PART 9

Plants and Mushrooms

CHAPTER 64

Plant-Induced Dermatitis

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Cutaneous exposure to plants may cause a wide array of skin problems. Plant-induced dermatitis can manifest in multiple ways, including weeping eczematous patches and plaques, vesicles and bullae, fine scaly patches, or any combination of these. Because the end result may be a generic response to injury, dermatitis is often an easy clinical diagnosis to make. However, determining the type of dermatitis affecting the patient can be difficult and frustrating. Acute care providers are often the first individuals to encounter and treat severe plant-induced dermatitis, so the ability to make a rapid and accurate diagnosis is crucial.

There are numerous subtypes of dermatitis: contact (irritant or allergic), photoallergic, nummular, asteatotic, stasis, seborrheic, atopic, and dyshidrotic. Dermatitis can manifest acutely with vesicles and bullae or in a chronic form with lichenification and hyperpigmentation. The acute nature of dermatitis is often itchy and uncomfortable, leading patients to seek emergency care. The history and physical examination are of the utmost importance in determining causality. A morphologic approach to the physical examination is a high-yield method for generating the appropriate differential diagnosis. Is the rash linear in nature? This often implies an external contactant. Is the rash in sun-exposed areas? This implies a photosensitive dermatitis.

In addition, the symptoms of the rash are important. Irritant reactions tend to decrescendo in severity, being the worst at presentation and gradually improving over time, whereas those that are allergic tend to crescendo, then decrescendo. They gradually build over 1 to 21 days to peak intensity, then slowly improve.

There are many clinical mimics of plant-induced dermatitis, including drug hypersensitivity reactions, connective tissue disease, superficial fungal infections, urticaria, and cutaneous T cell lymphoma. If a patient has persistent dermatitis that lasts longer than 1 month, a biopsy is often indicated to help differentiate possible mimickers. Pathology review of the biopsy specimen will help rule out other conditions and lead to appropriate therapy.

The subset of dermatitis discussed in this chapter is plant-induced dermatitis. Plant-induced dermatitis can be caused by contact with a wide variety of plants. Thousands of species of plants have been reported to cause dermatitis. The specific effects that each of these plants has on the skin have not been fully determined or described. The majority of medical literature regarding plant-induced dermatitis is anecdotal and has not been confirmed by independent observers. Few large-scale studies of the effects of plants have been performed. The exception is the *Toxicodendron* (poison ivy/oak/sumac) species of plants, because of their ubiquitous nature.

The most common injury to skin caused by plants is a simple scratch, laceration, or puncture wound. This can lead to bacterial or fungal infection. Plant-induced dermatitis reactions can be further subclassified. These include irritant contact dermatitis, allergic contact dermatitis, phototoxic dermatitis, and photoallergic dermatitis. Plants can also cause contact urticaria and foreign body reactions.

IRRITANT CONTACT DERMATITIS

A wide variety of plants cause irritant contact dermatitis, or nonallergic inflammation of the skin caused by direct contact with the offending plant. Most of these rashes are mild and self-limited, typically involving 1% to 2% body surface area (BSA). Irritant contact dermatitis causes transient redness and pruritus of the contacted skin. The spectrum of reactions ranges from linear scratch marks to weeping, ulcerated, red scaly plaques that may be difficult to link to the originating plant.

The most common cause of plant-induced contact dermatitis is irritant in nature. Irritant contact dermatitis can be further subdivided into traumatic (mechanical) and chemical causes. Most plants have the potential to cause traumatic skin injury. Some common plants in this category include rose thorns, cactus, orange trees, lemon trees, bougainvillea, and Euphorbiaceae.[37] Whether it is a thorn from a hawthorn tree, a cut from a sharp leaf edge, or scratches from briars, human skin is poorly prepared to protect itself from such insults (Figure 64-1).

Any foreign body embedded in the skin can cause a granulomatous reaction pattern. Some plants are more prone to causing this type of inflammatory reaction. Plants with thorns and barbs are the most likely culprits. Rose thorns and cactus spines are common offenders (Figure 64-2). Cacti are indigenous to the southwestern United States. They are popular as houseplants and can be grown indoors with proper care. Therefore, cactus injuries can be seen in a wide variety of locales.[116] The initial contact and acute injury may lead to chronic granulomatous inflammatory eruption, which typically takes 4 to 8 weeks to develop. It is the lag time that may make the diagnosis difficult. Clinically, the rash consists of erythematous and indurated papules, plaques, and nodules. The lesions are often grouped and localized, which is a clue to the diagnosis. Cactus spines may also penetrate so deeply into the skin that they cause pseudotumors of bone.[106]

The prickly pear (*Opuntia ficus-indica*) is found in North and Central America, as well as around the Mediterranean Sea. It is a member of the Cactaceae family. The fruit is covered with glochids. A unique example of mechanical trauma is from a glochid. Glochids are modified leaves that appear as tufts of barbed spines or hairs found on *Opuntia* species of cacti (Figure 64-3). They have sharp tips that penetrate skin and cause irritation by disrupting the epidermis. They are very loosely held to the cactus, release with the slightest touch, are quite irritating to skin, and cause variable amounts of discomfort and itching. They tend to break off from the cactus and work their way onto the skin, causing a granulomatous reaction that may resemble scabetic nodules.[106] They can also implant into the conjunctiva.[132] Glochids are present year-round and cause dermatitis in all seasons.

Similarly, penetrating injuries from a variety of cactus species, including *Echinopsis*, have been reported throughout the southwestern United States. Typical injuries manifest on the extremities as inflammatory papules. In rare cases, cactus spines can penetrate into bone and soft tissue spaces and cause inflammatory arthritis. Appropriate footwear and clothing, including gloves, are of utmost importance when encountering plants that can cause mechanical skin trauma. Treatment is to remove the spines from the skin. This is best done mechanically with a forceps under bright illumination and magnification if necessary[96,132] (Figure 64-4).

When biopsies are performed of the chronic (4 weeks after initial injury) inflammatory papules caused by cacti glochid implantation, a granulomatous reaction pattern is found.[79] Multiple multinucleated giant cells, histiocytes, granulomas, and organic plant material can be seen histologically under polarized light sources. Occasionally, a traumatic injury may implant one or more microbes. When performing a biopsy, one should also perform a tissue culture for bacteria, mycobacteria, and fungal species. This is especially true in cases with pustular morphologies.

FIGURE 64-1 Spiny thorns of the rose bush. *(Courtesy USDA-NRCS PLANTS Database; Herman DE, et al:* North Dakota tree handbook, *USDA NRCS ND State Soil Conservation Committee, Bismarck, ND, 1996, NDSU Extension and Western Area Power Administration.)*

FIGURE 64-3 Prickly pear cactus. *(Courtesy Jon Sullivan.)*

Initial treatment should be prompt extraction of the cactus spines. The smaller the spine, the more difficult the removal.[79] This is a particular problem when encountering injuries from the beaver tail cactus (Figure 64-5), which has very small glochids that can be quite difficult to remove. Many methods of removal have been employed to remove the spines. Tweezers are often the first line of removal, and various gels, glue, tape, and facial masks have been tried.[86] The best method is mechanical removal with a small forceps or fine needle. Once removal is accomplished, a topical corticosteroid can be employed. A midpotency topical corticosteroid, such as triamcinolone acetonide (Aristocort, Kenalog) 0.1% cream or ointment, is often all that is needed. The general recommendation is to use topical corticosteroids for 2 weeks at a time to avoid skin atrophy; however, reports in the literature suggest use twice daily for up to 3 months for this indication.[116] Most granulomatous reactions resolve within 2 to 4 months.[36] Often, removal attempts are unsuccessful, and the glochids work their way to the surface over months to years. Supportive care with cool compresses with aluminum acetate solution 1:40 in water used as soak, compress, or wet dressing is very helpful. Administering pain medication and initiating prompt therapy for any coinfection are integral parts of the overall treatment plan.

Infections may also be inoculated into the skin from mechanical plant injury. The most well known is *Sporothrix schenckii* fungal infection occurring after a prick or puncture from a rose thorn. *S. schenckii* is a common dimorphic fungus found in organic material. The characteristic lymphangitic spread is easily recognized (Figure 64-6). Typically, an ulcerating nodule develops at the site of inoculation; then, over the next 3 weeks (range, 3 days to 12 weeks), nodules develop along the draining lymphatic channels. The nodules eventually ulcerate, and patients develop chronic lymphangitis. First-line therapy is itraconazole, 200 mg orally (PO) once daily for 2 to 4 weeks after all lesions have resolved, usually for a total of 3 to 6 months.[26,90] There are many other infections caused by traumatic implantation of bacteria, fungus, and algae into skin or underlying subcutaneous tissues (Box 64-1).

Another common problem is direct implantation of plant organic material into the skin. This implantation causes a foreign body reaction, such as that seen with a splinter. The goals of treatment are to remove the foreign material promptly and treat infections with the appropriate antimicrobial agent(s).

Wood dust can also cause an eczematous dermatitis of either the irritant or allergic type. The victims are nearly always woodworkers who have been repeatedly exposed. Allergic contact dermatitis occasionally develops. Rarely, an erythema multiforme–like configuration is noted.[50] Respiratory hypersensitivity, including asthma, to wood dusts is well documented.[118] Solid wood

FIGURE 64-2 Many plants (including these from Peru) have evolved thorns and spines in self-defense. *(Courtesy Paul S. Auerbach.)*

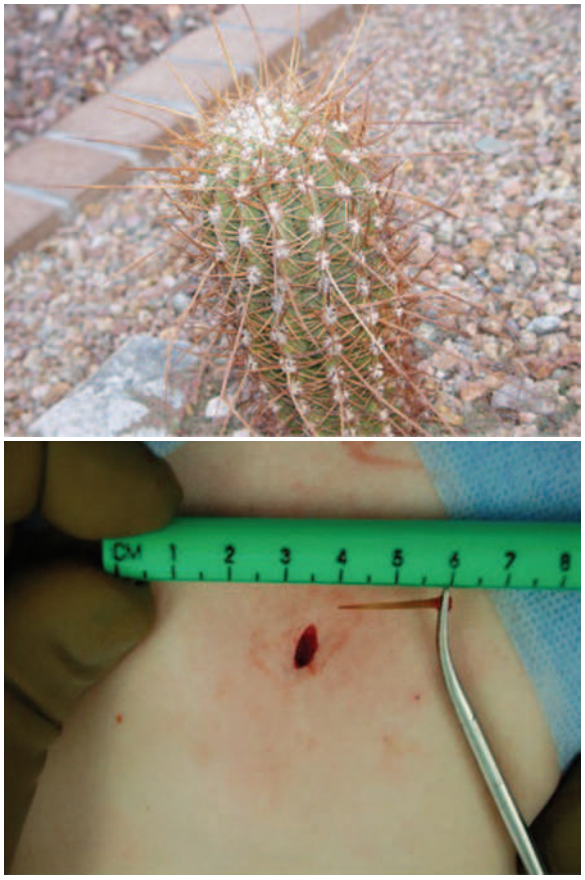

FIGURE 64-4 Penetrating cactus spine injury to mediastinum of a child. *(From O'Neill PJ, Sinha M, McArthur RA, et al: Penetrating cactus spine injury to the mediastinum of a child,* J Pediatr Surg *43:e33, 2008.)*

has very rarely been reported to cause dermatitis.[123] Table 64-1 lists the most commonly reported woods that cause contact dermatitis. Dermatitis from woods is almost entirely seen in occupational settings. Treatment includes avoidance of the offending agents and use of ultrapotent topical corticosteroids, such as clobetasol 0.05% ointment twice daily to the affected areas for up to 2 weeks.

The most common form of plant-induced irritant contact dermatitis is from plant-derived chemicals. Acids, enzymes, isothiocyanates, phorbol esters, calcium oxalate, and alcohols cause these reactions. The chemicals are directly toxic to the skin and work by altering inherent pH balance, dissolving protective lipids of the stratum corneum, and denaturing skin proteins. These reactions require direct contact of the plant material with the epidermis. Many factors can modify irritant reactions. The most important variables are duration of skin contact, concentration of the irritant, and underlying skin integrity and thickness.[8] Concentration of the irritant chemical in the plant will be at different levels in the stem, petals, roots, and leaves. Levels of the irritant also fluctuate at different times of the year, so someone could have a reaction in the summer months from contacting the leaves of an irritating plant and may not have the same reaction when touching the stem in winter.

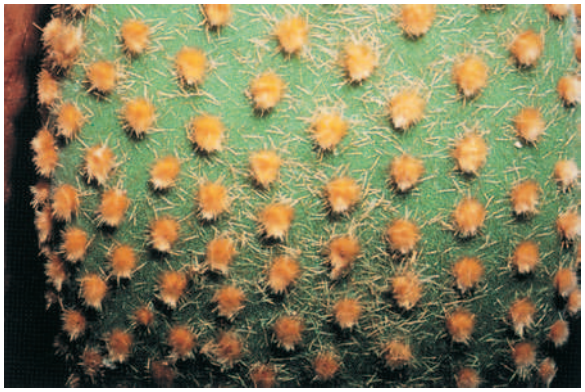

FIGURE 64-5 Beaver tail cactus. *(Courtesy Eric Lewis.)*

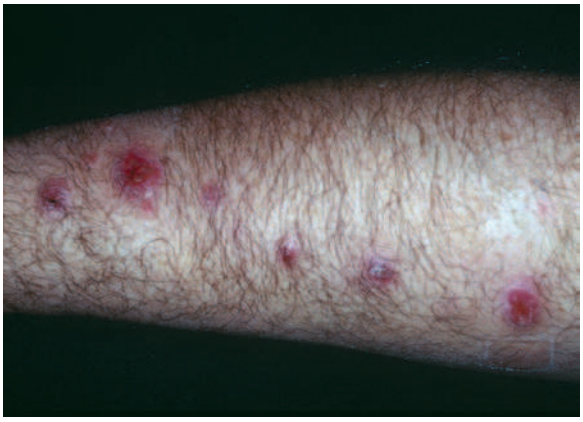

FIGURE 64-6 The characteristic red nodules that indicate lymphangitic spread of *Sporothrix schenckii.*

Plants in the spurge (Euphorbiaceae) family exude a milky sap when traumatized. This sap contains a chemical mixture of irritating diterpenes and phorbol esters.[44] After skin contact, the reactions can vary from mild stinging and burning to erythema, vesiculation, and bulla formation. Blister formation typically occurs within 24 hours. Eczematous weeping plaques can also be seen in the first 24 hours. Reactions can last for 2 to 3 weeks. The spurge family is a large family of plants with more than 7000 described members. These plants are found predominantly in tropical climates; in the United States, they can be found mainly in Florida and the southwestern states. Some well-known members of the Euphorbiaceae family include the croton plant, wolfsmilk, manchineel tree, and snow-on-the-mountain (Figure 64-7 and Table 64-2).

Plants of the genus *Croton* are also members of the spurge family. These tropical plants are the source of croton oil. This oil had been used in the past as a purgative and for many medicinal remedies. The plants contain a mixture of phorbol esters and diterpenes in their leaves, stems, and seeds.[18] These

BOX 64-1 Infections Associated with Mechanical Plant Injury

Bacterial
Staphylococcus aureus
Clostridium tetani

Chromomycosis
Fonsecaea pedrosoi
Phialophora compacta
Phialophora verrucosa
Cladosporium carrionii
Rhinocladiella aquaspersa

Phaeohyphomycosis
Exophiala jeanselmei
Wangiella dermatitidis

Mycetoma
Madurella mycetomatis
Actinomadura madurae
Actinomadura pelletieri
Nocardia brasiliensis
Nocardia cavae
Nocardia asteroides
Streptomyces somaliensis
Madurella grisea
Leptosphaeria senegalensis
Petriellidium boydii
Aspergillus nidulans

Protothecosis
Prototheca wickerhamii

Mycobacterial
Mycobacterium kansasii
Mycobacterium marinum
Mycobacterium ulcerans

Other Fungal
Blastomyces dermatitidis
Sporothrix schenckii
Histoplasma capsulatum

Data from references 71, 92, and 130.

TABLE 64-1 Sampling of Wood Trees That Cause Contact Dermatitis

Common Name	Botanical Name
African black walnut	*Mansonia altissima*
African blackwood	*Dalbergia melanoxylon*
Bolivian rosewood	*Machaerium acutifolium*
Brazilian box tree	*Aspidosperma* spp.
Cocobolo	*Dalbergia retusa*
Cordia	*Cordia goeldiana*
East Indian rosewood	*Dalbergia latifolia*
Ebony	*Diospyros celebica*
Honduran mahogany	*Swietenia macrophylla*
Iroko	*Chlorophora excelsa*
Litre	*Lithrea caustica*
Macassar ebony	*Diospyros celebica*
Mahogany	*Khaya* spp.
Milo wood	*Thespesia populnea*
Obeche	*Triplochiton scleroxylon*
Padauk	*Pterocarpus dalbergiodes*
Pao ferro	*Machaerium scleroxylum*
Perupok	*Lophopetalum dubicum*
Pine	*Pinus* spp.
Redwood	*Sequioa sempervirens*
Sapele wood	*Entandrophragma cylindricum*
Silky oak	*Grevillea robusta*
Sucupira	*Bowdichia nitida*
Tali wood	*Erythrophleum guineense*
Teak	*Tectona grandis*
Walnut	*Juglans nigra*
White ash	*Fraxinus americanus*
Zebrawood	*Astronium fraxinifolium*

Data from references 2, 3, 24, 25, 51, 52, 74, and 102.

TABLE 64-2 Common Members of the Euphorbiaceae Family

Common Name	Botanical Name
Poinsettia	*Euphorbia pulcherrima*
Candelabra cactus	*Euphorbia lactea*
Caper spurge	*Euphorbia lathyrus*
Chinese tallow	*Sapium sebiferum*
Crown-of-thorns	*Euphorbia splendens*
Cypress spurge	*Euphorbia cyparissias*
Manchineel tree	*Hippomane mancinella*
Pencil tree	*Euphorbia tirucalli*
Petty spurge	*Euphorbia peplus*
Sandbox tree	*Hura crepitans*
Snow-on-the-mountain	*Euphorbia marginata*
Sun spurge	*Euphorbia helioscopia*
Wolfsmilk	*Euphorbia purpurea*

Data from Asilian A, Faghihi G: Severe irritant contact dermatitis from cypress spurge, *Contact Dermatitis* 51:37, 2004; and Lovell CR: Irritant plants. In Lovell CR, editor: *Plants and the skin*, Oxford, 1993, Blackwell Scientific Publications, pp 42-95.

esters can cause immediate skin blistering, as well as a weeping eczematous eruption. These plants are found mostly in Central and South America, but approximately 40 species live in the southern United States. They typically appear as low-lying shrubs.

Some plants, such as those listed in Table 64-3, contain proteolytic enzymes, which cause skin irritation when contacted in sufficiently high concentrations. Plants such as *Mucuna pruriens* (cowhage) contain a proteolytic enzyme, mucunain, that causes intense itching immediately on contact. Its seed pods are covered with tiny stinging hairs called *trichomes,* which contain high concentrations of mucunain. This enzyme has been used for decades by practical jokers in its dried form as itch powder. Recently, medical researchers have made use of the irritant enzyme found in papaya. Papain is a proteolytic enzyme that is used in a number of commercial wound dressings to aid in degradation of necrotic tissue and to assist wound healing.[103]

FIGURE 64-7 Common plants that induce irritant phytophotodermatitis. **A,** Snow-on-the-mountain. **B,** Wolfsmilk. **C,** Croton bush. (***C** courtesy Yves Sell, Institute of Botany, Louis Pasteur University, Strasbourg, France.)*

TABLE 64-3 Common Plants with Irritant Enzymes

Common Name	Botanical Name	Proteolytic Enzyme
Cowhage	*Mucuna pruriens*	Mucunain
Crownflower	*Calotropis* spp.	Mudarin
Pineapple	*Ananas comosus*	Bromelin
Papaya	*Carica papaya*	Papain
Fig tree	*Ficus carica*	Ficin

Calcium oxalate is a common skin irritant. Calcium oxalate in plants is found in a crystalline needle-like form called *raphides*. It is present in irritating concentrations in many plants, including dumb cane, rhubarb, agave, daffodils, and hyacinths. Dumb cane (*Dieffenbachia* spp.) is a common houseplant well known to cause irritant skin and mucous membrane reactions (Figure 64-8).[30] The common name arises from the effect it has on persons who chew its leaves, which release calcium oxalate. Calcium oxalate causes irritation, swelling, salivation, pain, and blistering of mucous membranes. In an extreme case, the person is unable to speak normally.[133] When the sap of this plant contacts the eye, conjunctival swelling and corneal ulcers may occur.[87] Raphides are also found in *Agave* species. Irritant contact dermatitis has been reported in tequila distillery workers, who are in frequent contact with *Agave tequilana*.[110] Purpuric and irritant reactions have been reported after exposure to sap of *Agave americana*.[25,105] Immediate burning on exposure is characteristic of calcium oxalate toxicity.

Daffodils and hyacinths are among the many other species containing calcium oxalate, which is found in its highest concentration in the bulb.[121] Agricultural workers who gather these bulbs and flowers are at highest risk for irritant dermatitis, typically on the distal extremities where they came into contact with the plant.[62]

The family Solanaceae contains the peppers. These plant species contain several capsaicinoids, the most common of which is capsaicin. Capsaicin is a chemical compound that can cause skin and mucous membrane burning, itching, and in severe cases, vesiculation and bulla formation. Specialized cells of the plant's placenta produce capsaicin. Capsaicin binds to receptors on neurons and causes release of substance P from primary sensory neurons. With repeated applications, capsaicin causes depletion of substance P and desensitizes the neuron. This effect is used in clinical practice with topical application of capsaicin-containing compounds to skin in areas of chronic pain, such as for postherpetic neuralgia.

Brassicaceae (Cruciferae) is a large family of plants that causes irritant contact dermatitis. More than 3500 species live in temperate regions of the world.[32] Its members include horseradish (*Armoracia rusticana*), black mustard (*Brassica nigra*), and white mustard (*Sinapis alba*) (Figure 64-9). These plants contain glucosinolates, which are converted to isothiocyanate, which causes irritant dermatitis.[82] This reaction is catalyzed by the enzyme myrosinase. Substrate interacts with the enzyme after the plant is crushed, as in chewing.[32] Contact with these plants can cause a wide range of cutaneous reactions, including burning sensation, pain, red patches, and blister formation.

The Ranunculaceae family includes buttercups and Old Man's Beard (Figure 64-10). Table 64-4 lists a small sampling of plants in this family reported to cause irritant contact dermatitis. Protoanemonin is considered the primary irritant toxin in this group of plants. Reactions from these plants tend to be mild and rarely cause people to seek medical care. Table 64-5 includes plants and plant families that cause irritant phytocontact dermatitis and lists their primary irritant substance.[74,121]

It is currently believed that both irritation and contact sensitization are mediated by epidermally derived cytokines. Tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), macrophage inflammatory protein-2 (MIP-2), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are produced and secreted into tissue in response to both allergens and irritants. However, a number of other proteins are released only by allergenic stimulation.

In irritant contact dermatitis, the chemical irritant (which is usually an acid, alkali, surfactant, solvent, oxidant, enzyme, or toxin) damages keratinocytes. This damage is highly dependent on the concentration of the irritant. No sensitization or elicitation

FIGURE 64-8 *Dieffenbachia* species.

FIGURE 64-9 White mustard plant. *(Courtesy Yves Sell, Institute of Botany, Louis Pasteur University, Strasbourg, France.)*

FIGURE 64-10 Plants of the family Ranunculaceae. **A,** Buttercup. **B,** Old Man's Beard. *(**B** courtesy Yves Sell, Institute of Botany, Louis Pasteur University, Strasbourg, France.)*

phase occurs, as is seen in allergic contact dermatitis, which is a key discerning feature between the two types of plant-induced contact dermatitis. The damaged keratinocyte activates phospholipase A_2. This in turn cleaves arachidonic acid and diacylglyceride (DAG) from the cell membrane. Arachidonic acid is converted into various prostaglandins and leukotrienes. Prostaglandins and leukotrienes cause endothelial cells to dilate and become leaky, resulting in edema. They also act on mast cells to release histamine and are chemoattractants for lymphocytes and neutrophils. Further recruitment of lymphocytes and neutrophils is facilitated by expression of intercellular adhesion molecule-1 (ICAM-1) by keratinocytes.[84] The DAG causes upregulation of genes for cytokines such as interleukin-1 (IL-1) and GM-CSF. These proteins then act to stimulate T cells and neutrophils. All these inflammatory cells combined with release of various cytokines and vasoactive substances lead to the clinical findings of irritant contact dermatitis. This is a continuing area of investigation.[107,134]

TREATMENT

Treatment of primary irritant dermatitis requires multiple steps. The victim must be removed from exposure to the irritant chemicals. Gentle cleansing of the wound with antibacterial soap, cool compresses, and watching for infection are essential. Antihistamines, such as hydroxyzine 10 to 25 mg PO four times daily, or diphenhydramine 25 mg PO two to four times daily, can help with itching. The sedating antihistamines tend to work better than the newer, nonsedating types (fexofenadine, loratadine, and desloratadine), although some patients respond well to the nonsedating forms. Topical medium-strength corticosteroids, such as triamcinolone 0.1% cream, may be applied twice daily to the affected areas for up to 2 weeks without risk for atrophy. Clobetasol 0.05% cream or ointment (an ultrapotent topical corticosteroid) can also be used in severe cases. In the case of topical medium-strength and ultrapotent topical corticosteroids, care should be taken to avoid application in the groin, axillae, and face. Typical application regimens are twice daily for 1 to 2 weeks. Cool compresses with aluminum acetate solution (Domeboro, Burow's solution) diluted 1:40 in water are very helpful for soothing pruritus and exudative skin irritation. Dermatitis generally heals in less than 7 days if no complications develop and if tissue damage is minimal. If the patient is unable to be removed from the source of irritation, no medicine, cream, or soak will alleviate the problem. People are sometimes forced to change occupations or hobbies, or at the very least modify their environment.

TABLE 64-4 Irritant Plants in the Family Ranunculaceae

Common Name	Botanical Name
American prairie crocus	*Pulsatilla patens*
Buttercup	*Ranunculus* spp.
Christmas rose	*Helleborus niger*
Meadow rue	*Thalictrum foliosum*
Pasque flower	*Pulsatilla vulgaris*
Pilewort	*Ranunculus ficaria*
Staves-acre	*Delphinium* spp.
Traveler's joy	*Clematis vitalba*
Windflower	*Anemone nemorosa*
Wolfsbane	*Aconitum napellus*

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is a type IV delayed hypersensitivity reaction. This form of contact allergy is much more common than is contact urticaria. The most common acute presentation is linearly arranged eczematous, edematous patches and plaques with

TABLE 64-5 Plants Causing Irritant Phytocontact Dermatitis and Their Primary Irritant Chemicals

Common Name	Botanical Name	Irritant Chemical
Agave	*Agave americana*	Calcium oxalate
Black mustard	*Brassica nigra*	Isothiocyanates
Buttercup	*Ranunculus bulbosus*	Protoanemonin
Coral plant	*Jatropha*	Thioglycoside
Cowhage	*Mucuna pruriens*	Proteolytic enzymes
Croton	*Croton tiglium*	Phorbol esters
Daffodils	Amaryllidaceae family	Calcium oxalate
Dumb cane	*Dieffenbachia* spp.	Calcium oxalate
Hyacinths	Liliaceae family	Calcium oxalate
Manchineel tree	*Hippomane mancinella*	Phorbol esters
May apple	*Podophyllium peltatum*	Podophyllin resin
Pencil tree	*Euphorbia tirucalli*	Triterpene alcohols
Prickly pear	*Opuntia* spp.	Spines
Spurges	Euphorbiaceae family	Shorbol and diterpene esters
Mustard, radish, etc.	Cruciferae (Brassicaceae) family	Isothiocyanates
Buttercups, pilewort	Ranunculaceae	Protoanemonin
Common caper	Capparidaceae family (e.g., *Capparis spinosa*)	Isothiocyanates
Peppers	Solanaceae family	Capsaicin
Spider plant	Cleomaceae family (e.g., *Cleome* species)	Isiothiocyanates

Data from High WA: Agave contact dermatitis, *Am J Contact Dermat* 14:213, 2003; and Ricks MR, Vogel PS, Elston DM, et al: Purpuric agave dermatitis, *J Am Acad Dermatol* 40:356, 1999.

TABLE 64-6 *Toxicodendron* Species

Common Name	Botanical Name
Western poison oak	*Toxicodendron diversilobum*
Eastern poison oak	*Toxicodendron quercifolium*
Poison ivy	*Toxicodendron radicans*
Rydberg's poison ivy	*Toxicodendron rydbergii*
Poison sumac	*Toxicodendron vernix*

varying amounts of vesiculation and bulla eruption. Occasionally, the eruption is widespread. If the face is involved, there can be severe eyelid swelling. Patients are quite distressed by their appearance. In severe cases, they can have systemic symptoms of fever, chills, fatigue, and lethargy. In its more chronic form, as is seen with the Compositae family, allergic contact dermatitis presents with lichenified eczematous plaques in exposed areas.

TOXICODENDRON (POISON IVY/OAK/SUMAC)

The most common cause of acute allergic contact dermatitis in the United States is from exposure to poison ivy, oak, and sumac plants (Table 64-6). In the past, allergic contact dermatitis caused by poison ivy, oak, or sumac was referred to as *Rhus* dermatitis. Recent botanical nomenclature places the poison ivy, oak, and sumac plants in the Anacardiaceae family in the genus *Toxicodendron*. The *Rhus* genus contains plants that are not known to cause allergic contact dermatitis. Therefore, the term "*Rhus* dermatitis" should be abandoned.

Toxicodendron weeds are fastidious. They do not grow in Alaska or Hawaii and do not survive well above 1500 m (5000 feet), in deserts, or in rain forests. They grow best along cool streams and lakes and luxuriate if it is also sunny and hot. They are found in every state of the continental United States. The plants have different configurations in different regions, but generally, poison ivy grows east of the Rockies, poison oak grows west of the Rockies, and poison sumac grows best in the southeastern United States. Because avoidance is the best prevention, it is important to learn what the plants look like in a given area (Figure 64-11). Once contaminated with the oil (resin), an average person has 1 to 4 hours to wash it off with soap and water to prevent dermatitis.

Poison ivy (*T. radicans*) grows in moist shady regions east of the Rockies. The plants thrive at sea level and do very poorly above 1500 m (5000 feet). Poison ivy is never found on the U.S. West Coast. The leaflets are 10 to 30 cm (4 to 12 inches) long and are found in groups of three. The shape of the leaves is often ovate or obtuse. The leaves can be shiny, smooth, and hairless, or they can be rough, hairy, and velvety[12,32] (Figure 64-12). Its characteristic shape has led to the adage, "Leaves of three, let them be" (Figure 64-13). It is a climbing shrub commonly found growing up the trunks of large trees, with aerial roots that are quite prominent.

Poison oak (*T. diversilobum*) is found in the west coastal states of North America and is given the designation *western poison oak*. It is a common shrub with multiple stems that form three leaflets. The leaves are larger on plants that grow in shade than on those grown in full or partial sunny conditions. It has many brown aerial roots and clusters of yellow flowers that bloom in the spring.[32] The flowers bear cream-colored berries. In the California hills, poison oak grows like a forest, but in cooler, dry climates, it remains isolated in small patches.

Poison sumac (*T. vernix*) is a fast-growing small tree or shrub. Some plants grow as tall as 12 m (40 feet), but the average height is about 4.5 m (15 feet). The plants are found in wet marshy regions of the United States. Its leaves are unique among *Toxicodendron* species. They are configured as 7 to 13 smooth oval leaflets attached along a central stem.[32] The plant forms pale-colored fruit. Nonpoisonous sumacs can be recognized by their jagged leaf margins and red berries.

All *Toxicodendron* plants have many interconnected channels that contain sap. When the plant is traumatized and a channel is broken open, the sap is extruded and hardens as a black resin

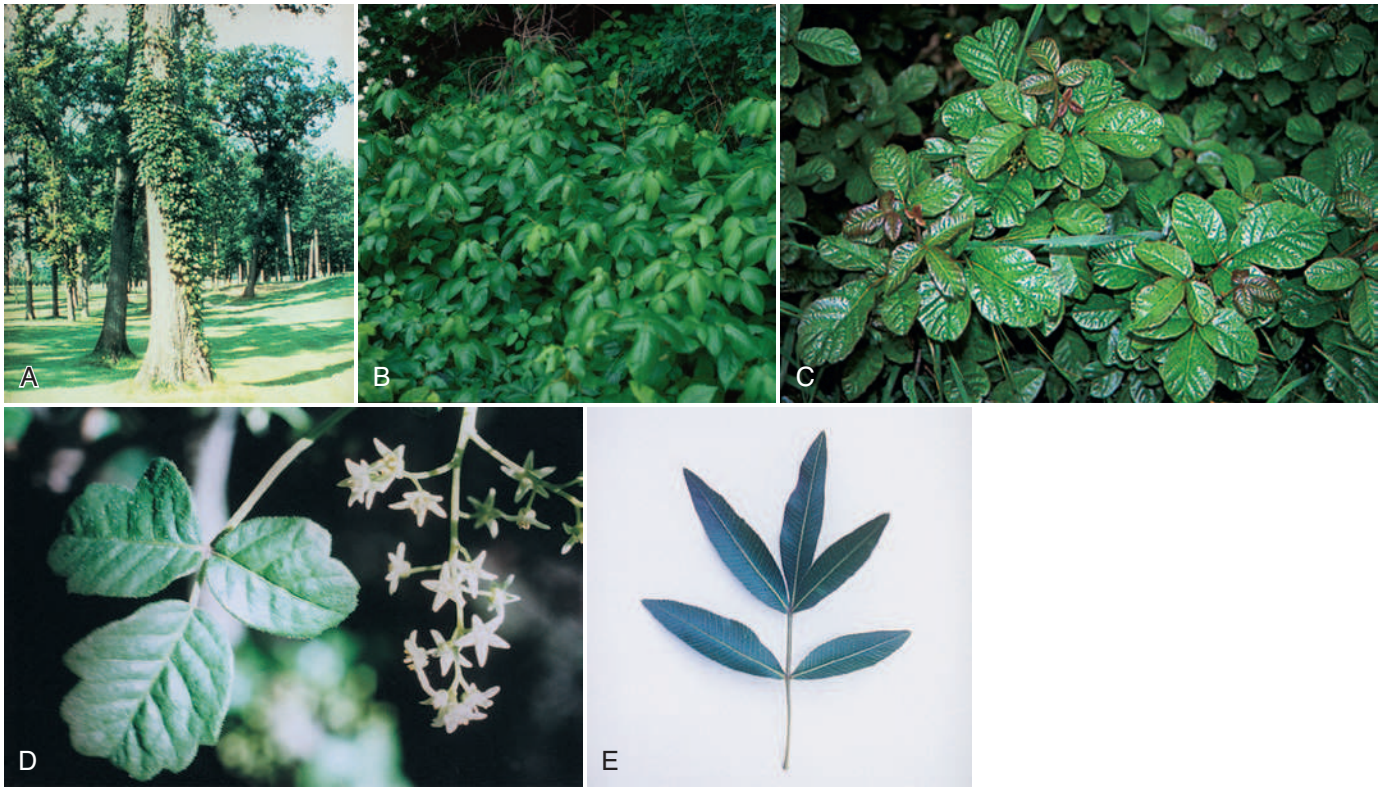

FIGURE 64-11 Plants in the *Toxicodendron* genus. **A,** Poison ivy. **B,** Poison ivy growing as a sea of vines. **C,** Poison oak. **D,** Poison oak, close-up. **E,** Poison sumac. (*C courtesy Paul S. Auerbach.*)

FIGURE 64-12 **A** to **D,** Poison ivy can have various appearances.

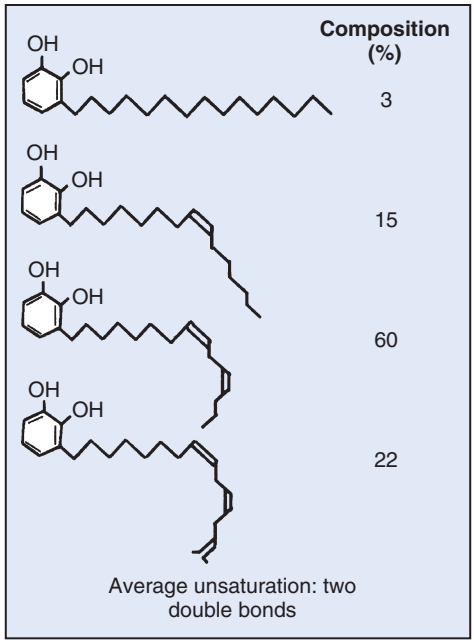

FIGURE 64-14 General structure and composition of poison ivy urushiol.

to seal off the damage. This sap is the material that contains the allergen urushiol.[32]

All parts of the plant contain the urushiol resin, which is a heavy, nonvolatile oil (Figure 64-14). In its natural state, the oil is colorless or slightly yellow. Because the oil is virtually invisible, many people fail to understand how they acquired the rash. It is not a vapor, because at 315° C (600° F) in a fire or oven, urushiol splatters like butter. In a camp or forest fire, it attaches to smoke particles and can be carried downwind. The oil also readily coats the fur of animals, which explains why people often contract the dermatitis from their outdoor pets. On exposure to air, the oil oxidizes, polymerizes, and turns black. This is a way to recognize the weeds, especially in autumn when the leaves fall off.

The amount of urushiol present in poison ivy and poison oak is roughly equal year-round, even when the plants are only sticks without leaves in the winter. As the leaves turn red and start to dry up in the fall, important nutrients, including urushiol, return to the stem and roots through subepidermal resin canals.[52] Therefore, dead leaves that fall to the ground are virtually devoid of urushiol.

Urushiol is exposed to skin when a plant that has been injured or bruised releases it to the surface of the leaf, petal, stem, or root. Clinical effects usually manifest 24 to 48 hours after contact in a previously sensitized individual[111] and 10 to 14 days after contact in a patient on first exposure. Typically, linear streaking of papulovesicles occurs; edema, weeping, and crusting are also often seen (Figure 64-15). A distinct linear nature is often a clue to the diagnosis of allergic contact dermatitis. On occasion, the eruption can appear to be urticarial in nature or can mimic cellulitis. Appearance of black dots on the skin in areas of involvement can be helpful in determining the etiology.[69] The black dots represent dried urushiol that has been oxidized by air (Figure 64-16). Severe itching leading to excoriations almost always accompanies the rash. This can lead to secondary infection.

FIGURE 64-13 Close-up views of the characteristic three-leaf pattern of *Toxicodendron*. *(Courtesy Peter Schalock, Massachusetts General Hospital, Boston, Mass.)*

The antigen is found in the milky sap, which is quickly absorbed into the skin. It is nearly impossible to wash off the sap quickly enough to prevent dermatitis. Once the sap touches the body, it is often spread by inadvertent transfer. This explains why patients often develop eruptions in sites distant from the initial contact with the plant. There are many unique urushiol chemicals. Collectively, they can be called *urushioids*. Each plant has a different urushioid concentration and composition. Urushioids have a structure that contains a benzene ring with a varying-length carbon side chain. Concentrations of the various urushioids of each plant depend on growing conditions and season, which also affect their antigenic properties. If the side chain is desaturated and longer, this increases the catechols' antigenicity. Conversely, if there is a substitution on the catechol ring, this reduces antigenicity.[84] Addition of an aliphatic side chain and presence of free phenolic groups also increase antigenicity.[121] Poison ivy contains predominantly urushiol III, poison oak contains mostly urushiol I, and poison sumac contains predominantly urushiol II.[32,84]

If the patient avoids repeat exposure, dermatitis resolves within 14 to 21 days in most cases. It is important to diagnose secondary impetiginization because this can lead to cellulitis if not treated with appropriate antibiotics. The most likely pathogens are *Staphylococcus aureus* and streptococcal species. Hyposensitization therapy has not proved practical or particularly effective and is rarely performed. Patients need to be informed to clean clothing thoroughly, through at least one complete automated hot-water wash and rinse cycle with detergent, and to clean any object that may have come in contact with the plant in order to avoid repeat exposure.

It is estimated that 50% to 70% of the population is sensitive to the causative antigen, urushiol. The amount of purified

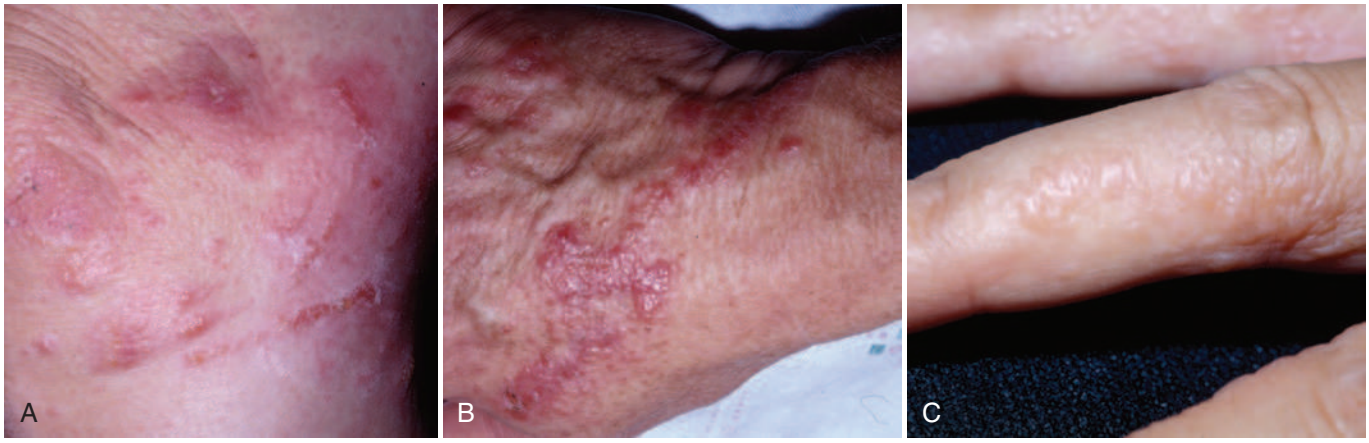

FIGURE 64-15 Representation of the linear nature of poison ivy–induced allergic contact dermatitis. **A,** Knee. **B,** Hand. **C,** Finger.

urushiol required to elicit a reaction is 2 to 2.5 mg.[47] Some people (~35%) are considered subclinically sensitive because they have negative skin test reactions to 2.5 mg of urushiol but react to higher concentrations, such as 5, 10, and 50 mg.[47] Clinically, this group is interesting because they invariably did not have poison ivy dermatitis as teenagers and often plucked the weeds with apparent impunity. However, usually in midlife after a bout of weed pulling, a rash spreads explosively. For unknown reasons, they have crossed the line into clinical sensitivity. If patch-tested with dilutions of urushiol, these individuals are often exquisitely sensitive and do not appear to lose their reactivity. The flare-up may last for several weeks, probably because of prior contamination of the home and workplace with urushiol oil. Treatment must be aggressive and more prolonged than usual.

A smaller group (10% to 15%) does not react to higher concentrations and cannot be sensitized by 1000 mg. This group was first detected and studied in passive transfer experiments in the 1950s.[48] These individuals are considered to be naturally tolerant, but it remains unclear whether they achieved that state by early antigenic exposure or by genetic luck. They have no inherent resistance to contact sensitization with other chemicals and otherwise appear healthy.[49] They may hold a clue to the molecular basis for immunologic tolerance.

From a practical standpoint, only 10% to 15% of Americans (up to 40 million people) can be categorized as exquisitely sensitive. Generally, these persons seek and need emergency medical care (Figure 64-17). They typically have had prior unpleasant experiences. Within 2 to 6 hours after exposure, swelling is accompanied by an erythematous, intensely pruritic, edematous, vesicular, and ultimately bullous eruption that can be associated with fever, malaise, and prostration (Figure 64-18). This true dermatologic emergency should be treated immediately and vigorously.

Extreme susceptibility tends to be familial; if one parent is supersensitive, children are likely to be as well. If both parents are sensitive, the chance of sensitive offspring is about 80%.[128] The level of individual sensitivity is not determined by severity of the initial bout of dermatitis, although almost one-half of patients admit to a memorable bout of dermatitis as a teenager. However, no more than 25% to 35% of patients at age 30 to 40 were stricken within the previous year.[42] When these patients are patch-tested with weak dilutions of urushiol, less than one-half react as might be expected from their history. An individual's level of reactivity does not change appreciably if he or she is tested monthly over a year; testing at less frequent intervals in very sensitive patients over 3 to 4 years has shown little or no change in the level of reactivity.[47] Repeated mild to moderate

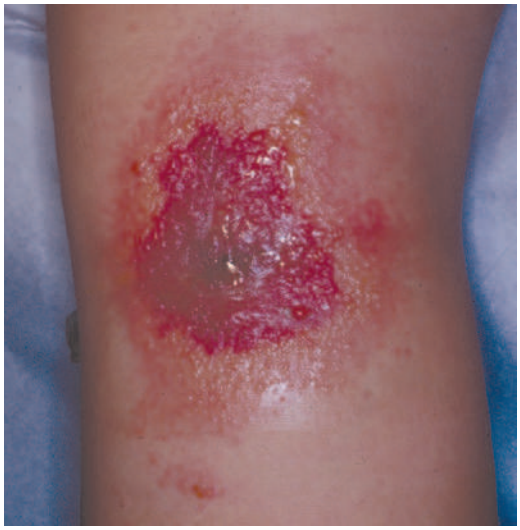

FIGURE 64-16 Poison ivy–induced allergic contact dermatitis after a young woman accidentally pinched some poison ivy leaves behind her knee. Note the central black dots, which represent the dried urushiol.

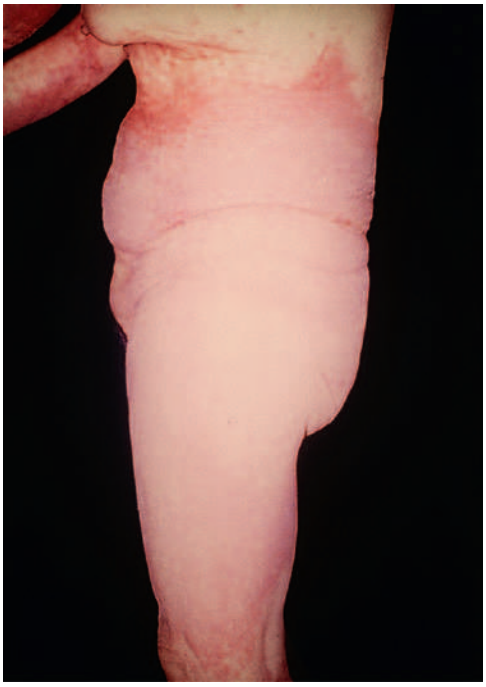

FIGURE 64-17 Generalized poison ivy dermatitis.

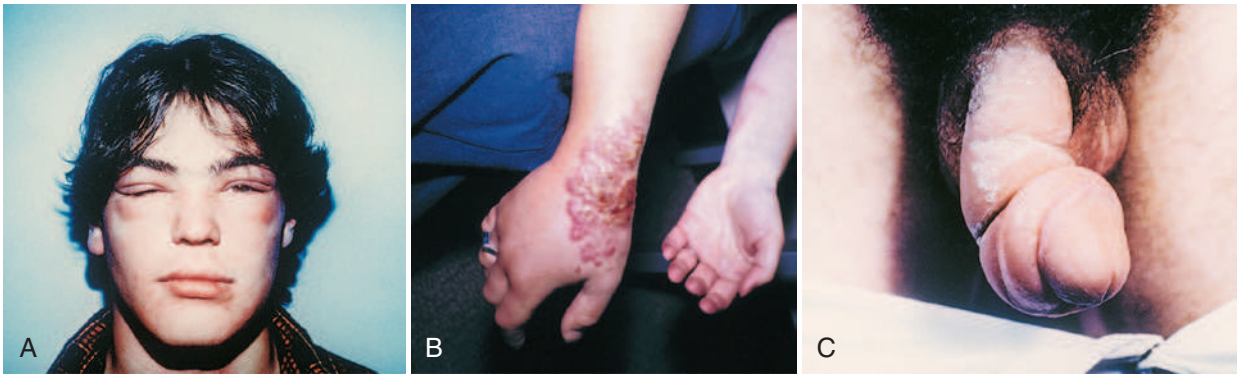

FIGURE 64-18 Severe acute poison oak dermatitis. **A,** Facial edema. **B,** Blisters. **C,** Penile edema. *(Courtesy Axel Hoke.)*

bouts of dermatitis maintain the sensitive state, whereas a single severe bout may produce a prolonged period of anergy or refractoriness, not unlike the clinical condition of "hardening" or unresponsiveness, which is well described in the industrial setting.[41,42,113]

The Anacardiaceae family accounts for most cases of allergic contact dermatitis in the United States. Table 64-7 catalogs the major members of this family and the plants most likely to cause dermatitis. Most individuals who spend a great deal of time outdoors know how to recognize these plants and appropriately avoid them. Figure 64-11 shows poison ivy, oak, and sumac. However, these are not the only plants that need to be considered. Table 64-8 lists some common plants causing allergic contact dermatitis.

In patients who have demonstrated allergic contact dermatitis to the *Toxicodendron* plants, there is a high risk of cross-reactivity with a number of other plants, including mango, oil from the cashew nut shell, fruit pulp from *Ginkgo biloba,* Japanese lacquer tree, and India marker ink tree. Mango dermatitis has been reported to be the leading cause of plant dermatitis in Hawaii.[121] (Figure 64-19). The allergens causing mango dermatitis are three resorcinol derivatives: heptadecadienylresorcinol, heptadecenylresorcinol, and pentadecylresorcinol.[95] Urushiol is found in the plant's leaves and stems and in its fruit's skin. Typically, people are exposed to the urushiol when they eat or manipulate the fruit that has yet to be peeled. Facial involvement, particularly of the lips, occurs after biting into a mango that still

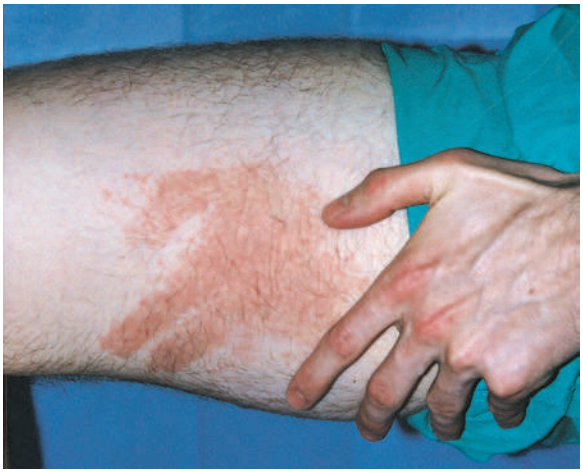

FIGURE 64-19 Pruritic and eczematous rash 3 days after onset. One week earlier, this 27-year-old man had peeled a mango, become distracted by a telephone call, and rested his left hand on his right leg. Three days later, contact dermatitis became apparent. When much younger, the patient had been sensitized to poison oak and poison ivy; the sap of the mango rind contains oleoresins that cross-react with the oleoresins of poison ivy. The rash resolved after 1 week of treatment with topical corticosteroids. *(From Tucker MO, Swan CR: Images in clinical medicine: The mango-poison ivy connection,* N Engl J Med *339:235, 1998.)*

TABLE 64-7 Anacardiaceae Family

Common Name	Botanical Name
Brazilian pepper	*Schinus terebinthifolius*
Cashew	*Anacardium occidentale*
El litre tree	*Lithraea caustica*
Ginkgo tree	*Ginkgo biloba*
Indian marking nut	*Semecarpus anacardium*
Japanese lacquer	*Rhus vernicifera*
Korean lacquer tree	*Rhus vernicifera stokes*
Mango	*Mangifera indica*
Pepeo tree	*Mauria puberula*
Poison ivy	*Toxicodendron radicans* and *T. rydbergii*
Poison oak	*Toxicodendron diversilobum* and *T. toxicarium*
Poison sumac	*Toxicodendron vernix*
Poisonwood	*Metopium toxiferum*
Renges tree	*Anacardium melanorrhoea*

Data from Marks JG Jr, Elsner P, DeLeo VA: *Contact and occupational dermatology,* ed 3, St Louis, 2002, Mosby, pp 13-15.

TABLE 64-8 Plants Causing Allergic Contact Dermatitis

Common Name	Botanical Name
(Various)	*Alstromeria* spp.
(Various)	*Compositae* spp. (~20,000)
(Various)	*Grevilla* spp.
Lichen	*Cladonia, Evernia,* and *Primelia* spp.
Liverwort	*Frullania* spp.
Pine tree	*Pinus* spp.
Poison ivy	*Toxicodendron radicans*
Poison oak	*Toxicodendron diversilobum*
Poison sumac	*Toxicodendron vernix*
Primrose	*Primula obconica*
Ragweed	*Ambrosia* spp.
Tulip	*Tulipia* spp.

Data from Marks JG Jr, Elsner P, DeLeo VA: *Contact and occupational dermatology,* ed 3, St Louis, 2002, Mosby, pp 13-15.

FIGURE 64-20 *Ginkgo biloba.*

carries its outer peel. The other common area of involvement is the hand after individuals peel the fruit.[82] Once peeled, mangos are no longer allergenic. Cross-hypersensitivity between mango contact allergens and urushiol has been reported.[95]

The ginkgo tree, *Ginkgo biloba,* is commonly found in cities, where the trees thrive. Its characteristic split leaves are easily recognized (Figure 64-20). It has been reported to cause allergic contact dermatitis in joggers who run through debris on sidewalks and roadways containing ginkgo leaves, flowers, and fruit.

Multiple plants are similar in appearance to the poison ivy plant and need to be differentiated. Table 64-9 lists some of the more common "imposters" for the poison ivy plant. The Virginia creeper, *Parthenocissus quinquefolia,* is frequently misidentified as poison ivy. Figure 64-21 shows poison ivy side by side with the Virginia creeper. English ivy, *Hedra helix,* is another plant that is often difficult to differentiate from poison ivy. *H. helix* has been reported to cause allergic contact dermatitis.[135]

TABLE 64-9 Imposters of the Poison Ivy Plant

Common Name	Botanical Name
Boston ivy	*Parthenocissus tricuspidata*
English ivy	*Hedra helix*
Skunkbush sumac	*Rhus trilobata*
Virginia creeper	*Parthenocissus quinquefolia*

Data from McGovern TW, LaWarre SR, Brunette C: Is it or isn't it? Poison ivy look-a-likes, *Am J Contact Dermat* 11:104, 2000.

FIGURE 64-21 Poison ivy on the left, with three leaves, adjacent to the plant (Virginia creeper, with five leaves) for which it is commonly mistaken (*bottom* and *right*).

IMMUNOLOGY OF POISON IVY AND POISON OAK DERMATITIS

The immunologic mechanism for allergic contact dermatitis is generally thought to be type IV cell-mediated delayed hypersensitivity.[43] An initial sensitization phase occurs, followed by an elicitation phase on subsequent exposure.

Allergic contact dermatitis is caused by haptens. Haptens are low-molecular-weight compounds, almost always 500 daltons or less, that exist as unprocessed antigen. They are lipid soluble, allowing them to pass into the stratum corneum.[77] Contact allergens are not immunogenic by themselves; they bind to epidermal proteins to generate new antigenic determinants.[66,76] Urushiol from poison ivy is a hapten. Percutaneous penetration of the hapten is followed by haptenization of self-proteins, which are then recognized by the innate immune system.[66] Sensing by Toll-like receptors (TLRs) and inflammasomes results in proinflammatory cytokines and chemokines that drive epidermal and dermal inflammation. Among these, TNF, IL-Iβ, and IL-18 are required for hapten-induced dendritic cell activation and migration from the skin to local lymph nodes.[66] Finally, antigen presentation by the skin dendritic cells at the lymph nodes to the naive and memory T cells leads to their activation and differentiation. These are the early immune events in the induction of allergic contact dermatitis.

Langerhans cells are the main antigen-presenting cells (APCs) in the skin. They are normally in a resting state, with minimal to no ability to stimulate T cells. In skin, keratinocytes are also part of the immune surveillance system. They respond quickly to every chemical insult, either irritant or allergenic, in antigen-dependent fashion, to produce a variety of cytokines. These function mainly to amplify future inflammatory responses.[10,93] Early on, they secrete TNF-α and ICAM.[1] Later, they release IL-1, IL-6, IL-8, and IL-10; still later, macrophage chemotactic factor and other cytokines are released.[9,55,56,93,100] These may in turn release acute-phase reactants from mast cells and endothelial cells, as seen in irritant responses.[10,93] Current research is attempting to identify which keratinocyte cytokines specify the allergic reaction, as distinct from simply injury. Nevertheless, it is known

that the catechol molecules of poison oak and poison ivy enter the skin and bind through nucleophilic attack at benzene ring positions 4, 5, and 6 to surface proteins on APCs, which are primarily epidermal Langerhans cells. These cytokines from the keratinocytes cause Langerhans cells to mature and enter into an active state. Active Langerhans cells are then able to recognize and internalize antigens.

Langerhans cells are responsible for immunosurveillance. In the sensitization phase, when a hapten such as urushiol is applied to skin, it penetrates the stratum corneum. Urushiol then activates the skin's innate immune response, leading to upregulation of proinflammatory cytokines and eventual recognition of the antigen by activated APCs. These cells internalize the urushiol by pinocytosis. Proteolytic enzymes in lysosomes then process the urushiol. This processing consists of proteolytic degradation of the protein into smaller antigenic peptides. The antigenic peptides that have undergone chemical degradation associate with class II major histocompatibility complex (MHC) molecules and are expressed on the surface of the APCs.

The APCs then leave the epidermis and travel to regional lymph nodes, where they present processed antigen on the cell surface in context with a class I MHC molecule to the T cell receptor (TCR) complex on a CD8+ T cell, or in context with the class II MHC molecule to the TCR complex on a CD4+ T cell. Presence or absence of an urushiol-specific TCR is genetically determined. During early fetal development, the thymus interacts with various T cells. Through gene rearrangements, thousands of unique TCRs are produced that recognize unique antigens. If no T cell is present that recognizes the antigen complex on the APC, no reaction occurs, and the patient does not develop allergic contact dermatitis. To complete the sensitization signal, another surface protein (the B7 antigen) forms a co-stimulatory signal by binding to the CD28 ligand on the T cell. This then activates the T cell, which divides repeatedly to form a clone of urushiol-specific CD8+ and CD4+ cells. These subsequently expand into clones of circulating activated T effector and T memory lymphocytes.[65,81]

In the elicitation phase, with a new challenge by urushiol, the hapten enters the epidermis and again is internalized by Langerhans cells. It is processed and expressed by the MHC molecules, which then interact with the clone of T cells now specifically ready to interact with this MHC-antigen complex. This leads to the appearance of allergic contact dermatitis, typically within 24 to 72 hours of exposure. Langerhans cells in the skin that interact with T cells secrete IL-1, which stimulates the T cells to secrete IL-2 and express IL-2 receptors, which directly leads to activation, proliferation, and expansion of the T cell clone. Activated T cells will also secrete IFN-γ, which acts on keratinocytes to express ICAM-1, which allows them to interact directly with T cells.[84] Keratinocytes also secrete many cytokines that cause expansion and proliferation of these T cells. The CD8 lymphocytes elicit a cell-mediated cytotoxic immune response at the site of contact characterized by erythema, edema, and vesiculation resulting from destruction of epidermal cells and activation of the dermal vasculature. The clinical reaction is driven by the CD8 cytotoxic, effector T cells. This can be modified by CD4 T cells that may be either T helper type 1 (Th_1) or, more likely, Th_2 in nature.[65,81] In an individual patient, this determines the severity of dermatitis after exposure to the poisonous weeds. In addition, alternate pathways exist that account for the varying presentations of ACD. An acute eruption can begin within hours of initial exposure. Some have emphasized the presence of basophils in these hyperacute poison oak and poison ivy lesions and have proposed a role for basophil mediators in the pathogenesis of an early-onset acute reaction.[39] Others have proposed alternate hyperacute mechanisms involving mast cell degranulation, or a CD4 T cell–mediated induction of IgE reactivity.[64,67]

Suppressor pathways to decrease the extent of these pathways also exist. These mechanisms are poorly understood but include a number of specific pathways, such as elimination of primed dendritic cells by effector CD8 T cells, release of antiinflammatory cytokines, and activation of suppressor T cells.[128] These responses are generated to counterbalance or downregulate the type IV hypersensitivity reaction. It is the exposure to antigen through noncutaneous routes that leads to these suppressor pathways or, if there is a massive exposure, to antigen at the sensitization phase.[84] The final resulting skin reaction is a balance of sensitization and suppression of these antigen-specific reactions.

TREATMENT

Systemic corticosteroids are widely accepted as the first line of treatment for moderate to severe disease, especially given early and in large, therapeutic doses. In mild cases, ultrapotent topical steroids alone, such as clobetasol 0.05% ointment twice daily to the affected areas for 2 weeks, may suffice. If the reaction is of less than 2 hours' duration, intravenous (IV) hydrocortisone (adult dose 100 to 200 mg) or methylprednisolone (adult dose 500 mg to 1 g) can be curative. After a patient has suffered 4 to 6 hours with massive edema, erythema, and pruritus, IV therapy is highly effective, but it must be followed by more prolonged oral or intramuscular (IM) administration of corticosteroids. Most patients in this category seek help after 8 to 16 hours of discomfort, at which point IV therapy is less effective. In these circumstances, oral prednisone, 1 mg/kg/day for 3 to 4 days, followed by a slow taper over 2 to 3 weeks, helps many patients, but the danger lies in a sudden flare-up, which becomes poorly responsive to corticosteroids, at the end of therapy. This more often happens with rapid prednisone tapers. Whenever considering systemic corticosteroids for acute allergic contact dermatitis, the physician should evaluate the patient for active infection, vascular accident, endocrinopathy, or familial history of glaucoma. Side effects from oral corticosteroids include hypertension, increased risk for infection, adrenal insufficiency, glaucoma, cataracts, increased blood glucose, mood changes, osteoporosis, osteonecrosis, edema, weight gain, hypokalemia, peptic ulcer disease, bowel perforation, myopathy, Cushing's syndrome, adrenal suppression, and stunted growth in adolescents.

If dermatitis has been present for more than 24 hours, which is typically the case in clinical practice, the aggressive regimen is less successful. When the onset of dermatitis is delayed for several days and the eruption is mild or moderate, systemic therapy offers less benefit. In the situation of a mildly to moderately sensitive patient with delayed onset, topical corticosteroids are the mainstay of therapy. Typically, an ultrapotent topical steroid, such as clobetasol (Temovate), is used twice daily for no more than 14 days. Table 64-10 lists the most common topical corticosteroids and their classification. Prolonged use of ultrapotent corticosteroids may lead to skin atrophy. The face, axillae, and groin are highly susceptible to atrophy, so use of ultrapotent products should be avoided in these regions. In most mild cases of dermatitis, a medium- to high-potency topical corticosteroid and 15- to 30-minute cool compresses three or four times daily with a 1:40 dilution of aluminum acetate (Domeboro, Burow's solution) will suffice. A bath with 1 cup of Aveeno oatmeal per tub of water, in addition to therapy with antihistamines such as hydroxyzine or diphenhydramine, is helpful for the itching. Treatment is usually required for 1 to 2 weeks.

In more severe cases with the eyelids, hands, or more than 10% BSA involvement, a systemic corticosteroid, such as prednisone, in a tapering dose starting at 1 mg/kg, or triamcinolone (Kenalog), 40 mg IM, is employed, tapering slowly over a course of 2 to 3 weeks to avoid rebound. Antihistamines, such as hydroxyzine, 10 mg PO four times daily (up to 100 mg/day), or diphenhydramine, 25 mg PO two or three times daily, can be used to suppress itching. Calamine lotion and aluminum acetate compresses also help with the itching.

Topical immunomodulators, such as pimecrolimus (Elidel) 1% cream and tacrolimus (Protopic) 0.03% or 0.1% ointment, offer a noncorticosteroid treatment alternative. There is no risk of atrophy with these two agents. Studies show them to be helpful in alleviating allergic and irritant contact dermatitides, but expense is often a limiting factor.[5,6]

Most patients visit a pharmacy looking for over-the-counter (OTC) preparations; usually, they are disappointed. The eruption heals spontaneously in 7 to 10 days, so the most helpful option is an inexpensive agent, such as calamine lotion, which is comforting and helps form a crust. Aluminum acetate (Domeboro,

TABLE 64-10 Classification of Corticosteroids

Generic Name	Trade Name	Preparations Available
Ultrapotent		
Betamethasone dipropionate	Diprolene	0.05% cream or ointment
Clobetasol propionate	Temovate, Cormax	0.05% cream or ointment
Diflorasone diacetate	Psorcon	0.05% cream or ointment
Halobetasol propionate	Ultravate	0.05% cream or ointment
High Potency		
Amcinonide	Cyclocort	0.1% cream or ointment
Desoximetasone	Topicort	0.25% cream or ointment
Fluocinonide	Lidex	0.05% cream or ointment
Halcinonide	Halog	0.1% cream or ointment
Medium Potency		
Betamethasone valerate	Luxiq	0.1% cream or ointment, 0.12% foam
Fluocinolone acetonide	Synalar	0.025% cream or ointment
Fluticasone propionate	Cutivate	0.005% ointment or 0.05% cream
Hydrocortisone butyrate	Locoid	0.1% cream
Hydrocortisone valerate	Westcort	0.2% cream or ointment
Triamcinolone acetonide	Aristocort, Kenalog	0.1% cream or ointment
Low Potency		
Alclometasone dipropionate	Aclovate	0.05% cream or ointment
Clocortolone pivalate	Cloderm	0.1% cream
Desonide	DesOwen, Tridesilon	0.05% cream or ointment
Hydrocortisone acetate	Cortaid, Corticaine	0.5% cream or ointment

Burow's solution) 1:40 diluted in plain water and used as a soak, compress, or wet dressing is helpful, as is a 1% acetic acid wet dressing (white vinegar) in water. The soaks are performed for 15 to 30 minutes at a time and can be repeated as often as necessary. Regardless of the therapy chosen, time is required for healing.

Although field workers have mentioned that *Aloe vera* latex empirically improves wound healing, a major study in contact dermatitis showed that it was ineffective.[136] Topical lotions with anesthetics or antihistamines offer no additional benefit and may induce contact sensitization to the chemical additives. Allergic contact dermatitis is a self-healing disease if iatrogenic influences are avoided. Secondary superficial infections may occur in children, during hospitalization, or in cases with prolonged pruritus and scratching. Use of antibacterial soaps usually prevents this complication.

As the dermatitis heals and scales form after 10 to 14 days, the patient may note a resurgence of pruritus, which left untreated can lead to subacute lichenoid neurodermatitis (Figure 64-22). Judicious use of almost any corticosteroid cream or ointment, such as triamcinolone acetonide 0.025%, desonide 0.025%, or hydrocortisone 2.5%, helps alleviate symptoms.

PREVENTION

Prevention involves a combination of avoidance and destruction of plants. This can be done directly, by educating individuals at risk to recognize and avoid these plants, or indirectly, by wearing protective clothing and gloves when coming into contact with them. Rubber gloves that are the thickness of surgical gloves are inadequate protection because urushiol is able to penetrate through rubber. Vinyl gloves are more protective, as are other plastic gloves. Leather gloves are acceptable. Many herbicides are available to kill the plants. Unfortunately, none is specific to *Toxicodendron* species. Proper cleaning of clothing is essential. Washing immediately with soap (detergent) and water has been shown to destroy urushiol. A lotion containing the organoclay quaternium-18 bentonite is very effective in preventing this type of dermatitis. If applied before contact with the urushiol resin, it has been proven to decrease poison ivy, oak, and sumac dermatitis by inactivating the resin.[85]

The best approaches to prophylaxis, based on an intimate understanding of the chemistry of urushiol and the biology of the weeds, are recognition and avoidance.[45] When this is not possible, protective clothing that is either disposable or washable should be worn. Wool is the best material to use as a protective barrier because it binds the allergen readily.[32] Clothing should be washed with detergent or, preferably, bleach to inactivate urushiol. Tools and other inanimate objects are best cleaned with a dilute solution of bleach. Bleach rapidly inactivates urushiol, and organic solvents such as alcohol, gasoline, and acetone can extract it from contaminated surfaces. For cleansing the skin after contact, a variety of products are available, some more useful than others. A commercially available OTC solvent is Tecnu, but this is merely an inexpensive petroleum solvent sold at a high price and should not be used for therapy. An excellent choice is rubbing (isopropyl) alcohol, which should be applied liberally for decontamination and followed by liberal use of water wash-off to avoid spreading the oil on the skin. Care should be taken to limit contact time with the skin, particularly with children, who may be susceptible to transcutaneous alcohol toxicity.

Use of soap is inferior to better solvents. The newer topical agent Zanfel has been shown to experimentally decrease urushiol-induced contact dermatitis. It is a mixture of alcohol solubles and anionic surfactants that binds to the urushiol antigen and renders it unable to induce an allergic reaction. If applied soon enough after exposure, it has the potential to decrease urushiol-induced allergic contact dermatitis.[35] The idea of using barrier preparations has become popular again, even though in the past, such creams and ointments proved disappointing.[97] The current favorite, an organoclay called IvyBlock, was developed to protect forestry workers against these weeds during national firefighting escapades.[46] This approach was confirmed in a multicenter

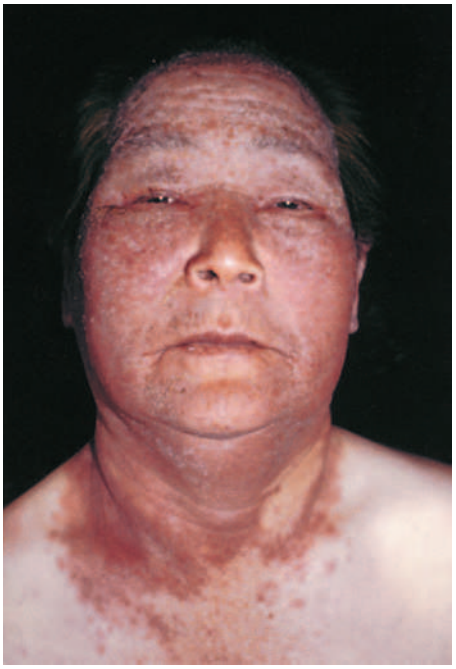

FIGURE 64-22 Resurgence of pruritus, leading to patch of subchronic lichenoid neurodermatitis.

FIGURE 64-23 Compositae members. **A,** Dahlia. **B,** Chrysanthemum. **C,** Daisy. *(**C** courtesy Yves Sell, Institute of Botany, Louis Pasteur University, Strasbourg, France.)*

study.[85] The lotion can be obtained readily from a pharmacist or by major marketers. Oak-N-Ivy-Armor is a product marketed to be used as a preventive lotion. It actively binds urushiol and keeps it from contacting the skin. Similar topical preventive products include büji Block and Ongard. Stokogard outdoor cream, composed of a linoleic ester dimer, was removed from the market for lack of U.S. Food and Drug Administration (FDA) approval but is still available in industrial supply houses that are not regulated.[98] When the cream is first applied, it has a foul smell (like dead fish), resulting from release of the ester. The odor disappears in about 20 minutes, and the cream acts like a barrier to delay the penetration of urushiol oil. It must be washed off in 4 to 6 hours for protection.

COMPOSITAE FAMILY

There are more than 20,000 species of plants in the Compositae family. Box 64-2 provides a brief list of some of the more common members, and Figure 64-23 shows a few highly recognizable members. Compositae species have worldwide distribution. The allergens found in these plants are sesquiterpene lactones. More than 3000 individual sesquiterpene lactones have been identified.[33,54] The lactones are made in the trichomes found on the plant's surface. The allergen is not highly sensitizing; thus the individuals typically affected have repeated contact with the allergen and are usually involved in daily handling of plants: florists, nursery workers, horticulturists, and produce handlers. Rarely, home gardeners or other people who spend long periods outdoors are affected. Allergenicity is increased by the presence of an α-methylene group attached to the lactone ring.[111] The dermatitis is fairly characteristic across the Compositae family. The clinical scenario is often a chronic lichenified eruption resembling photodermatitis.[84] Clues that this is not photodermatitis include involvement of the upper eyelids and submental region of the neck, areas that are classically spared in true photodermatitis. Definitive diagnosis can be made by patch-testing the patient to various portions of the actual leaf, stem, and petal against appropriate controls. A screening mixture of sesquiterpene lactones is available, but this mixture will miss some relevant allergies to Compositae plants. It is prudent to patch-test the patient with the actual plant that is suspected of causing the allergic reaction.

Ragweed (*Ambrosia* spp.) is a member of the Compositae family of plants; thus its allergen is a sesquiterpene lactone. Figure 64-24 shows a photo of common ragweed. Ragweed pollen likely contains two individual antigens, one that can cause respiratory ailments, such as asthma or allergic rhinitis, and another that contains sesquiterpene lactones and causes allergic

BOX 64-2 Familiar Compositae Plants

- Artichoke
- Black-eyed Susan
- Butterweed
- Chamomile
- Chicory
- Chrysanthemum
- Cornflower
- Daisy
- Dahlia
- Dandelion
- Endive
- Feverfew
- Goldenrod
- Ironweed
- Lettuce
- Marigold
- Mugwort
- Pyrethrum
- Ragweed
- Ragwort
- Sagebrush
- Sneezeweed
- Stinking mayweed
- Sunflower
- Tansy
- Tarragon
- Thistle
- Yarrow
- Zinnia

Data from Marks JG Jr, Elsner P, DeLeo VA: *Contact and occupational dermatology,* ed 3, St Louis, 2002, Mosby, pp 13-15.

FIGURE 64-24 Ragweed, *Ambrosia* species.

FIGURE 64-25 A familiar cut flower, Peruvian lily (*Alstroemeria* spp.).

contact dermatitis. Clinically, patients show involvement of the head and neck region and other areas not covered with clothing. The dermatitis is chronic in nature and tends to mimic photocontact dermatitis. In this case, the upper eyelid and submental regions may be involved, which is not the case in photocontact dermatitis. *Ambrosia deltoidea* is a weed in the Compositae family found in the southwestern United States that has also been reported to cause airborne allergic contact dermatitis. This plant bears little resemblance to common ragweed.[112]

Wild feverfew (*Parthenium hysterophorus*) is a weed in the Compositae family found throughout the western hemisphere. It is an acute cause of allergic contact dermatitis, although in clinical practice, it most often manifests as chronic lichenified dermatitis in areas chronically exposed to the allergen. Feverfew caused epidemic outbreaks of dermatitis in India after it was accidentally transplanted there. It is not a native plant to India and has thrived in its new environment. The epidemics have become so severe that it has been nicknamed the "scourge of India."[84]

Peruvian lily (*Alstroemeria* spp.) is a very popular cut flower. Its allergen is tuliposide A or α-methylene-γ-butyrolactone (Figure 64-25). Allergic contact dermatitis to this plant is the most common cause of allergic contact dermatitis in florists. Florists who repeatedly cut the flowers and stems are chronically exposed to the allergen. Consequently, they have the highest sensitization rate. It is a very rare cause of allergic contact dermatitis in individuals outside of the floral industry.

Liverworts (*Frullania* spp.) are members of the Jubulaceae family (related to mosses) that usually live on tree bark. They are small, reddish brown plants found most often in the Pacific Northwest. There are hundreds of species of *Frullania* plants. Similar to members of the Compositae family, this plant causes chronic lichenified dermatitis that is rarely seen in the acute phase. The allergen is sesquiterpene lactone. Allergic contact dermatitis caused by *Frullania* is a problem among lumberjacks and forest workers, but it may affect any individual who takes a walk in the woods.[84]

Grevillea banksii and *G. robusta* have been implicated as causing allergic contact dermatitis. These plants are native to Australia but have been transplanted around the globe. They grow as shrubs and are used in domestic landscaping. The allergen is a resorcinol. Similarly, *Dittrichia graveolens* (stinkwort) is a weed native to the Mediterranean but has become naturalized initially in Australia and now in the United States. It has recently been reported as a cause of allergic contact dermatitis in outdoor workers.[124]

Allergic contact dermatitis to lichens is seen most often in forestry workers and gardeners. Lichens live worldwide and grow just about anywhere (Figure 64-26). They are composed of algae and fungi that live in a symbiotic relationship. The allergens are

FIGURE 64-26 Close-up view of lichen. *(Courtesy Peter Schalock, Massachusetts General Hospital, Boston, Mass.)*

usnic acid, atranorin, and evernic acid.[84] The clinical picture is very similar to that of Compositae dermatitis.[125]

The false heliotrope plant (*Phacelia crenulata*) is found in deserts of the southwestern United States. It causes acute allergic contact dermatitis in the direct areas of contact. A linear papulovesicular reaction, not unlike the reaction to *Toxicodendron,* is usually seen.

Two common, easily recognized plants that can cause allergic contact dermatitis are the tulip and primrose. The tulip (*Tulipia* spp.) is an early-spring flowering plant (Figure 64-27). Its allergen is tuliposide A, the same allergen found in *Alstroemeria* (Peruvian lily, discussed earlier). The allergen has its highest concentration in the epidermis of the bulb, from which originate the clinical findings of "tulip fingers," a chronic fissured and scaly eczematous rash of the fingertips in people who routinely handle the bulbs (Figure 64-28).[58] This is most common in commercial

FIGURE 64-27 Tulip, *Tulipia* species.

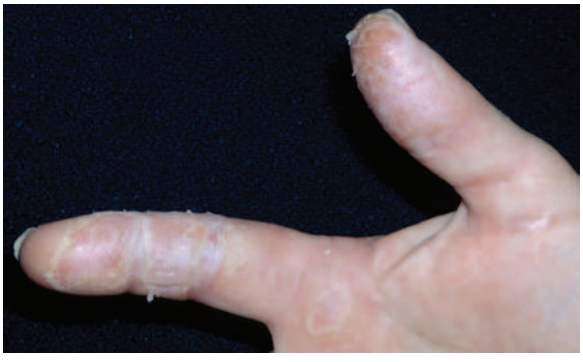

FIGURE 64-28 Eczematous scaly patches on the fingers of a floral worker.

FIGURE 64-29 Primrose, a common houseplant.

gardeners; occasionally, an avid home gardener is affected. People who are allergic to tulips should avoid *Alstroemeria*.

Primrose (*Primula obconica*) is a common houseplant reported to cause allergic contact dermatitis in home gardeners (Figure 64-29). Its allergen is primin (2-methoxy-6-pentyl-1,4-benzoquinone). The allergen is found in the highest concentration in the trichomes of the stem and leaves. A genetically altered hybrid has been produced that does not make primin and thus has no potential to induce allergic contact dermatitis. This hybrid is likely responsible for the decrease noted in incidence of primin-induced allergic contact dermatitis.[28]

The creosote bush (*Larrea* spp.) is found throughout North and South America (Figure 64-30). It is a shrubby bush with leaves covered by a resinous substance. There are a few reports of this resin causing allergic contact dermatitis.[75]

The Hydrophyllaceae family of plants contains a class of chemicals called *phacelioids*.[104] These substances are related to urushiol and can be potent allergens. However, they do not cross-react with urushiol. The *Cineraria* hybrid has also been described as a cause of allergic contact dermatitis in the Compositae family.[29]

Not all cases of Compositae-induced dermatitis are allergic in nature. The glove artichoke (*Cynara solumus*) has been associated with an irritant vesicobullous reaction affecting the fingertips, although patch-test results have been negative.[101] Some patients have even presented with erythrodermic presentations, especially from the *Parthenium hysterophorus* (wild feverfew) species.[2]

Botanical extracts in cosmetics and topical medications can cause contact dermatitis.[61] This dermatitis is often irritant in nature, but allergic contact dermatitis has been reported in susceptible individuals. Plant products associated with cosmetic contact dermatitis include Compositae plants, tea tree oil, peppermint, lavender, lichens, and henna. In addition to the plant product, other allergens in these cosmetics include ingredients such as fragrance, preservative, dye, and sunscreen.[61]

Currently, resources are limited for patch-testing patients to plant irritants. The European and American baseline series includes sesquiterpene-lactone mix for Compositae and *Frullania*. Special plant series exist for testing Compositae, *Frullania,* Liliaceae, Alstroemeriaceae, Alliaceae, and the genus *Citrus*. However, testing for Anacardiaceae, Cruciferae, Capparaceae, Ginkgoaceae, Araliaceae, and Apiaceae is not currently available.[109]

FIGURE 64-30 Leaves of the creosote bush are covered with a resinous substance. *(Courtesy Jon Sullivan.)*

CONTACT URTICARIA: IMMUNOLOGIC AND NONIMMUNOLOGIC SUBTYPES

Contact urticaria can be classified as immunologically or nonimmunologically induced. The immunologic subtype is caused by an immediate hypersensitivity reaction requiring antibody formation to a particular substance. These type I hypersensitivity reactions show a broad clinical spectrum, from mild skin hives to anaphylaxis. Prick testing and radioallergosorbent test (RAST) are of benefit in determining the cause in certain cases. The immunologic form of urticaria depends on the individual patient's immune activity or hyperactivity. There is no predictable manner to determine to which plants a person may develop a type I reaction. Food handlers and persons otherwise constantly exposed to plant products are likely to be more at risk. Many plant species have been reported to cause contact immunologic urticaria.[70,82] Patients typically present with urticarial wheals in areas of exposure within 1 to 2 hours of handling a particular plant. Occasionally, there is oral involvement with tongue and lip swelling. When there is prominent oral involvement, one must also consider consumed fruit as a cause. Box 64-3 provides a partial list of plants causing contact immunologic urticaria. Atopic individuals have been reported to be at higher risk for type I contact urticaria.[82]

Nonimmunologic plant contact dermatitis is caused by direct release of urticating substances onto or into the skin. There are four main families of plants contain stinging hairs or spines that can cause contact urticaria: Euphorbiaceae, Hydrophyllaceae, Loasaceae, and Urticaceae.[82] Most of these plants are found in the tropics, with the exception of stinging nettles, which have worldwide distribution and are found throughout the United States. Box 64-4 lists some of the more common nettle plants. The most common plant causing contact urticaria is the stinging nettle *Urtica dioica* (Figure 64-31). Within the *Urticaceae* family reside other plants capable of producing contact urticaria by means of the nonimmunologic route. Urticarial reactions are typically acute and resolve spontaneously, so the advice of a physician is rarely sought. Persistent paresthesias lasting hours have been reported.[88]

In the case of nonimmunologic urticaria, release of histamine from mast cells with vasodilation and leakage of fluid appears

BOX 64-3 Plants That Cause Immunologic Urticaria

Fruits
Apple
Carrot
Celery
Parsley
Potato
Tomato

Plants
Tulip

Spices
Cinnamon
Garlic
Mustard
Rapeseed

Trees
Birch pollen
Western red cedar

Vegetables
Chives
Grains
Lettuce
Onion

BOX 64-4 Plants in the Nettle Family

- *Urtica chamaedryoides*
- *Urtica dioica*
- *Urtica gracilis*
- *Urtica ferox*
- *Urtica membranacea*
- *Urtica urens*
- *Urtica pilulifera*
- *Urtica parviflora*

to be an early direct chemical change leading to clinical hives.[38,114] The molecular events in mast cell degranulation are thought to be similar to those described for immunogenic urticaria, with certain discrete differences. There is no evidence for a selective membrane receptor, such as the high-affinity immunoglobulin E (IgE) receptor that is now well characterized and required for immunologic degranulation of mast cells.[114,119] Instead, a receptor-independent mode of action occurs for all nonimmunologic histamine liberators, acting directly on a pertussis toxin–sensitive G protein to initiate a signal through phospholipase C activation, which degranulates mast cells of their histamine content.[91] There does not seem to be a requirement for methylation of the membrane phospholipids. Rather, a high intracellular calcium accumulation must occur, and the reaction is rapidly terminated without delayed mediator release.[108] Arachidonic acid metabolites are not formed in any amount.[14]

Figure 64-32, *A* and *B,* shows the stinging nettle plant and a close-up view of its spines. Contact with spines on the plant causes release of biologically active substances from the spines. These include histamine, acetylcholine, 5-hydroxytryptamine (serotonin), leukotriene B_4 (LTB_4), and leukotriene C_4 (LTC_4).[7,27,34,40] These chemicals lead directly to urticaria. There is no standardized therapy for stinging nettle dermatitis. Often the symptoms resolve in several hours. If pruritus is severe, treatment with diphenhydramine, 25 to 50 mg every 6 to 8 hours as needed, is indicated. Figure 64-32, *C,* illustrates the faint urticarial papules seen after contact with the stinging nettle plant.

Numerous plants have been associated with release of urticating substances. These include chili pepper (*Capsicum* spp.) and cowhage (*Mucuna pruriens*). In the case of chili pepper, the released chemical is capsaicin; with cowhage, it is mucanain.[84]

The pathogenesis of immunogenic contact urticaria is a variation of immediate type I hypersensitivity. The central cytologic reactor in skin is the mast cell, which has high-affinity IgE receptors in its membrane. An IgE molecule binds to the receptor by its Fc portion, exposing the Fab segments as recognition sites for circulating proteins. When a divalent protein antigen appropriately bridges two IgE molecules, a series of biochemical events transpires that leads to mast cell degranulation. Initially, the plasma membrane is perturbed. Several lipids are phosphorylated and G proteins are activated, which in turn activate phospholipase C to hydrolyze phosphatidylinositol 4,5-bisphosphate (PIP_2) and yield two messengers: diacylglycerol (DG) and inositol triphosphate (IP_3).[20] IP_3 binds to its receptor on the endoplasmic reticulum, forming a calcium channel to release free calcium ions (Ca^{2+}) into the cytosol.[11,15,60,94] Simultaneously, DG activates protein kinase C in the plasma membrane, opening calcium channels and allowing entrance of extracellular Ca^{2+}, which further loads the cytosol with free Ca^{2+}, an important "messenger" in the stimulus secretion process.[78] G proteins interact with and release the nucleotide complexed to protein α-chains, some of which probably inhibit or stimulate cyclic adenosine phosphate and its actions as a second messenger.[20,122]

The result of the extensive alteration in intracellular milieu is activation of a serine proteinase and exocytosis of mast cell granule contents.[38,114] These come in three forms: preformed and rapidly released; preformed, bound to the granule matrix of heparin, and slowly released; and newly formed mediators. In addition, mast cells produce a variety of cytokines, including IL-1, IL-3, IL-4, IL-5, and IL-6; GM-CSF; and TNF-α.[120] These cytokines interact with cells and structures, such as endothelium in the skin, to amplify the various inflammatory responses.[38,114,120] In acute urticaria, the rapidly released preformed mediators account for most of the signs and symptoms. These mediators include histamine, chemotactic factors, and arylsulfatase. If the lesions persist or extend, other mediators, such as newly formed leukotrienes, heparin (or heparin fragments), cytokines, and a number of proteases, may be involved in the continuing tissue damage.

The sequence of inflammatory events leading to acute urticaria occurs most often in people with an atopic background, especially those with pollen allergies.[70] The patients with significant pollen allergies are also at risk for pollen-fruit allergy syndrome, described as a mucosal contact urticaria typically seen when these patients are exposed to *Betula pendula* (silver birch), *Artemisia vulgaris* (mugwort), or timothy grass (*Phleum pratense*).[68] Cross-reacting foods include apple, pear, carrot, celery, tomato, cherry, carrot, celery, aniseed, and peach. This group of people, mainly women and especially health care workers, have been found in recent years to be exquisitely sensitive to latex rubber gloves and sensitive to proteins in the natural latex from rubber trees in Asia.[22,73,83,115,126]

In the past decade, latex sensitivity has increasingly become a problem. More than 200 polypeptides are produced in natural latex rubber, many of them contact sensitizers, so that a single antigen is not likely to be identified for a given patient. In the clinical realm, IgE-mediated immediate-type hypersensitivity and thus the potential for anaphylaxis is a disastrous complication. In addition to the polypeptides appearing in natural rubber latex, many are found in a number of plants, particularly those consumed as food. One theory is that the cross-reacting allergens are "defense proteins" with a role to protect the plant from attack by pathogens.[72] Whether this is true requires further investigation, but it is also possible that by plant engineering, these allergens may be genetically removed from foods we consume.

In addition to fruit and nuts, mustard has been implicated in anaphylaxis.[99] In less severe cases, vesicular, eczematous rashes have been noted within hours of eating mustard or rapeseed, which is used widely in production of vegetable oils and margarine.[89] Recent reports also describe contact urticaria to raw potato, as well as the Solanaceae and Alliaceae families of plants, which include tomato, green bell pepper, jalapeño, chive, red leaf lettuce, serrano pepper, pasilla pepper, leek, red bell pepper, garlic, and yellow onion.

In contrast to urticarial reactions, erythema multiforme–like eruptions are well recognized after contact with bracelets and ornamental necklaces made of exotic woods, such as *Dalbergia nigra*.[50] Erythema multiforme has also been seen after exposure to more common plants, such as poison ivy, primula, and mugwort.[50,131] It is theorized that multiforme lesions result from vasculitis caused by deposition of immune complexes in or around the blood vessels.

FIGURE 64-31 *Urtica dioica*, or stinging nettle. *(Courtesy Peter Schalock, Massachusetts General Hospital, Boston, Mass).*

FIGURE 64-32 **A,** Stinging nettle. **B,** Close-up view of the stinging nettle spines. **C,** Urticarial papules induced after contact with the stinging nettle.

Diagnosis of immunogenic contact urticaria can be confirmed by simple tests. As a useful test, application of the suspected plant product to the antecubital fossa twice a day for several days may reproduce the wheal response. Open and closed patch tests, with examination of test sites in 2 to 6 hours, can be useful, as can more conventional prick, scratch, or scratch-chamber tests, in which the results are read in 15 to 20 minutes.[70] It is critical to determine whether urtication is immunologic or nonimmunologic, because this helps to quantify the risk for anaphylaxis.[53,70] For complete evaluation, an allergist obtains RASTs to quantify specific IgE in the patient's serum. More refined serologic tests include crossed radioimmunoelectrophoresis (CRIE) and CRIE inhibition.[23]

Patients with contact urticaria typically visit the emergency department when an eruption is extensive or extreme or if it is associated with stridor, wheezing, and collapse. Because mast cell degranulation is the central problem, epinephrine is the drug of choice because it stimulates cyclic adenosine monophosphate formation that opposes further degranulation. All patients at risk for severe urticaria should carry a method for epinephrine injection (e.g., EpiPen) with them at all times. Other supportive treatments for anaphylactic shock, such as albuterol, oxygen, or IV hydrocortisone, may be required. In less severe cases, antihistamines are valuable. IM or IV diphenhydramine in an adult dose of 25 to 50 mg usually stops progression of wheal formation and can be followed by oral hydroxyzine (10 to 25 mg three times daily) or cyproheptadine (4 mg three times daily) for 2 to 5 days. Pure H_1 blockers, such as fexofenadine (60 mg twice daily), are also effective and do not depress the central nervous system, although the prescriber must be aware of any unique adverse reactions. It is important to make certain the patient is not inadvertently exposed to hidden parts of the plant on the body, in clothing, or in a towel, blanket, or knapsack. Recrudescence of the urticarial response usually can be traced to continuing unknown contact with the offending agent. In patients with high risk for urticarial eruptions and airway involvement, education regarding avoidance of the offending plant is crucial to maintenance of a symptom-free lifestyle.

PHYTOPHOTODERMATITIS

Plants and their components can interact with ultraviolet (UV) rays of the sun and produce a clinically distinct entity known as phytophotodermatitis. The two types of phytophotodermatitis are phototoxic and photoallergic. *Phototoxic* reactions, which appear clinically as an exaggerated sunburn, are analogous to irritant contact dermatitis. *Photoallergic* reactions, which appear eczematous, are analogous to allergic contact dermatitis. Phototoxic reactions are encountered more frequently and are often recognized by a clinician's knowledge of offending agents and the morphology of the exanthem. The reactions most frequently appear as linear red patches and plaques with or without edema, but also can be bullous in nature.[127] A characteristic finding is postinflammatory hyperpigmentation lasting for months to

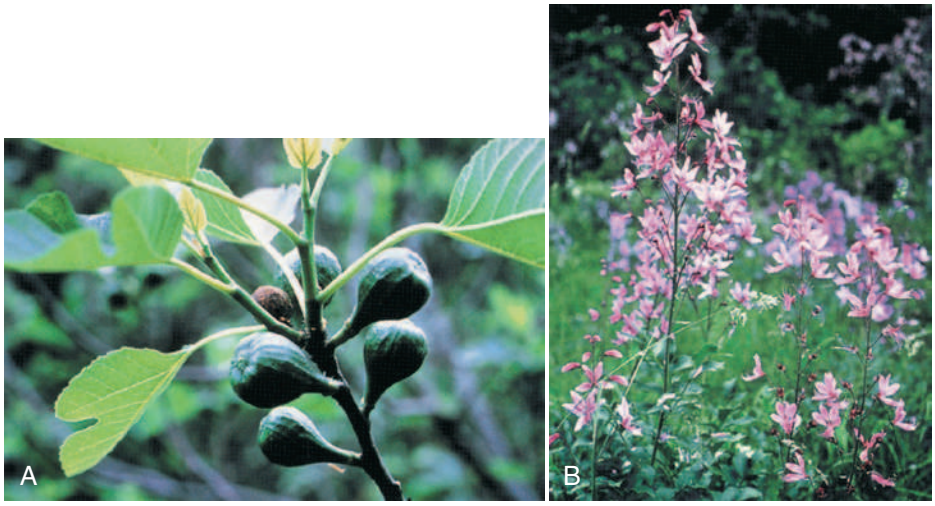

FIGURE 64-33 Phototoxic plants. **A,** Fig tree. **B,** Gas plant. *(**B** courtesy Yves Sell, Institute of Botany, Louis Pasteur University, Strasbourg, France.)*

years.[37] Most of these reactions are likely to go unreported or unrecognized, most often because of their mild nature, but also because it is often difficult to pinpoint the exact cause of the problem.

Phototoxic reactions are typically dose dependent and can occur in anyone if sufficient concentrations of UV light and the toxic plant material are achieved. In general, the wavelength of light needed to induce the most severe reactions is in the ultraviolet A (UVA) range, 320 to 400 nm.

For most phototoxic reactions, the plant toxin is a furocoumarin (psoralen). Furocoumarins intercalate into cellular DNA and cause formation of pyrimidine dimers, which interrupt DNA synthesis. This leads to cell damage and clinical effects. When UV light interacts with the psoralen molecule, it raises the energy level from the ground to an excited state. When the excited molecule returns to its ground state, energy is released that causes cross-linking of two strands of DNA. This interferes with DNA synthesis and ultimately cell division. This reaction is used to medical advantage in treatments such as PUVA (psoralen plus ultraviolet A) light therapy and in extracorporeal photopheresis. PUVA therapies are used for conditions ranging from vitiligo and psoriasis to cutaneous T cell lymphoma (CTCL). With extracorporeal photopheresis, a patient is connected by an IV line to a pheresis machine. Blood is drawn from the patient, and then leukocytes are isolated and exposed to a photoactive drug (psoralen), followed by exposure of blood to UVA light. This blood is then returned to the patient. This process causes cross-linking of DNA in the pathogenic T cells and death of these cells. This treatment is used almost exclusively for patients with CTCL and graft-versus-host disease (GVHD).

PHYTOPHOTOTOXIC CONTACT DERMATITIS

Furocoumarins include psoralen, 5-methoxy-psoralen (bergapten), 8-methoxy-psoralen (xanthotoxin), angelicin (isopsoralen), 5-hydroxy-psoralen (bergaptol), 8-hydroxy-psoralen (xanthotoxol), and limettin.[13,127] Psoralens are modified furocoumarins. Most of these chemicals are found in four plant families: Apiaceae, Rutaceae, Moraceae, and Leguminosae. Figure 64-33 shows a few examples of these plants. Figure 64-34 shows an example of the dermatitis that can result from exposure. Note the well-demarcated, angulated, hyperpigmented streaks that are characteristic of the disease.

Table 64-11 lists members of the families implicated in phytophototoxic contact dermatitis. Apiaceae, or Umbelliferae, is a well-recognized family that has an umbrella-like configuration to its flowers. In the United States, this family of plants is the most common cause of phytophototoxic dermatitis. The Moraceae and Leguminosae families are rare causes in the United States.[121]

So-called meadow dermatitis (dermatitis bullosa striata pratensis) occurs after exposure of wet human skin to psoralen-containing plants during daylight hours.[13] The most common offending plants are the yellow-flowered wild meadow parsnip and wild yellow flowered herb.[106] Bizarre linear configurations, such as an imprint, are often found on the lower extremities on bare skin after a walk through a field of a psoralen-containing weed.

Agriculture field work and grocery store work, in particular celery handling, have been the most frequently reported

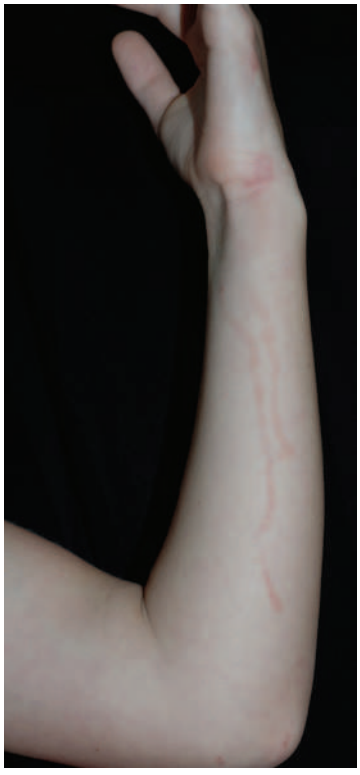

FIGURE 64-34 Phototoxic dermatitis induced by furocoumarins. *(Courtesy Richard A. Johnson, Massachusetts General Hospital, Boston, Mass.)*

TABLE 64-11 Common Members of the Umbelliferae, Rutaceae, Moraceae, and Leguminosae Families Found to Cause Phototoxic Contact Dermatitis

Common Name	Botanical Name
Umbelliferae (Apiaceae)	
Angelica	*Angelica gigas*
Celery	*Apium graveolens dulce*
Carrot	*Daucus carota*
Cow parsley	*Heracleum sphondylium*
Cow parsnip	*Heracleum lanatum*
Dill	*Anethum graveolus*
False bishop's weed	*Ammi majus*
Fennel	*Foenialum vulgare*
Giant hogweed	*Heracleum mantegazzianium*
Parsley	*Petroselinum crispum*
Parsnip	*Pastinaca sativa*
Queen Anne's lace	*Ammi majus*
Spring parsley	*Cymopterus watsonii*
Moraceae	
Fig	*Ficus carica*
Rutaceae	
Bergamot lime	*Citrus bergamia*
Berry rue	*Cneoridium dumosum*
Common rue	*Ruta graveolens*
Gas plant (burning bush)	*Dictamnus albus*
Grapefruit	*Citrus paradissi*
Lemon	*Citrus limon*
Lime	*Citrus aurantifolia*
Mexican lime	*Citrus aurantifolia*
Mokihana	*Pelea anisata*
Orange	*Citrus sinensis*
Zabon	*Citrus maxima*
Leguminosae	
Babchi (scurf-pea)	*Psoralea corylifolia*
Citrina	*Coronilla glauca*

Data from references 17, 19, 55, 59, 74, and 116.

occupations associated with phytophototoxic dermatitis. Another occupation with reports of phytophototoxic dermatitis is bartending. Handling limes while mixing drinks, if combined with UV light, may cause this dermatitis.[4,31,50,57,117,129]

Berloque (pendant- or drop-like) dermatitis is perfume-induced phytophotodermatitis. Typically, a patient seeks care for hyperpigmented macules on the head and neck, with no obvious preexisting rash or dermatitis. Unfortunately, the hyperpigmentation can last for years. The original cause of this reaction was the oil of bergamot, which is derived from bergamot oranges and used in many perfumes. The oil contains a mixture of psoralens, including 5-methoxy-psoralen (5-MOP).

Pseudophytophotodermatitis is a reaction that has been reported to occur after prolonged human exposure to celery that has been infected with a psoralen-producing fungus (*Sclerotinia sclerotiorum*), more commonly known as "pink rot." This occurs primarily in field workers who are responsible for harvesting the celery plants.[121]

BOX 64-5 Some Insecticides, Fungicides, and Herbicides That Cause Irritant Dermatitis (Pseudophytodermatitis)

- Captan
- Captofol
- Difolatan
- Dithiocarbamates
- Folpet
- Mancozeb (manganese and zinc ethylene-*bis*-dithiocarbamate)
- Maneb (manganese ethylene-*bis*-dithiocarbamate)
- Organophosphates
- Paraquat
- Phtahan
- Randox
- Sulfur

Data from Craigmill AL, editor: *Environmental Toxicology Newsletter,* University of California, Davis, 3:1, 1982; and Mark K, Brancaccio RR, Soter NA, et al: Allergic contact and photoallergic contact dermatitis to plants and pesticide allergens, *Arch Dermatol* 135:67, 1999.

Pseudophytodermatitis has been used to describe dermatitis caused by arthropods that live on the plant or chemical agents that have been applied to plants.[121] One common arthropod causing dermatitis is the grain itch mite *Pediculoides ventricosus,* which can infest straw or hay. Numerous chemicals that are purposefully applied to plants can also cause contact dermatitis. Most often, these are insecticides, herbicides, or fungicides (Box 64-5). Waxes or azo dyes applied to various fruits and vegetables can also cause pseudophytodermatitis. Azo dyes are synthetic dyes containing the azo group (two connected nitrogen atoms) and are used in many industries, including the food industry.

PHYTOPHOTOALLERGIC CONTACT DERMATITIS

The phytophotoallergic reaction is exceedingly rare. Clinically, it manifests as an eczematous eruption localized to sun-exposed areas of the body that came into contact with the offending plant. It is likely underrecognized and underreported. Rare case reports are found throughout the literature. The plants reported to cause this reaction are tromso palm (*Heracleum laciniatum*), feverfew (*Parthenium hysterophorus*), garlic (*Allium sativum*), *Frullania,* and some coumarin (psoralen)–containing plants.[3,16,21,63,80,82] The clinical importance of these reactions is unknown. In the future, better screening methods may increase recognition of these reactions. Until then, only clinicians with access to extended patch-testing series or with sufficient suspicion and knowledge will recognize these reactions.

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CHAPTER 65

Toxic Plant Ingestions

KIMBERLIE A. GRAEME

More than 46,000 plant exposures were reported to 57 American poison control centers (PCCs) in 2013, representing 2.25% of all human toxic exposures that year. This is likely an underrepresentation of plant exposures in the United States, because not all exposures are reported. The plant exposures most frequently reported to American PCCs were *Phytolacca americana* (American pokeweed), *Spathiphyllum* species (peace lily), *Prunus* spp. (cherry), *Ilex* spp. (holly), *Philodendron* spp., *Caladium* spp. (elephant ear), and *Malus* spp. (apple). Three deaths caused by plant poisoning were reported to PCCs in 2013.[226] The vast majority of reported plant exposures are accidental and occur in children. These exposures tend to produce mild symptoms. In fact, many exposures in children are to nontoxic or minimally toxic plants.

Worldwide, *Atropa belladonna* (deadly nightshade), *Datura* spp. (jimsonweed), *Brugmansia* spp. (angel's trumpet), *Hyoscyamus niger* (black henbane), *Conium maculatum* (poison hemlock), *Areca catechu* (betel nut), *Cascabela thevetia* (previously called *Thevetia peruviana,* or yellow oleander), *Nerium oleander* (common oleander), *Cerbera manghas* (sea mango), *Veratrum album* (hellebore), *Aconitum carmichaeli* (aconite), *Taxus* spp. (yew), *Chelidonium* spp. (greater celandine), *Colchicum autumnale* (autumn crocus), *Gloriosa superba* (glory lily), *Ricinus communis* (castor bean), *Atractylis gummifera* (bird-lime or blue thistle), and *Blighia sapida* (ackee fruit) cause significant morbidity and mortality.[101,108,111,145,203,209,338,354] The most serious poisonings generally occur in adults who have ingested the poisonous plants with intent for self-harm.[203,226,270] When plants are consumed with suicidal intent, the severity of symptoms is similar to other, nonplant, suicidal exposures.[270,304]

Serious poisoning can occur in wilderness exposure after persons consume meal-size portions of toxic plants that are mistaken for edible foods. These include hemlocks (*Conium maculatum* and *Cicuta maculata*) mistaken for wild carrots or parsnips, and autumn crocus (*Colchicum autumnale*) or death camas (*Zigadenus* spp.) mistaken for wild garlic or onion, respectively. War and famine can compel desperate, intentional, and prolonged ingestion of toxic plants. This may produce epidemics of chronic, devastating illnesses, such as Konzo from cassava (*Manihot esculenta*) and lathyrism from grass pea (*Lathyrus sativus*) consumption.

Although plants have been used for centuries as medications and mind-altering substances, there is a progressive trend of natural plant use as herbal medications (*Aconitum* spp., or aconitine) and to achieve legal intoxication (*Mitragyna speciosa,* or kratom, and *Argyreia nervosa,* or Hawaiian baby woodrose). Many medications prescribed by allopathic medical professionals have plant-based origins. Colchicine is derived from autumn crocus, a plant that was recommended for arthritis symptoms in *Des Materia Medica* in the first century AD. Furthermore, many popular drugs of abuse have plant-based origins. Ancient Incas used coca leaves (family Erythroxylaceae) medicinally. Cocaine was extracted from the leaves and abused recreationally. Bath salts, or synthetic cathinones, share a similar chemical structure to cathinone, found in khat (*Catha edulis*), a plant chewed socially in Arabia for millennia. Reasons for human exposure to toxic plants vary, but clinical presentations can be predicted if the plant species ingested is known. When identity of the ingested plant is unknown, general familiarity with toxic plant exposures and an organ system–based approach to evaluating patients may facilitate care.

GENERAL CONSIDERATIONS

Prompt and precise identification of the plant causing toxicity may not be feasible. Supportive care takes priority over plant identification. Airway, breathing, and circulation are assessed, including hydration status, end-organ perfusion, and urine output. Oral administration of activated charcoal (1 g/kg), up to 50 g, may aid gastrointestinal (GI) decontamination. However, recommendations on when to administer activated charcoal are challenging, because this has not been prospectively studied for most plant ingestions. If a patient is actively vomiting, activated charcoal likely will not contribute to decontamination. If the patient has depressed mental status or is likely to seize, administration of activated charcoal may result in pulmonary aspiration of charcoal and associated respiratory complications. Opinions on when to administer activated charcoal vary among toxicologists.

After emergency care is provided and the patient stabilized, a history should include time of ingestion, amount and part of plants ingested, initial symptoms, and time between ingestion and onset of symptoms. Method of preparation (e.g., drying, cooking, boiling) and number of persons who ate the same plant are important considerations. Plant identification may be aided by communication with PCC personnel and by Internet searches.[15,345,346]

Laboratory studies depend on clinical presentation and suspected plant exposure. Complications of poisoning include aspiration pneumonia, rhabdomyolysis, and deep vein thrombosis. Differential diagnosis is initially kept broad so that other illnesses, such as infection and trauma, are not missed. Table 65-1 provides signs and symptoms of toxic plant ingestions.

PLANT TOXINS

The discussion of plant toxins in this chapter is arranged on the basis of the organ systems primarily affected: central nervous, cardiovascular, gastrointestinal, hepatic, renal, hematopoietic, endocrine/metabolic, and reproductive system. Some plants contain toxins that injure many organ systems, especially if the toxins alter general cell functions, such as protein synthesis, production of adenosine triphosphate (ATP) in the mitochondria, or cell division. The discussion may note the chemical group to which the plants belong based on chemical structure. Most fall into one of the following categories: alkaloids, glycosides, resins, oxalates, or phytotoxins.

Alkaloids

Alkaloids are nitrogen-containing organic compounds that act as bases and form salts with acids. Plant alkaloids are soluble organic acid-alkaloid salts that contain nitrogen in a ring structure that is heterocyclic or aromatic, or both. Alkaloids are generally distributed throughout a given plant, so all ingested parts are toxic. Further subdivision into chemical groups is based on ring structure (Table 65-2).

TABLE 65-1 Effects of Toxic Plants on Organ Systems

System Involved	Syndrome	Common Name	Genus	Signs and Symptoms of Syndrome
Central nervous†	Anticholinergic*	Jimsonweed	*Datura*	See Box 65-1
		Angel's trumpet	*Brugmansia*	
		Deadly nightshade	*Atropa*	
		Black henbane	*Hyoscyamus*	
		Mandrake	*Mandrogora*	
	Nicotinic*	Tobacco	*Nicotiana*	See Box 65-2
		Poison hemlock	*Conium*	
		Betel nut	*Areca*	
		Blue cohosh	*Caulophyllum*	
		Golden chain tree	*Laburnum*	
		Kentucky coffee tree	*Gymnocladus*	
		Mescal bean bush	*Sophora*	
	Hallucinogenic*	Morning glory	*Ipomoea*	Hallucinations
		Nutmeg	*Myristica*	
		Marijuana	*Cannabis*	
		Peyote	*Lophophora*	
		Ibogaine	*Tabernanthe*	
		Khat	*Cathus*	
	Sedating†	Poppy	*Papaver*	Sedation
	Paralyzing‡	Yellow jessamine	*Gelsemium*	Weakness
	Epileptogenic*§	Strychnine	*Strychnos*	Twitching
		Water hemlock	*Cicuta*	Seizures
		Wild wisteria	*Securidacea*	Hyperreflexia
		Myrtle-leaved coriaria	*Coriaria*	GI distress
				Altered mental status
Cardiovascular†	Na^+,K^+ ATPase inhibitors	Foxglove	*Digitalis*	GI distress
		Common oleander	*Nerium*	Visual changes
		Yellow oleander	*Cascabela* (previously, *Thevetia*)	Altered mental status
		Squill	*Urginea*	Dysrhythmias
		Sea mango	*Cerbera*	Hypotension
		Lily of the valley	*Convallaria*	Hyperkalemia
		Ouabain	*Strophanthus*	
		King's crown	*Calotropis*	
	Sodium channel openers‡	Monkshood	*Aconitum*	GI distress
		Hellebore	*Veratrum*	Visual disturbances
		Death camas	*Zigadenus*	Paresthesias
		Rhododendron	*Rhododendron*	Altered mental status
		Azaleas	*Rhododendron*	Weakness/paralysis
				Dysrhythmias
				Hypotension
	Na^+ and Ca^+ transport inhibitors	Yew	*Taxus*	GI distress
				Altered mental status
				Dysrhythmias
				Widening of QRS
				Hypotension
Oral and gastrointestinal‖	Oral irritants	Philodendron	*Philodendron*	Hypersalivation
		Dumb cane	*Dieffenbachia*	Oropharyngeal edema
		Peace lily	*Spathiphyllum*	Vesicles
		Elephant's ear	*Colocasia*	Dysphagia
		Giant elephant's ear	*Alocasia*	Aphonia
				Airway compromise
	Gastrointestinal irritants	Chinaberry tree	*Melia*	GI distress
		Nightshade	*Solanum*	Neurologic symptoms
		Pokeweed¶	*Phytolacca*	Vomiting
				Foamy diarrhea
				Dehydration
				Altered mental status
				Plasmablasts
	Protein synthesis inhibitors	Castor bean	*Ricinus*	GI distress
		Rosary pea	*Abrus*	Dehydration
		Purging nut	*Jatropha*	Elevated liver enzymes
		Black locust	*Robinia*	Multiorgan failure

Continued

TABLE 65-1 Effects of Toxic Plants on Organ Systems—cont'd

System Involved	Syndrome	Common Name	Genus	Signs and Symptoms of Syndrome
	Hepatotoxins	Groundsel	*Senecio*	Venoocclusive disease
		Gordolobo	*Senecio*	Hepatomegaly
		Tansy ragwort	*Senecio*	Jaundice
		Comfrey	*Symphytum*	
		Mate	*Ilex*	
		Rattlebox	*Crotalaria*	
Renal	Oxalates	Rhubarb	*Rheum*	Hypocalcemia
		Sorrel	*Rumex*	Tetany
				Renal failure
	Other	Aloe	*Aloe*	Renal insufficiency
		Birthwart	*Aristolochia*	Renal failure
		Djenkol bean	*Pithecolobium*	
		Oduvan	*Cleistanthus*	
Hematopoietic	Anticoagulating	Yellow sweet clover	*Melilotus*	Bleeding
		Tonka bean	*Coumarouna*	
		Woodruff	*Galium*	
	Bone marrow inhibitors	Autumn crocus	*Colchicum*	GI distress
		Christmas bells	*Sandersonia*	Dehydration
		Glory lily	*Gloriosa*	Pancytopenia
		Podophyllum	*Podophyllum*	Weakness
	Hemolytic	Fava bean	*Vicia*	Hemolysis
				Hemoglobinuria
				Anemia
				Jaundice
Endocrine and metabolic	Hypoglycemia inducers§	Ackee fruit	*Blighia*	Vomiting
		Wild yams	*Dioscorea*	Seizures
		Cocklebur	*Xanthium*	Hypoglycemia
		Bird-lime	*Atractylis*	Metabolic acidosis
		Ox-eye daisy	*Callilepis*	Liver disease
	Mineralocorticoid inducers	Licorice	*Glycyrrhiza*	Hypertension
				Edema
				Weakness
				Rhabdomyolysis
				Hypokalemia
	Cyanogenic	Apple seed	*Malus*	GI distress
		Cherry pits	*Prunus*	Bitter almond breath
		Peach pits	*Prunus*	Agitation/seizures
		Plum pits	*Prunus*	Coma
		Apricot pits	*Prunus*	Metabolic acidosis
				Dysrhythmias

*Anticholinergic and nicotinic plants can be hallucinogenic and epileptogenic.
†Many plants that affect the central nervous system and cardiovascular system can result in sedation and seizures.
‡Cardiovascular agents that open sodium channels may also produce weakness or paralysis.
§Hypoglycemic agents are also epileptogenic.
‖The majority of toxic plants cause some gastrointestinal (GI) distress.
¶Also a hematopoietic poison.

Glycosides

Sugars in the form of acetals are called glycosides. In glycosides, a glycosyl group replaces an alcohol or a hydroxyl group. On hydrolysis, glycosides yield sugars (glycones) and aglycone compounds. The aglycone moiety accounts for most of the toxicity, although the sugar may enhance solubility and absorption. (Figure 65-1). Glycoside-producing plants include cardioactive, cyanogenic, saponin, anthraquinone, and coumarin glycoside compounds.

Resins

Resins are highly toxic compounds of diverse chemical and plant origin united by the physical characteristics of insolubility in water, absence of nitrogen, and solid or semisolid state on extraction at room temperature. Resins are usually mixed with other compounds, such as volatile or essential oils (oleoresins), gum (gum resins), and sugars (glycoresins).

Oxalates

Oxalates occur naturally in plants as soluble (sodium or potassium) or insoluble (calcium) oxalates or acid oxalates. Oxalates have corrosive effects and bind serum calcium, causing hypocalcemia.

Phytotoxins

Phytotoxins, or toxalbumins, are among the most toxic substances of plant origin. They are composed of large protein molecules that resemble bacterial toxins in structure and in their ability to act as antigens (Figure 65-2).

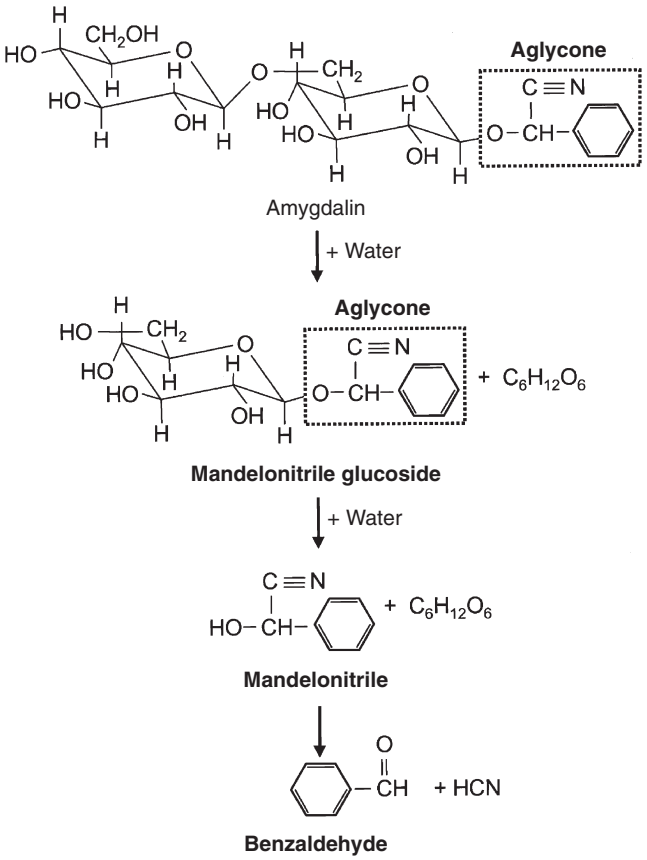


FIGURE 65-1 Hydrolysis of amygdalin, with its toxic aglycone group, yields hydrogen cyanide. The enzyme β-glucosidase, called emulsin, contained in plants can catalyze amygdalin hydrolysis.

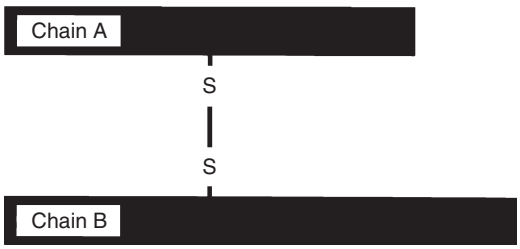
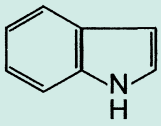
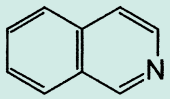
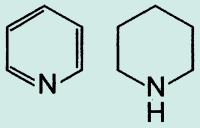
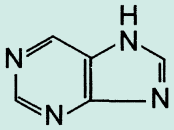
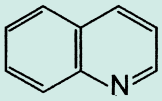
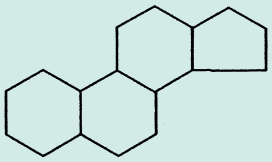
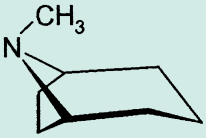


FIGURE 65-2 The structures of ricin and abrin (phytotoxins isolated from the castor bean plant and the jequirity bean plant, respectively) are similar in structure to biologic toxins such as botulinum. These glycoproteins are composed of two peptide chains, designated A and B, connected by a disulfide bond.

TABLE 65-2 Plant Alkaloids and Their Structures

Alkaloid Type	Alkaloid Structure	Examples
Indole		Ergonovine (ergots) Strychnine Physostigmine (calabar beans) Rauwolfia alkaloids (reserpine)
Isoquinoline		Opium alkaloids Emetine (ipecac)
Pyridine/ piperidine		Nicotine (tobacco) Arecoline (betel nut) Lobeline (Indian tobacco)
Purine		Caffeine Theobromine (cacao)
Quinoline		Cinchona alkaloids (quinidine)
Steroid		Veratrum alkaloids (false hellebore) Aconite (monkshood)
Tropane		Atropine (belladonna) Hyoscyamine Hyoscine (scopolamine)

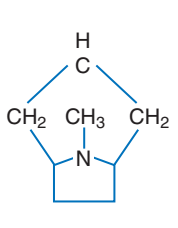
CENTRAL NERVOUS SYSTEM TOXINS

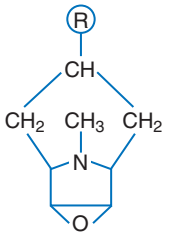
ANTICHOLINERGIC PLANTS (TROPANE ALKALOIDS)

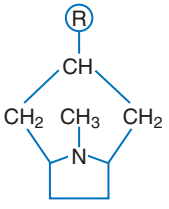
The plants discussed in this section produce an anticholinergic syndrome. Anticholinergic syndromes are more accurately termed *antimuscarinic syndromes*, because the syndrome is produced by antagonism of muscarinic receptors, with sparing of nicotinic receptors. However, the term *anticholinergic syndrome* is more frequently used and therefore is used here.

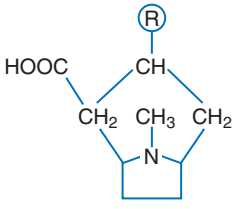
Plants contain tropane alkaloids (often called "belladonna alkaloids"), including atropine, hyoscyamine (the levorotatory isomer of atropine), and hyoscine (scopolamine).* Structures of the tropane alkaloids follow.

Tropane alkaloids are found in approximately 25 genera and 2000 species of plants. Plants causing human toxicity include









*References 51, 107, 166, 169, 209, 215, 217, 293, 324.

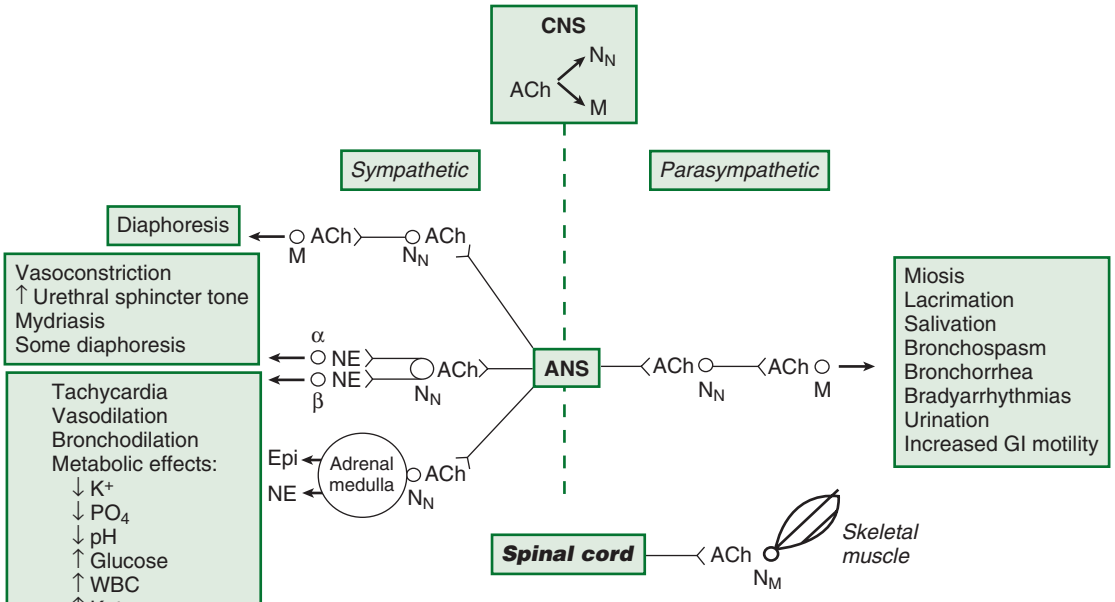


FIGURE 65-3 Nicotinic and muscarinic receptors of the central nervous system (*CNS*), autonomic nervous system (*ANS*), and peripheral skeletal muscles. Anticholinergic toxins (e.g., tropane alkaloids) antagonize muscarinic receptors, causing confusion, agitation, abnormal movements, hallucinations, and coma centrally, and mydriasis, anhidrosis, tachycardia, urinary retention, and ileus peripherally. Direct nicotinic agonists (e.g., arecoline, coniine, cytisine, lobeline, nicotine) stimulate nicotinic receptors; however, prolonged depolarization at the receptor causes eventual blockade of nicotinic receptors. *ACh,* Acetylcholine; *Epi,* epinephrine; *GI,* gastrointestinal; *M,* muscarinic receptor; *NE,* norepinephrine; N_M, nicotinic receptor at skeletal muscle; N_N, nicotinic receptor in nervous system.

Atropa belladonna (deadly nightshade), *Mandragora* spp. (mandrake), *Hyoscyamus niger* (black henbane), *Datura* spp. (jimsonweed), *Brugmansia* spp. (angel's trumpet), *Solanum* spp., and *Duboisia* spp. (corkwood tree).* The Solanaceae family includes *Solanum* and *Scopolia carniolica,* sources of scopolamine.

Anticholinergic Syndrome

Toxicity may occur after ingesting or smoking plant parts. Tropane alkaloids competitively inhibit postsynaptic muscarinic receptors, producing the classic anticholinergic syndrome[58,125,136,257,266,293] (Figure 65-3 and Box 65-1). A useful clinical sign of anticholinergic toxicity is lack of perspiration in the axillae. Anticholinergic findings suggestive of poisoning may be remembered using the following mnemonic[266,307]:

Hot as a hare (or Hot as Hades),
Blind as a bat,
Dry as a bone,
Red as a beet,
Mad as a hatter.

*References 51, 136, 149, 166, 169, 209, 217, 257, 259, 265, 293, 308.

BOX 65-1 Anticholinergic Syndrome

Central
Central nervous sytem excitation
Agitation
Hallucinations
Lethargy
Coma
Respiratory depression
Mumbling speech
Muteness
Undressing behavior
Repetitive picking behavior

Peripheral
Tachycardia
Mydriasis
Blurred vision
Inability to accommodate (visually)
Flushed skin
Hyperthermia
Absent bowel sounds
Urinary retention
Dry mucous membranes

Jimsonweed

Datura species are generally known as jimsonweed or thorn apple, and *Brugmansia* species are generally known as angel's trumpet (Figure 65-4).[134,136,335] Young, thin, and tender stems of jimsonweed contain the highest concentration of tropane alkaloids.[217] However, the seeds also contain high concentrations of the alkaloids, and as little as one-half teaspoonful of seeds may cause death from cardiopulmonary arrest. The word "jimsonweed" is thought to be derived from Jamestown, Virginia, where British troops reportedly behaved bizarrely after consuming *Datura* in 1676. *D. stramonium* has reportedly been used in Haitian zombification rituals.[85,134,136] This plant is referenced in Homer's Odyssey and in the Shakespeare plays *Romeo and Juliet, Anthony and Cleopatra,* and *Hamlet*.[161] In cigarette form, jimsonweed has been used to treat asthma, heralding the current use of ipratropium bromide. *Datura* is still used as an herbal medicine, called Buah Kecubung, to treat allergic rhinitis in Malaysia.[219]

Reports of abuse of *Datura* and *Brugmansia* as hallucinogens continue to be reported in the United States and Europe.[136,215,276,324] Clusters of poisonings among adolescents are typical.[58,86,134,161,166,215,285,324] Frequently, a tea of the plant parts is brewed.[166] Smoking and ingesting various plant parts is described.[215] Report of toxicity after using a homemade *Datura* toothpaste has been reported.[260] Mass poisonings have occurred in Botswana and Slovenia after consumption of foods made with sorghum flour and buckwheat flour contaminated with seeds of *D. stramonium*.[245,261] Similar outbreaks have occurred elsewhere. In Athens, *Datura innoxia* was mistaken for blites (*Amaranthus blitum*) and consumed with vegetables, producing mass poisoning.[249]

Symptoms may appear within minutes and can last for days.[86,257,324] Tachycardia, dry mouth, nausea, vomiting, decreased GI motility with decreased bowel sounds, incoherence, disorientation, slurred speech, muteness, agitation, auditory and visual hallucinations, paranoia, mydriasis, hyperthermia, flushed skin, urinary retention, and hypertension have been

FIGURE 65-4 Jimsonweed (*Datura* spp.) is a bush with trumpet-like flowers **(A)** and thorny seedpods that contain numerous small, kidney-shaped seeds **(B).** A nickel is shown for size comparison. Angel's trumpet (*Brugmansia* spp.) is a tree **(C)** with trumpet-like flowers **(D).** *(Courtesy Kimberlie A. Graeme, MD, and Phillip Saba, MD.)*

reported.[86,166,215,257,266,285,324] Blurred vision and photophobia may be secondary to mydriasis. Isolated mydriasis and cycloplegia, including anisocoria, may be noted after topical contact to the eyes.[148,156,198,294,335] Anticholinergic poisoning should be suspected when patients are observed to communicate with imaginary friends with mumbling speech, while demonstrating repetitive picking behavior.[134,308] With severe toxicity, seizures, flaccid paralysis, and coma may ensue. Focal neurologic signs and posturing have been reported.[107,207,245,251,257,324] Users may be amnestic of events.[215] Studies may show leukocytosis, mild transient elevation of liver enzymes, elevated creatine phosphokinase (CPK) levels and other evidence of rhabdomyolysis, and changes on electrocardiogram (ECG) that are consistent with tachycardia and dysrhythmias.[86,107,136]

Death may result from behavioral changes, leading to trauma, drowning, or environmental exposure associated with hyperthermia or hypothermia.[166] Autopsy has revealed edema of the brain and lungs with focal hemorrhages within the alveoli, ischemic lesions and edema of the heart, and hyperemia of the sinusoidal tracts of the liver.[44]

Deadly Nightshade

Ingestion of *Atropa belladonna* (deadly nightshade) is less common than *Datura* or *Brugmansia* ingestion. All parts of deadly nightshade contain tropane alkaloids, but the highest concentrations are in the ripe fruit and green leaves; each berry may contain up to 2 mg of atropine. The berries may be mistaken for bilberries (hurtleberries) or blueberries. A family of eight had acute exposures to *A. belladonna* after eating both raw and cooked berries in a pie. The most severely poisoned patient had anticholinergic symptoms, with hypertonia, hyperthermia, respiratory failure, and coma, and required mechanical ventilation. Urine drug screens detected only atropine and not scopolamine, which is generally present in much smaller quantities.[221,293,308] A review of 49 children with acute deadly nightshade intoxication found that children most often demonstrated meaningless speech, tachycardia, mydriasis, and flushing; lethargy and coma were seen in the most severely poisoned children.[51] A patient with seasonal chronic ingestion presented with recurrent tachycardia, mydriasis, inability to concentrate, visual hallucinations, delusions, inappropriate laughter, dizziness, and headache.[169] The less frequently ingested velvet nightshade (*Solanum erianthum,* or potato tree) may produce anticholinergic syndromes.[162]

Mandrake

Mandragora officinarum (mandrake), which has a folklore history of being able to increase fertility, has recently been used as an aphrodisiac.[236] *Mandragora autumnalis* (autumn

mandrake) has been mistaken for *Borago officinalis* (starflower or borage). Both autumn mandrake and borage grow in Mediterranean areas and have similar leaves and small, blue-violet flowers. Consumption of mandrake produces an anticholinergic syndrome.[265,266] All plant parts of the *Mandragora* spp. contain tropane alkaloids.[236]

Additional (Rare) Signs and Symptoms Seen with Anticholinergic Plants

Along with anticholinergic signs and symptoms, QT prolongation has been reported with some *Hyoscyamus reticulatus* exposures.[16] Polyneuropathies have been reported with angel's trumpet (*Brugmansia*) and *Hyoscyamus* spp. ingestions.[16,246,295,355]

Treatment

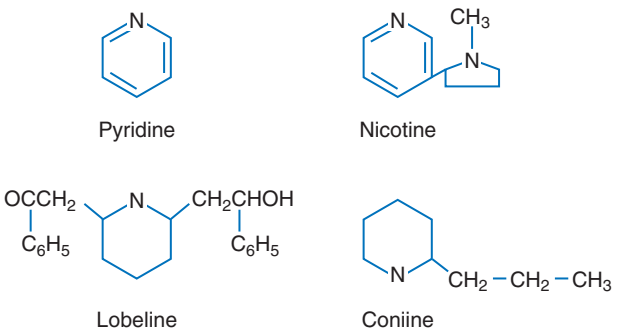
Treatment of anticholinergic plant exposure consists primarily of decontamination and supportive care, including airway protection, intravenous (IV) fluids, and vasopressors for hypotension resistant to IV fluids. Hyperthermia should be assessed and treated if significant. Agitation can be treated with careful administration of benzodiazepines. Haloperidol and phenothiazines should not be used, because these agents may worsen toxicity. Foley catheterization or nasogastric tube placement may be necessary if there is bladder distention or decreased gut motility, respectively.[125,166,169,251,293]

Some authorities recommend treating severe central anticholinergic syndrome with carefully titrated physostigmine, which is derived from the calabar bean of *Physostigma venenosum*. This cholinesterase inhibitor blocks acetylcholine degradation, resulting in accumulation of acetylcholine that overcomes the competitive inhibition from tropane alkaloids. Rapid, but often transient, reversal of peripheral and central nervous system (CNS) effects can ensue. However, bradycardia, asystole, ventricular arrhythmias, hypotension, bronchospasm, bronchorrhea, and seizures have been reported after rapid IV administration of physostigmine, limiting its use. Persons with cardiac conduction abnormalities are particularly susceptible to the cardiac complications. Use of physostigmine generally does not shorten hospital stay.[58,125,166,251,266,285,308,324]

Most patients with anticholinergic poisoning can be managed safely and effectively with supportive care alone.[307] If physostigmine is used, the patient should be on a cardiac monitor, with pulse oximetry, and a physician at the bedside should slowly administer graduated doses of the drug.[50,125,308]

NICOTINIC PLANTS (PYRIDINE AND PIPERIDINE ALKALOIDS)

The pyridine-piperidine group contains the major alkaloids nicotine, coniine, lobeline, arecoline, piperine, and isopelletierine. Structures of some pyridine/piperidine alkaloids follow:



Plants containing nicotinic alkaloids include *Nicotiana* spp. (tobacco plants), *Conium maculatum* (poison hemlock), *Areca catechu* (areca palm, betel nut), *Caulophyllum thalictroides* (blue cohosh, squaw root), *Laburnum anagyroides* (golden chain tree), *Sophora secundiflora* (mescal bean bush, Texas mountain laurel), and *Sophora microphylla* (kowhai).[304]

BOX 65-2 Nicotinic Syndrome

Early Stage	Late Stage
Hypertension	Hypotension
Tachycardia	Bradyarrhythmias
Vomiting	Paralysis
Diarrhea	Coma
Muscle fasciculations	
Convulsions	

Nicotinic Syndrome

Peripherally, acetylcholine is a neurotransmitter for autonomic and somatic motor fibers. It is stored in vesicles within the presynaptic neuron and released by calcium-dependent exocytosis into the synapse, where it binds to receptors and is eventually degraded by acetylcholinesterase. Acetylcholine can bind to two receptor types, nicotinic and muscarinic. Nicotinic receptors are located on postganglionic autonomic neurons (N_N receptors) and at skeletal neuromuscular junctions (N_M receptors). Plant toxins that are direct nicotinic agonists (e.g., arecoline, coniine, cytisine, lobeline, nicotine) prolong depolarization at these receptors and eventually cause blockade of nicotinic receptors. Clinical evidence of stimulation followed by blockade is apparent. Vomiting, diarrhea, abdominal pain, salivation, hypertension, tachycardia, bronchorrhea, tachypnea, muscle fasciculations, spasms, tremor, agitation, confusion, and convulsions (the stimulation) are followed by hypotension, bradyarrhythmias, asystole, respiratory failure, hyporeflexia, paralysis, and coma (the blockade). When it occurs, death is generally caused by respiratory paralysis[57,77,213,218,291,301,304] (Box 65-2; see also Figure 65-3).

Green tobacco sickness is a mild form of nicotine poisoning seen in tobacco-naive field workers with dermal exposure to leaves of green tobacco in wet environments. Nicotine, a water-soluble alkaloid, is absorbed dermally. The syndrome is characterized by weakness, salivation, nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, visual and hearing disturbances, respiratory depression, and occasionally fluctuations in blood pressure and heart rate. Neuromuscular blockade may result in death. A urinary nicotine metabolite, cotinine, may be helpful diagnostically.[20,213,291,313]

Tobacco Plants

Tobacco contains nicotine and related alkaloids with similar pharmacologic properties, such as anabasine, which is found in *Nicotiana glauca* (wild tree tobacco) (Figure 65-5). *N. glauca* has been mistaken for *Amaranthus hybridus* (marog) and eaten with porridge in South Africa. Ingestion of *N. glauca* is generally fatal. Anabasine, an isomer of nicotine that appears to be more toxic than nicotine, probably accounts for much of the toxicity of *N. glauca, N. debneyi,* and *N. rotundifolia*. Anabasine concentrations can be particularly high in the roots of the plants. Although there are more than 60 *Nicotiana* spp., some other, more common tobacco family members include *N. rustica* (Mapacho), *N.*

FIGURE 65-5 Tree tobacco (*Nicotiana glauca*).

FIGURE 65-6 *Nicotiana trigonophylla* (desert tobacco) and other *Nicotiana* spp. are characterized by narrow, tube-like flowers. *(Courtesy Kimberlie A. Graeme, MD.)*

tabacum (cultivated or common tobacco), *N. trigonophylla* (desert tobacco) (Figure 65-6), and *N. attenuata* (coyote tobacco). *N. tabacum* is the major source of commercial tobacco and contains 0.5% to 9% nicotine. *N. rustica* (Mapacho) tends to contain higher concentrations of nicotine than does *N. tabacum*. Lobeline, derived from the Indian tobacco plant *Lobelia inflata,* is a high-affinity nicotinic ligand. It can cause nicotine-like effects but is generally less toxic than is nicotine.[81]

Nicotine alkaloids are rapidly absorbed from the oral, GI, and respiratory tracts, as well as dermally. The kidneys excrete nicotine promptly after biotransformation in the liver and lungs. The half-life is 1 to 2 hours. Although the lethal dose of ingested nicotine is not well established, 2 to 5 mg may cause nausea, and 40 to 60 mg may be lethal in adult humans. In children, 1 mg/kg nicotine may produce significant toxicity. One to two cigarettes or less than 1 teaspoon of a nicotine solution used to refill electronic cigarettes could be lethal in a child if ingested and absorbed.[213,218,291,301,313]

Poison Hemlock

Conium maculatum, or poison hemlock, also known as spotted hemlock, California fern, Nebraska fern, stinkweed, fool's parsley, or carrot weed, is often mistaken for an edible plant, such as parsley, parsnip, or anise (Figure 65-7). However, it has a mousy odor, unpleasant bitter taste, and may irritate the mouth and throat. The stem is hollow with purplish to reddish brown spots. Its long taproot is solid and parsnip-like. Although all plant parts are poisonous, the unripe fruit is especially toxic. Poisonings are more common in the spring and summer. Poisoning may ensue after eating birds that have consumed poison hemlock. Coniine and γ-coniceine, the principal alkaloids in *C. maculatum,* are pyridine derivatives similar to nicotine. Coniine is more toxic than γ-coniceine. The alkaloid is volatile and susceptible to drying and heating.[37,291,338,346]

Conium maculatum was used in ancient times for capital punishment and murder. The primary action of the toxins is activation and then blockade of nicotinic acetylcholine receptors. Initially, stimulation causes sialorrhea, nausea, vomiting, diarrhea, abdominal cramping, hypertension, tachycardia, tremor, ataxia, confusion, and blurred vision, followed by dry mucosae, GI hypotonia, diminished cardiac contraction, hypotension, bradycardia, lethargy, and weakness, as with nicotinic syndrome. Muscles rapidly swell and stiffen, with multifocal necrosis of myocytes and associated muscle pain. Muscle fasciculations may be followed by flaccid paralysis, including respiratory paralysis. Rhabdomyolysis followed by acute tubular necrosis with renal failure may occur. Liver function tests (LFTs) and CPK and may be followed to assess rhabdomyolysis. Death is usually from respiratory failure. Autopsy may reveal congestion of the lungs and liver.[37,95,115,116,125,142,291,338,346]

FIGURE 65-7 Poison hemlock (*Conium maculatum*).

Betel Nut

Areca catechu (areca palm) produces betel nut, a common masticatory drug in the Far East, Asia, India, and the South Pacific; it is shipped elsewhere (Figure 65-8). An estimated 10% to 25% of the world's population chews "betel quid." It is generally chewed with slaked lime paste (calcium hydroxide) wrapped in leaves of betel pepper (*Piper betel*), known as "quid," "punsupari," and "pan masala." Occasionally, tobacco is added. Quid is sucked in the lateral gingival pocket. Commercially, areca nut is marketed in the form of sweetened areca nut, known as "supari." *A. catechu* contains arecoline and guvacoline, which are hydrolyzed to arecaidine and guvacine, respectively. These are strong inhibitors of γ-aminobutyric acid (GABA) uptake. These arecal

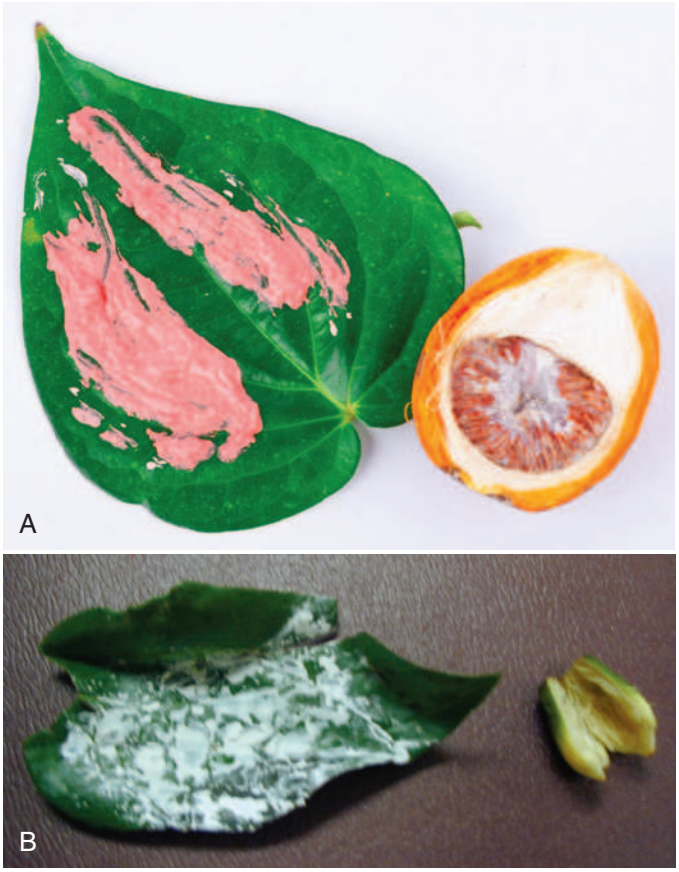
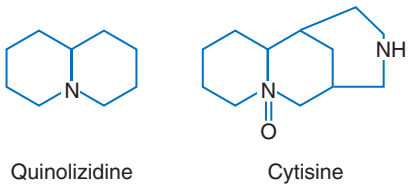


FIGURE 65-8 Betel nut (*Areca catechu*). (***A*** *copyright iStockphoto.com/nine_far;* ***B*** *courtesy Daniel Brooks, MD, and Tammy Tyree, NP.)*

alkaloids are nicotinic and muscarinic. Betel pepper leaves contain betel oil, which contains psychoactive phenols and cadinene. These possess cocaine-like properties. Clinical effects resemble nicotinic syndrome, stimulant effects, and cholinergic toxicity, including CNS effects (dizziness, euphoria, subjective arousal, altered mental status, hallucinations, psychosis, convulsions), cardiac effects (tachycardia, hypertension, palpitations, arrhythmias, bradycardia, hypotension, chest discomfort, acute myocardial infarction in susceptible individuals), pulmonary effects (bronchospasm, tachypnea, dyspnea), GI effects (salivation, vomiting, diarrhea), urogenic effects (urinary incontinence), and musculoskeletal effects (weakness, paralysis). Use with calcium salts may result in hypercalcemia, hypokalemia, and metabolic acidosis with renal potassium wasting and renal insufficiency. Betel nut use is also associated with flushing, diaphoresis, warm sensations, red- or orange-stained lips, oral mucosa and saliva, and dark-brown– or black-stained teeth. Precancerous oral lesions may occur with chronic use. Areca nut chewing is associated with increased risk of oral and esophageal squamous cell carcinoma.[42,67,89,163,202, 203,232,297,315]

Golden Chain Tree

All parts of *Laburnum anagyroides* (golden chain tree) are toxic and contain the nicotinic alkaloids cytisine and *n*-methylcytisine. Cytisine is a quinolizidine alkaloid but is often classified with the pyridine and piperidine alkaloids. These alkaloids stimulate nicotinic ganglia. The toxins are concentrated in the seeds. Toxicity is generally only mild to moderate; however, an unusual fatality occurred in which 23 seedpods were found in the stomach of an adult at autopsy. Other plants that contain cytisine include Kentucky coffee tree (*Gymnocladus dioica*), necklace pod sophora (*Sophora tomentosa*), and mescal bean bush (*Sophora secundiflora*) (Figure 65-9) (see Hallucinogenic Plants, later). Structures follow[291]:



Quinolizidine Cytisine

Blue Cohosh

Caulophyllum thalictroides is known as blue cohosh or squaw root. All parts of the plant contain the nicotinic alkaloid *n*-methylcytisine, which is much less potent than nicotine. Teas made from *C. thalictroides* have been used to induce labor and have reportedly resulted in newborn death and perinatal complications of stroke, congestive heart failure, respiratory failure, and circulatory collapse. The infant toxicity is thought to result from the toxic saponins, caulosaponin and caulophyllosaponin, rather than from the nicotinic alkaloids.[291]

Treatment

Treatment of nicotinic syndromes consists of supportive care with particular attention to airway protection and ventilation. Administration of activated charcoal has been used because it adsorbs nicotine in vitro. However, nicotine and related alkaloids are absorbed rapidly and often produce vomiting, which may limit usefulness of activated charcoal. These alkaloids may induce altered mental status, which can increase the risks associated with activated charcoal. Benzodiazepines and barbiturates are given for seizures. High urine output is maintained with aggressive IV fluids. Consider urine alkalinization. Treating initial excessive adrenergic stimulation with adrenergic antagonists is not advised, because this complicates the nicotinic blockade that typically follows. Symptomatic bradycardia may be treated with atropine. Atropine may also help to treat bronchorrhea. Hypotension can be treated with IV fluids and inotropic agents, if needed.[291,304]

OTHER NEUROMUSCULAR BLOCKING PLANTS

The nicotinic plants previously discussed produce a nondepolarizing neuromuscular blockade. Ingestion of yellow jasmine and exposure to the stinging nettle plant can produce weakness and paralysis.

Yellow Jasmine

Gelsemium sempervirens (Carolina or yellow jessamine) is a woody perennial evergreen vine with fragrant yellow flowers. It contains multiple indole alkaloids, including gelsemine, gelseminine, and gelsemoidin. Gelsemine binds to acetylcholine receptors at the neuromuscular junction (peripheral nicotinic acetylcholine receptors) and, to a lesser extent, at muscarinic receptors. A toddler who ate the blossoms of *G. sempervirens* experienced neuromuscular blockade with ataxia, dysarthria, facial weakness (including bilateral ptosis), extremity weakness, and transient coma. The child recovered without sequelae.[38]

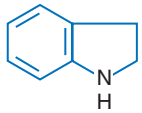
Stinging Nettle

Urtica ferox is found in New Zealand. Dermal exposure most often produces pain, inflammation, urticaria, and allergic reactions (including anaphylactic reactions) when the leave tips break off and fine needles penetrate the skin. With large skin exposures, rapid onset of systemic symptoms may occur, including paresthesias, muscle weakness, paralysis, and respiratory failure. Peripheral neuropathy has been described. The toxin responsible for paralysis is not known.[304]

FIGURE 65-9 Mescal bean bush (*Sophora secundiflora*) **(A)** is characterized by bean pods that contain burnt-red seeds **(B)** and by purple blooms **(C).** *(Courtesy Phillip Saba, MD, and Kimberlie A. Graeme, MD.)*

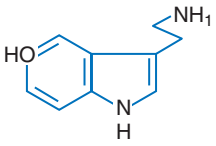
HALLUCINOGENIC PLANTS (INDOLES, PHENYLALKYLAMINES)

Many psychoactive plants are indole derivatives, which are among the most potent psychoactive compounds in nature and have the following structure:

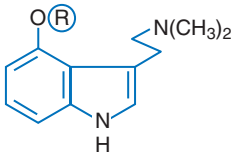


Indole nucleus

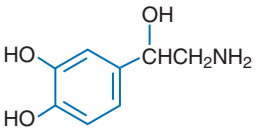
Chemical relationships exist among serotonin, psilocybin (*Psilocybe* spp.), and D-lysergic acid diethylamide (LSD). Striking structural similarities exist between many potent psychoactive plant compounds and biochemically important neurotransmitters, as follows:



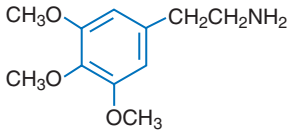
Serotonin



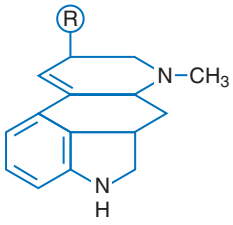
Psilocybin



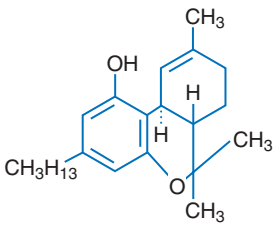
Norepinephrine



Mescaline



Lysergic acid diethylamide



Tetrahydrocannabinol

Morning Glory

The active component of the naturally occurring hallucinogen found in the seeds of morning glory (*Ipomoea violacea*) (Figure 65-10) and Hawaiian baby woodrose (*Argyreia nervosa*) is ergine, or (+)-lysergic acid amide (LSA), an indole derivative.[134,253,254] Compared to LSD, LSA has a lower binding affinity for most serotonergic receptors, produces weaker psychedelic effects, and produces more sedation.[253] However, LSA may still produce psychosis through serotonergic and dopaminergic effects.[183,253] Hypertension has been reported.[183] Nonetheless, about 300 morning glory seeds, or enough to fill a cupped hand, are equivalent to 200 to 300 mg of LSD and have reportedly produced similar systemic and hallucinatory effects. Ingestion of Hawaiian baby woodrose seeds (*A. nervosa*), which also contain LSA, has similar effects.[124] *A. nervosa* is used in tribal medicine in parts of India.[253] Tutorials on the Internet provide instruction for ingestion of dried or fresh *A. nervosa* seeds and for preparation of aqueous and alcoholic extracts.[253,254] *Rivea corymbosa* (Ololiuhqui) also contains LSA. Some have postulated that fungal infection of these plants with ergoline alkaloid biosynthesis may be responsible for the LSA found in the hallucinogenic plants.[177]

FIGURE 65-10 Morning glory (*Ipomoea violacea*).

Nutmeg

Myristica fragrans is used to make the spices nutmeg and mace (Figure 65-11). Mature rinds of the fruit split, revealing a bright-red, fringed, fleshy coating on the outside of its seed. The coating contains mace, and the seed contains nutmeg. Nutmeg contains myristicin, which is structurally similar to mescaline in peyote (*Lophophora williamsii*) and to kawain in kava (*Piper methysticum*), discussed later. Other alkylbenzene derivatives, such as safrole and elemicin, are also found in nutmeg. Nutmeg has been abused for its alleged hallucinogenic effects but may produce euphoria, lethargy, or obtundation. At very high doses, tachycardia, palpitations, anxiety, and anticholinergic-type signs are seen. Hallucinations and paranoid behavior can be observed at these higher doses. Nutmeg is most often abused by persons with limited access to more pleasant and more potent psychotomimetic agents. A person who ingested one grated nutmeg seed (7 g) had nausea, weakness, loss of coordination, vertigo, fainting, and paresthesias but no hallucinations.[26,303]

Cannabis

Cannabis preparations are largely derived from the female *Cannabis sativa* plant. The primary psychoactive component is δ-9-tetrahydrocannabinol (THC), which is most concentrated in the flowering tops. Marijuana generally contains 0.5% to 5% THC; however, sinsemilla and Netherwood varieties may contain up to 20% THC, and hashish and hashish oils have higher concentrations. Cannabinoids can be smoked or ingested. More recently, cannabis oils, or butter, with extremely high THC concentrations, have been promoted for "vaping," which involves using a vaporizer. A typical marijuana cigarette contains 0.5 to 1.0 g of cannabis, and the THC delivered varies from 20% to 70%, with bioavailability of 5% to 24%. As little as 2 mg of available THC produces effects in occasional users.[144]

FIGURE 65-11 Nutmeg (*Myristica fragrans*). *(Courtesy Daniel Brooks, MD, and Tammy Tyree, NP.)*

FIGURE 65-12 Peyote (*Lophophora williamsii*).

Cannabinoids bind to specific cannabinoid receptors in areas of the brain involved with cognition, memory reward, pain perception, and motor coordination. Cannabinoids act as neuromodulators in release and action of neurotransmitters (e.g., acetylcholine, glutamate).[93,144] Endogenous ligands for these receptors are endocannabinoids. The first endocannabinoid identified was anandamide, named after the Sanskrit word *ananda,* which means "bliss."

Desirable effects include mild mood-altering qualities, euphoria, altered perceptions, time distortion, and intensification of ordinary sensory experiences (e.g., gustatory, visual, and auditory sensations). Adverse effects include nausea, vomiting, anxiety, impairment of short-term memory and attention, mydriasis and slowly reactive pupils, and impairment of motor skills and reaction time. Psychotic symptoms have been reported in persons vulnerable to psychosis. Clinically, tachycardia may occur within minutes of THC exposure and last a few hours. Minor changes in blood pressure may occur. Exposed toddlers may present with lethargy, slurred speech, ataxia, and shaking.[39,144,340]

Peyote

Peyote use dates back to more than 5000 years ago.[54] The hallucinogenic peyote cactus *Lophophora williamsii* contains alkaloids that are phenylethylamines or isoquinolines, rather than indoles (Figure 65-12). Mescaline (3,4,5-trimethoxy-β-phenylethylamine), the primary psychoactive component of peyote, is structurally similar to the neurotransmitters norepinephrine and epinephrine and to hallucinogenic amphetamines. Pharmacologically, however, mescaline is similar to hallucinogenic indoles. Mescaline may affect the action of norepinephrine and serotonin, evidenced clinically by sympathomimetic effects, followed by marked visual hallucinations. Mescaline produces slight rises in blood pressure and heart rate, tachypnea, mydriasis, perspiration, flushing, nausea, salivation, hyperreflexia, ataxia, agitation, paranoia, psychosis, and urination. Type B botulism was associated with consumption of a ceremonial tea made from peyote that was stored in a jar by members of the Native American Church. Affected members had bilaterally symmetric, flaccid weakness in all extremities, dysphagia, nasal speech, and diplopia.[12,55,152]

San Pedro Cactus (*Echinopsis* or *Trichocereus* spp.)

Mescaline is also found in some *Trichocereus* spp. (or *Echinopsis* spp.), such as *T. pachanoi* (or *E. pachanoi*; the San Pedro cactus) and *E. peruviana* (Peruvian torch cactus). These cacti have been used medicinally by South American shamans.[242,55] The San Pedro cactus (*E. pachanoi* or *T. pachanoi*) also contains other psychoactive phenethylamines, including lophophine, homopiperonylamine, and lobivine, as does peyote.[47] *Trichocereus* spp. contain 3,4-dimethoxyphenethylamine, which has been isolated from these cacti and sold illicitly[250] (personal communication, Arizona police department).

Dona Ana Cactus

Coryphantha macromeris (Engelm) Br. and R. and its *runyonii* (Br. and R.) L. Benson variety contain methylated catecholamines, including the phenethylamine normacromerine (*N*-methyl-3,4-dimethoxy-β-hydroxyphenethylamine), which are believed to be psychoactive.[173]

MESCAL BEAN BUSH

The mescal bean bush or Texas mountain laurel (*Sophora secundiflora*) of the pea family (Fabaceae) produces dark-red hallucinogenic beans (mescal beans; see Figure 65-9). The beans contain the toxic alkaloid cytisine, which causes nausea, numbing sensations, hallucinations, unconsciousness, convulsions, and death through respiratory failure. The beans may be boiled in water and the mixture consumed, producing a delirium or "visionary trance." The origin of mescalism in modern peyote religion is debated. Mescal beans are worn during some peyote ceremonies.[12]

Iboga

Tabernanthe iboga (iboga or eboka) contains indole alkaloids, including ibogaine. The root of this plant is used in West Africa to communicate with ancestors, reportedly producing "visions" and "waking dreams." More recently, the roots have been ingested as a hallucinogenic substance of abuse. It produces altered states of consciousness, delusions, hallucinations, altered time perception, synesthesias (auditory, olfactory, and gustatory), mydriasis, tachycardia, tremor, and ataxia. Convulsions, paralysis, and lethal respiratory arrest have been reported. A man was found dead after ingesting a powdered root bark of *T. iboga* shrub mixed with sweet concentrated milk. Autopsy revealed pulmonary edema with hemorrhagic alveolitis and vascular congestion.[53,182,211]

Gifbol

Boophone disticha (gifbol, tumbleweed, veld fan, or windball) was historically used in Africa to poison arrow tips. It is now reportedly abused by teenagers for its hallucinogenic effects. In rats, it produces flaccid paralysis.[127]

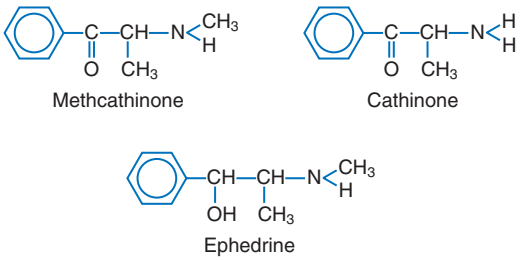
Khat

The evergreen khat tree, *Catha edulis,* grows in East Africa and Arabia (Figure 65-13). Khat is also known as chat, qat, kat, kath, gat, eschat, miraa, murungu, qaad, and jaad. As early as 1237, khat was advocated in Arabic medical literature as a mood-elevating and hunger-suppressing agent. Khat leaves and bark continue to be chewed, with juice of the masticated plant being swallowed for stimulatory effects. Khat contains *cathinone* (2-amino-1-phenyl-1-propanone), cathine (norpseudoephedrine), and norephedrine. Cathinone, a phenylalkylamine, is the

FIGURE 65-13 Khat (*Catha edulis*). *(Courtesy Daniel Brooks, MD, and Tammy Tyree, NP.)*

major psychoactive constituent. Structurally, cathinone is similar to amphetamines, and khat has been referred to as a "natural" amphetamine. Synthetic cathinones (known as "bath salts") have been manufactured and used illicitly. As with amphetamines, cathinone is an indirect sympathomimetic, inducing release of dopamine, serotonin, and norepinephrine.[4,6,9,53,56,154,235,240,252,327]

The structures of methcathinone, cathinone, and ephedrine follow:



Cathinone in fresh plant material must be extracted by masticating laboriously; this results in gradual absorption. As the leaf wilts, cathinone content decreases and the leaf loses its potency as a psychostimulant. Because only fresh leaves produce the desired stimulatory effects, in the past, khat use was generally limited to countries where khat was produced (e.g., North Yemen, Ethiopia, Kenya); however, khat is now air-freighted to Europe and the United States. Khat is transported damp, rolled in a banana leaf bundle called a marduff.

Desirable effects of khat include increased energy and alertness, feelings of increased endurance and self-esteem, enhanced imaginative ability, higher capacity to associate ideas, and euphoria. Cathinone has both positive chronotropic and inotropic effects. Tachycardia, increased blood pressure, tachypnea, and mydriasis are seen. Adverse effects include anorexia, hypomania, insomnia, delusions, paranoid psychosis, aggression, depression, anxiety, hyperthermia, stomatitis, oral lesions/cancers, gastritis, and endocrine disturbances. Khat use has been associated with vasoconstriction, acute myocardial infarction, leukoencephalopathy, and increased incidence of acute cerebral infarction. Khat is known to be habit forming and has been classified as a substance of abuse by the World Health Organization. Cathinone is a Schedule I controlled substance under federal regulations in the United States.*

ANTICHOLINERGIC PLANTS

Henbane (*Hyoscyamus niger*). jimsonweed (*Datura stramonium*), angel's trumpet (*Brugmansia* spp.) and mandrake (*Mandragora officinarum*) contain tropane alkaloids and can produce hallucinations, as discussed earlier.

Treatment

Treatment of patients exposed to hallucinogenic plants is generally supportive. First-line treatment for agitation is generally benzodiazepines.

SEDATING PLANTS

Poppy

Papaver somniferum flowers are large and white with purple stains at the base of each petal. They yield opium, a complex of more than 20 alkaloids, including morphine, codeine, and papaverine. Morphine was the first plant alkaloid isolated, by pharmacist Friederich Wilhelm Adam Serturner in 1806.[141] Seeds of *P. somniferum* are used in foods and beverages, including bagels, muffins, pastries, curry sauce, rice, and teas. Opiate toxicity from poppy seed exposure occurred in a 6-month-old infant given 75 mL of strained milk made with 200 g of poppy seeds in 500 mL of milk, resulting in respiratory arrest requiring ventilation. Opiate toxicity has occurred after ingestion of a boiled poppy plant and after ingestion of spaghetti with poppy seeds. Poppy seed tea has been injected intravenously as a form of drug abuse, resulting in vomiting, hyperthermia, tachycardia, tachypnea, hypoxia, hypotension, myalgias, dyspnea, and rigors. Systemic reaction to foreign substances may account for much of the syndrome seen with injection. Poppy dependence has been described. Ingestion of poppy seeds can result in detectable levels of morphine and codeine by urine drug screen testing.[176,190,220,258,333]

PLANTS PRODUCING SPASTIC PARAPARESIS/QUADRIPARESIS (NEUROTOXIC AMINO ACIDS)

Grass Pea

Lathyrus sativus (grass pea, chickling pea, vetchling, khasari, guaya, shan li dou, and pois carre), *Lathyrus cicero* L. (red pea), and *Lathyrus clymenum* L. contain the neuroexcitatory amino acid β-(*N*)-oxalyl-amino-L-alanine acid (BOAA), previously called β-*N*-oxalyl-L-2,3-diaminopropanoic acid (β-ODAP). Neuroexcitation is caused by BOAA being structurally similar to glutamate and acting as a glutamate receptor agonist. The toxic BOAA is thought to produce excessive and damaging neuroexcitation via glutaminergic pathways. Mitochondrial dysfunction is seen.

Chronic *L. sativus* (grass pea) ingestion may produce neurolathyrism, an upper motor neuron disease characterized by spastic lower-extremity paraplegia and occasionally quadriplegia. Mentation is generally unaffected. The illness was described in 46 BC by Hippocrates: "All men and women who continuously fed on the pulse were attacked by a weakness on the legs which remained permanent." Since that time, neurolathyrism epidemics have been reported during wartime, famine, and natural disasters. The most recent epidemics have been in Bangladesh, India, and Ethiopia. Toxicity is generally only seen when a person eats grass peas for 2 to 3 months and as 30% to 50% of their total dietary intake, or 400 to 500 g of seeds per day for several months. Despite chronic accumulation of toxin, the disease can appear to have a dramatically acute onset; however, detailed histories generally reveal some report of subacute weakness, myalgias, cramps, or stiffness.[25,349] Clinically, neurolathyrism appears similar to neurocassivism, or konzo (see Cyanogenic Plants, later).

CONVULSANT PLANTS (INDOLES, RESINS)

Strychnine

Strychnine, an indole found in seeds of the tree *Strychnos nux-vomica,* is a powerful CNS stimulant. Poisoning may occur after ingestion of rodent poisons containing strychnine, with use of illicit drugs contaminated with strychnine, or with use of herbal remedies contaminated with strychnine. Strychnine is especially concentrated in seeds and roots of the plant. The bark of *S. nux-vomica* also contains the alkaloid brucine, which is less potent than strychnine but produces similar toxicity when consumed. The *S. nux-vomica* tree has been confused with *Alstonia scholaris* (blackboard tree), resulting in fatal consumption of its bark due to brucine toxicity.[1]

Strychnine is a selective, competitive antagonist of glycine, a major inhibitory neurotransmitter, at its postsynaptic receptors in the spinal cord and brainstem. Poisoning produces an excitatory state, with hyperreflexia, hypersensitivity to stimuli, migratory rippling movements of muscles, twitching, rigidity, and spinal convulsions (generally, flexor spasm of upper limbs, extensor spasm of lower limbs, opisthotonic posturing, and jaw muscle spasms, all without loss of consciousness or postictal states). Minimal stimulation elicits diffuse muscle contractions. In between spasms, which last from 30 seconds to 2 minutes, muscles become completely relaxed. Respiratory and secondary cardiac failure may ensue during severe convulsions.

Treatment consists of supportive care, benzodiazepines, and barbiturates. Chemical paralysis with a nondepolarizing

*References 2, 4-6, 9, 19, 65, 90, 132, 154, 174, 208, 223, 235, 240, 252.

agent, endotracheal intubation, and mechanical ventilation may be required for severely poisoned patients. Hyperthermia, rhabdomyolysis, renal failure, and acidosis may occur secondary to convulsions. These complications often require treatment. Occasionally, death ensues despite aggressive treatment.[1,33,60,114,205,229,241,263,296,351]

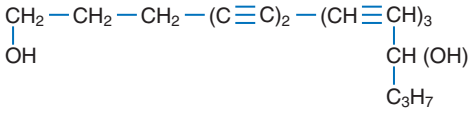
Some *Strychnos* spp. in Africa contain alkaloids that produce curare-like effects. These alkaloids act through nondepolarizing and competitive mechanisms at the neuromuscular junction, competing with acetylcholine for the receptor and thus blocking nerve-to-muscle transmission. This results in paralysis; however, paralysis is not seen after ingestion of these species, because the toxic alkaloids are not absorbed from the GI tract.[263]

Wild Wisteria

The root of *Securidacea longepedunculata* (violet tree or wild wisteria) has been used as an intravaginal suicidal poison and abortifacient. The distilled oil of the root is primarily methyl salicylate; however, wild wisteria also contains the alkaloid securinine, a GABA-A receptor antagonist, which produces hyperreflexia, hypertonia, and seizures. Death can result within hours of placing the root intravaginally and is generally preceded by vomiting, diarrhea, and dehydration.

Water Hemlock

Water hemlock (*Cicuta maculata*) is one of the most toxic resin-containing plants. The resin of *C. maculata,* an unsaturated aliphatic alcohol called cicutoxin, has the following structure:



Cicutoxin

Species within the Umbelliferae (also called Apiaceae) family are divided into the *Cicuta* and *Oenanthe* genera. Nine subspecies of *Cicuta* are poisonous (Figure 65-14). *C. virosa* is common European water hemlock, whereas *C. maculata* and *C. douglasii* are found in North America. *Oenanthe crocata* (hemlock water dropwort) is found in Europe and North America. *Oenanthe* spp. contain oenanthotoxin.[118] Other common names for *Cicuta* spp. include cowbane, five-finger root, snake weed, snake root, wild carrot, dead man's fingers, death-of-man, poison parsnip, wild parsnip, beaver poison, children's bane, muskrat weed, spotted hemlock, spotted cowbane, musquash root, false parsley, fever root, mock-eel root, wild dill, spotted parsley, and carotte à Moreau. Roots have a parsnip- or carrot-like odor, and *Cicuta* spp. are often mistaken for edible plants, such as water parsnip, pignut, sweet flat, watercress, wild celery, wild ginseng, kvanne, and wild carrots. The taste has been diversely described as unpleasant, resembling pine, or sweet tasting. Mature roots have air-filled chambers and extend from hollow stems. The plant is most toxic in the spring. All parts of the plant are toxic, but the roots contain the highest concentration of cicutoxin. Ingestion of as little as 2 to 3 cm of the root may be fatal to an adult. The severity of poisoning and latency to symptoms are proportional to the amount of plant ingested. The principal toxins, cicutoxin and oenanthotoxin, act as noncompetitive GABA antagonists in the CNS, resulting in unabated neuronal depolarization that manifests as seizures, including status epilepticus.[118,125,157,292]

Water hemlock poisoning should be considered in any patient who presents with cholinergic-like poisoning and abrupt onset of seizures. Early symptoms include muscarinic effects and involve primarily the GI tract: abdominal pain, nausea, vomiting, and diarrhea. Marked diaphoresis, salivation, and respiratory distress may be seen. Nicotinic effects are less prominent (see Figure 65-3). Tachycardia and hypertension or bradycardia and hypotension may be seen. Dysrhythmias may occur. Ataxia, paresthesias, muscle spasms, weakness, and coma have been reported. With severe poisoning, epileptiform seizure activity or spastic and tonic movements, including opisthotonos without electroencephalographic (EEG) seizure activity, may occur. Rhabdomyolysis and renal failure have been reported. Deaths may be associated with persistent seizures, cerebral edema, pulmonary edema, ventricular fibrillation, cardiopulmonary arrest, and disseminated intravascular coagulation. Survival beyond 8 hours generally indicates a good prognosis. Laboratory abnormalities include metabolic acidosis and elevated CPK and LFTs.

Treatment of water hemlock poisoning includes securing an airway, ventilation, and treating seizures with benzodiazepines and barbiturates. Phenytoin is contraindicated because it is ineffective for seizure control. Anticholinergic agents are not recommended because these agents do not reduce seizure activity. Continuous EEG monitoring may be helpful. Treatment of hypoxia, acidosis, hyperthermia, rhabdomyolysis, and cerebral edema should be provided. Hypotension can be treated with IV fluids and vasopressors. Recovery can take up to 4 days, and some patients never completely recover. Although survival has improved with aggressive supportive care, death may still ensue. Autopsies reveal pulmonary and cerebral edema, brain hemorrhages, and renal necrosis.[118,125,157,292]

Myrtle-Leaved Coriaria

Coriaria myrtifolia (myrtle-leaved coriaria, Currier's sumach, or Redoul sumach) grows in the western Mediterranean area. *C. myrtifolia* contains coriamyrtin, an analog of picrotoxin. The toxin is found in high concentrations in the berries, which resemble blackberries. Ingestion of only a few fruits can produce significant toxicity. The leaves are toxic. Rarely, individuals have become poisoned after eating snails acquired off the plant, after drinking the milk of goats that had been eating the plant, and

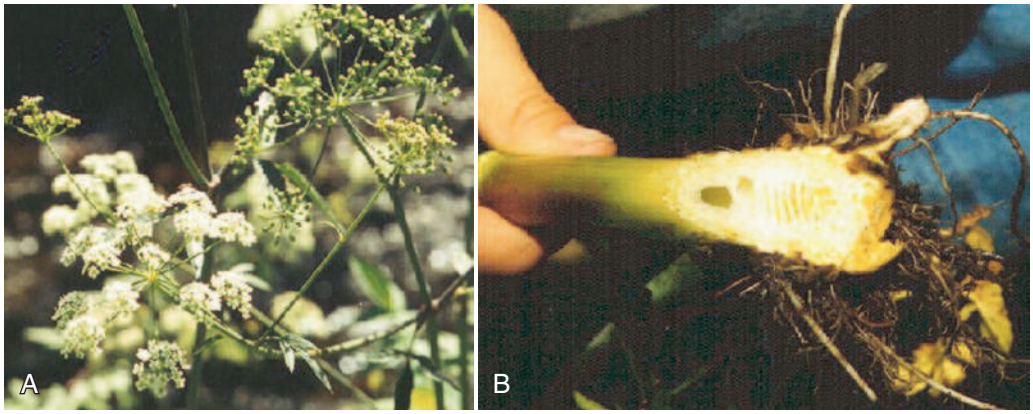


FIGURE 65-14 *Cicuta* species have characteristic flowering tops, typical of the Umbelliferae family **(A),** and roots with air-filled chambers at the ends of hollow stems **(B).** *(Courtesy Steven Curry, MD.)*

after consuming honey contaminated by its nectar. The leaves have been eaten when mistakenly thought to be the leaves of senna (*Cassia senna* L.). Initially, vomiting, abdominal pain, and drunken intoxication are seen. This may be followed by twitching, seizures (including status epilepticus), coma, and apnea. Death may occur. Treatment with benzodiazepines and barbiturates should be considered.[87]

Tutu

Tutu refers to the *Coriaria* spp. found in New Zealand, which include *C. angustissim, C. arborea, C. lurida, C. plumose, C. pteridoides*, and *C. sarmentosa*.[31] Although these plants are generally shrubs, *C. arborea* (tree tutu) may become an evergreen tree, reaching 6 m (20 feet) in height. The primary toxic is tutin, which is picrotoxin-like and produces GABA-A receptor suppression, resulting in anxiety and seizures. Some children who have eaten the attractive, seed-containing berries have died. The berries reportedly have a sweet, blueberry-like flavor. The whole plant is toxic, with the exception of the soft, black or purple petals, which are fleshy and called "berries."[31] Unfortunately, these "berries" contain highly toxic seeds that may be consumed with the berries. As described with other toxic plants, bees that have used tutu nectar have produced toxic, tutin-containing honey. The toxic derivative of tutin, hyenanchin (a hydroxytutin), may be present. Ingestion of the honey may produce vomiting, prolonged delirium, status epilepticus, and death. The seizures may present suddenly without warning. Ingestion of the plant may produce nausea, diarrhea, blurred vision, excitement, tremor, muscle spasms, weakness, incoordination, and coma. Nausea and vomiting may be delayed for 2 to 6 hours after consumption, followed by tonic-clonic seziures and respiratory compromise. The patient may report chest pain and rhonchi before respiratory arrest. If death occurs, it is generally within 24 hours. In survivors, the illness may last for several days, and patients may be amnesic on recovery. Practitioners in New Zealand recommend ECG, serum electrolytes, and a 12-hour observation period, with hospital admission if symptoms develop. There are no antidotes, and treatment is supportive. Benzodiazepines are often helpful and can be given prophylactically.[31]

Kratom

Kratom (*Mitragyna speciosa*) is a tree native to Southeast Asia; however, its plant parts are now popular as herbal drugs of abuse.[329] It contains the toxic alkaloids mitragynine, mitraphylline, and 7-hydroxymitragynine. Mitragynine is thought to have opioid effects, although stimulant effects are seen with ingestion of low doses of kratom. Other receptors besides opioid receptors are likely involved in toxicity. Toxicity is manifested as GI distress, palpations, nystagmus, tremor, altered mental status, and seizures. Psychosis may be seen with chronic abuse. A withdrawal syndrome featuring myalgias, insomnia, fatigue, and chest discomfort has been reported.[329]

Star Fruit

Patients with chronic renal disease are at risk of convulsions after ingesting star fruit (*Averrhoa carambola*). The proconvulsant toxin is caramboxin, a phenylalanine-like molecule with two carboxylic acid moieties. It is structurally similar to ibotenic acid, a toxin found in inebriating mushrooms. Caramboxin is able to activate NMDA glutamate (excitatory) neuroreceptors. Clinically, patients with kidney disease present with intractable hiccups, confusion, and status epilepticus. Toxicity occasionally progresses to death.[130]

Other Convulsants

Anticholinergic and nicotinic plants may produce seizures. Ingestion of plants that produce hypoglycemia, such as ackee (*Blighia sapida*), wild yam (*Dioscorea* spp.), cocklebur (*Xanthium* spp.), bird-lime (*Atractylis gummifera*), and ox-eye daisy (*Callilepis laureola*), are associated with seizures and discussed later. Ingestion of plants that produce multisystem organ failure, such as *Ricinus communis*, *Colchicinum autumnale*, *Poldophyllum* spp., and cyanogenic plants, may produce seizures. Plant-derived essential oils, such as eucalyptus oil, oil of wormwood (*Artemisia absinthium*), oil of wintergreen, and camphor, may produce seizures (see Table 65-4, later). Ingestion of plants that produce liver failure, such as *Chelidonium* (greater celandine), may produce seizures, as discussed later.

BOX 65-3 Cardiovascular Toxins Found in Plants

Alkaloids
Steroid (e.g., aconite, veratrum alkaloids)
Taxane (e.g., taxines)

Glycosides
Cardiac (e.g., lanatosides, oleandrin, thevetin)

Resins
Grayanotoxins (e.g., o-acetyl-andromedol)

CARDIOVASCULAR TOXINS

Cardiovascular toxins found in plants are listed in Box 65-3.

CARDIOTOXINS THAT INHIBIT SODIUM/POTASSIUM ADENOSINE TRIPHOSPHATASE (CARDIAC GLYCOSIDES)

More than 200 naturally occurring cardiac glycosides have been identified. Plant cardiac glycosides are composed of a steroid backbone, an attached five-membered unsaturated lactone ring (six-membered for *Helleborus*), and either a carbohydrate or a sugar moiety in glycosidic linkage. The toxic aglycones are released by acid and enzymatic hydrolysis. The attached sugar moiety has no inherent cardiac action but may enhance solubility, absorption, and toxicity of the aglycone moiety. Cardiac glycosides bind to the membrane-bound enzyme sodium/potassium adenosine triphosphatase (Na^+/K^+ ATPase), increasing intracellular Na^+ and calcium ion (Ca^{2+}) levels and automaticity (Figure 65-15).[274] Cardiac glycosides are found in *Digitalis purpurea* (foxglove) (Figure 65-16), *Digitalis lanata, Nerium oleander*

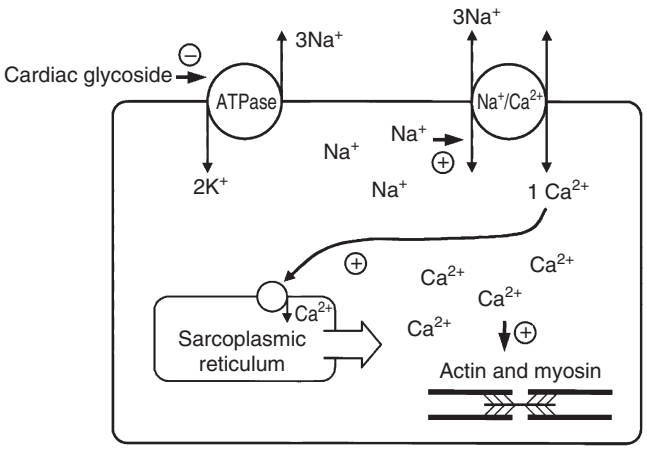


FIGURE 65-15 Cardiac glycosides bind to and inhibit the membrane-bound enzyme Na^+/K^+ ATPase in cardiac myocytes (shown), baroreceptor cells, and skeletal muscle cells. Inhibition of Na^+/K^+ ATPase in cardiac myocytes results in accumulation of intracellular Na^+, which results in accumulation of Ca^{2+} within myocytes via Na^+,Ca^{2+} exchangers. The resultant increase in intracellular Ca^{2+} stimulates further release of Ca^{2+} from the sarcoplasmic reticulum. The increased intracellular Ca^{2+} interacts with troponin C of the actin-myosin complex to cause increased contractions, seen as increased automaticity (e.g., premature ventricular contractions on electrocardiogram). Inhibition of membrane-bound enzyme Na^+/K^+ ATPase in baroreceptor cells and skeletal muscle cells contributes to increased vagal tone and hyperkalemia, respectively.

FIGURE 65-16 *Digitalis purpurea* (foxglove). *(Courtesy Kimberlie A. Graeme, MD.)*

(common oleander) (Figure 65-17), *Thevetia peruviana* (also called *Cascabela thevetia* and yellow oleander) (Figure 65-18), *Convallaria majalis* (lily of the valley) (Figure 65-19), *Urginea maritima* (squill or sea onion) (Figure 65-20), *U. indica, Cerbera manghas* (sea mango), *C. odollam* (pink-eyed cerbera), *Strophanthus* spp. (ouabain, poison rope), *Asclepias* spp. (balloon cotton, red-headed cotton-bush, and common milkweeds), *Calotropis procera* (king's crown), *Carissa spectabilis* (wintersweet), *C. acokanthera* (bushman's poison), *Plumeria rubra* (frangipani), *Cryptostegia grandifolia* (rubber vine), *Adenium multiflorum* (impala lily), *Euonymus europaeus* (spindle tree), *Cheiranthus, Erysimum* (wallflower), and *Helleborus niger* (henbane).* Cardiac glycosides are found in the African plant genera *Acokanthera, Boophone, Strophanthus, Adenium,* and *Catharanthus roseus* (Madagascar periwinkle). *C. roseus* contains vinca alkaloids that are antimitotic and produces metaphase arrest (as does colchicine from *Colchicum autumnale,* discussed later). *C. roseus* is the source of the antineoplastic drugs vincristine and vinblastine. *C. roseus* has hypoglycemic effects.[225,231]

Foxglove

Digitalis purpurea grows wild in parts of the United States and is cultivated as a garden ornamental plant. *D. purpurea* contains digitoxin, not digoxin. Withering reported medicinal use of extracts of *D. purpurea* based on a recipe for treating "dropsy."[155,239] The leaves have been consumed in a risotto when they were mistaken for borage (*Borago officinalis*) leaves, in a salad when mistaken for dandelion leaves, and in an herbal tea when mistaken for comfrey (*Symphytum officinale*).[52,204,234] Toxicity has been reported from consumption of contaminated field water with *Digitalis* plants growing nearby.[234] *D. lanata* (wooly foxglove or Grecian foxglove) was mistakenly substituted for plantain in herbal products, with resultant human cardiotoxicity.[305] *D. lanata* contains lanatosides A, B, and C, which yield digoxin and digitoxin. Intentional overdoses occur.[189,234]

*References 40, 98, 103, 125, 140, 142, 155, 193, 234, 300, 331, 334.

Oleander

All parts of *Nerium oleander* and *Thevetia peruviana* (*Cascabela thevetia*) are toxic, but the seeds contain more glycoside than do other parts of the plant. Yellow oleander (*T. peruviana* or *C. thevetia*), a native plant of tropical America, grows abundantly in the United States. Ingestion of a couple of seeds of yellow oleander, known as "lucky nuts," can result in death; however, the number of seeds ingested is a poor guide to the degree of poisoning. Yellow oleander contains the cardiac glycosides thevetin A and B, thevetoxin, neriifolin, peruvoside, ruvoside, and others. It is a popular suicide agent in Sri Lanka and India. Of patients admitted with yellow oleander poisoning in Sri Lanka, 43% had arrhythmias, many required temporary cardiac pacing, and 6% died shortly after admission. Common oleander (*N. oleander*), a native plant of the Mediterranean, grows abundantly in the United States. Common oleander contains the principal cardiac glycosides oleandrin and neriine, as well as folinerin and digitoxigenin. Severe toxicity has been reported after consumption of unprocessed common oleander leaves and prepared teas. Chronic toxicity has occurred with criminal intentional poisoning. Topical application of homemade *N. oleander* solutions onto psoriatic wounds has caused toxicity.[4,98,99,125,135,193,195,238,274,348]

Squill

Urginea maritima was used by ancient Egyptians and Romans as a diuretic, heart tonic, expectorant, emetic, and rat poison.

FIGURE 65-17 *Nerium oleander* (common oleander) plants have white or pink flowers **(A)** and long, narrow seedpods **(B).** *(Courtesy Kimberlie A. Graeme, MD.)*

FIGURE 65-18 *Thevetia peruviana* (yellow oleander) has yellow flowers **(A)** with smooth seedpods, known as "lucky nuts," composed of green flesh surrounding a hard brown seed **(B)**. *(Courtesy Kimberlie A. Graeme, MD.)*

Squill contains several cardiac glycosides, including scillaren A, glucoscillaren A, scillaridin A, and scilliroside.[103,331,343]

Suicide Tree

Cerbera odollam (suicide tree, pong-pong tree, pink-eyed cerbera, yellow-eyed cerbera) contains cerberin, a cardiac glycoside. Ingestion of the seeds with suicidal and homicidal intent is reported in South Asia. Less often, suicidal ingestion occurs in the Western world, and has occurred after purchase of the seeds online. Anecdotal clinical improvement has been noted when toxicity is treated with digoxin-specific Fab fragments.[171]

FIGURE 65-19 Lily of the valley (*Convallaria majalis*). *(Courtesy Donald Kunkel, MD.)*

Sea Mango

Cerbera manghas (sea mango) is similar to *C. odollam* (suicide tree). This tree grows in India, Vietnam, Cambodia, Sri Lanka, Myanmar (previously Burma), Madagascar, and Australia. The plant has large, white flowers that smell like jasmine. When the fruit is still green, it looks like a small mango. The inner fruit kernel is white, but on exposure to air turns violet, then dark gray, and then black. The crushed, white, fleshy kernel is often consumed as a suicide poison in India and Sri Lanka. The seeds are quite toxic. The leaves are less toxic. These plants contain the toxins cerberoside, cerberin, and odollin. After ingestion, death can occur within hours.[100,128,203,330]

Clinical Presentation

The onset of symptoms and duration of action are well known for certain glycoside preparations, such as digoxin, digitoxin, and

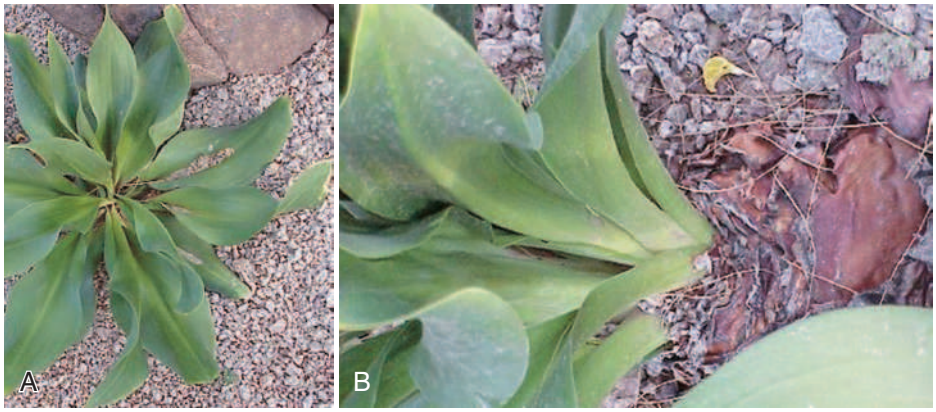


FIGURE 65-20 *Urginea* species (squill or sea onion) have broad leaves **(A)** and a red, underground bulb (some varieties have a white bulb) **(B).** *(Courtesy Kimberlie A. Graeme, MD.)*

ouabain, but may vary considerably after plant ingestions. For example, oleandrin exhibits protracted binding times to cardiac myocardial tissues.[193] Generally, cardiac glycoside toxicity produces nausea, vomiting, diarrhea, abdominal tenderness, visual changes (appearance of yellow and green colors, "halos," geometric shapes, scintillations, photophobia), mydriasis, mental status changes (disorientation, psychosis, lethargy, stupor, dysarthria, weakness, dizziness, restlessness, seizures), cardiac disturbances (palpitations, premature ventricular beats, bradycardia, atrioventricular block, sinus node block, paroxysmal atrial tachycardia with block, junctional tachycardia, bidirectional ventricular tachycardia, ventricular arrhythmias, myocardial depression with cardiogenic shock, syncope), hyperkalemia, and death. When it occurs, death is generally caused by cardiotoxicity. The ECG may reveal nonspecific ST-segment and T-wave changes, similar to digoxin-induced changes.[96,135,195,204,234,274,305,347] Serum digoxin levels may be elevated after exposure to plants containing cardiac glycosides, because antibody-based digoxin assays cross-react nonquantitatively with many cardiac glycosides. Digoxin immunoassays can only predict the presence of the glycoside, not the degree of toxicity.[99,140,193,331,204] Conversely, the degree of hyperkalemia often correlates with severity of toxicity.[99,128,204]

Treatment

Continuous cardiac monitoring for at least 24 hours is recommended because of the risk for arrhythmias. Cardiac glycoside toxicity from plant ingestions has been successfully treated with a single dose or multiple repeated doses of activated charcoal, cardiac pacing, antiarrhythmic agents, and digoxin-specific Fab fragments (e.g., Digibind, DigiFab). Maintenance of fluid and electrolyte balance is important. Potassium levels should be checked frequently. Correction of hyperkalemia with insulin and dextrose is recommended. Sodium polystyrene sulfonate resin is not recommended because total-body hypokalemia may ensue. Theoretically, administration of exogenous calcium could be harmful because of high intracellular calcium concentrations of poisoned myocytes. It is hypothesized that the heart may perform one final contraction without relaxation, a state termed *stone heart*. However, some have questioned the withholding of calcium, because some case reports and retrospective review suggest that calcium administration is generally not detrimental. Bradyarrhythmias have been managed with atropine and β-adrenergic agents. However, there is a theoretical risk for increasing tachyarrhythmias, which may be more difficult to treat. Some have advised against use of atropine and β-adrenergic agents unless bradycardia is life threatening. Some believe that cardiac pacing is a better alternative, although this may precipitate tachyarrhythmias as well. Ventricular tachycardia may persist despite electrical cardioversion, and electrical cardioversion can precipitate ventricular fibrillation or asystole. Therefore, electrical cardioversion is reserved for resistant cases.

For patients with tachyarrhythmias, lidocaine has been advocated. The role of magnesium is not known, although some have subjectively noted death after yellow oleander poisoning treated with IV magnesium. Amiodarone, quinidine, and calcium channel blockers are contraindicated because they may increase digitalis concentration; β-blockers are contraindicated because they may worsen heart block. Digoxin-specific Fab antibody fragments may couple to circulating cardiac glycosides and limit binding of cardiac glycosides to Na^+/K^+ ATPase. Administration of digoxin-specific Fab antibody fragments to reverse cardiotoxicity from plant glycosides has been successful in several animal and human studies. Clinical trials in Sri Lanka revealed that IV administration of 1200 mg of digoxin-specific antibody fragments reversed life-threatening cardiac arrhythmias and corrected hyperkalemia after yellow oleander poisoning. High doses of digoxin-specific Fab antibody fragments (e.g., 10 to 20 vials) may be needed. Animal studies indicate that fructose-1,6-diphosphate may be a beneficial treatment of cardiac glycoside poisoning. This is being studied in humans currently, but is not an established treatment.*

*References 74, 99, 100, 101, 128, 135, 171, 179, 193, 199, 204, 234, 274, 277, 279, 305.

FIGURE 65-21 Monkshood (*Aconitum* spp.).

CARDIOTOXINS THAT OPEN SODIUM CHANNELS (STEROID ALKALOIDS, RESINS)

Steroid alkaloids form principal toxic components of several common cardiotoxic plants: *Aconitum* spp. (monkshood, wolfsbane, helmet flower), *Veratrum viride* (American hellebore, green hellebore), and *Zigadenus* spp. (death camas). Aconite is found in *Aconitum* spp., and veratrum alkaloids are found in *V. viride, V. nigrum* var. *japonicum* (false hellebore), *V. californicum* (skunk cabbage), *V. album* (white hellebore), *Z. paniculatus* (death camas), *Z. venenosus, Z. nuttallii,* and *Z. gramineus.*

Aconite

Aconite poisonings have become more common because of the use of *Aconitum* spp. (*A. napellus* [monkshood]; (Figure 65-21), *A. carmichaeli* (Chuanwa, Fuzi, Bushi), *A. brachypodium, A. vulparia,* and *A. kusnezoffii* (Caowu) in herbal products. *Delphinium* spp. (larkspur) demonstrate similar toxicity. All parts of these plants are toxic, with the roots being most toxic. *Aconitum* spp. contain diterpenoid-ester alkaloids, particularly aconitine, but also mesaconitine, hypaconitine, and yunaconitine, which are neurotoxins and cardiotoxins. Boiling these plants in water hydrolyzes aconite alkaloids to less toxic benzoylaconine and aconine derivatives. Soaking or boiling, termed *decoction,* is generally done when these plants are used as herbal medicines. The estimated lethal dose of wild plant is 1 g.[10,61-63,72, 120,125,200]

Aconite alkaloids activate voltage-sensitive sodium channels and affect excitable membranes of neural, cardiac, and muscle tissues. Aconite alkaloids bind to open voltage-gated sodium channels, producing a hyperpolarized state, with permanent activation of the channels. Hypaconitine affects sodium channels of the nerve membrane more selectively than aconitine and is more potent than aconitine and mesaconitine in producing neuromuscular block. These neurotoxins produce conduction block and paralysis through voltage-sensitive sodium channels in axons. In cardiac tissues, prolonged depolarization prevents repolarization of excitable membranes. Enhancement of the transmembrane inward sodium current during the plateau phase of the action potential prolongs repolarization in cardiac myocytes and induces delayed and early afterdepolarizations. Delayed afterdepolarizations result in increased automaticity, such as premature ventricular beats. Early afterdepolarizations produce lengthening of the QT interval. Hypotension and bradycardia may be induced by activation of the ventromedial nucleus of the hypothalamus.[10,62,61,72,120,125,200]

Symptoms begin within 3 minutes to 6 hours of aconite ingestion and may persist for several days. Nonspecific GI symptoms (nausea, vomiting, diarrhea) are accompanied by neurotoxicity and cardiotoxicity. Visual impairment, dizziness, vertigo, ataxia, paresthesias (e.g., numbness of mouth and extremities), hyporeflexia, weakness, paralysis, coma, restlessness, and convulsions may occur. Patients may present with chest pain, palpitations,

and syncope. Cardiac effects are clinically similar to cardiac glycoside toxicity, with enhanced vagal tone, bradycardia, heart block, ectopic beats, supraventricular tachycardia, bundle branch block, junctional escape rhythms, ventricular tachycardia, bifascicular ventricular tachycardia, polymorphic ventricular tachycardia, torsades de pointes, ventricular fibrillation, asystole, and hypotension. Bidirectional ventricular tachycardia, which is generally considered suggestive of cardiac glycoside toxicity, has been reported with aconite poisoning. Elevated CPK and troponin levels, with or without evidence of myocardial infarction, may occur. Myocardial necrosis and myocarditis have been reported. Hypokalemia, metabolic or respiratory acidosis, respiratory alkalosis, and renal and hepatic impairment may be noted. Occasionally, death ensues, generally from ventricular arrhythmias, such as refractory ventricular fibrillation. Respiratory paralysis may result in death.* A 17-year-old man ate immature *Delphinium* root and developed seizures, ventricular fibrillation, and cardiac arrest. He survived and later reported that he had experienced a floating or flying sensation.[328]

Veratrum Alkaloids

Veratrum and *Zigadenus* spp. belong to the lily family. All parts of these plants are toxic, with the rhizomes being more toxic than the tops. *Veratrum* spp. have been found in sneezing powders and have been accidentally ingested when mistaken for *Gentiana lutea* (yellow gentian). Gentian wines are usually made from *G. lutea*. When accidentally made from *Veratrum* spp., these wines can be toxic. *V. viride* has been mistaken for skunk cabbage, ramps, and pokeweed (*Phytolacca americana*), producing toxicity after ingestion. *Zigadenus* spp. (foothill camas, death camas, mountain camas) have been accidentally ingested when mistaken for nontoxic wild onions (*Allium macropetalum*) and sego lilies (*Calochortus nuttallii*). *Amianthium muscitoxicum* (fly poison) and *Schoenocaulon officinale* (Sabadilla) contain veratrum alkaloids. Veratrum alkaloids include protoveratrine, veratridine, cevadine, jervine, zygadenine, and zygacine, which are found in the entire plant, although the bulb and flower usually cause toxicity. These alkaloids are extremely toxic and rapidly increase permeability of voltage-sensitive sodium channels in excitable cell membranes. This results in initial depolarization and then subsequent loss of membrane potential. Stimulation of vagal fibers may result in bradycardia and hypotension.†

Symptoms generally occur within 30 minutes to 4 hours and resolve within 24 to 48 hours, although symptoms may persist for many days. Toxicity is characterized by headache, diaphoresis, salivation, nausea, vomiting, diarrhea, abdominal pain, hypotension, bradycardia, and shock. Syncope, respiratory depression, scotomata, paresthesias, fasciculations, muscle spasticity, hyperreflexia, vertigo, ataxia, dizziness, coma, seizures, and death may occur. ECG findings may mimic cardiac glycoside toxicity, including repolarization abnormalities (e.g., abnormal T waves and ST segments), sinoatrial and atrioventricular blocks, and prolonged QT intervals.[113,137,262,290,345,354]

Grayanotoxins

Resins called grayanotoxins are found in rhododendrons, mountain laurels, and azaleas. They produce toxicity similar to that seen with the steroid alkaloids veratrum and aconite. They act by binding to myocardial sodium channels and increasing their permeability and by increasing vagal tone. Grayanotoxins inhibit cardiac and respiratory actions within the CNS. Poisoning may result from ingestion of leaves, flowers, or nectar. Grayanotoxin-contaminated honey, termed "mad honey," is the most common source. The nectar of *Rhododendron* spp. contains the grayanotoxin *o*-acetyl-andromedol, formerly andromedotoxin, which is transferred to humans through consumption of honey produced by bees using the plant's nectar. "Mad honey" was reportedly used as a biologic weapon against the Romans in 67 BC. Poisonings still occur in Asia Minor. "Mad honey" is sometimes taken in hopes of enhancing sexual performance but may result in toxicity. Symptoms include diaphoresis, hypersalivation, nausea, vomiting, bradycardia, arrhythmias (atrioventricular blocks, junctional rhythms), chest pain, hypotension, shock, dizziness, syncope, circumoral and extremity paresthesias, incoordination, and muscular weakness. A patient presented with acute myocardial infarction with normal coronary arteries after "mad honey" ingestion.[168,302] Patients generally recover in 1 to 2 days. In Korea, the blossoms of azaleas (*R. mucronulatum*) are used to make wine, honeyed flower juice, and griddle cakes, with reported toxicity.[3,69,71,88,168,180,191,196,339]

Treatment

Treatment of poisoning from cardiotoxins that open sodium channels is supportive, with attention to fluid and electrolyte balance. Atropine for bradycardia and vasopressors for fluid-resistant hypotension are appropriate. Patients may require mechanical ventilation and cardiopulmonary resuscitation. Magnesium may suppress early afterdepolarizations and polymorphic ventricular tachycardia. Lidocaine, procainamide, flecainide, amiodarone, and hemoperfusion have been used to treat ventricular arrhythmias secondary to aconite poisoning, as reported in various case reports. Ventricular dysrhythmias may be resistant to cardioversion and antiarrhythmic agents. Cardiopulmonary bypass, extracorporeal membrane oxygenation, and ventricular assist device placement have been used successfully for treatment of aconite poisoning.*

OTHER CARDIOTOXINS

Taxine Alkaloids

Taxus spp. include *T. baccata* (English yew), *T. brevifolia* (Western yew), *T. cuspidata* (Japanese yew), and *T. sumatrana* (Sumatra or Chinese yew). The toxic alkaloids include taxines A and B. Yew plants also contain nitriles, ephedrine, and irritant oils. All parts of *Taxus* plants are toxic except the pulp, or aril, which contains very little taxine. The seeds, which are surrounded by the aril, may be toxic if chewed sufficiently to allow absorption of taxine. The plant is most toxic in the winter. Taxine B, believed to be the primary cardiotoxic alkaloid, inhibits both calcium and sodium transport across cell membranes.†

Most *Taxus* exposures occur in children, are accidental, and are not associated with significant toxicity. However, serious toxicity and death have occurred after intentional ingestions of *Taxus* spp.. The lethal oral dose of yew leaves is 0.6 to 1.3 g/kg body weight. GI toxicity is most common; dizziness, mydriasis, muscle weakness, altered mental status, and convulsions have been reported. Severe toxicity is characterized by bradycardias, heart blocks, ventricular tachycardia, ventricular fibrillation, widened QRS complexes, hypotension, cardiac arrest, and death. Brugada syndrome pattern has been noted on the ECG during toxicity; it resolved with recovery. Hemolysis with multiorgan failure has been reported.‡ Autopsies have revealed dilated cardiac ventricles and congestion of the organs with pronounced cerebral and pulmonary edema.[138] Plant parts are often found in the stomach and small bowel on autopsy. 3,5-Dimethoxyphenol demonstrated by gas chromatography–mass spectrometry of blood or urine is a marker of *Taxus* poisoning.[119,138,268,270,344]

Reported yew-induced arrhythmias in humans are consistent with arrhythmias induced by blockade of voltage-gated sodium channels. These are described as bradycardia with wide QRS complexes, despite normal electrolytes. Two patients who ingested yew presented with severe cardiotoxicity and a wide QRS complex, which appeared to respond favorably to administration of hypertonic sodium bicarbonate.[216,267,283] However, sodium bicarbonate administration did not narrow the widened QRS complex of *Taxus*-poisoned swine.[283] Because there is minimal risk to administering sodium bicarbonate and possible significant benefit, this treatment should be considered if widened

*References 61, 62, 72, 120, 125, 175, 200, 201, 203, 222, 243, 306, 353.
†References 113, 125, 129, 137, 158, 262, 271, 290, 345, 354.

*References 10, 61, 62, 69, 71, 97, 125, 129, 137, 196, 201, 222, 243, 262, 290, 306, 345, 353.
†References 119, 138, 185, 194, 203, 267, 268, 326, 336, 337, 347.
‡References 138, 185, 203, 216, 228, 267, 283, 326, 336, 337, 347.

QRS is noted. Lidocaine administration and cardiac pacing have been reportedly beneficial for treatment of humans poisoned with yew.[270,337]

ORAL AND GASTROINTESTINAL TOXINS

ORAL IRRITANTS (GLYCOSIDES, OXALATES)

Daphne

Coumarin glycosides may produce pronounced irritant effects. An example is daphne (*Daphne mezereum*), with its fragrant, succulent berries. The widely cultivated daphne presents a significant risk to curious children, for whom only a few ingested berries may be lethal. The fruits contain a coumarin glycoside and a diterpene that irritate mucous membranes, with swelling of the tongue and lips. Blisters form if berries are rubbed on the skin, and in the oral and GI tract if ingested. Severe gastroenteritis with GI bleeding may occur after ingestion. In addition, progressive weakness, paralysis, seizures, and coma may develop. Treatment is supportive.

Insoluble Oxalates

Plant exposures involving *Philodendron, Dieffenbachia* (dumb cane), *Spathiphyllum* spp. (peace lily) (Figure 65-22), *Colocasia* spp. (elephant's ear, common calla), and *Brassaia* (octopus tree, Queensland umbrella tree) are frequently reported.[184,206,256] *Alocasia macrorrhiza* (giant elephant's ear, taro), *Monstera deliciosa* (fruit salad plant, split-leaf philodendron), *Anum* spp. (dragon lily, voodoo lily), *Arisaema amurense* (cobra lily), and *Zantedeschia aethiopica* (calla lily, arum lily) can produce similar toxicity.[40,203,284] These plants contain insoluble oxalates arranged in numerous crystalline needles of calcium oxalate (raphides) contained in specialized cells (idioblasts). When stimulated, as by mastication, idioblasts forcefully release raphides that become embedded in exposed tissues, resulting in painful oropharyngeal edema, hypersalivation, vesicle formation, dysphagia, and aphonia. On occasion, airway obstruction occurs. These plants also contain trypsin-like proteases, histamine, and kinin-like substances that may contribute to toxicity.[206,284,320,342] In a mass foodborne illness in Chicago, patients presented with oral burning and facial edema after lunch in an office cafeteria serving a Chinese vegetable entrée found to contain raphides.[342]

Dieffenbachia is commonly known as "dumb cane" because of the person's inability to speak after chewing the plant. As with other plants containing insoluble oxalates, vesicle, bulla, and ulcer formation of the oral mucous membranes and epiglottis or esophageal erosions may occur after mastication and ingestion.[8] Respiratory obstruction resulting from edema and sudden death have been reported. Treatment is supportive, with special attention to maintaining a patent airway. Severe edema and potential for airway obstruction may warrant intensive care monitoring. After massive ingestions, hypocalcemia and its effects should be anticipated.[206,256,320,342]

GASTROINTESTINAL IRRITANTS (RESINS, ALKALOIDS)

Gastrointestinal toxins found in plants are listed in Box 65-4.

Chinaberry Trees

Melia azedarach plants are found throughout the southern United States and Hawaii (Figure 65-23). The chinaberry tree, also known as China tree, Texas umbrella tree, or white cedar tree, contains tetranortriterpenes (resins) identified as meliatoxins A_1, A_2, B_1, and B_2, which are enterotoxic and neurotoxic. The bark contains toosendanin. Gastroenteritis can occur after

FIGURE 65-22 Plants that are oral irritants. *Philodendron* **(A),** *Dieffenbachia* **(B),** *Spathiphyllum* **(C).** *(Courtesy Kimberlie A. Graeme, MD.)*

BOX 65-4 Gastrointestinal Toxins Found in Plants

Alkaloids
Amine (e.g., colchicine)
Isoquinoline and quinoline (e.g., emetine in ipecac)
Pyrrolizidine
Steroid (e.g., solanine)

Glycosides
Coumarin
Saponin (e.g., phytolaccatoxin)

Resins
Cicutoxin
Meliatoxins

Phytotoxins
Abrin
Curcin
Ricin

FIGURE 65-23 Chinaberry (*Melia azedarach*) tree **(A)** and berries **(B).** *(Courtesy Kimberlie A. Graeme, MD.)*

ingestion of any part of the plant, but typically occurs after berries are ingested by children. Immature berries are green but turn yellow and wrinkle with age. After ingestion of only one berry, severe gastroenteritis may ensue, often with bloody diarrhea. Symptoms may be rapid in onset or delayed by several hours after ingestion. In Chinese medicine, *M. azedarach* bark has been boiled and drank, with resultant nausea, vomiting, abdominal discomfort, diarrhea that can be bloody, dizziness, muscle soreness, weakness, ataxia, areflexia, coma, blurred vision, ptosis, numbness, and headache. Muscle tremors, convulsions, and death have been reported in children after ingestion of berries of the African variety of chinaberry tree. Fatalities are generally caused by respiratory arrest. Mild elevation of liver enzymes and CPK, as well as hypokalemia and acidosis, has been reported. Autopsy has revealed cerebral edema, midbrain necrosis, intracranial hemorrhage, pulmonary congestion, GI hemorrhage, yellow discoloration of the liver, and congestion of the kidneys. Treatment is supportive, with replacement of fluids and electrolytes. Patients with tachycardia and hypotension generally respond to IV fluids.[150,264]

Solanum

The genus *Solanum* makes up the largest group of steroid alkaloid–containing plants and includes *S. tuberosum* (potato), *S. gracile* (wild tomato), *S. carolinense* (horse nettle), *S. pseudocapsicum* (Jerusalem cherry), *S. dulcamara* (woody nightshade), *S. americanum* (black nightshade), and other nightshade plants. *Solanum* species are used medicinally in some countries. Solanine, a glycoalkaloid with a steroid-like moiety, has been isolated from more than 1700 different *Solanum* spp. It is found throughout the plants but is most concentrated in unripe fruits. Solanine generally produces gastroenteritis, but bradycardia, weakness, and CNS and respiratory depression may be seen. Treatment is supportive, with replacement of fluids and electrolytes. If hypotension ensues, patients generally respond to IV fluids. Atropine may be beneficial if bradycardia develops. Spontaneous recovery usually occurs in 1 to 3 days.[78,133]

Plants Containing Saponin Glycosides

Saponin glycosides are found throughout the plant kingdom, for example, in pokeweed (*Phytolacca americana*), English ivy (*Hedera helix*), tung tree (*Aleurites* spp.), ginseng (*Panax ginseng* or *P. quinquefolium*), and licorice (*Glycyrrhiza glabra*).[125] Saponins are GI irritants that facilitate their own intestinal absorption. Saponins may induce lysis of erythrocytes, causing hemolytic anemia. In addition, most saponins are found in combination with other toxins, resulting in diverse clinical syndromes.

Pokeweed. *Phytolacca americana,* or *P. decandra,* is most commonly known as pokeweed but is also called Virginia poke, inkberry, pocan, pigeonberry, American cancer-root, garget, red ink, American nightshade, scoke, jalap, and redwood. It may be mistaken for horseradish, parsnip, or Jerusalem artichoke. *P. americana* has green leaves with red stalks. Berries are green when immature and turn deep purple with maturity. Pokeberries typically leave a purple stain. The root is the most toxic part of the plant. *P. americana* is ingested intentionally in pokeweed salad and pokeberry teas. When prepared for ingestion, leaves should be parboiled, which entails boiling the leaves first in water that is discarded before boiling the leaves again and rinsing them with fresh water. However, parboiling does not necessarily offer complete protection against toxicity.[125]

The saponin glycosides phytolaccatoxin and phytolaccagenin account for the GI injury, which manifests as fulminant gastroenteritis, with vomiting and diarrhea 2 to 4 hours after ingestion. Diarrhea may appear foamy from the sudsing effect of saponin glycosides. Hypotension may follow significant GI fluid losses. Severe toxicity may include weakness, loss of consciousness, seizures, and respiratory depression.[125]

P. americana also contains mitogenic, hemagglutinating, and antiviral proteins. Pokeweed mitogen may induce morphologic changes in lymphocytes and plasma cells. An increased number of circulating plasmablasts and proplasmacytes, eosinophilia, and thrombocytopenia can be seen after ingestion or after handling *P. americana* with broken skin.

FIGURE 65-24 Castor bean plant (*Ricinus communis*) **(A)** contains ricin and is characterized by broad, serrated leaves, with fresh beans encased within a soft, thorny, red seedpod. With age, the seeds and their surrounding seedpod become brown, and the seeds develop hard shells that are difficult to penetrate **(B).** *(Courtesy Phillip Saba, MD, and Kimberlie A. Graeme, MD.)*

Treatment for acute toxicity includes fluid replacement for dehydration secondary to GI losses. Airway support may be needed. Seizures should be treated with benzodiazepines. Hematologic changes generally resolve within weeks.[125]

TOXINS THAT INHIBIT PROTEIN SYNTHESIS (PHYTOTOXINS)

Toxalbumins (Ricin, Abrin, Curcin, Robin, Phasin)

Toxalbumins are found in *Abrus precatorius* (jequirity bean, rosary pea, prayer bead; contains abrin), *Ricinus communis* (castor bean; contains ricin) (Figure 65-24, *A*), *Jatropha curcas* (purging nut) and *J. multifida*, which contain curcin, and *Robinia pseudoacacia* (black locust; contains robin and phasin). These toxins inhibit protein synthesis and cause cell death. The toxins are glycoproteins composed of two peptide chains, designated A and B, connected by a disulfide bond (see Figure 65-2). Chain B binds to the cell membrane. The toxin penetrates the cell by endocytosis. Chain A binds irreversibly and inactivates the ribosomes through glycosidase activity, which disrupts protein synthesis and results in cell death. Much of the toxicity is the result of endothelial cell damage, which causes increased capillary permeability, fluid and protein leakage, and edema.*

Ricin poisoning generally results from eating or chewing on the nut or seed; however, consumption of leaves may also produce toxicity.[270] Fresh, immature castor beans are encased within a soft, thorny, red seedpod. With age, the seeds and surrounding seedpod become brown, and the seeds develop hard shells that are difficult to penetrate, but can be punctured by teeth (Figure 65-24B). After a latent period of 1 to 6 hours, nausea, vomiting, diarrhea, hemorrhagic gastritis, abdominal pain, thirst, dehydration, hypotension, coma, hyporeflexia, seizures, respiratory compromise, and shock may occur. Liver disease, with elevated LFTs, is common. Death may occur from dehydration and electrolyte imbalances. Convulsions may precede death. Death on the third day or later is usually caused by multiorgan failure. Autopsy may reveal GI tract ulcerations, necrosis of the lymph nodes and liver, nephritis, and pulmonary edema.[45,92,94,145,187,247,269]

The oral lethal dose is estimated to be 1 mg/kg; theoretically, only one bean in a child and 8 to 10 beans in an adult could be fatal, although this rarely is the case. A discrepancy between the serious toxicity of isolated ricin exposure and the milder toxicity of ingested seeds of *Ricinus communis* is recognized. A young adult consumed 10 to 15 seeds of *R. communis* and experienced severe cramping abdominal pain and vomiting 4 hours after ingestion, without GI bleeding or abdominal guarding. He received IV fluids. By the third day, he had recovered completely. Other cases of oral ingestion of masticated seeds indicate that GI distress may be followed a few days later by elevated liver enzymes or hyperbilirubinemia, followed by complete recovery. In contrast, a Bulgarian broadcaster who was injected with isolated ricin died from severe gastroenteritis and multiorgan failure. Ingested *R. communis* is much less toxic than is parenteral ricin. The degree of mastication of castor beans may determine the degree of toxicity seen with oral ingestions. Fresh, soft seeds are likely to be more toxic than aged seeds that are enveloped by a hard coat. Although deaths have been reported with ingestions of a couple of seeds, toxicity is unlikely if mature seeds are swallowed intact. Furthermore, some of the toxin, which is a protein, is likely digested in the GI tract.[7,45,92,94,247]

Similarly, deaths have been reported after ingestion of fresh jequirity beans (*Abrus precatorius*) if the soft, immature bean is chewed or if the hard shell of the mature bean is adequately penetrated. The estimated human fatal dose of abrin is 0.1 to 1 mcg/kg. One-half a seed has been reported to cause toxicity in a child, and one chewed bean could be fatal. However, as with castor beans, the mature bean shell is often not penetrated; therefore significant toxicity is not often seen. For example, a 15-month-old child ingested more than 20 jequirity beans with only minor clinical toxicity, including mild hepatomegaly and mild elevation of aspartate aminotransferase/transaminase (AST).[92,112,269]

Symptoms generally begin within a few hours. Mild symptoms involve diarrhea alone. More severe symptoms include persistent vomiting, diarrhea, and abdominal pain, with associated hypovolemia and hypokalemia. Hemorrhagic gastritis with bloody diarrhea may ensue. Dehydration may be associated with shock and hepatorenal dysfunction. Severely ill patients may present with hyperthermia, mental status changes, and seizures. Systemic injury may appear in a delayed fashion as the cumulative effects of inhibition of protein synthesis mount. Delayed effects may occur 1 to 5 days after ingestion. Terminally, elevated serum LFTs and creatinine levels may be seen, indicating hepatorenal failure. If death occurs, it is generally 3 to 5 days after ingestion and is associated with seizures, tachycardia, GI distress, mucosal changes of the GI tract (including edema and hemorrhage of the Peyer's patches), focal necrosis and failure of the liver and kidneys, and retinal hemorrhage. Cerebral and pulmonary edema, hypertension, and pancreatitis have been observed.[7,92,112,269]

Jatropha species have attractive, sweet-flavored fruit that may entice children. Children may consume the seeds out of curiosity. Presentation of toxicity may be mistaken for organophosphate poisoning, with diaphoresis, vomiting, diarrhea, obtundation, and miosis reported in one case. Mydriasis has also been reported. Other cases have manifested with hemorrhagic gastroenteritis, hypotension, muscle spasm, and hyperpnea. Leukocytosis may be noted.[181,187]

Treatment

Treatment of toxalbumin poisoning is supportive, including fluid and electrolyte replacement. Patients who remain asymptomatic

*References 7, 36, 45, 92, 94, 145, 164, 187, 247, 269.

for 4 to 6 hours after ingestion of seeds may be discharged, with instructions to return if symptoms develop. Laboratory follow-up for delayed liver toxicity may be appropriate. Studies indicate that ricin antibody administered intravenously shortly after exposure could be beneficial. Animal studies indicate that vaccination with abrin and ricin toxoids may offer protection against subsequent abrin and ricin challenges, respectively. However, there does not appear to be cross-immunity between abrin and ricin toxoids. Toxoids and antibodies are not readily available. Detection kits for toxalbumins are being developed.[36,45,68,92,94,247,269]

HEPATOTOXIC AGENTS

Pyrrolizidine Alkaloids

It is estimated that 3% of the world's flowering plants contain toxic pyrrolizidine alkaloids.[281] Plants containing pyrrolizidine alkaloids include *Senecio vulgaris* (groundsel), *S. longilobus* (gordolobo), *S. jacobaea* (tansy ragwort), *S. latifolius* (Dan's cabbage or muti), *Symphytum officinale* (comfrey), *Gynura segetum, Ilex paraguanyensis* (mate), *Heliotropium* spp., *Crotalaria* spp. (rattlebox), *Amsinckia intermedia* (fiddle neck or tar weed), *Baccharius pteronoides, Astragulus lentiginosus, Gnaphalium, Cynoglossum, Echium, Tussilago farfara,* and *Adenotyles alliariae* (alpendost). These plants are consumed in herbal preparations, in breads made with grains that are contaminated with pyrrolizidine-containing weeds ("bread poisoning"), and in teas. For example, *Senecio* and *Crotalaria,* which are used to make "bush tea" in Jamaica, have been associated with hepatotoxicity. Less frequently, contaminated animal meat, milk, or honey from exposed animals or bees may be the source of exposure.

Pyrrolizidine alkaloids are heterocyclic compounds that act as alkylating agents and are activated in the liver. Activation by cytochrome P-450 and mixed-function oxidase systems forms reactive pyrrolic metabolites that alkylate proteins and DNA, thereby inhibiting protein and nucleic acid synthesis. The metabolites can also bind to glutathione, resulting in glutathione depletion. Toxicity results from a hepatic sinusoidal obstruction syndrome that presents as hepatic venoocclusive disease, hepatomegaly, cirrhosis, and Budd-Chiari syndrome, which is characterized by obstruction of the trunk or large branches of the hepatic vein.[49,122,275,278,281,309]

Young patients seem more susceptible than adults. Ingestion of 10 mg of pyrrolizidine alkaloid is probably enough to produce acute or chronic venoocclusive disease. Venoocclusive liver disease is characterized by nonthrombotic occlusion of the central veins of hepatic lobules. Histologic liver findings include central vein dilation, sinusoidal congestion, centrilobular necrosis, and fibrosis. Clinical evidence of intrahepatic portal hypertension may include painful hepatomegaly, ascites, weight gain, and jaundice. Hepatic failure and death may ensue. Neonatal death secondary to hepatotoxicity has been reported after intrauterine exposure to pyrrolizidine alkaloids from an herbal preparation. Neonatal ascites, skin edema, hepatomegaly, and anemia were noted. Elevated LFTs and bilirubin, as well as hyponatremia, may be seen. Occasionally, laparoscopic liver biopsy and hepatic and portal decompression are helpful in diagnosis and treatment, respectively. Treatment, including albumin infusions, diuretics, and therapeutic paracentesis, is supportive. *N*-acetylcysteine may reduce toxicity. Defibrotide, which has been used to treat venoocclusive liver disease of other etiology, may theoretically be useful. Cirrhosis and portal hypertension may be persistent.*

Kava Kava

Piper methysticum (kava kava) is used recreationally and medicinally in Polynesia and Micronesia. Traditionally, kava kava extracts are prepared from kava kava roots macerated with water or coconut milk. Kava kava is associated with yellowing of the skin and reddening of the eyes, termed *kava dermopathy,* and may be hepatotoxic.[49,121,207] More recent studies question the hepatotoxicity of kava kava. Some suggest that a contaminant, rather than *P. methysticum*, may be the culprit.[323]

*References 29, 49, 70, 122, 275, 278, 309, 310, 314, 356.

Greater Celandine

Chelidonium majus (greater celandine) is hepatotoxic. Patients are generally exposed through herbal use. Patients generally present with jaundice and elevated aminotransferases (transaminases), consistent with cholestatic hepatitis. Seizures may occur. The hepatotoxicity appears to be an idiosyncratic reaction.[49,270,321]

Black Cohosh

Cimicifuga racemosa (black cohosh), not to be confused with *Caulophyllum thalictroides* (blue cohosh), is hepatotoxic and produces an idiosyncratic hepatitis.[104] Exposure tends to be secondary to herbal use. It produces hepatonecrosis. Patients present with constitutional symptoms, jaundice, right-upper-quadrant abdominal pain, and elevated liver enzymes. Liver biopsy has revealed liver necrosis, with evidence of oxidative damage and protein adducts that may provoke an autoimmune response. Patients can make a full recovery.[104]

Coffee Senna

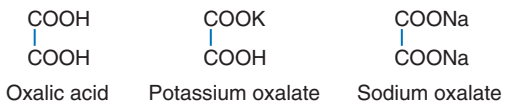
Cassia occidentalis (coffee senna, negro coffee, coffee weed, kasondi) ingestion is associated with hepatic failure, myopathy, and encephalopathy, with a high fatality rate. Young children may eat the beans and have fatal outcomes. Patients may present with fever, GI distress, lethargy, and abnormal behaviors (irritable, violent, self-mutilating). Physical examination may reveal hepatomegaly. Laboratory studies reveal elevated liver enzymes and coagulopathy. Histopathology may reveal myodegeneration of the skeletal muscle and fatty change with centrilobular necrosis of the liver.[237]

Other hepatoxic plants include chaparral (*Larrea tridentate,* also known as the creosote bush or greasewood), aloe (*Aloe barbadenis miller*), germander (*Teucrium polium, T. chamaedrys*), senna, and mistletoe.[49,79,233,273,322] These are usually taken as herbal supplements. Chaparral contains the hepatotoxin nordihydroguaiaretic acid.[131] Plants that contain mitochondrial toxins (discussed later) may present with multiorgan failure, including liver failure.

RENAL TOXINS

SOLUBLE OXALATES

Soluble oxalates are found in rhubarb (*Rheum* spp., including *Rheum rhaponticum*) and sorrel (*Rumex* spp.) plants. Other plants containing oxalate include *Halogeton glomeratus* (saltlover), *Oxalis caerulea* (blue woodsorrel), *Oxalis corniculata* (creeping woodsorrel), *Portulaca oleracea* (common purslane), and *Tetragonia tetragonioides* (New Zealand spinach). Consumption of rhubarb leaves as a substitute for spinach resulted in several deaths in England during World War I. Soluble oxalates are rapidly absorbed by the GI tract. The oxalates may produce some corrosive effects on the GI tract, and mild toxicity may include only vomiting, diarrhea, and irritation of the oral and GI tracts. With more significant exposures, generalized disturbance of monovalent and divalent cation metabolism occurs. Serum ionized calcium levels may drop rapidly. Weakness, paresthesias, tetany, hyperreflexia, muscle twitches and cramps, hypotension, and seizures may develop. Acute renal failure may occur if calcium oxalate precipitates in urine and obstructs the renal tubules. Calcium oxalate crystals may be found in the myocardium and birefringent crystals in vascular walls.[27,110,288] The structures of oxalates follow:



Oxalic acid | Potassium oxalate | Sodium oxalate

Sodium bicarbonate lavage should be avoided because of the risk for sodium oxalate formation. IV calcium is recommended for tetany, prolonged QT interval, or low serum ionized calcium. Urine output should be maintained with generous fluid replacement to prevent deposition of calcium oxalate crystals in renal

tubules. Of note, hemodialysis easily removes oxalate from the blood.[27]

OTHER NEPHROTOXINS

Aloe species contain aloins and aloinosides and can cause parenchymatous nephritis and acute renal failure. Initially, inflammation of the GI tract with bloody diarrhea is present, followed by fluid and electrolyte loss. Arthralgias and palpable purpura, followed by hematuria, proteinuria, renal failure, and death, were reported in a man who ingested juice extracted from four to five leaves of *Aloe vera* (*Aloe barbadenis*).[43,312]

Aristolocia clematitis (birthwart) contains aristolochic acid, which is nephrotoxic, producing interstitial nephropathy, called "aristolochic acid nephropathy." Recently, Balkan endemic nephropathy has been associated with *Aristolocia* seeds. Aristolochic acids are also carcinogenic. Wheat and other crops grown in close proximity to *Aristolocia* spp. are thought to take up aristolochic acids from the soil; there is concern of food crops becoming secondarily poisonous.[255,312]

Pithecolobium lobatum or *Archidendron jiringa* (djenkol bean, jering) has a sulfur-containing amino acid, djenkol acid. Djenkol beans resemble a flattened horse chestnut and are contained in large, dark-purple pods that grow on large trees. The beans are consumed intentionally as a delicacy in Indonesia, Malaysia, southern Thailand, and Myanmar. Poisoning is characterized by nausea, vomiting, spasmodic pain, hematuria, oliguria, and acute renal failure. A sulfurous odor may be noted on the breath and in the urine. Urine may contain needle-like crystals (djenkolic acid crystals). Animal studies and human renal biopsy results reveal acute tubular necrosis. Symptoms generally resolve with supportive care. Alkalinization of the urine may increase dissolution of djenkol crystals.[24,312]

Cleistanthus collinus (Vadisaaku, Oduvan, Oduvanthalai) is used as a suicidal and homicidal poison in India. All parts of the plant are toxic. Fresh leaves or extract of boiled leaves are generally consumed. *C. collinus* contains diphyllin glycosides, cleistanthins A and B, which are thought to be responsible for toxicity. The toxins inhibit proton pumps of the distal renal tubular cells. Toxicity is usually not evident until 3 to 4 days after ingestion. Distal renal tubular acidosis results, with urinary potassium wasting and metabolic acidosis. Renal failure may follow. The toxin antagonizes α-adrenergic receptors, causing hypotension. GI distress, altered mental status, dysrhythmias (bradycardia more often than tachycardia), hypotension, hypoxia, acute respiratory distress syndrome (ARDS), and muscle weakness are reported. Muscle weakness may manifest as dysarthria, dysphagia, ptosis, ocular palsies, and weak neck muscles leading to inability to hold up the head. Coagulopathy, elevated liver enzymes, elevated CPK, hypokalemia, hyponatremia, hyperchloremia, and urinary alkalosis are noted. Marked hypokalemia (<3 mEq/L) during hospitalization is associated with a worse prognosis. Treatment is supportive. Neostigmine and atropine have been advocated in case reports and animal studies. Animal studies indicate *N*-acetylcysteine may be beneficial. Mortality rates of 20% to 30% are reported, despite medical care. Death is usually caused by cardiac or respiratory failure.[21,32,80,230,317]

HEMATOPOIETIC TOXINS

PLANTS WITH ANTICOAGULANT PROPERTIES (LACTONE GLYCOSIDES)

Dipteryx odoratum (Dutch tonka bean) and *Coumarouna* (or *Dipteryx*) *oppositofolia* (English tonka bean) were among the first historically mentioned medical sources of coumarin. *Melilotus officinalis* (yellow sweet clover, yellow melilot, common melilot), *Asperula odorata,* and *Galium odoratum* (woodruff) contain significant quantities of coumarin. These coumarin-containing products have been consumed in teas. Yellow sweet clover poisoning is caused by dicumarol, a fungal metabolite produced from coumarin substrates in spoiling plants. Dicumarol interferes with synthesis of vitamin K–dependent coagulation factors, inducing coagulopathy. Generally, this has been a problem in livestock rather than humans.[186,272,278]

TOXINS THAT INHIBIT CELL DIVISION AND BONE MARROW

Colchicine

Colchicine toxicity can occur after ingestion of *Sandersonia aurantiaca* (Christmas-bells, Chinese lantern lily), *Gloriosa superba* (glory lily, flame lily), *Colchicum persicum,* and more often, *Colchicum autumnale,* all of the lily family. *C. autumnale* is commonly known as autumn crocus, wild saffron, meadow saffron, naked lady, naked boy, and son-before-the-father. It can be mistaken for an edible plant, such as leek, wild garlic, or bear's garlic (*Allium ursinum*). *C. autumnale* is found in Europe, North America, and Asia. All parts of the plant contain colchicine, an amine alkaloid, but the highest concentrations are found in the underground bulb. Colchicine binds selectively and reversibly to tubulin and prevents its polymerization into microtubules. This disrupts cell division, cell shape, mobility, and phagocytosis. Cells with the highest turnover rates, such as those of the GI mucosa and bone marrow, are affected most severely. Cell arrest in metaphase and abnormal nuclear morphology are seen at autopsy; the clumps of chromatin material seen in the nuclei are called colchicine bodies.*

Acute poisoning may occur after a latent period of several hours. Repeated ingestion of lower doses may have a latent period of days before onset of symptoms. Initial GI effects are severe abdominal pain, nausea, vomiting, diarrhea, and hemorrhagic gastroenteritis, which may result in electrolyte abnormalities, volume depletion, acidosis, shock, arrhythmias, and multiorgan failure. Muscular weakness and ascending paralysis may cause respiratory arrest, which may occur suddenly and with a clear sensorium. Respiratory arrest may be associated with pulmonary edema and cardiomegaly from hypertrophic myocytes. Patients may present comatose or convulsing. Myocardial toxicity, rhabdomyolysis, and pancreatitis have been reported. Initially, leukocytosis may be seen, but bone marrow depression with pancytopenia may follow, predisposing to hemorrhage and infection. Autopsy reveals hypocellular bone marrow. Autopsy may reveal diffuse vacuolization in the cytoplasma of hepatocytes and congestion of the liver, kidneys, spleen, lungs, and brain. Occasionally, hemorrhagic edema is seen. Isolated mitotic structures within the epithelium of the colon have been reported at autopsy. If a patient survives, it may take weeks to recover. Patients who survive severe toxicity may develop alopecia days to weeks after poisoning.†

Because of the severity of poisoning and frequent lethal outcomes after significant ingestion, aggressive decontamination should be considered. Colchicine-specific Fab antibody fragments have been used with success in France for management of acute poisoning with the drug form of colchicine, but this treatment is not commercially available. Therefore, treatment is symptomatic and supportive. Pulmonary function tests can be used to monitor respiration, assessing for fatigue and progressive ascending paralysis. Assisted ventilation is used as needed. Parenteral analgesics are given cautiously to relieve severe abdominal pain, because colchicine sensitizes patients to CNS depressants. Fluid and electrolyte replacement and occasionally blood component replacement and granulocyte colony-stimulating factor (G-CSF) may be necessary. Maintain adequate urine output and assess for infection.[11,17,46,48,101,126,151,165,350]

Podophyllum

Podophyllum peltatum is most commonly known as the mayapple but has also been called American mandrake. Because of this common name, it has been occasionally confused with true mandrake (*Mandragora officinarum),* an unrelated plant with anticholinergic properties. Toxicity from *P. peltatum* exposure is caused by the glucoside podophyllotoxin. *Dysosma pleiantha* also contains podophyllotoxin.[203] Acute toxicity after ingestion of *P. peltatum* may occur after a latent period of several hours, manifested by GI distress and associated hypovolemia. Nervous

*References 11, 46, 48, 82, 101, 123, 126, 172, 178, 203, 287, 312, 350.

†References 11, 46, 48, 82, 101, 109, 151, 165, 172, 178, 203, 287, 312, 350.

system effects (confusion, delirium, coma, peripheral neuropathy), bone marrow depression, and multiorgan failure may follow as a result of the antimitotic effect of podophyllotoxin. Treatment is similar to that for colchicine poisoning.[117]

PLANTS THAT INDUCE HEMOLYSIS

Fava Beans

Fava beans (*Vicia faba*) contain vicine and convicine, two metabolically inactive glycones that may be cleaved by β-glycosidase to produce toxins such as divicine and isouramil. Divicine, isouramil, and convicine are thought to be the primary toxins that account for the oxidative stress and hemolytic crisis seen in patients deficient in glucose-6-phosphate dehydrogenase (G6PD) who consume fava beans. Methemoglobinemia may occur. Favism has been reported in infants who ingest breast milk from mothers who have recently ingested fava beans and in fetuses of mothers who consumed fava beans. Clinically, favism is characterized by hemoglobinuria, anemia, and jaundice, secondary to hemolysis. Patients may present with fever, cyanosis, malaise, weakness, lethargy, nausea, vomiting, headache, and lumbar or abdominal pain. When methemoglobinemia occurs, cyanosis may be absent due to severe anemia from hemolysis. Levels of carboxyhemoglobin, a byproduct of hemolysis, may rise. Renal failure may ensue, secondary to hemolysis. With methemoglobinemia, patients with hypoxia, as determined by pulse oximetry, may appear unresponsive to supplemental oxygen. Methemoglobinemia causes unreliable and erroneous pulse oximeter readings. Arterial blood gas determination using multiwavelength co-oximetry is reliable and will generally reveal normal oxygen tension in the patient with methemoglobinemia. Supportive care is the mainstay of treatment. Occasionally, blood transfusions, exchange transfusions, and hemodialysis are needed. Remember that methylene blue treatment of methemoglobinemia may induce hemolysis in patients with G6PD deficiency; therefore, transfusion is preferable, when needed.[75,147,153,197]

ENDOCRINE AND METABOLIC TOXINS

PLANTS THAT INTERFERE WITH STEROID METABOLISM

Licorice

Licorice use predates the Babylonian and Egyptian empires. Its genus name, *Glycyrrhiza,* is derived from the Greek word for "sweet root." Adverse effects with chronic ingestion of *Glycyrrhiza glabra* (natural licorice) result from altered steroid metabolism. *G. glabra* contains glycyrrhizic acid, which is converted to 18-β-glycyrrhetinic acid in the GI tract. Both acids inhibit 11-β-hydroxysteroid dehydrogenase, an enzyme essential to in vivo conversion of cortisol to cortisone. Excessive local cortisol binds to and activates mineralocorticoid receptors in the kidneys, producing a hypermineralocorticoid syndrome, characterized by water and sodium retention with potassium excretion. Signs and symptoms of chronic ingestion include hypertension, edema, hypokalemia, metabolic alkalosis, headache, paresthesias, weakness, paralysis, tetany, and muscle cramps. Myopathy, myoglobinuria, and rarely thrombocytopenia have been reported. Heart failure, arrhythmias (e.g., torsades de pointes, ventricular fibrillation), and cardiac arrest have been attributed to licorice root ingestion.

Treatment consists of discontinuing exposure to licorice, maintaining good urine output, and alkalinizing the urine of patients with rhabdomyolysis. Occasionally, potassium-sparing diuretics (e.g., triamterene, spironolactone) are useful. Patients with torsades de pointes may respond to magnesium and potassium infusions.[30,59,105,109,139,167,214,312]

PLANTS WITH MITOCHONDRIAL TOXINS

Ackee Fruit

Blighia sapida trees, or ackee (akee) fruit trees, are indigenous to West Africa and prevalent in the West Indies, Central America, and southern Florida. Unripe ackee fruit has a closed yellow aril that is toxic. Ripe ackee fruit, with a spontaneously opened red aril, is nontoxic. The seeds contain hypoglycin B and are toxic regardless of the maturation of the aril. Unripe ackee fruit contains hypoglycin A, or L(R,S)-2-amino-3-methylenecyclopropylproprionic acid, a water-soluble amino acid that is converted to methylenecyclopropylacetyl-coenzyme A in vivo. Both compounds are hypoglycemic agents; the second is a suicide inhibitor of β-oxidation of fatty acids. Inhibition of fatty acid metabolism results in microvesicular steatosis of the liver, hyperammonemia, metabolic acidosis, and hypoglycemia. Laboratory and histopathologic findings are indistinguishable from those of Reye's syndrome, but urine shows increased concentrations of glutaric and ethylmalonic acids after hypoglycin A exposure.[28,170,212,298]

Ackee fruit constitutes a traditional Jamaican breakfast and has been associated with Jamaican vomiting sickness. Ingestion of unripe ackee fruit caused an outbreak epidemic of fatal encephalopathy in West Africa, primarily affecting children ages 2 to 6 years, who experienced vomiting, hypotonia, convulsions, and coma. All children died within 48 hours of the onset of vomiting. Autopsy revealed massive liver steatosis and severe hypoglycemia. Urine concentrations of dicarboxylic acids were elevated. Similarly, an epidemic of more than 100 cases occurred in Haiti, associated with vomiting, abdominal pain, loss of consciousness, convulsions, and many deaths. Hypoglycemia was noted. The carnitine derivatives octanoylcarnitine and hexanoylcarnitine were noted in the urine, confirming exposure to hypoglycin. Fatal ackee fruit poisoning is more common in children than in adults. Adults are more likely to present with self-resolving cholestatic jaundice.[170,212,227,298,299]

Treatment is largely supportive and consists of securing an airway and administering IV fluids and dextrose. Before hypoglycemia was recognized, mortality rates of symptomatic unripe ackee fruit exposure approached 80%. Frequent glucose and electrolyte measurements with appropriate replacement are essential. Seizures are treated with benzodiazepines and barbiturates, remembering that serum glucose should be assessed and hypoglycemia treated in all seizing patients. Theoretically, riboflavin, clofibrate, glycine, methylene blue, and L-carnitine may be beneficial, although their efficacy is not established. Carnitine may facilitate transport of fatty acids into mitochondria and has been used for other toxins (e.g., valproate) that inhibit β-oxidation of fatty acids.[28,188,298,299]

Wild Yams

Dioscorea species contain dioscorines and dioscines. They are tuberous plants, commonly known as yams, used as a staple food in Africa and Asia. The tubers are usually detoxified in running water, soaking in salt water, boiling for several hours, squeezing out the juice, and roasting. The nondetoxified plant has been used in homicide, suicide, and hunting. CNS irritability with seizures, liver failure, and renal failure are seen. Hypoglycemia is reported.[312]

Cocklebur

Cocklebur (*Xanthium strumarium* and *X. spinosum*) has worldwide distribution and can be found along riverbanks, beaches, and lake shores. The stem is angled with red or black spots. The fruit is hard, brown, and woody; it contains two seeds that taste like sunflower seeds. The seeds and seedlings contain carboxyatractyloside, a sulfonated diterpenoid glycoside. This toxin inhibits oxidative phosphorylation and translocation of adenosine diphosphate (ADP) and ATP across mitochondrial membranes. Carboxyatractyloside is an analog of atractyloside, which is found in *Callilepis laureola* (ox-eye daisy) and *Atractylis gummifera* (bird-lime, blue thistle), discussed next. Drying of seeds does not diminish toxicity.

Patients present with acute abdominal pain, nausea, vomiting, diaphoresis, palpitations, drowsiness, and dyspnea, followed by respiratory depression. With severe poisoning, seizures, coma, and death may occur. Seizures may be repetitive, frequent, and difficult to treat. Patients may appear pale or with icterus and may be clammy, without pyrexia. Hepatomegaly and rhabdomyolysis may be noted. Laboratory findings may reveal elevated liver enzymes, elevated blood urea nitrogen and creatinine, hyponatremia, transient hyperglycemia followed by marked hypoglycemia, elevated CPK and CPK-MB, metabolic acidosis, and evidence of a consumption coagulopathy (diminished

fibrinogen and prolonged prothrombin time). ECG may show ST-segment abnormalities. Death may occur within 2 days of ingestion. Autopsy findings include centrilobular hepatic necrosis, renal proximal tubular necrosis, microvascular hemorrhage of the cerebrum and cerebellum, and leukocytic infiltrates in the muscles, pancreas, lungs, and myocardium. Increased vascular permeability is suspected.

Treatment is supportive. Phenylbutazone, a nonsteroidal anti-inflammatory drug that is generally unavailable because of its toxicity, has been shown to reduce cytotoxic effects of carboxyatractyloside in rats.[311,332]

Bird-Lime/Blue Thistle

Atractylis gummifera (bird-lime, blue thistle) is found in North Africa and the Mediterranean region. It has a sugary taste and has been confused with edible wild artichoke. *A. gummifera* contains two poisonous glucosides: atractyloside and carboxyatractyloside. The glucosides inhibit oxidative phosphorylation, block transport of ADP at the mitochondrial membrane, and block conversion of ADP to ATP. The toxins inhibit the actions of P-450 and b_5 cytochromes. Clinically, headache, abdominal pain, vomiting, hematemesis, diarrhea, and dizziness are followed by liver failure, associated with jaundice and hepatitis. Seizures, coma, dysrhythmias, and renal failure may be seen. Laboratory studies reveal hypoglycemia, metabolic acidosis, uremia, and hyperkalemia. Death is generally from multiorgan system failure. Autopsy reveals lesions, necrosis, and congestion of the liver and kidneys.[145,146,311,312,332]

Ox-Eye Daisy

Callilepis laureola (ox-eye daisy, wildemagriet, impila) has been used as a medicinal plant in South Africa. It is administered to pregnant women to facilitate childbirth, but approximately 1500 deaths are reported each year from its use. In Natal, autopsies have shown hepatic and renal tubular necrosis. *C. laureola* contains the poisonous glucosides atractyloside and carboxyatractyloside.[40,341,231] Toxicity and treatment are similar to those for cocklebur and bird-lime exposure, as discussed earlier. Mortality has been reported at 90% by 5 days. *N*-acetylcysteine may be beneficial in treatment of plant toxicity from atractyloside and carboxyatractyloside.[49]

KARAKA

Corynocarpus laevigatus (karaka, New Zealand laurel) is a tall evergreen tree native to New Zealand. It contains the toxin karakin, which is hydrolyzed to 3-nitropropionic acid (3-NP), a toxic metabolite. *Astragalus mise* (timber milkvetch) also contains 3-NP, as does sugar cane infected by fungus. 3-NP is structurally similar to succinic acid, a substrate in the tricarboxylic acid (Krebs) cycle. 3-NP is an irreversible, competitive inhibitor of succinate dehydrogenase, the enzyme that converts succinic acid into fumarate. This results in inhibition of the Krebs cycle, which reduces ATP synthesis and interferes with energy production. Succinic acid and lactic acid accumulate. Excitotoxic and neurodegenerative effects are characterized by hypokinesia, dystonia, and chorea. It is thought that ingestion of one karaka kernel may produce toxicity. Initially, nausea, vomiting, diarrhea, and abdominal pain occur. Additionally, headache, altered mental status, nystagmus, tremor, and dizziness may be seen. With severe toxicity, coma, seizures, and respiratory failure occur. There may be delayed neurodegenerative disease that resembles Huntington's disease, with dystonia, choreoathetoid movements, and dyskinesia. Magnetic resonance imaging can reveal hypodensity of the basal ganglia (putamen and globus pallidus). Treatment is supportive, including benzodiazepines and barbiturates for seizures. Levodopa does not appear helpful for the neurodegenerative sequelae.[304]

GIFBLAAR

Dichapetalum cymosum (gifblaar) contains fluoracetate, which inhibits the Krebs cycle, reducing cellular respiration and often resulting in death. This is primarily a concern for cattle in Africa.[40]

CYANOGENIC PLANTS

Glycosides that yield hydrocyanic acid on hydrolysis are known as cyanogenic glycosides (see Figure 65-1). Cyanogenic glycosides include amygdalin, prunasin, linamarin, lotaustralin, and triglochinin.[64] Amygdalin (D-mandelonitrile-β-D-glucoside-6-β-glucoside), abundant in the Rosaceae family, is the cyanogenic compound found in seeds of *Malus* spp. (apples) and pits of *Prunus* spp., including cherries, peaches, plums, and apricots. Deaths have been reported after ingestion of apricot, apple, cherry, and other fruit seeds.[289] Black or wild cherries (*Prunus serotina*) are considered the most dangerous. Poisonings have resulted from milkshakes that contained apricot kernels and from apricot kernels sold in health food stores as snacks.[318] Linseeds (*Linum usitatissimum*) and cycad seeds (*Cycas* spp.) are also cyanogenic.[64,280]

Bamboo (*Dendrocalamus aspe*, *Bambusa nutans*, *B. mulfiplex*, *Thyrsostachys siamensis*) produces cyanogenic glycosides, including taxiphyllin (2-[β-D-glucopyranosyloxy]-2-[4-hydroxyphenyl] acetonitrile). When bamboo shoots are cut, a glycosidase enzyme in the shoot hydrolyzes the glycoside and produces hydrogen cyanide gas, which can be inhaled and has proved fatal. Ingestion of bamboo does not appear to produce cyanide toxicity.[286]

Cassava (*Manihot esculenta*) contains the cyanogenic glucoside linamarin, which is rapidly hydrolyzed to acetone cyanohydrin, which breaks down into hydrogen cyanide and acetone.[106,282] Both chronic and acute cyanide toxicity have been reported after ingestion of cassava. Chronic ingestion produces an upper motor neuron disease known as Konzo, or tropical spastic paraparesis. Konzo occurs after recurrent consumption of improperly prepared cassava during droughts in areas where cassava is a staple food, such as in Africa. To remove cyanogens, roots should be soaked; however, when water is scarce, this soaking process is limited.[22,23,106]

Cyanide combines with and inhibits many enzymes. It possesses great affinity for the ferric iron in cytochrome oxidase of the electron transport chain, accounting for most of its toxicity (Figure 65-25). By combining with cytochrome oxidase, cyanide prevents electron transport, thereby preventing ATP production by oxidative phosphorylation. Metabolic acidosis ensues. Humans detoxify cyanide by transferring sulfane sulfur to cyanide to form thiocyanate. Numerous sulfur sources are most likely acted on by various sulfurtransferases to form the sulfane sulfur needed to convert cyanide to thiocyanate. Administration of exogenous sulfane sulfur, such as sodium thiosulfate, can greatly facilitate detoxification.[76]

Clinically, GI distress, bitter almond breath, CNS changes (agitation, anxiety, excitement, weakness, numbness, hypotonia, spasticity, coma, seizures), respiratory changes (hyperpnea, dyspnea, apnea, cyanosis), cardiovascular changes (tachycardia and hypertension followed by bradycardia and hypotension, heart block, ventricular arrhythmias, asystole), and metabolic changes (anion gap metabolic acidosis) are seen. Skin color may be pink or cyanotic, and the partial pressure of oxygen may be normal in cyanide poisoning. ECG may reveal T-on-R phenomenon as a result of progressive shortening of the ST segment. Multiorgan failure and death may occur.[76,203,282]

Treatment

Red blood cell or plasma cyanide levels can be determined; however, treatment should be initiated promptly, without confirmation of exposure, in patients with evidence of toxicity. Patients with cyanogenic glycoside poisoning may respond to treatment with 100% oxygen and cyanide antidote kits. The traditional antidote kit contains sodium nitrite (3% solution given intravenously on the basis of hemoglobin and weight; generally, 300 mg in a nonanemic adult), and sodium thiosulfate (12.5 g in an adult). Traditional cyanide antidote kits are designed to induce methemoglobinemia through nitrite exposure. Cyanide binds preferentially to the ferric ion of methemoglobin rather than to that of cytochrome oxidase in the electron transport chain. Forming methemoglobin limits inhibition of electron transport by cyanide and restores cellular respiration. Sodium thiosulfate in

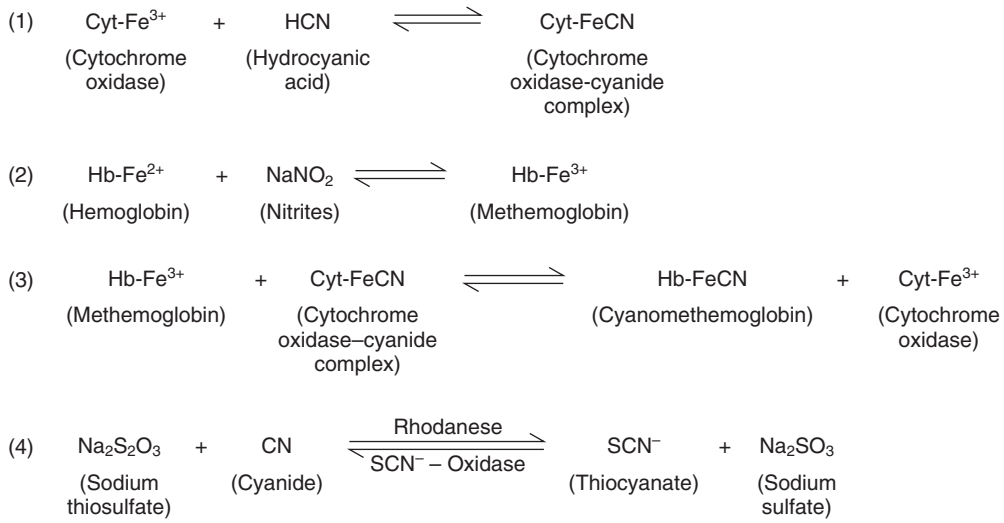


FIGURE 65-25 Principal steps in hydrocyanic acid poisoning and detoxification. *1,* Breakdown of cellular respiration resulting from the binding of cyanide to cytochrome oxidase. *2,* Conversion of the ferrous (Fe^{2+}) form of hemoglobin to the ferric (Fe^{3+}) form (methemoglobin) via nitrites. *3,* Preferential binding of cyanide to methemoglobin, liberating cytochrome oxidase and restoring cellular respiration. *4,* Providing exogenous thiosulfate to aid in formation of the less toxic thiocyanate via various sulfurtransferases, such as rhodanese. Thiocyanate is then excreted from the body. The reaction is slowly reversible via the enzyme thiocyanate oxidase, and rebound may occur.

the cyanide kit provides exogenous sulfane sulfur groups that bind to cyanide and form thiocyanate, which is much less toxic than cyanide. More recently available in the United States, hydroxocobalamin (Cyanokit) is also used to treat cyanide toxicity. Cyanide combines with hydroxocobalamin to form cyanocobalamin, which is excreted in the urine and bile. Sodium thiosulfate may be given with hydroxocobalamin, with theoretical synergistic therapeutic effects. Supportive care, including mechanical ventilation, IV fluids, and vasopressors, may also be used.[76,282,318]

REPRODUCTIVE TOXINS

Some plants that have been used as abortifacients are shown in Table 65-3.[34,73,101,224,231,352] Generally, a plant is not feticidal unless it produces severe toxicity or fatality in the mother.

Human teratogenesis from plant exposure is difficult to assess, because humans rarely chronically ingest toxic plants. Discussion of teratogenesis in livestock can be found in other sources.[248]

OTHER TOXINS

OILS

Irritant oils, including various mustards (*Brassica* spp), horseradish (*Amoracia lapathifolia*), and protoanemonin from the buttercup family (Ranunculaceae), induce gastroenteritis. Essential oils, often found in combination with resins (oleoresins), are extracted commercially for use as rubefacients, salves, and liniments. Essential oils are summarized in Table 65-4.

ACKNOWLEDGMENT

I am grateful for having known Donald Kunkel, an exceptionally kind mentor, who guided me in the early editions of this chapter.

TABLE 65-3 Abortifacient Plants

Common Name	Genus	Species	Toxicity
Blue cohosh (or squaw root)	*Caulophyllum*	*thalictroides*	Nicotinic syndrome
Bryony	*Bryonia*	*dioica*	Nephrotoxic
Glory lily (or flame lily)	*Gloriosa*	*superba*	Toxins that inhibit cell division and bone marrow
Green hellebore	*Helleborus*	*viridis*	Cardiotoxic
Pennyroyal	*Mentha*	*pulegium*	Hepatotoxic
Nutmeg	*Myristica*	*fragrans*	Neurotoxic (hallucinogenic)
Potato tree	*Solanum*	*erianthum*	Neurotoxic (anticholinergic)
Ruda (or fringed rue)	*Ruta*	*chalepensis*	Multiorgan toxicity
Syrian rue (or espand)	*Peganum*	*harmala*	Neurotoxic (convulsant, paralytic, hallucinogenic)
Wild wisteria	*Securidacea*	*longepedunculata*	Neurotoxic (convulsant)
Yellow oleander	*Thevetia* or *Cascabela*	*peruviana* *thevetia*	Cardiotoxic

TABLE 65-4 Toxic Essential Oils

Common Name Of Oil	Genus and Species of Plant from Which Oil Is Derived	Toxin	Toxic Effect
Camphor[66]	*Cinnamomum camphora, Dryobalanops aromaticum, Ocotea usambarensis, Ocimum kilimandscharicum,* and others	Camphor	GI distress, headache, tremor, twitching, convulsions (including status epilepticus), delirium, coma, death
Clove[102]	*Syzygium aromaticum*	Eugenol	Hepatic failure
Eucalyptus[14,83,325]	*Eucalyptus globulus*	1,8-Cineole (eucalyptol)	Diaphoresis, CNS depression (hyporeflexia, weakness, ataxia, slurred speech, agitation, confusion, coma, respiratory depression, convulsions), GI upset (vomiting, diarrhea, abdominal pain), respiratory effects (bronchospasm, pneumonitis, pulmonary edema), metabolic acidosis, rhabdomyolysis, hypotension, death
Lavender[192]	*Lavandula* spp.	Linalool, linalyl acetate, lavandulyl acetate, terpinen-4-ol	CNS depression, confusion
Pennyroyal[13,18,319]	*Hedeoma pulegioides, Mentha pulegium*	Pulegone (oxidized to the toxic metabolite, menthofuran)	Hepatic failure, altered mental status, seizures, cerebral edema, multiorgan failure, shock, death
Pine[210]	*Pinus sylvestris* and other pine trees	1-α-Terpineol (damage also induced by lipophilic hydrocarbons)	Respiratory irritation (hemorrhagic and necrotic lungs), CNS depression
Sage[143]	*Salvia officinalis*	Thujone, camphor, cineole	Seizures
Wintergreen[41,159]	*Gaultheria procumbens*	Methyl salicylate	Salicylate poisoning (metabolic acidosis, respiratory alkalosis, CNS excitation, CNS depression, hyperthermia), laryngeal edema
Wormwood[35,91,160,244,316] (in the green liqueur, absinthe)	*Artemisia absinthium, A. pontica*	α- and β-Thujone	Psychoanaleptic effects, vomiting, neurotoxicity (vertigo, delirium, hallucinations, convulsions, coma), respiratory failure, death

CNS, Central nervous system; *GI,* gastrointestinal.

APPENDIX

A Common Toxic Plants

Common Name	Genus	Species	Toxin	Toxic Effect
Ackee (akee)	*Blighia*	*sapida*	Hypoglycin	Hypoglycemic
Aconite	*Aconitum*	spp.	Aconitine, mesaconitine, hypaconitine, yunaconitine	Cardiotoxic
Angel's trumpet	*Brugmansia*	*suaveolens*	Atropine, hyoscyamine, hyoscine	Anticholinergic
Apple seeds	*Malus*	spp.	Cyanogenic glycosides	Cyanogenic
Apricot pits	*Prunus*	spp.	Cyanogenic glycosides	Cyanogenic
Autumn crocus	*Colchium*	*autumnale*	Colchicine	Hematopoietic
Azalea (see Rhododendron)				
Belladonna (see Deadly nightshade)				
Bellyache bush	*Jatropha*	*gossypiifolia*	Curcin	Protein synthesis inhibition
Betel nut	*Areca*	*catechu*	Arecoline, arecaine	Nicotinic
Birthwart	*Aristolocia*	*clematitis*	Aristolochic acids	Nephrotoxic
Black cherry	*Prunus*	*serotina*	Cyanogenic glycoside	Cyanogenic

Common Name	Genus	Species	Toxin	Toxic Effect
Black locust	*Robinia*	*pseudoacacia*	Robin, robitin (glycoside)	Protein synthesis inhibition
Black snake root (see Death camas)				
Blue cohosh	*Caulophyllum*	*thalictroides*	*n*-Methylcytisine, saponins	Nicotinic
Bushman poison bush (boesmansgif)	*Acokanthera*	*oppositifolia*	Cardenolides	Cardiotoxic
Carolina jessamine (aka yellow jessamine)	*Gelsemium*	*sempervirens*	Gelsemine, sempervirine	Psychoactive
Cassava (aka, manioc, tapioca)	*Manihot*	*esculenta*	Cyanogenic glycoside	Cyanogenic
Castor bean	*Ricinus*	*communis*	Ricin	Protein synthesis inhibition
Cherry	*Prunus*	spp.	Cyanogenic glycoside	Cyanogenic
Chinaberry tree	*Melia*	*azedarach*	Meliatoxin	GI irritant
Christmas rose	*Helleborus*	*niger*	Hellebrin, helleborin, helleborein	Cardiotoxic
Cobra lily	*Arisaema*	*amurense*	Calcium oxalate	Oral irritant
Coca	*Erythroxylon*	*coca*	Ecogonine	Psychoactive
Cocklebur	*Xanthium*	*strumarium*	Carboxyatractyloside	Metabolic toxin
Coral plant	*Jatropha*	*multifida*	Curcin	Protein synthesis inhibition
Corkwood tree	*Duboisia*	*myoporoides*	Tropane alkaloids	Anticholinergic
Daphne	*Daphne*	*mezereum*	Dihydroxycoumarin, diterpene mezerein	Coumarin glycosides
Day jessamine	*Cestrum*	*diurnum*	Tropane alkaloids	Anticholinergic
Deadly nightshade	*Atropa*	*belladonna*	Atropine	Anticholinergic
Death camas (aka black snakeroot)	*Zigadenus*	spp.	Zygacine, zygadenine	Cardiotoxic
Devil's trumpet (aka hairy thorn apple)	*Datura*	*metel*	Atropine, hyoscyamine, hyoscine	Anticholinergic
Dieffenbachia (aka dumb cane)	*Dieffenbachia*	spp.	Oxalate, asparagine	Oral irritant
Djenkol tree	*Archidendron Pithecolobium*	*jiringa lobatum*	Djenkol acid (amino acid)	Nephrotoxic
Elephant ear	*Colocasia*	*antiquorum*	Oxalates	Oral irritant
English bean (see Fava bean)				
False hellebore (aka Indian poke)	*Veratrum*	spp.	Veratrin	Cardiotoxic
Fava bean	*Vicia*	*faba*		Hemolytic anemia in patients with glucose-6-phosphate deficiency
Fishberry (or Levant nut)	*Anamirta*	*cocculus*	Picrotoxin	Convulsant
Foxglove	*Digitalis*	*purpurea*	Digitoxin, gitaloxin, gitoxin	Cardiotoxic
Glory lily	*Gloriosa*	*superba*	Colchicine-like alkaloids	Hematopoietic toxicity
Golden chain (aka golden rain)	*Laburnum*	*anagyroides*	Cytisine	Nicotinic
Horse bean (see Fava bean)				
Horse chestnut	*Aesculus*	spp.	Aesculin	Coumarin glycosides
Hyacinth bean	*Dolichos*	*lablab*	Cyanogenic glycosides	Cyanogenic
Hydrangea	*Hydrangea*	spp.	Cyanogenic glycosides	Cyanogenic
Inkberry (see Pokeweed)				
Jequirity pea (aka rosary pea, precatory bean)	*Abrus*	*precatorius*	Abrin	Protein synthesis inhibition
Jessamine (see Carolina jessamine)				
Jessamines	*Cestrum*	spp.	Tropane alkaloids	Anticholinergic
Jetbead	*Rhodotypos*	*tetrapetala*	Cyanogenic glycosides	Cyanogenic
Jimsonweed	*Datura*	*stramonium*	Atropine, hyoscyamine, hyoscine	Anticholinergic
Jonquil (see Daffodil)				
Kentucky coffee tree	*Gymnocladus*	*dioica*	Cytisine	Nicotinic
Larkspur	*Delphinium*	spp.	Aconitine-like (methyllycaconitine, lycoctonine)	Cardiotoxic Neurotoxic (curare-like in livestock)
Lily of the valley	*Convallaria*	*majalis*	Convallotoxin, convallarin, convallamarin	Cardiotoxic

Continued

Common Name	Genus	Species	Toxin	Toxic Effect
Lobelia (aka Indian tobacco)	*Lobelia*	spp.	Lobelamine, lobeline	Nicotinic
Mandrake (aka Satan's apple)	*Mandragora*	*officinarum*	Hyoscyamine, scopolamine	Anticholinergic
Marijuana	*Cannabis*	*sativa*	Tetrahydrocannabinol	Psychoactive
Mayapple	*Podophyllum*	*peltatum*	Podophyllotoxin	Hematopoietic
Mescal bean	*Sophora*	*secundiflora*	Cytisine	Psychoactive
(Common) Milkweed	*Asclepias*	*syriaca*	Asclepiadin	Cardiotoxic
Monkshood (aka aconite, wolfsbane)	*Aconitum*	spp.	Aconitine	Cardiotoxic and neurotoxic
Morning glory	*Ipomoea*	*violacea*	(+)-Lysergic acid amide	Psychoactive
Mountain laurel	*Kalmia*	*latifolia*	Andromedotoxin, arbutin, grayanotoxins	Cardiotoxic
Narcissus (see Jonquil)				
Night-blooming jasmine	*Cestrum*	spp.	Tropane alkaloids	Anticholinergic
Nutmeg	*Myristica*	*fragrans*	Myristicin	Psychoactive
Oleander	*Nerium*	*oleander*	Oleandrin, oleandroside, nevioside	Cardiotoxic
Oduvan(thalai)	*Cleistanthus*	*collinus*	Cleistanthin A and B	Nephrotoxic
Peach pits	*Prunus*	spp.	Cyanogenic glycosides	Cyanogenic
Peyote	*Lophophora*	*williamsii*	Mescaline, lophophorine	Psychoactive
Philodendron	*Philodendron*	spp.	Oxalate	Oral irritant
Physic nut (aka purging nut)	*Jatropha*	*curcas*	Curcin	Protein synthesis inhibition
Pigeonberry (see Pokeweed)				
Plum pit	*Prunus*	spp.	Cyanogenic glycosides	Cyanogenic
Poison hemlock	*Conium*	*maculatum*	Coniine, Coniceine	Nicotinic
Pokeweed	*Phytolacca*	*americana*	Triterpene saponins	GI irritant and hematopoietic
Potato tree	*Solanum*	*erianthum*	Tropane alkaloids	Anticholinergic
Purging nut (see Physic nut)				
Rattlepod (aka scarlet, wisteria tree)	*Sesbania*	spp.	Pyrrolizidine alkaloids	Hepatotoxic
Rhododendron (aka laurel, azalea)	*Rhododendron*	spp.	Grayanotoxins	Cardiotoxic
Rhubarb	*Rheum*	*rhabarbarum*	Oxalates	Nephrotoxic
San Pedro cactus	*Trichocereus*	*pachanoi*	Mescaline, lophophorine, and 3,4-dimethoxyphenethylamine	Psychoactive
Sea mango	*Cerbera*	*manghas*	Cerberoside, cerberin, and odollin	Cardiotoxic
Senecio (aka groundsel)	*Senecio*	*longilobus*	Pyrrolizidine alkaloids	Hepatotoxic
Squill	*Urginea*	*maritima*	Cardiac glycosides	Cardiotoxic
Star of Bethlehem	*Ornithogalum*	*umbellatum*	Cardiac glycosides, amine alkaloids	Cardiotoxic
Star fruit	*Averrhoa*	*carambola*	Caramboxin (phenylalanine-like)	Convulsant
Strawberry bush (see Burning bush)				
Suicide tree (or Pong-pong tree)	*Cerbera*	*odollam*	Cerberin	Cardiotoxic
Texas mountain laurel (see mescal bean)				
Tobacco	*Nicotiana*	*tabacum*	Nicotine	Nicotinic
Tree tobacco	*Nicotiana*	*glauca*	Anabasine	Nicotinic
Trumpet lily	*Datura*	*arborea*	Atropine, hyoscyamine, hyoscine	Anticholinergic
Tutu	*Coriaria*	*arborea*	Tutin (picrotoxin-like)	Convulsant
Water hemlock	*Cicuta*	*maculata*	Cicutoxin	Convulsant
Wild cherry (see Black cherry)				
Woody nightshade (see Nightshade)				
Yellow jessamine (see Carolina jessamine)				
Yellow oleander (aka be still tree, lucky nut tree)	*Thevetia* or *Cascabela*	*peruviana* *thevetia*	Thevetin, thevetoxin	Cardiotoxic
Yew	*Taxus*	spp.	Taxine	Cardiotoxic

APPENDIX

B Nontoxic Plants

African violet (*Saintpaulia ionantha*)
Air plant (*Kalanchoe pinnata*)
Aluminum plant (*Pilea cadierei*)
Aralia, false (*Dizygotheca elegantissima*)
Aralia, Japanese (*Fatsia japonica*)
Asparagus fern (*Asparagus plumosus*), berry
Baby's breath (*Gypsophilia paniculata*)
Baby's tears (*Helxine* [or *Soleirolia*] *soleirolii*)
Begonia (*Begonia rex*)
Bird of paradise* (*Strelitzia reginae*)
Bird's nest fern (*Asplenium nidus*)
Boston fern (*Nephrolepsis exaltata bostoniensis*)
Bromeliad family
California poppy (*Eschscholzia californica*)
Camellia (*Camellia japonica*)
Christmas cactus (*Schlumbergera bridgesii*)
Coffee tree (*Coffea arabica*)
Coleus
Coral berry* (*Aechamea fulgens, Ardisia crispa*)
Cornstalk plant (*Dracaena fragrans*)
Crape myrtle (*Lagerstromea indica*)
Creeping Charlie* (*Pilea nummularifolia*)
Crocus* (spring-blooming only)
Croton* (*Codiaeum variegatum*)
Dahlia
Dandelion (*Taraxacum officinale*)
Dogwood (*Cornus*)
Donkey's tail (*Sedum morganianum*)
Dragon tree (*Dracaena draco, Dracaena marginata*)
Easter cactus (*Schlumbergera bridgesii*)
Easter lily (*Lilium longiflorum*)
Echeveria: Mexican snowball, painted lady, plush plant
Emerald ripple (*Peperomia caperata*)
Fiddleleaf fig (*Ficus lyrata*)
Fig tree, weeping (*Ficus benjamina*)
Forget-me-not (*Myosotis alpestris, Myosotis sylvatica*)
Forsythia
Fuchsia
Gardenia
Geranium* (*Pelargonium*)
Gloxinia (*Sinningia speciosa*)
Grape ivy (*Cissus rhombifolia*)
Hawaiian ti plant (*Cordyline terminalis*)
Hawthorne (*Crataegus*), berry
Heavenly bamboo (*Nandina domestica*), berry
Hibiscus
Honeysuckle berry (*Lonicera*)
Ice plant
Impatiens walleriana
Jade plant (*Crassula argentea*)
Jasmine (*Jasminum rex*), Madagascar jasmine
Kalanchoe: maternity plant, monkey plant, panda bear plant
Lace plant, Madagascar (*Aponogeton senetralis*)
Lady, lady's slipper (*Cypripedium, Paphiopedilum*)
Lily of the Nile (*Agapanthus*)
Lipstick plant (*Aeschynanthus radicans*)
Maidenhair fern (*Adiantum*)
Marigold, African/American tall (*Tagetes*)
Moon cactus (*Gymnocalycium*)
Mother-in-law's tongue or snake plant (*Sansevieria trifasciata*)
Mother of pearls (*Grapetopetalum paraguayense*)
Nandina berry
Natal plum (*Carissa grandiflora*)
Norfolk Island pine (*Araucaria heterophylla*)
Old man cactus (*Cephalocereus senilis*)
Olive tree (*Olea europaea*)
Orchid (*Cattleya, Cymbidium, Oncidium*)
Oregon grape (*Mahonia aquifolium*)
Palm, bamboo (*Chamaedorea erumpeus*)
Pansy flower (*Viola*)
Paradise (*Howea* [or *Kentia*] *forsterana*)
Parlor (Chamaedorea [or Kentia] elegans)
Peanut cactus (*Chamaecereus sylvestri*)
Pellionia
Peony flower (*Paeonia*)
Peperomia
Petunia
Phlox
Piggyback plant (*Tolmiea menziesii*)
Pigmy date palm (*Phoenix roebelenii*)
Pocketbook (*Calceolaria herbeohybrida*)
Polka dot or freckle face plant (*Hypoestes sanguinolenta*)
Prayer plant (*Maranta leuconeura*)
Pussy willow (*Salix discolor*)
Pyracantha berry
Queen's tears (*Billbergia nutans*)
Rabbit's foot fern (*Davallia fejeensis*)
Rainbow plant (*Billbergia saundersii*)
Raphiolepsis
Rattlesnake plant (*Calathea insignis*)
Ribbon plant (*Dracaena sandriana*)
Rock rose (*Cistus*)
Rosary pearls (*Senecio rowleyanus*)
Rosary vine (*Ceropegia woodii*)
Roses (*Rosa*)
Rubber plant (*Ficus elastica*)
Schefflera plant (*Brassaia* [or *Schefflera*] *actinophylia*)
Sedum
Sensitive plant (*Mimosa pudica*)
Sentry (*Howea belmoreana*)
Silver heart (*Peperomia marmorata*)
Snake plant or mother-in-law's tongue (*Sansevieria trifasciata*)
Snapdragon (*Antirrhinum majus*)
Spider plant (*Anthericum, Chlorophytum comosum*)
Staghorn fern (*Platycerium bifurcatum*)
Starfish flower (*Stapelia*)
String of beads* (*Senecio rowleyanus, Senecio herreianus*)
String of hearts (*Ceropegia woodii*)
Swedish ivy (*Plectranthus australis*)
Sword fern (*Nephrolepsis cordifolia, Nephrolepsis exaltala*)
Tahitian bridal veil (*Gibasis geniculata, Tripogandra multiflora*)
Umbrella tree (*Schefflera actinophylla*)
Vagabond plant (*Vriesea*)
Velvet plant, purple (*Gynura aurantiaca*)
Venus fly trap (*Dionaea muscipula*)
Violet (Viola)
Wandering Jew (*Tradescantia albiflora*)
Wandering Jew—red and white (*Zebrina pendula*)
Wax plant (*Hoya exotica*)
Yucca
Zebra plant (*Aphelandre squarrosa*)
Zinnia

*This species has not been reported to cause illness, but other species may be toxic.

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CHAPTER 66

Toxic Mushroom Ingestions

SANDRA M. SCHNEIDER AND TIMOTHY J. WIEGAND

> Had nature any outcast face? Could she a son condemn? Had nature an Iscariot?
> That mushroom—it is him. *Emily Dickinson*

Mushrooms are often considered the vermin of the vegetable world, likened to snakes, slugs, and worms. Some are regarded as mystical and others as delicacies. The locations of tasty morels are passed on from generation to generation, closely guarded from strangers. Each autumn and spring, foragers scour the woods for known delicacies and new ones untried. Some mushroom foragers search for "little brown mushrooms," not for their taste, but to evoke hallucinations.

Eating unidentified or misidentified species can be dangerous. In the vast majority of toxic ingestions (perhaps up to 95%), the mushroom was incorrectly identified. More than 40,000 species of fungi are currently described, with a few thousand new ones added each year. Only 100 species are toxic.[41]

The fungi kingdom contains molds, smuts, rusts, mildews, yeasts, and mushrooms, which are different from plants because they lack chlorophyll. *Yeasts* are single-cell organisms that divide using budding. *Mold* is any fungus that grows with thread-like connections and a fuzzy appearance. *Mildew, rust,* and *smut* are all fungi related to mushrooms and break down vegetable matter, leaving behind a white, red, or black powder, respectively. *Toadstool* is often used to describe toxic mushrooms. This chapter differentiates toxic mushrooms by their toxins and scientific names.

The body of a fungus is a dense network of branching filaments, or hyphae. The mushroom is the fruiting body of the fungus, containing the spores. The hyphae and mycelia generally occur in an underground network supporting the visible mushroom. Mushrooms often grow in large rings radiating from a central network of mycelia. In the past, these "fairy rings" were thought to have mystical influence (Figure 66-1). A fairy ring in northeast Oregon has been found to occupy an area over 10 km^2 (3.9 square miles). This ring is thought to be between 2000 and 8000 years old, making it the oldest and largest single organism on the planet. Fungi are largely *saprophytic* (i.e., growing on decaying vegetable matter), involved with the decomposition of rotting materials, usually wood. They can also be *parasitic* (i.e., living on another living organism, injuring the host) or *symbiotic* (i.e., living together with each benefiting). Some emerge only after significant environmental changes, such as the large quantity of morels that may be found where a forest fire has recently occurred.

FIGURE 66-1 "Fairy ring" of mushrooms. *(Copyright iStockphoto.com/FairytaleDesign.)*

As a mushroom emerges from the ground, it is covered with a membrane or veil (Figure 66-2). As the mushroom grows (Figure 66-3), the membrane breaks, leaving residual marks known as *warts* on the cap of the mushroom (Figure 66-4). These warts may remain firmly attached to the mushroom or may remain as only residual spots, depending on the species of mushroom and environmental conditions. The emerging cap

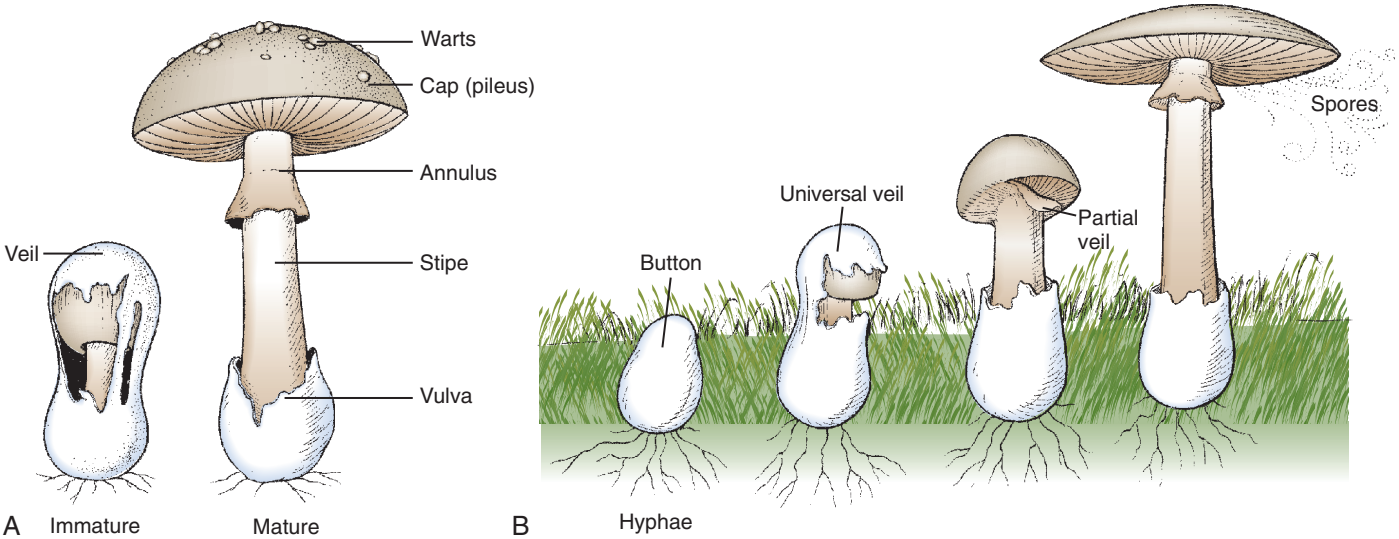

FIGURE 66-2 Structural characteristics **(A)** and life cycle **(B)** of mushrooms.

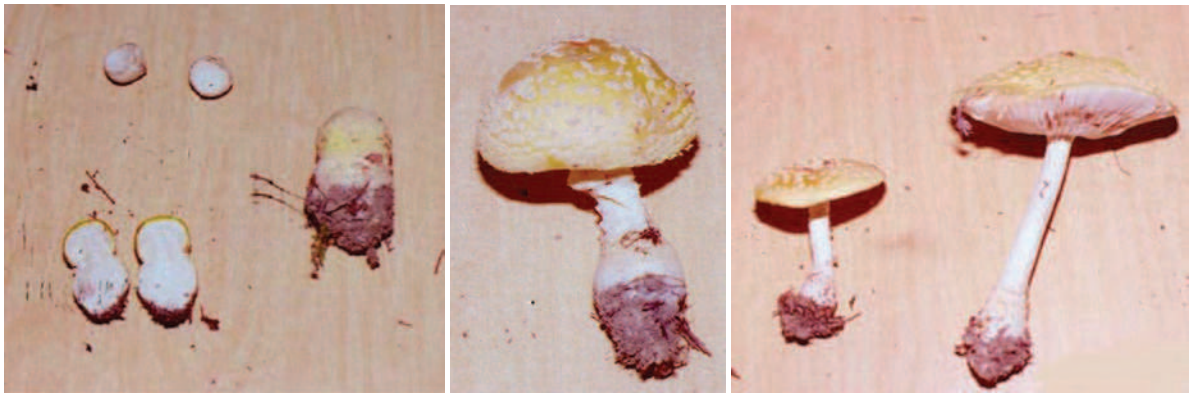

FIGURE 66-3 Growth of an *Amanita* species.

FIGURE 66-4 Warts on *Amanita muscaria*. *(By Peter Rosbjerg from http://www.flickr.com. Used with permission.)*

FIGURE 66-6 *Amanita phalloides*. (Grüner Knollenblätterpilz). *(By Maja Dumat from http://www.flickr.com. Used with permission.)*

takes on a shape consistent with the specific species, ranging from cylindrical to convex to funnel-shaped.

Gills located under the cap contain the spore-producing bodies. Some gills are covered with a second membrane or partial veil, which later pulls away to form an annulus, or ring, midway down the stalk of the mushroom. Gills may be attached firmly to the stalk, sometimes running down the stalk, or only to the cap itself (free gills) (Figure 66-5). Attachment of the gills is an important aid to identification of some poisonous mushrooms, such as *Amanita phalloides* (Figure 66-6).

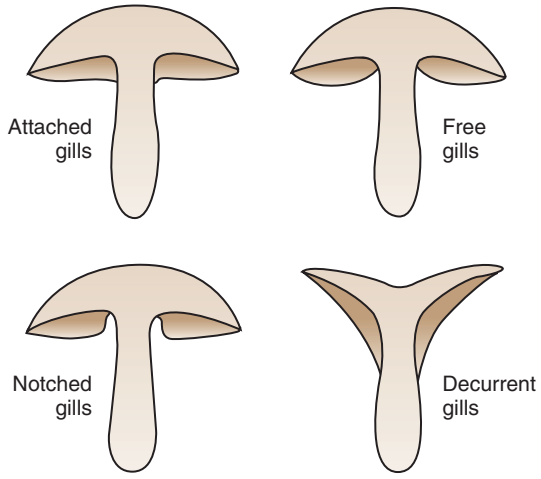

FIGURE 66-5 Mushroom gill types.

The stalk (stipe) begins at the cap and ends either underground or in a cup (vulva) (Figure 66-7). A vulva at or just below ground level often is seen in a poisonous species. The stipe is generally located in the center of the cap and may or may not be tapered. The stipe of many poisonous species enlarges below the cap, ending in a bulb. The stipe may have a ringed membrane as evidence that the partial veil formerly protected the gills (Figure 66-8). Spores are produced by spore-forming bodies on the gills and expelled into the air after they mature.

Spores vary in size, color, and shape but are usually unicellular. They average 5 to 10 μm in diameter. Spores are useful in identifying mushroom species (Figure 66-9 and Box 66-1). They can be obtained by cutting the stipe of a fresh specimen close

FIGURE 66-7 Death cap (*Amanita phalloides*).

FIGURE 66-8 Typical features of an *Amanita* mushroom. *(By Tomasz Przechlewski from http://www.flickr.com. Used with permission.)*

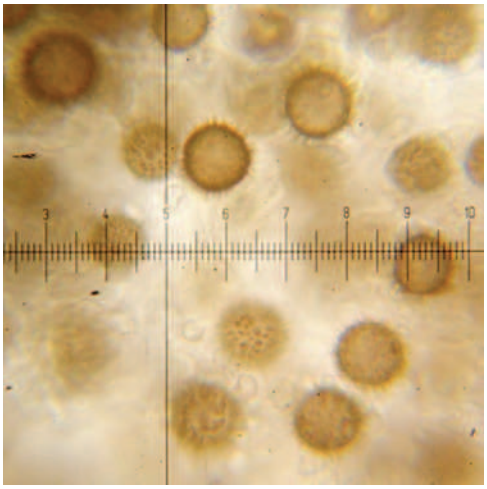

FIGURE 66-9 Spores from a mushroom. *(By Jason Hollinger from http://www.flickr.com. Used with permission.)*

to the gills, then laying the cap gill-side down on white paper for a few hours at room temperature. The initial color seen after removal of the gills is used for identification. With drying, the color may fade or change. Additional information about spores can be acquired by staining with Melzer's reagent (a solution of iodine and chloral hydrate). Spores that stain blue are called *amyloid,* indicating the presence of starch (Figure 66-10). This technique may be particularly useful in spore identification from gastric aspirates. Spores of *Amanita* species are amyloid. Thin-layer chromatography of spores available from a mycology laboratory, mushroom farm, or botany department is a more accurate aid to identification.

There are many species of mushrooms, including several that are hunted, that have no caps, gills, or stipe. They have developed alternative methods of releasing their spores. The "puffball" mushrooms are well known by the cloud of spores they release through a pore on the top surface of their spherical fruiting bodies (Figure 66-11). This spore release occurs when the spores are mature and may be initiated by a falling branch, errant placement of a deer's hoof, or the squeezing fingers of a curious child.

Mushrooms are composed of approximately 90% water, with 3% proteins and other nitrogen-containing compounds. The remainder is largely carbohydrate, fat, and a few vitamins. Some

BOX 66-1 Obtaining Spore Prints

1. Obtain a fresh specimen.
2. Cut off stalk close to the gills.
3. Lay cap, gill side down, on white paper for several hours at room temperature.
4. Note color of spores on paper immediately after removal of cap. Drying may alter spore appearance.

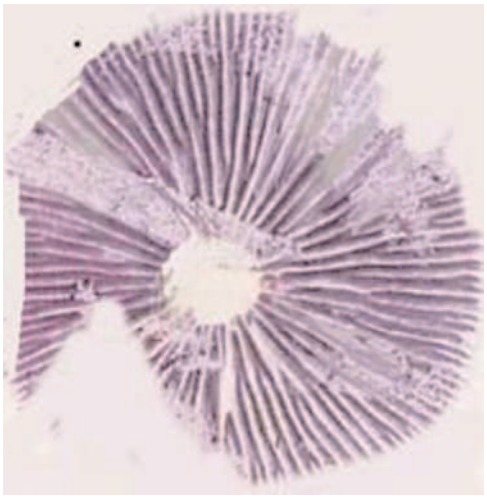

FIGURE 66-10 Spore print staining positive for amyloid.

mushrooms may have high levels of minerals, such as selenium, iron, and potassium. Nutritionally unimpressive, mushrooms are consumed primarily for their taste and texture. Wild mushrooms have the additional allure of being free. This is changing in many parts of the northwestern United States, where some species of mushroom have become so profitable that pickers have had to buy commercial permits, and gun battles have erupted over territorial disputes.

Of the many varieties of wild mushrooms, few are deadly or cause serious illness. All mushrooms, including toxic ones, are safe to handle without gloves; however, handwashing after handling is strongly recommended. Many experts will even bite off and chew a small piece of mushroom to gather taste information before spitting it out. As in wine tasting, a thorough rinsing is recommended after each taste.

The American Association of Poison Control Centers (AAPCC) reports between 7000 and 9000 mushroom exposures annually, with most exposures occurring between June and October. Most of these occur in children younger than 6 years and are not serious or result only in mild gastroenteritis. These exposures are usually caused by ingestion of a small amount of mushroom growing in the backyard. More serious ingestions can occur when young adults or foragers confuse toxic mushrooms for edible or hallucinogenic species. More serious exposures with potentially life-threatening toxic effects occur in less than 1% of all cases reported to poison control centers.[59]

Many immigrants fail to realize that the nontoxic mushrooms from their native lands have toxic look-alikes in America. This is particularly true of Southeast Asian immigrants, who are attracted to the large *Amanita* species. Entire families have been poisoned, with many fatalities. The Russian roulette played by mushroom foragers is statistically safe. Some self-proclaimed experts are simply lucky; occasionally, they are not.

FIGURE 66-11 Puffball mushrooms (edible).

FIGURE 66-12 *Agaricus bisporus* (edible).

NONTOXIC MUSHROOMS

The most common commercially available mushroom in the United States is *Agaricus bisporus* (Figure 66-12). It is cultivated in abandoned mine shafts and caves. This small white mushroom with dark gills is often picked before the gills are fully exposed. Although the mushroom is considered nontoxic, hypersensitivity reactions and gastrointestinal (GI) symptoms have been reported. In some parts of the United States, close relatives of this common mushroom account for the largest percentage of toxic mushroom cases. Most often, *A. bisporus* causes GI disturbance. *Agaricus* species may be confused with the deadly *Amanita* species (Figure 66-13). The popular portobello mushroom is a type of *Agaricus bisporus*. *A. bisporus* can also be found in the wild.

Nontoxic mushrooms may carry environmental toxins, such as heavy metals and pesticides. Mushrooms with high lead concentrations have been gathered near highways.[36] High mercury concentrations are found in mushrooms from industrial sites.[98] Regular consumption of wild-grown edible mushrooms from areas surrounding former mercury mining sites in Slovakia led to concerning levels of heavy metals. Many mushrooms fruit among cultivated plants and may contain toxic levels of pesticides. Human toxicity has not been reported.

Fungi may cause allergic reactions. Molds that grow in damp locations in buildings have been suspected to cause a variety of patient complaints. They are one cause of the "sick building" syndrome that has resulted in some structures being vacated or

FIGURE 66-13 *Amanita rubescens.*

FIGURE 66-14 Shiitake mushroom.

demolished when the problem could not be remedied by conventional methods. Acute anaphylaxis from mushroom ingestion is rare, despite the presence of haptens capable of inciting an allergic response.[62] More often, symptoms develop from inhalation of spores.[84] Patients may present with anaphylaxis or, more frequently, with chronic hypersensitivity pneumonitis. Hypersensitivity reactions are described in workers exposed to cultivation of *A. bisporus* (the most popular commercially grown mushroom in America)[69] and shiitake (*Lentinus edodes*), the popular Japanese mushroom (Figure 66-14).[102] Asthma symptoms developed in almost 10% of shiitake-exposed workers. In one study, all workers had positive skin and inhalation challenge tests.[113] Spore counts correlate with asthma symptoms.

Gastroenteric symptoms after ingestion of mushrooms may not be caused by toxins. Bacterial food poisoning may occur in foods that coincidentally contain mushrooms. Small bowel obstruction occurred in a person who consumed 500 g of the edible mushroom *Cantharellus cibarius* (chanterelle) (Figures 66-15 and 66-16).[38] This was largely a result of poor mastication, because entire mushrooms were recovered from the patient's intestines. Improper preparation of edible mushrooms can result in severe toxicity. Staphylococcal food poisoning has been reported from improperly canned mushrooms.[66] Most wild mushrooms are nontoxic, and many are delicious. Morels (*Morchella esculenta* [Figure 66-17] or *M. deliciosa*) are highly prized delicacies. Chanterelles (*C. cibarius*) (see Figures 66-15 and 66-16) and several species of *Boletus* (Figures 66-18 and 66-19) are particularly tasty. The chicken mushroom (*Laetiporus sulphureus*) (Figures 66-20 and 66-21) is often used in place of chicken in Chinese dishes. Extracts of the shiitake mushroom, *L. edodes,* may have antimalarial properties.[136]

TYPES OF MUSHROOM TOXICITY

Mushroom toxicity can be classified into several types, which are summarized in Box 66-2. Detailed discussions of each type are presented in the sections that follow. Box 66-3 provides a method for identifying what type of mushroom may have caused a patient's illness.

FIGURE 66-15 *Cantharellus cibarius* (edible).

FIGURE 66-16 *Cantharellus cibarius* (chanterelles). *(By Tomasz Przechlewski from http://www.flickr.com. Used with permission.)*

FIGURE 66-18 *Boletus edulis* (edible).

FIGURE 66-20 Chicken mushroom, *Laetiporus sulphureus* (edible).

FIGURE 66-17 Morels (*Morchella esculenta*).

FIGURE 66-19 *Boletus luridus. (By Tomasz Przechlewski from http://www.flickr.com. Used with permission.)*

FIGURE 66-21 *Laetiporus sulphureus. (By Carl Mueller from http://www.flickr.com. Used with permission.)*

BOX 66-2 Types of Mushroom Toxicity

- Gastrointestinal irritants
- Disulfiram-like toxins
- Neurotoxins
  - Muscarinic
  - Isoxazole derivatives
  - Psilocybin-hallucinogenic
- Protoplasmic
  - Gyromitrin—hepatotoxic
  - Amatoxin—hepatotoxic
  - Orellanine—nephrotoxic

BOX 66-3 Guide to Mushroom Identification

1. Collect any specimens left at home—preferably uncooked.
2. Collect fresh specimens from gathering site(s).
3. Transport and store mushrooms in paper bags.
4. Spores can be recovered from gastrointestinal fluid.
5. Note initial toxicity and time since ingestion. Note symptoms or lack of symptoms among others ingesting mushrooms.
6. Contact a regional poison information center for assistance in locating an expert in identification.
7. When symptoms are not consistent with identified species, consider that the patient might have ingested another type of mushroom.

GASTROINTESTINAL TOXINS

Most toxic mushrooms fall into the group of GI irritants. This large, heterogeneous group of mushrooms causes GI distress, consisting of nausea, vomiting, and diarrhea, beginning 1 to 2 hours after ingestion and resolving in 6 to 12 hours. Even *A. bisporus,* the common cultivated mushroom, may cause brief gastroenteritis in some individuals.[114] The mechanism is unknown.

CAUSATIVE MUSHROOMS

A large number of unrelated mushrooms cause GI symptoms with varying host responses (Box 66-4). *Chlorophyllum molybdites* (also known as *Lepiota morganii*) (Figure 66-22) is the most frequently ingested toxic mushroom in America. Most persons who ingest *C. molybdites* confuse it with *A. bisporus,* which it closely resembles. The common name for *C. molybdites,* green-spored parasol, describes the characteristics of this summer mushroom. The whitish cap is 10 to 40 cm (4 to 16 inches), initially smooth and round, and becomes convex with maturity. Tan or brown warts may be present. The gills are free from the stalk, initially white to yellow, and become green with maturity. The stalk is 5 to 25 cm (2 to 10 inches) long, smooth, and white. The ring is generally brown on the underside. Spores are green. The mushroom is common in most of eastern and southern North America and in California. In southern California, it is a common lawn mushroom.

Text continued on p. 1474

BOX 66-4 Mushrooms Reported to Cause Gastrointestinal Irritation

Agaricus
albolutescens
hondensis (Figure 66-23)
placomyces
silvaticus
silvicola
xanthodermus (Figure 66-24)

Amanita
brunnescens (Figure 66-25)
chlorinosma
flavoconia (Figure 66-26)
flavorubescens (Figure 66-27)
frostiana
parcivolvata
spissa
spreta
volvata

Boletus
luridus (see Figure 66-19)
pulcherrimus
satans
sensibilis

Chlorophyllum
molybdites (*Lepiota morganii*) (Figure 66-28)

Entoloma (Rhodophyllus)
lividum
nidorosum
rhodopolium
salmoneum (Figure 66-29)
strictius
vernum

***Cantharellus* (Figure 66-30)**
bonari
floccosus
kauffmanii

Hebeloma
crustuliniforme
fastibile
mesophaeum
sinapizans

Lactarius
chrysorrheus (Figure 66-31)
glaucescens
helvus
representaneus
rufus (Figure 66-32)
scrobiculatus
torminosus (Figure 66-33)
uvidus

Lepiota
clypeolaria (Figure 66-34)
cristata (Figure 66-35)
lutea (Figures 66-36 and 66-37)
morganii
naucina

Lycoperdon
marginatum
subincarnatum

Morchella (Figures 66-38 and 66-39)
angusticeps
crassipes
deliciosa
esculenta (Figure 66-40)
semilibera (Figure 66-41)

Naematoloma (Hypholoma)
fasciculare

Omphalotus
olearius
illudens (Figure 66-42)
olivascens (Figure 66-43)

Paxillus
involutus

Ramaria (Clavaria)
formosa (Figure 66-44)
gelantinosa

Russula
emetica (Figure 66-45)

Scleroderma
aurantium
cepa (Figure 66-46)

Tricholoma
album
muscarium
pardinum
pessundatum
saponaceum
sejunctum
sulphureum
venenatum

Verpa
bohemica

FIGURE 66-22 *Chlorophyllum molybdites* (also known as *Lepiota morganii*). *(By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-23 *Agaricus hondensis. (By Dan Bennett from http://www.flickr.com. Used with permission.)*

FIGURE 66-24 *Agaricus xanthodermus. (By Damon W. Smith from http://www.flickr.com. Used with permission.)*

FIGURE 66-25 *Amanita brunnescens. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-26 *Amanita flavoconia. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-27 *Amanita flavorubescens.*

FIGURE 66-28 *Chlorophyllum molybdites* (*Lepiota morganii*). *(By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-29 *Entoloma* (*Rhodophyllus*) *salmoneum. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-30 *Cantharellus* mushroom. *(By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-31 *Lactarius chrysorrheus. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-32 *Lactarius rufus. (By aSIMULAtor from http://www.flickr.com. Used with permission.)*

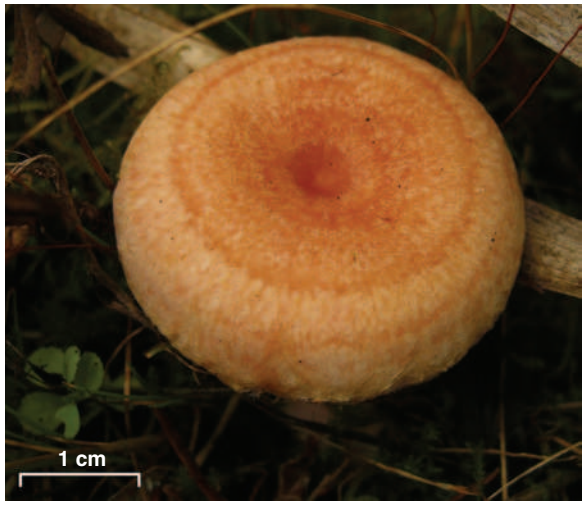

FIGURE 66-33 *Lactarius torminosus. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-34 *Lepiota clypeolaria. (By Tomasz Przechlewski from http://www.flickr.com. Used with permission.)*

FIGURE 66-35 *Lepiota cristata. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-36 *Lepiota lutea. (By Lara604 from http://www.flickr.com. Used with permission.)*

FIGURE 66-37 *Lepiota lutea. (By Lara604 from http://www.flickr.com. Used with permission.)*

FIGURE 66-38 *Morchella* sp. *(By Damon W. Smith from http://www.flickr.com. Used with permission.)*

FIGURE 66-39 Inside of a Morchella mushroom. *(By Damon W. Smith from http://www.flickr.com. Used with permission.)*

FIGURE 66-40 *Morchella esculenta. (By Jason Sturner from http://www.flickr.com. Used with permission.)*

FIGURE 66-41 *Morchella semilibera. (By Jason Sturner from http://www.flickr.com. Used with permission.)*

FIGURE 66-42 *Omphalotus illudens. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-43 *Omphalotus olivascens. (By Nathan Wilson from http://www.mushroomobserver.org/image/show_image/621 from http://www.flickr.com. Used with permission.)*

FIGURE 66-44 *Ramaria (Clavaria) formosa. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-45 *Russula emetica. (By Maja Dumat from http://www.flickr.com. Used with permission.)*

FIGURE 66-46 *Scleroderma cepa. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

Another common mushroom causing GI symptoms is the jack-o'-lantern. Its botanical classification is not completely settled. Most often, it is referred to as *Omphalotus illudens* (see Figure 66-42), *Omphalotus olearius,* or *Omphalotus olivascens* (see Figure 66-43). The mushroom is a bright orange-yellow mushroom with sharp-edged gills and often grows in clusters at the base of stumps or on buried roots of deciduous trees. The cap is 4 to 16 cm (1.6 to 6.3 inches) in diameter on a stalk that is 4 to 20 cm (1.6 to 8 inches) long. Gills are olive to orange, with white to yellow spores. The mushroom shows characteristic luminescence lasting 40 to 50 hours after collection. Members of this family are found in both eastern and western North America, generally in autumn and early spring. They may be mistaken for the edible species *C. cibarius* (see Figure 66-15). Some European reports have documented hepatic impairment and muscarinic effect following ingestion.[122] It is not clear whether the mushroom and its toxins are the same on both sides of the Atlantic.

Although the genus *Amanita* is most famous for its deadly member *A. phalloides* (see Figure 66-6), the genus also contains tasty nontoxic mushrooms (e.g., *Amanita caesarea* [Figure 66-47], *A. calyptrata, A. velosa*). Several *Amanita* species cause GI symptoms indistinguishable from those caused by jack-o'-lantern mushrooms or *C. molybdites* (see Figure 66-28). *Amanita brunnescens* (see Figure 66-25) and *Amanita flavorubescens* (see Figure 66-27) are frequently listed as containing GI toxins, although they are occasionally listed as edible. Both have broad, yellowish to brown caps (3 to 15 cm [1.2 to 6 inches]) with loosely attached warts. The stalks are 3 to 18 cm (1.2 to 7.1 inches) long, enlarging toward the base with a superior ring. *A. brunnescens* stains reddish brown when bruised. As with most *Amanita,* these mushrooms are found in summer or fall associated with hardwoods or conifers.

Several members of the genus *Agaricus,* particularly *Agaricus albolutescens, A. silvaticus,* and *A. xanthodermus* (Figure 66-24), can cause GI symptoms. They resemble the cultivated mushrooms in grocery stores and are found in meadows and lawns in the summer and autumn. Table 66-1 lists the look-alike toxic and nontoxic mushrooms in this group.

FIGURE 66-47 *Amanita caesarea. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

TOXINS

A variety of toxins have been extracted from these mushrooms, although their structures are poorly described. Most are protein based and heat labile, although toxicity may not be completely eliminated with cooking. In some cases the toxin may be destroyed by heating (temperature and duration vary by species), parboiling, or even preserving in salt. Host response to a toxin varies; some persons can eat such mushrooms without harm, whereas others become quite ill. Some mushrooms also contain hemolysins and toxins that cause hemorrhage and hepatitis in animals.[63,118] Human hemolysis has not been reported.[63]

TABLE 66-1 Gastrointestinal Irritant Mushrooms Mistaken for Edible Species

Gastrointestinal Irritant	Edible Species
Agaricus *albolutescens* *silvaticus* *xanthodermus* (see Figure 66-24)	*Agaricus bisporus*
Amanita brunnescens (see Figure 66-25)	*Amanita flavorubescens* (see Figure 66-27) *Amanita inaurata* (Figure 66-48)
Chlorophyllum molybdites (see Figures 66-22 and 66-28)	*Lepiota* spp. (Figure 66-49) *Agaricus bisporus* (see Figure 66-12)
Entoloma spp. (see Figure 66-29)	*Pluteus cervinus* *Entoloma abortivum*
Hebeloma crustuliniforme	*Rozites caperata* (Figure 66-50)
Naematoloma fasciculare	*Armillaria mellea* (Figures 66-51 to 66-53) *Naematoloma sublateritium* *Naematoloma capnoides*
Paxillus involutus	*Lactarius* spp. (Figure 66-54)
Ramaria formosa (see Figure 66-44) *Ramaria gelatinosa*	*Ramaria* spp.
Scleroderma aurantium	*Lycoperdon perlatum* (Figure 66-55)
Tricholoma pessundatum	*Cantharellus cibarius* (see Figure 66-16)
Omphalotus olearius (see Figure 66-42)	*Laetiporus sulphureus* (see Figure 66-21) *Armillaria mellea* (see Figures 66-51 to 66-53)

FIGURE 66-48 *Amanita inaurata. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-49 *Lepiota* species—some are toxic.

FIGURE 66-51 *Armillaria mellea. (By Nathan Wilson from http://www.mushroomobserver.org/image/show_image/621 from http://www.flickr.com. Used with permission.)*

FIGURE 66-50 *Rozites caperata. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-52 *Armillaria mellea. (By Maja Dumat from http://www.flickr.com. Used with permission.)*

FIGURE 66-53 *Armillaria mellea. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-54 *Lactarius* sp. *(By Maja Dumat from http://www.flickr.com. Used with permission.)*

CLINICAL PRESENTATION

Within 1 to 2 hours of ingestion of these mushrooms, nausea, vomiting, intestinal cramping, and diarrhea develop. Stools are usually watery and occasionally bloody with fecal leukocytes. Chills, headaches, and myalgias may occur. Symptoms remit spontaneously in 6 to 12 hours. Most patients require only fluid and electrolytes replacement. A few serious cases reported in the literature have been associated with severe dehydration. In a review of 106 cases, all patients responded well to fluid and electrolyte replacement and occasional antiemetic or antidiarrheal medications.[23] Admitted patients were discharged in an average of 2 days. Persons whose symptoms are delayed (beginning 4 hours or more after ingestion) probably have ingested a more toxic mushroom, possibly *Amanita, Galerina, Lepiota,* or *Gyromitra*. Those who ingest these more toxic mushrooms present with very severe GI distress and may develop hepatic failure. Because nausea and vomiting are common symptoms seen with various types of mushroom exposures, careful attention to onset and timing of these symptoms is important in differentiating more severe, or even life-threatening, toxicity from relatively benign ingestions.

Recent reports of ingestion of jack-o'-lantern mushrooms describe mildly elevated liver transaminases.[122] Cases of metabolic acidosis and dehydration, and even death, are attributed to *C. molybdites*[15,116] (see Figure 66-22).

TREATMENT

Treatment is largely supportive and does not depend on the type of mushroom ingested (Box 66-5). Intravenous (IV) fluid and electrolytes replacement may be required. Although there is no evidence, in a severe case, an antiemetic, such as ondansetron, 8 mg orally (PO/ODT) or intravenously (IV), or promethazine, 25 mg IV, may prevent further emesis. If a patient presents within 1 hour of ingestion and vomiting has not occurred, activated charcoal (1 g/kg) without cathartic is given PO or through nasogastric (NG) tube, although no evidence shows that its use decreases toxicity. Once vomiting starts, activated charcoal is likely useless. Most cases are self-limited.

Care should be taken not to dismiss early GI symptoms when several types of unknown mushrooms have been ingested. Individuals may ingest both GI irritant mushrooms and mushrooms containing serious toxins. Persons with prolonged gastroenteritis from unidentified mushrooms should be observed for 24 to 48 hours for development of delayed hepatic damage. Special efforts should be made in these cases to identify the ingested mushrooms.

BOX 66-5 Treatment of Gastrointestinal Irritant Mushroom Ingestion

1. Note time since ingestion. If more than 2 hours between ingestion and symptoms, a more serious protoplasmic toxin ingestion may have occurred. Monitor liver transaminases.
2. Provide fluid and electrolytes replacement.
3. Provide antiemetic and antidiarrheal medications as needed.

DISULFIRAM-LIKE TOXINS

A fascinating toxicity is caused by some members of the *Coprinus* genus, known as "inky caps" (Figure 66-56). Individuals who ingest these mushrooms and subsequently ingest alcohol have symptoms similar to those of an alcohol-disulfiram (Antabuse) reaction.

CAUSATIVE MUSHROOMS

Several members of the *Coprinus* genus may contain disulfiram-like toxins (Box 66-6), but symptoms are most common with *Coprinus atramentarius*. The mushroom has a 2- to 8-cm (0.8- to 3.1-inch) cylindrical cap on a thin, 4- to 5-cm (1.6- to 2-inch) stalk. The cap is white or occasionally orange or yellow at the

FIGURE 66-55 *Lycoperdon perlatum. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-56 *Coprinus* sp. *(By Damon W. Smith from http://www.flickr.com. Used with permission.)*

BOX 66-6 Mushrooms Suspected of Causing or Reported to Cause an Alcohol-Disulfiram Reaction

Coprinus (Figure 66-57)
atramentarius
comatus (see Figure 66-56)
insignis
micaceus

Clitocybe
clavipes (Figure 66-58)

top. The mature cap often develops cracks, which turn up at its margins. The cap blackens as it matures and then liquefies into the "inky cap." A ring may be present low on the stalk. Spores are black. *C. atramentarius* grows throughout North America in clusters of three or more in grass or wood debris. It often appears overnight after a rain. Several members of the *Coprinus* genus, including *C. atramentarius,* are edible if no alcohol is ingested for the next 72 hours. Other mushroom species contain coprine-like toxins. *Lepiota aspera* has caused disulfiram-like reactions in individuals who eat this mushroom and simultaneously consume ethanol.

TOXIN

Mushrooms causing a disulfiram reaction contain the toxin coprine, first isolated from the mushroom *C. atramentarius* in 1975.[46] Coprine is distinct from disulfiram and is most likely a derivative of glutamine. It probably is not present in the raw mushroom, but rather a hydrolyte created during cooking.[67]

Coprine (or its derivative L-aminocyclopropanol) inhibits acetaldehyde dehydrogenase, similar to the action of disulfiram. Acetaldehyde accumulates, leading to flushing, diaphoresis, headache, tachycardia, nausea, and vomiting. Some clinicians believe that coprine is a relatively poor inhibitor of acetaldehyde dehydrogenase and suggest that symptoms result from altered neurotransmitter levels.[86]

CLINICAL PRESENTATION

A history of wild mushroom ingestion within days before symptoms is rarely offered. Ingestion of the mushroom imparts sensitivity to alcohol, which begins 2 to 6 hours after ingestion and

FIGURE 66-57 *Coprinus* sp. *(By Jason Hollinger from* http://www.flickr.com*. Used with permission.)*

FIGURE 66-58 *Clitocybe* mushrooms—some are toxic.

may last up to 72 hours. Within minutes of subsequent alcohol ingestion, the person experiences severe headache, flushing, and tachycardia. Hyperventilation, shortness of breath, and palpitations may occur. Chest pain and orthostatic hypotension occur in severe cases. Symptoms can be confused with an allergic reaction or acute myocardial infarction. Symptoms typically resolve spontaneously within 3 to 6 hours.

TREATMENT

Supportive and symptomatic treatments are suggested for patients with coprine toxicity (Box 66-7). Because these disulfiram-like symptoms may have other, more severe causes, baseline laboratory tests (blood urea nitrogen [BUN], creatinine, electrolytes, and glucose) should be drawn. Urine output should be monitored. IV fluids should be given to keep urine output at 50 mL/hr (children, 1 mL/kg/hr). Activated charcoal is not beneficial. Charcoal does not adsorb alcohol, and the coprine has already been absorbed by the time the reaction occurs. Hypotension generally responds to IV fluid administration. Severe hypotension refractory to fluid replacement should be treated with norepinephrine (initially 2 to 4 mcg/min; 0.05 to 0.1 mcg/kg/min in children and increased as necessary); norepinephrine stores are depleted in a true disulfiram reaction. Propranolol (0.5 to 3 mg IV; 0.01 to 0.02 mg/kg IV up to 1 mg in children) is used for severe symptomatic supraventricular tachycardia. Propranolol may be repeated as needed after 5 to 10 minutes.

NEUROLOGIC TOXINS

MUSCARINE

Muscarine was first isolated from the mushroom *Amanita muscaria* more than 150 years ago (Figures 66-59 and 66-60). A classic muscarinic reaction includes salivation, lacrimation, urination, diaphoresis, GI upset, and emesis (SLUDGE syndrome). Buddhist adepts may have used *A. muscaria* in the second to ninth centuries to achieve enlightenment.[43]

BOX 66-7 Treatment of Coprine Toxicity (Disulfiram-Like Toxin)

1. Generally requires only supportive care.
2. Hypotension responds to fluid or, if necessary, intravenous norepinephrine (2 to 4 mcg/min, or 0.05 to 0.1 mcg/kg/min in children, increasing as needed every 5 to 10 minutes).
3. Severe symptomatic supraventricular tachycardia can be controlled with intravenous propranolol (0.5 to 3 mg in adults, or in children, 0.01 to 0.02 mg/kg up to a maximum of 1 mg per dose, repeated after 5 to 10 minutes as needed).

FIGURE 66-59 *Amanita muscaria. (By Kevin L. Cole from http://www.flickr.com. Used with permission.)*

Causative Mushrooms

Amanita muscaria has a cap 5 to 30 cm (2 to 12 inches) in diameter that is scarlet red with white warts. The stalk tapers upward and is white, often hollow, and grows 15 to 20 cm (6 to 8 inches) in length. It has a prominent vulva and numerous rings. Gills are free and white, as are the spores. The mushrooms grow in eastern North America and throughout much of the western United States, often near *Boletus edulis*. They grow under hardwoods and conifers from summer to autumn.

Potentially toxic amounts of muscarine are found in some *Inocybe* (Figure 66-61) and *Clitocybe* mushrooms (Figure 66-62, Box 66-8, and Table 66-2; see also Figure 66-58). *Inocybe* mushrooms (see Figure 66-61) are small brown mushrooms with conical caps up to 6 cm (2.4 inches) in diameter. Stalks are 2 to 10 cm (0.8 to 4 inches) long, covered with fine, brown to white hairs. Gills are brown and notched; spores are brown. They are found typically under hardwoods and conifers in the summer and fall. All members of this family are considered poisonous.

In contrast, many *Clitocybe* mushrooms (see Figure 66-58) are edible, but except for *Clitocybe nuda* and its close relatives, they are not very tasty. A few contain muscarine. All *Clitocybe* mushrooms are whitish tan to gray mushrooms with caps 15 to 33 mm (0.6 to 1.3 inches) long on hairless stalks 1 to 5 cm (0.4 to 2 inches) long. Gills are decurrent (run down the stalk), and spores are white. They are usually single specimens (not clustered) found on lawns in the summer and fall.

FIGURE 66-60 *Amanita muscaria. (By Damon W. Smith from http://www.flickr.com. Used with permission.)*

FIGURE 66-61 *Inocybe* mushrooms—some are toxic.

FIGURE 66-62 *Clitocybe* sp. *(By Damon W. Smith from http://www.flickr.com. Used with permission.)*

BOX 66-8 Mushrooms Reported or Suspected of Containing Muscarine

Amanita
gemmata
muscaria (see Figures 66-59 and 66-60)
pantherina (Figure 66-63)
parcivolvata

Boletus
calopus
luridus
pulcherrimus
satanas

Clitocybe (see Figures 66-58 and 66-62)
aurantiaca
dealbata
nebularis

Hebeloma crustuliniforme

Inocybe (see Figure 66-61)
fastigiata
geophylla
nappies
patouillardii
pudica

Mycena pura (Figure 66-64)

Omphalotus (see Figure 66-42)
olivascens (see Figure 66-43)
olearius
illudens (see Figure 66-42)

FIGURE 66-63 *Amanita pantherina. (By Maja Dumat from http://www.flickr.com. Used with permission.)*

Many *Inocybe* and *Clitocybe* mushrooms contain larger concentrations of muscarine than does *A. muscaria*. Other toxins (e.g., ibotenic acid) are present in *A. muscaria* and contribute to its toxicity.

Toxin

Muscarine is a quaternary trimethyl ammonium salt of 2-methyl-3-oxy-5-(amino) tetrahydrofuran. Muscarine stimulates postganglionic cholinergic receptors (muscarinic receptors), mimicking the action of acetylcholine. Muscarine stimulation of the GI tract leads to increased secretory activity, contraction amplitude, and peristalsis. Stimulation of the urinary tract leads to bladder contraction and increased peristalsis of the ureters. Stimulation of secretory tissue leads to salivation and lacrimation. Bronchoconstriction, flushing, and diaphoresis result from additional stimulation of bronchial and vascular tissues. Cardiac effects include reflex tachycardia or, more often, bradycardia and decreased atrioventricular conduction. Central nervous system (CNS) effects include headache, ataxia, and visual disturbances. The sensorium is generally not affected (except in ingestion of *A. muscaria,* which contains other CNS toxins).

FIGURE 66-64 *Mycena pura. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

TABLE 66-2 Look-Alikes of Mushrooms Causing Muscarine Poisoning

Toxic Species	Edible Species
Clitocybe dealbata	*Marasmius oreades* (Figure 66-65)
Inocybe species (see Figure 66-61)	*Marasmius oreades*

FIGURE 66-65 *Marasmius oreades. (By Becky Dewdney-York from http://www.flickr.com. Used with permission.)*

Clinical Presentation

Symptoms develop within 15 to 30 minutes after ingestion of muscarine-containing mushrooms. Typical symptoms include salivation, urination, lacrimation, diarrhea, diaphoresis, abdominal pain, nausea, and emesis. Bradycardia, bronchospasm, and constricted pupils are also noted. Copious bronchial secretions may cause respiratory failure requiring mechanical ventilation.

Symptoms remit spontaneously in 6 to 24 hours. In Europe, some deaths are reported from *Inocybe patouillardii*.[67] Although this mushroom is rarely eaten, ingestion carries a mortality rate of 6% to 12%, particularly among persons with preexisting pulmonary or cardiac disease. Most deaths occur within the first 12 hours as a result of respiratory failure or cardiovascular collapse.

Treatment

Treatment of muscarinic toxicity is outlined in Box 66-9. Many patients require supportive care with oxygen, suctioning, and IV fluid replacement. Activated charcoal and cathartics are rarely given because of the prominent emesis and diarrhea. Atropine is a muscarine antagonist but should be used only to control secretions or profound bradycardia. It should not be given prophylactically or for asymptomatic bradycardia because it may worsen the delirium, ataxia, and hallucinations induced by *A. muscaria*. Atropine is dosed at 0.01 mg/kg IV for children and 1 mg IV for adults. When secretions are life threatening, that

BOX 66-9 Treatment of Muscarinic Toxicity

1. Supportive care with oxygen, suctioning, and endotracheal intubation as needed.
2. Fluid and electrolyte replacement.
3. Atropine (if symptoms are life threatening) 0.01 mg/kg intravenously every 5 to 10 minutes until secretions are controlled. There is no upper limit to the dose if secretions are excessive. Atropine may worsen central nervous system effects of some mushrooms such as *Amanita muscaria.*

BOX 66-10 Mushrooms Reported or Suspected of Containing Ibotenic Acid, Muscimol, or Related Compounds

Amanita
cokeri
gemmata
muscaria (see Figures 66-59 and 66-60)
pantherina (see Figure 66-63)

Panaeolus campanulatus

Tricholoma muscarium

initial dose may be doubled on subsequent doses. There is no upper limit on the dose of atropine if secretions are severe and potentially life threatening. Symptoms resolve spontaneously within 24 hours.

ISOXAZOLE REACTIONS

The isoxazole derivatives ibotenic acid and muscimol produce CNS symptoms, including excitement and alteration in visual perception.

Causative Mushrooms

Several mushrooms contain ibotenic acid (Box 66-10 and Table 66-3). *A. muscaria* is described previously. *Amanita pantherina* (see Figure 66-63) is 5 to 15 cm (2 to 6 inches) long with a cap 5 to 15 cm in diameter. The cap is generally white to pink in the young specimen but becomes reddish brown or brown, often darker at the rim, with maturity. Fragments of the universal veil form warts on the cap but may be washed off by rain. The stalk has a distinct ring, with a vulva at the bottom. When the flesh is cut or injured (e.g., by insect larvae), it develops a pinkish tinge. Gills are free and produce white spores. The raw mushroom has minimal smell and tastes similar to a raw potato. It grows from June to November in woodlands throughout North America. *A. muscaria* and *A. pantherina* have been identified for sale in markets in Japan and elsewhere.

Toxin

Ibotenic acid is found in the bright-red cap of *A. muscaria* and undergoes decarboxylation during drying to form muscimol, which is more toxic than ibotenic acid. The potency of the cap remains high despite drying. Muscimol is a γ-aminobutyric acid (GABA) receptor agonist.[51] Muscimol increases CNS serotonin levels and decreases catecholamine levels. Ibotenic acid resembles GABA and in animals can act as GABA acts. Liquid chromatography (LC) can identify these compounds.[80,120] Ibotenic acid and muscimol are rapidly absorbed in the GI tract and excreted in urine. They can be identified by gas chromatography–mass spectometry (GC/MS) in the urine of patients that ingest *A. muscaria* or *A. pantherina*.[117]

Clinical Presentation

Ingestion of 10 mg of *A. muscaria* produces mild intoxication, dizziness, and ataxia. Ingestion of 15 mg leads to pronounced ataxia and visual disturbances.[39,78] Delirium or manic behavior may develop. Physical activity is accelerated, with inability to judge size. Visual hallucinations, seizures, and muscle twitching are common. Some patients complain of residual headache for up to 48 hours. Nausea, vomiting, hallucinations, restlessness, psychomotor agitation, and somnolence were common symptoms reported in a series of acute poisonings with fly agaric (*A. muscaria*) and panther cap (*A. pantherina*) ingestion.[71]

Symptoms begin within 30 minutes of ingestion and generally last 2 hours. Rare fatalities have been reported. Some people have ataxia and paralysis of ocular convergence.[39] In rare cases, symptoms last as long as 48 hours, depending on the dosage

TABLE 66-3 Look-Alikes of Mushrooms Containing Isoxazole Toxins

Toxic Species	Edible Species
Amanita muscaria (see Figures 66-59 and 66-60)	*Amanita caesarea* (see Figure 66-47) *Amanita rubescens* (see Figure 66-13) *Armillaria mellea* (see Figures 66-51 to 66-53)
Amanita gemmata *Amanita pantherina* (see Figure 66-63)	*Russula* spp. (see Figure 66-45) *Amanita rubescens* (Figures 66-66 and 66-67)

FIGURE 66-66 *Amanita rubescens. (By Danel Solabarrieta from http://www.flickr.com. Used with permission.)*

FIGURE 66-67 *Amanita rubescens. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

BOX 66-11 Treatment of Isoxazole Toxins or Psilocybin Toxin

1. Supportive care.
2. Sedation as needed with benzodiazepine (diazepam, 2 to 5 mg IV every 10 minutes as needed) or phenobarbital (30 mg IV hourly).
3. If hyperpyrexia occurs (primarily seen in children), consider external cooling.

IV, Intravenously.

and individual host effect. There is a case report of psychosis lasting 5 days after ingestion of *A. muscaria*.[12] Ingestion of *A. pantherina* produces similar symptoms. In severe cases, seizures and CNS depression are observed[103] and rarely, death.[90]

Treatment

Treatment of patients with isoxazole reactions consists of supportive care (Box 66-11). Emesis caused by the toxin is unusual. Gastric emptying and activated charcoal administration are difficult because of CNS disturbances, have no proven effectiveness, and therefore are not recommended. Appropriate sedation with phenobarbital (30 mg IV hourly in adults, 0.5 mg/kg in children) or diazepam (2 to 5 mg IV repeated every 10 to 15 minutes in adults as needed, 0.1 to 0.3 mg/kg IV in children) is often necessary but requires caution. Phenobarbital or diazepam administered to treat *A. muscaria* ingestion may lead to unexpected apnea, flaccid paralysis, or both. Airway support and ventilatory assistance should be immediately available. Atropine may worsen the hallucinations, agitation, and delirium associated with isoxazole derivatives and should therefore be withheld unless the secretions or bradycardia are life threatening.

HALLUCINOGENIC MUSHROOMS

Perhaps the most sought-after mushrooms are "magic mushrooms," which are available as whole mushrooms in the wild and as spores (to grow your own) through mail-order catalogs. These mushrooms have been used for centuries for their hallucinogenic effects. Small, stone mushroom icons believed to be 3500 years old were found in Meso-American ruins.[67] Honey laced with *Psilocybe* can be purchased at Dutch coffee shops.

Causative Mushrooms

The most common hallucinogenic mushrooms are species of the *Psilocybe* genus (Box 66-12 and Table 66-4), which includes more than 100 species, not all of which cause hallucinations. These are "little brown mushrooms" (LBMs) (Figure 66-72). The cap is 0.5 to 4 cm (0.2 to 1.6 inches) in diameter (depending on the species), is usually smooth, and becomes sticky or slippery when wet. The stalk is slender and 4 to 15 cm (1.6 to 6 inches) long. Gills are gray to purple-gray; spores are dark, nearly black. The flesh of these mushrooms often turns blue or greenish when bruised or cut. The mushrooms are often mistaken for more poisonous species (e.g., *Galerina* [Figure 66-73] or *Inocybe* [see Figure 66-61]). These mushrooms also resemble *A. bisporus*. Regular grocery store mushrooms laced with lysergic acid diethylamide (LSD) or other hallucinogens are sold on the street as *Psilocybe*. Hallucinogenic mushrooms grow in a variety of habitats and are found throughout the world.

Other mushrooms, including members of the *Panaeolus* (see Figure 66-70) and *Gymnopilus* genera (see Figure 66-69), may contain psilocybin. *Panaeolus* mushrooms are also LBMs about the same size as *Psilocybe*. Gills are dark gray or black with black spores. They grow on dung throughout the tropics and subtropics of North America. Unlike *Psilocybe,* their caps do not become sticky or slippery when wet. The hallucinogenic effect and quantity of toxin varies among *Panaeolus* species.

Some *Gymnopilus* species (e.g., *Gymnopilus aeruginosus*) contain hallucinogens. These medium-sized mushrooms (cap, 5 to 15 cm [2 to 6 inches]; stalk, 5 to 12 cm [2 to 4.7 inches]) are variable in color (green, yellow, salmon, and red), with yellowish

BOX 66-12 Mushrooms Reported or Suspected of Containing Psilocybin or Psilocin or Both

Amanita
citrina (Figure 66-68)
porphyria

Conocybe
cyanopus
siligineoides
smithii

Gymnopilus (Figure 66-69)
aeruginosus
purpuratus
spectabilis
validipes

Naematoloma
popperianum

Panaeolus
campanulatus
castaneifolius
cyanescens
fimicola
foenisecii (Figure 66-70)
phalaenarum
semiovatus
sphinctrinus
subbalteatus

Psathyrella Sepulchralis

Psilocybe
baeocystis
caerulescens
caerulipes
cyanescens
cubensis
pelliculosa
semilanceata
strictipes
stuntzii

Stropharia
aeruginosa
coronilla
hornemannii
squamosal

TABLE 66-4 Look-Alikes of Mushrooms Containing Psilocybin or Psilocin

Toxic Species	Edible Species
Panaeolus foenisecii (see Figure 66-70)	*Psathyrella candolleana* (Figure 66-71)
	Agrocybe pediades
	Marasmius oreades (see Figure 66-65)
Panaeolus species (see Figure 66-70)	*Coprinus* spp. (see Figures 66-56 and 60-57)

FIGURE 66-68 *Amanita citrina. (By Tomasz Przechlewski from http://www.flickr.com. Used with permission.)*

FIGURE 66-69 *Gymnopilus* mushroom—some are toxic.

gills and rusty spores. They grow on stumps or sawdust in the U.S. Pacific Northwest.

Visual hallucinations and ataxia were reported in a person ingesting *L. sulphureus* (see Figures 66-20 and 66-21), previously thought to be harmless.[3] It is not clear whether this mushroom contained hallucinogenic material or the individual ingested an additional mushroom.

FIGURE 66-70 *Panaeolus foenisecii. (By Jason Hollinger from* http://www.flickr.com*. Used with permission.)*

FIGURE 66-71 *Psathyrella candolleana. (By Jason Hollinger from* http://www.flickr.com*. Used with permission.)*

FIGURE 66-72 *Psilocybe caerulipes.*

Psilocybe sclerotia, or "magic truffles," have also been reported to contain psilocybin alkaloids. These have been a popular source of the psychoactive alkaloids because they had not typically been included in laws banning the sales of psilocybin-containing mushrooms.[92]

Toxin

Psilocybin and its somewhat unstable metabolite psilocin are indole compounds derived from tryptamine. These two toxins were first isolated by Albert Hofmann,[49] known as the father of LSD. Chemically, the toxins resemble 5-hydroxytryptamine (5-HT) and LSD and have similar effects. They maintain their potency in dried specimens.

Psilocybin, as well as LSD, inhibits the firing rate of serotonin-dependent neurons, particularly at the presynaptic receptors. It induces euphoria, hallucinations, and loss of time sensation. Many of these symptoms are similar to those seen with LSD. Some species contain phenylethylamine, which may be responsible for tachycardia and other adverse reactions.[5] In human volunteer studies, peak plasma levels were reached at 105 minutes.[45]

Clinical Presentation

Ingestion of 5 mg of psilocybin (10 mg of fresh *Psilocybe cubensis*) causes moderate euphoria. Ingestion of 10 mg leads to hallucinations and loss of time sensation. Heightened imagination occurs within 15 to 30 minutes of ingestion. Hallucinations may last for 4 to 6 hours. Serious side effects are rarely seen, but fever and seizures have been reported in children.[75] Up to 50% of patients have tachycardia and hypertension.[91] Ingestion resulting

FIGURE 66-73 *Galerina marginata. (By Tomasz Przechlewski from* http://www.flickr.com*. Used with permission.)*

in myocardial infarction has been reported.[9] Flashbacks have been reported to occur in some persons for up to 4 months after ingestion.[7] Multifocal cerebral demyelination has been reported after ingestion of psilocybin-containing mushrooms.[115] Suicide while intoxicated with psilocybin-containing mushrooms has been reported in individuals with mental health or psychiatric disorders.[82]

Treatment

Recommendations for psilocybin toxicity are similar to those for isoxazole toxin (see Box 66-11). Initially, the patient should be placed in a quiet, supportive environment. Gastric emptying and activated charcoal administration are often impossible and may only enhance hallucinations. These modalities should be considered in patients with large ingestion who are brought early for treatment. Sedation can be accomplished when necessary with a benzodiazepine (e.g., diazepam, 0.1 mg/kg IV in children, or 2 to 5 mg IV in adults, repeated every 5 minutes as needed), phenobarbital (0.5 mg/kg IV in children, 30 mg IV in adults, repeated every 60 minutes as needed), chlorpromazine (50 to 100 mg intramuscularly [IM]), or haloperidol (5 mg IM). There is no evidence for the use of newer antipsychotic medications. Seizures can be controlled with diazepam in the doses just listed. Hyperpyrexia, seen primarily in children, is best treated with external cooling.

PROTOPLASMIC POISONS

GYROMITRA TOXIN

False morels (*Gyromitra esculenta* [Figure 66-74]) were once thought to be edible. During times of famine in Europe, ingestion of *Gyromitra* was encouraged.[44] Since 1793, these mushrooms have been suspected of causing toxicity, and since World War II, they have been known to cause hepatic failure, neurologic symptoms, and death. At present, they are collected, sold fresh, canned, and exported ("morschels") in Europe (Figure 66-75).[81] Symptoms appear 4 to 50 hours (usually 5 to 12 hours) after ingestion, with timing similar to that of *A. phalloides* poisoning. *Gyromitra* grows primarily in the spring and *A. phalloides* in the fall. Because of this difference in seasons and their distinct appearance, the identity of the two mushrooms is rarely confused.

Causative Mushrooms

Gyromitra esculenta (Figure 66-76) is approximately 5 to 16 cm (2 to 6.3 inches) in height with a reddish brown to dark-brown, irregularly shaped cap. The cap's surface is curved and folded, resembling a brain. The stalk is often as thick as the cap. The insides of the cap and stalk are hollow. This mushroom grows in the spring near pines and in sandy soil throughout North America. It is particularly common in Germany, Poland, and other eastern European countries. Mature species, particularly those with cap decay, may have increased toxicity. These mushrooms may be mistaken for morels, which are considered among the most delicious of wild mushrooms (Table 66-5).

Other members of the *Gyromitra* family contain gyromitrin. None of these mushrooms has been reported to cause toxicity in humans.

Toxin

Gyromitrin (*N*-methyl-*N*-formylhydrazone) was first isolated in 1967. This toxin is moderately volatile and heat sensitive. Cooking the mushrooms thoroughly and discarding the cooking liquid may decrease or eliminate the toxin. Symptoms have occurred despite proper cooking.

Once gyromitrin enters the stomach, hydrolysis yields *N*-methyl-*N*-formylhydrazine (MFH), which forms *N*-methylhydrazine or monomethylhydrazine (MH),[81] a component of rocket fuel. MH is a competitive inhibitor of pyridoxal phosphate, which interferes with enzyme systems (including decarboxylases, deaminases, and transaminases) requiring pyridoxine as a cofactor.[4] As a result, levels of GABA fall, interfering with neurotransmission.[61] It is believed that this decrease in GABA leads to altered mental status,

FIGURE 66-74 *Gyromitra esculenta,* which contains the hepatoxin gyromitrin. *(From Phillips R: Mushrooms of North America, Boston, 1991, Little, Brown.)*

FIGURE 66-75 False morel fungi (*Gyromitra esculenta*) for sale at a department store in Helsinki. *(Courtesy Ilmari Karonen; Wikimedia Commons.)*

FIGURE 66-76 *Gyromitra esculenta. (By Jason Hollinger from* http://www.flickr.com*. Used with permission.)*

TABLE 66-5 Look-Alike of Mushrooms Containing Gyromitrin

Toxic Species	Edible Species
Gyromitra esculenta (see Figure 66-76)	*Morchella esculenta* (see Figures 66-38 to 66-40)

seizures, or both. Recent questions have been raised about this widely accepted theory, because MH may cause seizures without a change in brain GABA levels.[74]

Both MFH and MH undergo oxidation in the liver into two highly reactive intermediates: a free methyl radical and an unstable diazonium compound.[81] These substances appear to produce local hepatic necrosis by blocking the activity of hepatic cytochrome enzyme systems, glutathione, and other hepatic biomolecules. There are significant concerns about long-term toxicity associated with repeated consumption of this mushroom. Each kilogram of fresh *G. esculenta* contains 3 to 100 mg gyromitrin. Fresh mushrooms contain 50 to 300 mg of MH per kilogram, and dried mushrooms up to 400 mg/kg. The human median lethal dose (LD_{50}) is suspected to be 20 to 50 mg/kg for adults and 10 to 30 mg/kg for children, or 0.4 to 1 kg of fresh mushrooms for an adult (average, 30 mushrooms) and 0.2 to 0.6 kg for a child.[81]

Clinical Presentation

Symptoms of gyromitrin toxicity are summarized in Box 66-13. They are generally delayed for 4 to 50 (average, 5 to 12) hours after ingestion. Initial symptoms include nausea, vomiting, and severe diarrhea. Some patients may have dizziness, weakness, muscle cramps, and loss of muscle coordination. In a severe ingestion, delirium, seizures, and coma are present. Hepatic failure develops over several days after ingestion, although hepatic damage is generally mild. Hypoglycemia, hypovolemia, severe hepatic failure, and death may occur.

Symptoms from gyromitrin toxin depend on amount consumed, toxin concentration, nature of the mushrooms, and other host factors. The variability of symptoms after ingestion of gyromitrin mushrooms is much greater than with other mushroom species. Some individuals can consume large quantities of *Gyromitra* with few or no symptoms. A second meal by the same person may lead to severe toxicity. Repeated consumption may increase the risk for a severe reaction.

Several drugs, including isoniazid, hydralazine, and probably MH,[18] are metabolized through acetylation of a hydrazine or amino group by the liver. Individuals vary greatly in the rapidity of acetylation. Two major human groups are termed "fast" and "slow" acetylators, with slow acetylation being an autosomal recessive trait. Slow acetylators in general have greater and more prolonged toxicity after ingestion of these drugs. Similar variation in toxicity in fast and slow acetylators is seen when *Gyromitra* mushrooms are ingested.

Treatment

Symptoms develop several hours after ingestion of *Gyromitra*. Treatment is summarized in Box 66-14. Activated charcoal (1 g/kg PO or via gastric tube) is of no value if given more than 1 hour after ingestion. At that time, most patients are asymptomatic and unaware that they have ingested a toxic mushroom. Pyridoxine has been useful in patients with neurologic disorders such as seizures and coma from MH toxicity and is of theoretical benefit in those with gyromitrin toxicity. Persons who ingest *G. esculenta* and develop significant neurologic symptoms should receive pyridoxine (25 mg/kg IV initial dose, up to 20 g/day).[4,60,133] No evidence indicates that pyridoxine alters the course of hepatic disease. High-dose pyridoxine therapy may cause acute peripheral neuropathies.[2]

Baseline measurements of liver transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), BUN, creatinine, complete blood cell count (CBC), platelet count, glucose, and electrolytes should be performed. ALT, AST, PT, PTT, INR, BUN, and creatinine should be monitored at least daily for 3 to 4 days for the development of hepatic failure. Rapid deterioration of the liver (ALT or AST >2000 international units [IU], PTT >50 seconds) mandates immediate transfer to a tertiary center with liver transplantation capability. Persons with significant hepatic failure may require monitoring of blood glucose level every 2 to 4 hours and supplemental glucose administration for symptomatic hypoglycemia.

No specific antidote or treatment is available for the fulminant hepatic failure. The appropriate timing or necessity of liver transplantation is uncertain. In persons with fulminant hepatic failure from infectious causes, the presence of an abnormal PT (unresponsive to fresh-frozen plasma) and development of hepatorenal syndrome, grade II hepatic encephalopathy, hypoglycemia, and uncorrectable metabolic acidosis are used as signs that transplantation is needed on an emergent basis. Persons with fulminant hepatic failure from toxic ingestion, elevated bilirubin level, and young age are important indicators of a poor prognosis. As discussed later, the model for end-stage liver disease (MELD) score for assessing liver failure provides the best prognostic information. Mortality from gyromitrin poisoning is reported to be 15% to 35%.[32]

BOX 66-13 Symptoms of Gyromitrin Toxicity

1. Onset of nausea, vomiting, and diarrhea within 4 to 50 (average, 5 to 12) hours.
2. Neurologic symptoms of dizziness, weakness, and loss of muscle coordination. Severe neurologic symptoms include coma, delirium, and seizures.
3. Hepatic failure begins 2 to 4 days after ingestion. Hepatic failure is often associated with hypoglycemia.

BOX 66-14 Treatment of Gyromitrin Toxicity

1. Activated charcoal if the patient presents within 1 hour of ingestion. Note that most of these patients will be asymptomatic.
2. Fluid and electrolyte replacement as needed.
3. Glucose replacement. Treat hypoglycemia with glucose infusion.
4. Pyridoxine, 25 mg/kg up to 20 g/day intravenously, to control seizures or coma.[6] If significant hepatic failure occurs, transfer patient to transplant facility.

RENAL TOXICITY

Although originally thought to be an edible mushroom, *Cortinarius orellanus* was associated with 81 cases of renal toxicity in the 1950s.[42] This led to isolation of the toxin orellanine, which is found in the mushrooms *C. orellanus, Cortinarius speciosissimus,* and *Cortinarius gentilis*. Most cases occur in Europe and Japan.

Causative Mushrooms

Cortinarius orellanus has a small, smooth, brown to brownish red cap 30 to 80 cm (12 to 31 inches) in diameter. The stalk is somewhat yellow, often darker closer toward the soil. Gills are orange to rust with rust-colored spores. It grows in deciduous woods, most frequently in sandy soil underneath oaks and birches. It is ubiquitous throughout Europe. Some other species of *Cortinarius* are found in the United States and may be toxic (Figure 66-77 and Box 66-15). *Amanita smithiana*, which grows in the Pacific Northwest, has been associated with renal failure in the U.S. patients.[131] It may be mistaken for *Tricholoma magnivelare*.[129] *Amanita proxima* in France and *Amanita pseudoporphyria* in Japan have caused similar symptoms.[104]

Toxin

The two toxins isolated from *C. orellanus,* orellanine and orelline, are structurally related to paraquat and diquat. Their mechanism of action remains a mystery. These are heat-stable compounds,

FIGURE 66-77 *Cortinarius* sp. (United States).

unaffected by cooking. The toxin appears to cause intense interstitial nephritis with early fibrosis.[50] The toxin can be identified with thin-layer chromatography (TLC).[52] Orellanine is being evaluated as a potential chemotherapeutic agent for certain types of cancers, including metastatic renal cancer. High-performance liquid chromatography (HPLC) analysis is able to detect orellanine in urine and in extracts of Cortinaceae members.[47] *Amanita* species contain aminohexadrienoic acid,[104,129] which appears to be responsible for its renal toxicity.

Clinical Presentation

Persons who ingest these mushrooms are generally asymptomatic for 2 to 20 days. During this latent period, acute renal failure develops. Some persons develop neurologic changes, including paresthesias, taste impairment, and cognitive disorders.

Symptoms vary greatly. One case report described 26 soldiers who ate soup made of *C. orellanus* in nearly identical quantities.[11] Acute renal failure developed in 12 patients on or around day 11. Eight individuals later recovered normal renal function, whereas four required long-term dialysis or kidney transplantation. The other 14 soldiers showed no rise in BUN or creatinine levels but developed leukocyturia and hematuria that persisted for more than 1 month. Renal failure reportedly occurs in 30% to 46% of persons who ingest these mushrooms and become ill. Renal function returns in approximately 50% of affected patients.

Renal biopsy in patients with orellanine-induced renal failure shows changes in tubular epithelial cells and in actin filaments within their cytoplasm.[87] These biopsy changes may persist for up to 3 months.[11]

Treatment

In most persons who ingest nephrotoxic mushrooms, unexplained acute renal failure develops many days later. If a person presents within 1 hour after eating orellanine-containing mushrooms, gastric emptying and activated charcoal administration (1 g/kg PO or via gastric tube) is theoretically indicated to prevent some absorption, decreasing the resultant toxicity. There is no evidence for its use. Early presentation is rare.

Once acute renal failure develops, baseline and repeated monitoring of BUN, creatinine, electrolytes, CBC, differential, and urinalysis should be performed to monitor renal function. Urine output should be monitored, and if it decreases, fluid administration should be used to achieve optimal hydration. Serum potassium, calcium, and magnesium should be monitored closely. If renal failure progresses, the patient should be transferred to a facility for hemodialysis and possible renal transplantation. Renal function may return to normal after months of dialysis dependency.

BOX 66-15 Mushrooms Reported as Causing Renal Failure

Amanita
proxima
pseudoporphyria
smithiana (Figure 66-78)

Cortinarius
gentilis
orellanus
rellanus
rubellus
speciosissimus
splendens
venenosus

FIGURE 66-78 *Amanita smithiana. (By Heather Gardner-Madras from http://www.flickr.com. Used with permission.)*

AMATOXINS

The mushrooms that contain amatoxins are responsible for more than 95% of fatalities caused by mushrooms (Box 66-16 and Table 66-6). *A. phalloides* is most common in central and eastern Europe; immigrants to the United States may have carried mushroom spores in wood products from eastern Europe. *Amanita verna* and *Amanita virosa* are more common in the United States. Toxicity has occurred from cooked or frozen mushrooms and even tea made from *Amanita* mushrooms.[94]

Causative Mushrooms

Mushrooms reported or suspected of containing amatoxins are listed in Box 66-16. The common names of *A. phalloides* (Figure 66-79; see also Figures 66-6 and 66-7) and its relatives, *A. verna* and *A. virosa* (Figures 66-80 and 66-81), are death cap, death angel, and destroying angel, reflecting their association with fatal outcome. *A. phalloides* has a white to greenish cap 4 to 16 cm (1.6 to 6.3 inches) in diameter, often with remnants of the veil as warts. The stalk is generally thick, 5 to 18 cm (2 to 7 inches) long, with a large bulb at the base, often with a vulva. A thin ring is usually present on the stalk. Gills are generally free and white to green in color; spores are white. The mushrooms grow under deciduous trees in the autumn.

Amanita virosa (see Figures 66-80 and 66-81) is more common in the United States. It resembles *A. phalloides,* but the cap is more yellow or white. *A. verna* is characteristically white. All grow in deciduous woods. Even mushroom experts have been tempted by the large white mushroom, which is tasty. The fatality rate is 35% in adults and 50% in children. Unfortunately, mushroom gatherers may mistake amatoxin-bearing *Amanita* species for edible mushrooms (see Table 66-6).

Some *Lepiota* mushrooms (see Figure 66-34), including *Lepiota castanea* and *Lepiota josserandii,* contain high concentrations of amatoxin. There have been two deaths attributed to *L. josserandii* in upstate New York.

Mushrooms that contain amatoxin may have a positive Meixner test. This test was first described by Wieland[132] in 1949 and popularized by Meixner.[77] A drop of liquid is expressed from a fresh mushroom onto print-free (ligand-free) newspaper and

BOX 66-16 Mushrooms Reported or Suspected of Containing Amatoxins

Amanita
bisporigera
decipiens Jacquetant
hygroscopica Coker
ocreata
ocreata Peck
phalloides (see Figures 66-6, 66-7, and 66-80)
suballiacea Murr
tenuifolia Murr
verna
virosa (see Figures 66-80 and 66-81)

Conocybe
filaris

Galerina
autumnalis Smith and Singer (Figures 66-82 and 66-83)
badipes Kühn
beinrothil
fasciculata Hongo
helvoliceps
marginata
marginata Kühner (Figure 66-84)
sulciceps Boedjin
unicolor Sing
venenata AH Smith

Lepiota
brunneoincarnata Chodat and Martin
brunneolilacea Bon and Boiffard
castanea
castanea Quelet
citrophylla (Berk and Br.) Sacc.
clypeolaria (Bull.:Fr.) Kummer (see Figure 66-34)
clypeolarioides Rea
felina (Pers.:Fr) Karsten
fulvella Rea
fuscovinacea Moeller and Lange
griseovirens Maire
heimii Locq.
helveola
helveola Bres.
helveoloides Bon ex Bon and Andary
josserandii
josserandii Bon and Boiffard
kuehneri Huijsm. Ex Hora
langei Locq.
lilacea Bres.
locanensis Espinosa
ochraceofulva Orton
pseudohelveola Kühner ex Hora
pseudolilacea Huijsm.
rufescens Lange
subincarnata Lange
xanthophylla Orton

TABLE 66-6 Look-Alikes of Mushrooms Containing Amatoxin

Toxic Species	Edible Species
Amanita phalloides (see Figures 66-6 and 66-7)	*Amanita fulva* (Figure 66-85)
Amanita verna	*Lepiota flavovirens*
Amanita virosa (see Figure 66-80)	*Agaricus bisporus* (see Figure 66-12)

FIGURE 66-79 *Amanita phalloides*—toxic.

FIGURE 66-80 *Amanita virosa. (By Jason Hollinger from* http://www.flickr.com*. Used with permission.)*

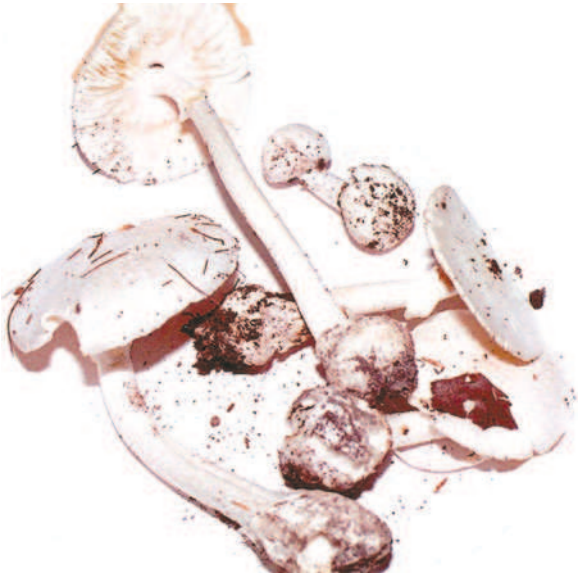

FIGURE 66-81 *Amanita virosa*—toxic.

FIGURE 66-82 *Galerina autumnalis. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

allowed to dry. A drop of concentrated (10 to 12 N) hydrochloric acid is added. A blue color develops within 1 to 2 minutes in the presence of amatoxins. Control tests on newspaper without mushroom juice and paper containing ligand should be conducted. False-positive results are common and can be elicited by excessive drying temperatures (>63°C [145.4°F]) or exposure to sunlight. The test can detect 2 mcg of α-amatoxin.[8] False-positive tests also occur from mushrooms containing psilocybin, terpenes, bufotenin, and other tryptamine compounds.[8] Almost 20% of gilled mushrooms that did not contain amatoxins tested positive in one study.[111] A positive test does not identify an amatoxin-containing mushroom, and further identification is necessary. TLC more accurately identifies the presence of amatoxin and can be done on mushroom liquid, human serum, or urine.[97] Radioimmunoassay (RIA), HPLC,[17] and a recently developed enzyme-linked immunosorbent assay (ELISA) test[89] can detect amatoxins in serum or urine.

Toxins

The mushroom *A. phalloides* contains two groups of toxins: amatoxins and phallotoxins. Each group contains several toxins. There are now eight identified amatoxins: α-amanitin, β-amanitin, γ-amanitin, ε-amanitin, amanin, amaninamide, amanullinic acid, and amanullin. Of these, α-amanitin is thought to be primarily responsible for human disease. α-Amanitin injected into animals produces hepatic toxicity characteristic of human ingestion of *A. phalloides*. In dogs, two phases of toxicity are seen. The first is cellular impairment with inhibition of protein and urea synthesis, followed by a second phase of hepatocellular changes, including condensation of nuclear chromatin and foaming of the cytoplasm.[73]

Phallotoxins include phalloidin, phalloin, phallisin, phallacidin, phallacin, phallisacin, and prophalloin. Phalloidin is the primary phallotoxin. Phallotoxins bind to F-actin, disrupting plasma membranes and causing massive efflux of calcium and potassium. Phallotoxins cause death in animals within 2 hours but are not

FIGURE 66-83 *Galerina autumnalis. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

FIGURE 66-84 *Galerina marginata. (By Tomasz Przechlewski from http://www.flickr.com. Used with permission.)*

believed to play a role in human toxicity.[33] Humans may not even absorb these toxins, although they may be responsible for local gastric irritation. *A. virosa* contains amatoxins and virotoxins. Virotoxins resemble phallotoxin biochemically and also bind F-actin and cause death in animals within a few hours. Six different virotoxins have been isolated, but none is thought to play a role in human *Amanita* hepatotoxicity.

Amatoxins are heat stable and not destroyed by cooking, freezing, or drying. *A. phalloides* mushrooms stored in a freezer for 7 to 8 months have resulted in death.[48]

Amatoxins are concentrated in the cap, gills, ring, and stalk. Very small amounts have been detected in the spores, although much less than in the other tissues.[76] α-Amanitin has been detected in most *Amanita* species in concentrations ranging from 50 to 6000 ppm.[124] Phallotoxins are more concentrated in the bulb and vulva. The concentration of toxin in a given mushroom depends on environmental factors and the soil.[20] After ingestion, amatoxins are absorbed from the gut and actively transported into the liver through transport systems shared by bile acids and xenobiotics. Amatoxins do not appear to cross the placenta.[125] α-Amanitin is rapidly cleared from plasma.[55] Amatoxins are not protein bound. They bind to ribonucleic acid (RNA) polymerase II and inhibit formation of messenger RNA (mRNA).[23] This in turn inhibits transcription, because the reservoir of mRNA is depleted.

FIGURE 66-85 *Amanita fulva. (By Jason Hollinger from http://www.flickr.com. Used with permission.)*

BOX 66-17 Symptoms of Amatoxin Ingestion

1. Delayed onset of nausea, vomiting, and diarrhea 4 to 16 hours after ingestion.
2. Resolution of gastrointestinal symptoms 12 to 24 hours later.
3. Onset of hepatic and occasionally renal failure 48 to 72 hours after ingestion.
4. Coagulopathy and pancreatitis may be seen with the hepatotoxicity.

Amatoxins are excreted into the bile, where they are reabsorbed and once again transported into the liver.[13] Interruption of this enterohepatic circulation could be a therapeutic tool. However, by the time clinical symptoms are present, enterohepatic circulation largely is complete, making its disruption ineffective.

Within the liver, α-amanitin may undergo some metabolism through the hepatic cytochrome system. Animal studies suggest that a more toxic metabolite may be produced through this metabolism, although this metabolite has never been isolated.[109,110] Nuclear fragmentation and condensation of chromosomal material have been observed within 15 hours of injection.[27] Glycogen is rapidly depleted, and fatty degeneration occurs within liver parenchymal cells. Mitochondria become swollen, and microvesicles appear throughout the cytoplasm.[27] Direct renal toxicity may occur.

Clinical Presentation

Symptoms of amatoxin poisoning are summarized in Box 66-17. People who ingest the mushroom *Amanita phalloides* feel well for 4 to 16 hours. Although nausea and vomiting are often reported with symptomatic mushroom exposures,[17] severe nausea, vomiting, abdominal cramps, and diarrhea follow this characteristic latent period with *A. phalloides* ingestion. Early complications include fluid and electrolyte imbalance (hypoglycemia, hypokalemia, and elevated BUN from dehydration). People in whom symptoms develop earlier (4 to 10 hours) are more likely to experience severe hepatotoxicity. Over the next 12 to 24 hours, the GI symptoms abate. The second latent period is followed by hepatic failure, which develops between 48 and 72 hours after ingestion in most patients. Hepatic failure may be of varying severity; it is frequently worse in children and depends minimally on the amount of mushroom ingested. Kidney failure can develop as a result of hepatic injury or possibly by direct renal toxicity to the kidneys.[37]

Children have greater toxicity and higher mortality, perhaps because of the relative quantity of mushrooms ingested or the varying metabolism in young children (differing levels of cytochrome enzymes). Previous experiments showed that ethanol concurrently ingested with *A. phalloides* decreased hepatotoxicity.[29] Therefore, decreased toxicity in adults could theoretically result from ingestion of ethanol with an *Amanita* mushroom dinner. More recently, however, ethanol failed to alter hepatotoxicity in an animal model poisoned with α-amanitin, which raises doubts about this explanation for increased toxicity in children.[108]

In addition to hepatic failure, endocrinopathies can develop, with hypocalcemia, decreased thyroid function, and elevated insulin levels in the presence of hypoglycemia.[58] Hypocalcemia may be caused in part by a loss of calcium through diarrhea or by a direct effect on osteoclasts. Renal failure may contribute to hypocalcemia. The thyroid abnormalities probably result from decreased hormone synthesis caused by overwhelming illness and blocked peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3). Thyroid-stimulating hormone (TSH) depression may result from decreased synthesis caused by inhibition of RNA polymerase II by amatoxin. Hypothyroidism has not been clinically significant. Hypoglycemia is probably the result of several processes, including impaired hepatic gluconeogenesis, increased insulin release from the initial hyperglycemia, and tissue destruction of the pancreas.[30] Bone marrow toxicity with decreased neutrophils, lymphocytes, and platelets has been noted. Disseminated intravascular coagulation and coagulopathies secondary to hepatic dysfunction are common.[101] Pancreatitis occurs in up to 50% of patients.[30] Hypophosphatemia is particularly common in children, for unknown reasons. Myopathy has been associated with *Amanita* toxicity.[40]

Hepatic biopsy shows diffuse and severe steatosis with periportal inflammation and necrosis. Renal biopsy shows acute tubular necrosis with hyaline casts.[26] Extremely high levels of hepatic enzymes are seen. Level of liver transaminases are not helpful in predicting the patient's prognosis. A precipitous drop in liver transaminases, often to normal levels, may occur just before death. In addition to the biochemical factors (e.g., high transaminases) and coagulopathy, hypoglycemia and thrombocytopenia are associated with increased likelihood of mortality in amatoxin poisonings. High urea levels and hyponatremia, as well as certain clinical characteristics, including low mean arterial pressure, encephalopathy, mucosal hemorrhage, and oliguria/anuria, have also been shown to be indicative of prognosis.

Treatment

Attempts to treat *A. phalloides* poisoning have ranged from scientific to purely empirical (Box 66-18). Noting that rabbits were able to eat the *A. phalloides* mushroom with impunity, clinicians fed ground raw rabbit to patients with *Amanita* poisoning, without success.[121] Hemodialysis was long recommended but now has been shown to be ineffective, because the toxin is rapidly cleared from the plasma. Amatoxin is taken up in liver cells within 5 hours after IV administration.[25] In a retrospective study of 205 cases of amatoxin ingestion,[30] hemodialysis worsened the prognosis, and charcoal hemoperfusion did not improve outcome. Plasmapheresis has been used, but this appears to be ineffective because the toxin is largely intracellular and has caused cellular damage by the time symptoms appear.[93]

Despite this scientific evidence, the literature continues to report the use of dialysis/hemofiltration,[17] hemoperfusion, and plasmapheresis.[57] Antigen-binding fragment (Fab) monoclonal antibodies against amatoxin were developed and tested in mice. Although hepatic toxicity was greatly lessened, renal toxicity was 50 times greater than in control animals, possibly because of dissociation of the amatoxin-Fab molecule in the kidneys.[24]

Previously, thioctic acid and benzylpenicillin were recommended as treatments. Both these treatments are now questioned. In a retrospective study, thioctic acid was more frequently associated in humans with fatal outcome.[30] A more recent review of patients treated with a variety of antidotes showed benzylpenicillin was more effective than simple supportive care, but less effective than silymarin or antioxidant therapy;[21] the authors suggested abandoning the use of penicillin. However, because silymarin has not been easily available in the United States, some poison control centers may still recommend penicillin. If benzylpenicillin is used, the recommended dose is high: 300,000 to 1 million units/kg/day IV. Side effects are significant and include allergy, hyponatremia,[22] and granulocytopenia.[85]

Silymarin is the active component of the milk thistle *Silybum marianum*. It is an antioxidant that accumulates in the liver.[64] Silymarin binds tightly to the plasma membrane, stabilizing it,[95,96] and hinders amatoxin from penetrating the cell wall.[56,126,127] It is a free radical scavenger,[31,72,130] inhibits lipid peroxidation,[10,14,31,83] and stimulates RNA polymerase I.[130] In both retrospective studies, silymarin has shown promising reductions in mortality.[21,28] The IV form has recently become available in the United States as

BOX 66-18 Treatment of Amatoxin Ingestion

Established

Activated charcoal (1 g/kg orally or via gastric tube) if the ingestion has occurred within 5 hours

Silymarin (silibinin), 20 to 40 mg/kg/day IV, 1.4 to 4.2 g/day orally

Experimental

Hyperbaric oxygen if available

Cimetidine, 4 to 10 g IV divided over 48 hours

If significant hepatic failure develops, transfer patient to transplant facility.

IV, Intravenously.

Legalon. The IV dose of silybin dihemisuccinate is 5 mg/kg over 1 hour, followed by 20 mg/kg/day for 6 days or until liver transaminases normalize. There have been no controlled trials assessing IV silibinin, but review of uncontrolled trials and case reports suggest a lower mortality rate compared with other treatments, including penicillin and penicillin with silibinin.[35,79] The oral preparation (70-mg capsules) is less well studied; dosage recommendation is 1.4 to 4.2 g/day. Silymarin is most effective when started within 24 hours of ingestion.[35] Some poison control centers recommend obtaining milk thistle seed extract from a local nutrition or health food store if Legalon is not available. Milk thistle seed extract typically consists of 65% to 80% silymarin. Silymarin contains both silybin A and B, with silibinin being a 1:1 combination of silybin A and B.

Gastric decontamination (ipecac, gastric lavage, whole-bowel irrigation) may be useful in patients who can tolerate the procedure and have presented early.[1,128] Unfortunately, by the time patients with *Amanita* ingestions present to the hospital, the ingestion is many hours old, and intense nausea and vomiting may limit ability to administer activated charcoal. Although amatoxin has enterohepatic circulation, no data support any therapy designed to disrupt the enterohepatic circulation unless the ingestion is noted within the first few hours.[21] Likewise, there are no data to support forced diuresis.

The French have used hyperbaric oxygen as a treatment for *Amanita* toxicity.[65] Hyperbaric oxygen has been shown to have efficacy in animal models.

Recent animal work has suggested the use of antioxidants. Cimetidine has been shown to be effective in animals[109] and has been reportedly used in humans[21] (4 to 10 g/day IV for adults; pediatric dose not described). Vitamin C and *N*-acetylcysteine (NAC) have been used with some success.[21,123] NAC was not found to prevent *Amanita*-induced hepatoxicity in a mouse model. However, its free radical and reactive oxygen species scavenging properties may be beneficial.[128] Other reported treatments include aucubin and kutkin, both plant derivatives.[21]

Intravenous normal saline or Ringer's lactate is needed to replace GI fluid losses. Electrolyte losses (particularly potassium) may be significant. BUN, creatinine, CBC with differential, platelet count, electrolytes, glucose, calcium, phosphorus, magnesium, urinalysis, PT, PTT, INR, fibrinogen, amylase, protein, and albumin should be initially measured and repeated at least daily to monitor liver and renal function. Hyperglycemia is common on the first day, but insulin is generally not required. Hypoglycemia occurs after 24 hours and may be severe, requiring IV concentrated glucose. Therefore, bedside determinations of glucose level should be performed at least every 6 hours.

The patient with liver failure from *Amanita* will appear similar to a patient with any other type of advanced liver disease, with jaundice and asterixis. Hepatic encephalopathy can develop with elevated ammonia level and increased intracranial pressure. Tests of liver damage, including ALT, AST, alkaline phosphatase, ammonia, PT, and PTT, should be repeated at least daily and two or three times a day if hepatic failure develops. Transaminases that rise rapidly or are in excess of 2000 IU or PTT greater than 50 seconds signal severe toxicity and the need for referral to a transplant center.

Once liver failure begins, it is treated the same as any other fulminant hepatitis. Hypoglycemia is common. Supplemental glucose should be readily available. Dietary protein should be limited to 0.5 g/kg/day. There is no need to supply supplemental thiamin or multivitamins. Oral lactulose, 30 to 45 mL every 6 to 8 hours, may reduce hepatic encephalopathy. In patients who do not tolerate lactulose, neomycin (1 g PO three times daily) can be tried. PT, PTT, and INR should be measured at least twice daily once hepatic failure begins, and vitamin K (100 mg IM), fresh-frozen plasma (2 to 6 units initially), or both should be used to correct abnormalities in coagulation.

If hepatic failure progresses, a liver transplant may be required. The timing of the transplant is highly controversial. Criteria used for other causes of fulminant hepatic failure are often applied to amatoxin poisoning. Factors associated with poor prognosis in acetaminophen-induced hepatic damage include metabolic acidosis, PT greater than 50 seconds, and elevated serum creatinine (>2.0 mg/dL).[88] The largest study suggests that a person with ALT or AST level greater than 2000 IU, grade II hepatic encephalopathy, or PT greater than 50 seconds is at serious risk for death and should be considered for an emergency liver transplant.[23] Persons who met these criteria have survived without transplant.[70,99] The MELD score appears to be more effective than the King's College or Clichy's criteria for assessing the need for hepatic transplant. There are many online calculators for the MELD score, which uses bilirubin, INR, and creatinine levels.[134] Increased reparative enzymes may correlate with hepatic recovery.[53] These enzymes, including α-fetoprotein, retinal binding protein, γ-glutamyl transferase, and des-γ-carboxyprothrombin, are thought to be released during the healing phase of liver disease. Because hepatic failure develops rapidly, victims with toxicity due to mushrooms who have significant hepatic dysfunction must be transferred early to a transplantation site. Patients undergoing liver transplantation for fulminant hepatic failure (not caused by *A. phalloides*) have a 60% to 80% survival rate.[21] There are no statistics specifically for patients with mushroom poisoning. In Europe, an extracorporeal liver assistance device, the molecular adsorbent recirculating system (MARS), has been developed and used successfully in four patients.[19,54,68,112] MARS has been suggested as a bridge to liver transplantation[112] and in combination with therapeutic plasma exchange.[135] Early use may offer more benefit with regard to toxin removal. A temporary liver transplant was performed on a child and sustained her while her own liver recovered.[100]

Some persons who survive acute hepatic failure caused by *Amanita* without needing hepatic transplant may have persistent elevation in liver transaminases. In one study of 14 patients with severe *Amanita*-induced hepatotoxicity, eight showed persisted elevations in AST and ALT without normalization over a 1-year follow-up period.[23] All had biopsy evidence of chronic active hepatitis with positive anti–smooth muscle antibody and cryoglobulins. It is not known whether these persons will have an increased risk for hepatoma or will develop more serious complications of chronic active hepatitis.

Amatoxin ingestion during pregnancy does not appear to have serious consequences. Several reports now suggest that amatoxin does not cross the placenta.[107,119] In one study, 22 pregnant women poisoned during their pregnancy had similar outcomes to a control group; however, only five ingested mushrooms in their first trimester.[119]

MISCELLANEOUS REPORTS OF TOXICITY FROM MUSHROOMS

Occasional toxicity has been reported with other mushrooms. Erythromelalgia has been reported after ingestion of *Clitocybe amoenolens*.[34,106,105] The mushroom contains the toxin clitidine, which resembles nicotinic acid. *Tricholoma equestre* or *Russula subnigricans* ingestion is associated with rhabdomyolysis, respiratory failure, and hepatic and renal dysfunction.[6,16,104] Deaths from acute myocarditis and renal failure have been reported.[6]

APPROACH TO THE PATIENT WITH MUSHROOM POISONING

Four types of individuals develop mushroom toxicity: foragers, children, those seeking hallucinogenic "highs," and rarely, victims of attempted homicide. Most patients seek medical care only after symptoms develop. If small children are observed chewing on lawn mushrooms, caregivers should be advised to call the nearest regional poison information center.

Persons with agitation, altered perceptions, or frank hallucinations temporally related to mushroom ingestion are probably intoxicated with isoxazole or hallucinogenic mushrooms. Whether the mushrooms are picked accidentally or ingested intentionally, the treatment and clinical course are identical.

Persons who develop muscarinic symptoms (salivation, urination, diaphoresis, GI upset, emesis) present such a classic picture that it is rarely confused with any other presentation. Some drugs (e.g., bethanechol) may cause similar symptoms when taken in

overdose. Patients with this variety of mushroom poisoning generally remain mentally clear and should be able to relate an appropriate history.

Patients with GI symptoms can be divided into those with early and those with delayed presentation. Those with early (within 2 hours of ingestion) GI symptoms generally have a benign course, except for persons with a mixed ingestion. Most guidebooks for mushroom hunters recommend eating only one variety of mushroom at a time, but more daring or foolish individuals mix multiple mushrooms and eat them frequently over the day. This makes diagnosis based on time of onset of symptoms difficult. Early onset of GI symptoms may mask more significant delayed symptoms. In these patients, identification of ingested mushrooms becomes essential to planning therapy.

Accurate botanical identification of the mushroom can be difficult. Only 800 of the 3000 species found in Europe can be identified without a microscope.[121] With the popularity of digital imaging, photos of suspicious mushrooms can be sent to poison control centers by e-mail and similarly can be forwarded to mycologists. This may save several hours of travel and may help initiate treatment, if needed, in a timelier manner. When multiple mushrooms are eaten together, the residual specimens brought from home may not be those causing toxicity. Cooking and refrigeration alter identifying features. Fresh mushroom specimens should be transported in a paper bag rather than in a plastic container to limit the effects of humidity. Finally, precise identification of even a good specimen can be difficult and should be done by an expert. Mycologists can be contacted through a poison control center, university, museum, or commercial mushroom grower.

In difficult cases, spores can be obtained from emesis or gastric-emptying procedures. Specimens should be refrigerated while awaiting analysis. More specific diagnosis can be made through TLC or RIA techniques. Botanical identification may not match the patient's symptoms. The patient should be treated according to time of onset of symptoms and condition when examined.

Patients with early-onset GI symptoms require supportive care with fluid and electrolyte replacement. For those with delayed GI symptoms or mixed ingestions containing amatoxin or gyromitrin mushrooms, treatment should begin as soon as possible. Toxic mushrooms can be differentiated by the season (spring: *Gyromitra*; autumn: *Amanita*).

Persons who have disulfiram-like reactions to alcohol should be questioned about prior mushroom ingestion. This situation is rarely correctly diagnosed because symptoms are thought to result from panic attacks, alcohol intoxication, or even an allergic reaction. Persons rarely relate their symptoms to the dinner of mushrooms eaten days earlier.

Any person with unexplained acute renal failure should be questioned about prior wild mushroom ingestion. Although *Cortinarius orellanus* is more common in Europe and Japan, it is found with increasing frequency in the United States. Because of the long delay before the onset of renal failure (1 to 2 weeks), the history of mushroom ingestion may be missed.

Mushroom poisoning cases remain relatively rare in the United States (they are still more common in parts of Europe and Asia), and until recently, up-to-date information was not accessible to the general public except through poison control centers. With the plethora of worldwide Internet connections, there are now mushroom experts readily available to answer questions about possible exposures within minutes to hours of contact. The active forager should use well-written field guides in addition to Internet sources and should cross-reference several sources before consuming any unknown mushrooms.

RECOMMENDED FIELD GUIDES

Arora D: *Mushrooms demystified,* Berkeley, Calif, 1986, Ten Speed Press.

Lincoff G: *The Audubon Society field guide to North American mushrooms,* New York, 1992, Knopf.

Lincoff G: *Simon & Schuster's guide to mushrooms,* New York, 1981, Simon & Schuster (European mushrooms).

Phillips R: *Mushrooms of North America,* Boston, 1991, Little, Brown.

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CHAPTER 67

Seasonal and Acute Allergic Reactions

JOHN TANNER AND THOMAS EGLIN

Allergic diseases are universal. Approximately 40% of people worldwide have one or more allergic diseases, and prevalence is increasing.[9,13,90] Allergic responses can range from annoying (e.g., allergic rhinitis) to life threatening (e.g., anaphylaxis).

Atopy is a predisposition to develop allergen-specific IgE hypersensitivity reactions (e.g., allergic rhinitis, bronchial asthma, atopic dermatitis, food allergy). It is often hereditary. Allergic rhinitis is the most common atopic disease and may be classified as seasonal (i.e., hay fever) or perennial. Aeroallergens (e.g., pollens) released from wind-pollinated plants (e.g., trees, grasses, weeds) cause seasonal allergic rhinitis. Perennial symptoms most often result from exposure to domestic allergens (e.g., dust mites, domestic pets, cockroaches, mold). In temperate climates, patients with perennial allergic rhinitis may also have worsening symptoms during warmer months because of seasonal allergens.

Allergic reactions may present with skin and soft tissue manifestations of urticaria and angioedema. Urticaria is common, with a lifetime incidence of 20%. These superficial, erythematous, slightly raised, and pruritic lesions may occur anywhere on the skin. Typically acute, they may also be chronic. Angioedema results from swelling of dermis and subcutaneous tissues. If angioedema occurs in the upper airway, it can be life threatening. Angioedema and urticaria can be IgE-mediated hypersensitivity reactions or caused by other mechanisms (e.g., hereditary angioedema).

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Anaphylaxis is the most severe form of allergic reaction and can be fatal if not treated promptly. Foods and medications are the most common causes of anaphylaxis. Anaphylaxis affects up to 2% of the worldwide population. Its incidence is increasing.[70,128] Anaphylactic reactions are likely underreported, particularly in cases of unexplained death. In one study, elevated tryptase levels (often found during acute anaphylaxis) were found in 13% of 68 cases of sudden unexpected death.[113]

ALLERGIC RHINITIS

Allergic rhinitis is an IgE-mediated inflammation of nasal mucosa characterized by nasal congestion, pruritus, rhinorrhea, and sneezing. It is the most common atopic disease and affects 10% to 30% of the global population.[90] For unclear reasons, prevalence of allergic rhinitis is increasing worldwide. Regional prevalence varies widely, from 5% in Tibet to greater than 40% in Australia.[29,30] Higher rates tend to occur in Western Europe, North America, and Australia. Lower rates are seen in Eastern Europe and south and central Asia.[21] Allergic rhinitis can lead to poor sleep, decreased school performance, decreased work productivity, and lower quality of life.[10,11,58,65,79,80,115]

EPIDEMIOLOGY AND RISK FACTORS

Allergic rhinitis typically first manifests in childhood or adolescence, then peaks in the second or third decade. Risk factors for allergic rhinitis are female gender, exposure to particulate air pollution, and history of maternal smoking during childhood.[21] The most important risk factor for development of allergic rhinitis is a family history of atopy, especially in cases with early onset. Risk is 30% greater if one parent or sibling is atopic and 50% or greater if both parents are affected.[85] Monozygous twins demonstrate a 45% to 60% concordance for allergic rhinitis.[32,34] Incomplete concordance for atopy in identical twins emphasizes the importance of environmental factors.[4] As with other atopic conditions (e.g., asthma, atopic dermatitis), allergic rhinitis tends to cluster in families. Multiple genes have been associated with allergic rhinitis.[24,35,100]

PATHOPHYSIOLOGY

Pathogenesis of allergic rhinitis consists of an acute allergic reaction and late inflammatory events. Acute clinical manifestations of allergic rhinitis are caused by a type I immediate hypersensitivity reaction. Late inflammatory events are mediated by cellular responses (i.e., by eosinophils, basophils, and T lymphocytes). Atopy is defined as the genetic predisposition to develop allergen-specific immunoglobulin E (IgE) antibodies. The underlying basis of immediate hypersensitivity is production of allergen-specific IgE (sensitization) antibodies. The sensitization process requires a cooperative effort between CD4 T lymphocytes and B lymphocytes (Figure 67-1). Sensitization begins with presentation by antigen-presenting cells (e.g., macrophages, dendritic cells) of an allergen to CD4 T lymphocytes in the context of a major histocompatibility complex. In response, CD4 T lymphocytes release cytokines, causing differentiation of B lymphocytes into immunoglobulin-secreting plasma cells; for example, release of the cytokine interleukin-4 (IL-4) or IL-13 from T lymphocytes promotes IgE switching.[27] Differentiation leads to isotype switching (i.e., production of specific antibody types) within the plasma cells. Once allergen-specific IgE antibodies are produced, allergens bind to mast cell surface IgE molecules in subsequent exposure, resulting in cross-linking of IgE molecules. Cross-linking causes mast cell or basophil degranulation that releases preformed and newly synthesized mediators. Histamine is the classic preformed mediator. Newly synthesized mediators include members of the arachidonic acid pathway (e.g., leukotrienes, prostaglandins, platelet-activating factor), neuropeptides (e.g., substance P), and cytokines (e.g., IL-4, IL-5).

Release of chemical mediators has various pathologic and clinical consequences. Stimulation of histamine receptors on sensory nerve endings causes sneezing and itching. Increased vascular permeability (produced by all the mediators) causes rhinorrhea. Leukotrienes and prostaglandins play major roles in nasal congestion.[132] Understanding of allergic rhinitis pathophysiology has been greatly enhanced by nasal challenge studies.[56] An allergic reaction consists of an early phase, characterized by mast cell or basophil degranulation, and a late phase, which occurs 4 to 6 hours after the early phase (see Figure 67-1).

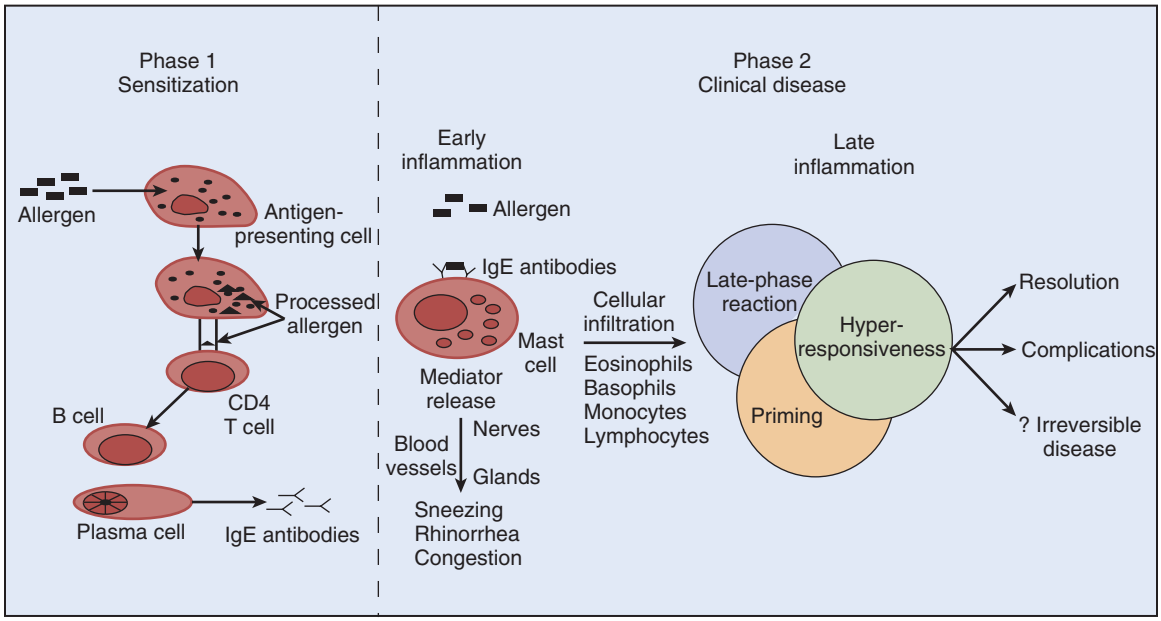

FIGURE 67-1 Natural history of allergic rhinitis (a simplified schematic). Individual becomes sensitized to an allergen in phase 1. Clinical disease develops in phase 2. Most individuals have an early response on reexposure to the allergen. Mast cell activation with mediator release dominates early response. After early response, individuals typically have cellular infiltration of nasal mucosa. This causes late inflammatory events, including spontaneous recurrence of mediator release (late-phase reaction), hyperresponsiveness to irritants, and increased allergen responsiveness (priming). *Circles* indicate heterogeneity of these late inflammatory events. Inflammation can resolve spontaneously, cause complications, or lead to an irreversible form of chronic rhinitis. *(From Naclerio R: Allergic rhinitis,* N Engl J Med *325:860, 1991.)*

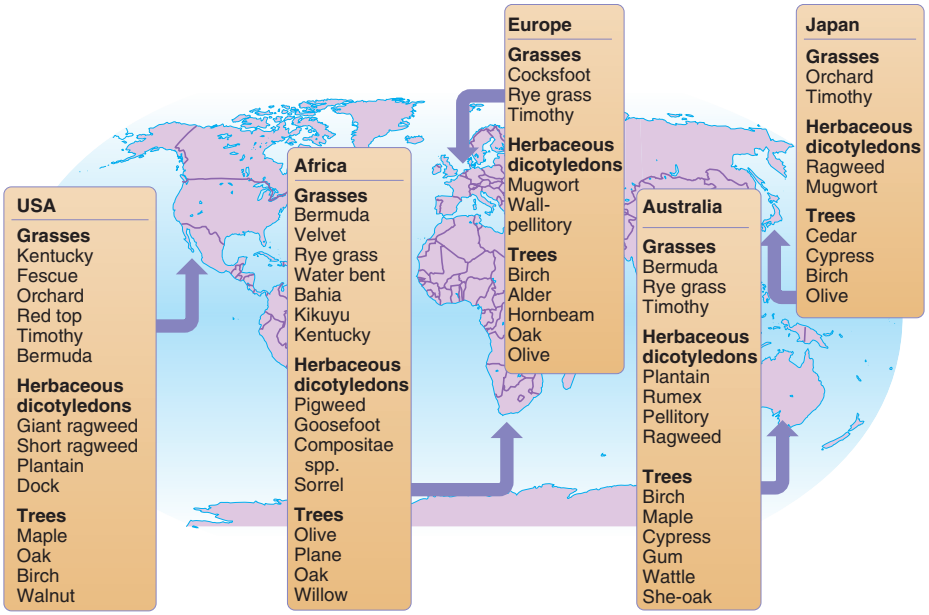

FIGURE 67-2 Selected worldwide distribution of clinically important pollen allergens. *(From Stewart GA, Peden DB, Thompson PJ, et al: Allergens and air pollutants. In Holgate ST, Church M, Broide D, et al, editors:* Allergy, *4th ed, Edinburgh, 2012, Elsevier.)*

The hallmark of the late-phase reaction is an influx of inflammatory cells (e.g., eosinophils, basophils, T lymphocytes).[3] Basophils cause further histamine release. T lymphocytes release additional cytokines that enhance IgE production (via IL-4) and eosinophil activation (via IL-5). This cellular response leads to a recrudescence of symptoms many hours after initial allergen exposure. Leukotrienes, prostaglandins, and cytokines released in an early-phase reaction play an important role in recruiting late-phase cellular components to the inflammatory site. Although inhaled corticosteroids block both early- and late-phase reactions, systemic corticosteroids block only the late-phase reaction.

ALLERGENS

Airborne allergens are the primary etiologic agents of allergic rhinitis. Although many potential allergenic proteins exist, relatively few are clinically important and even fewer have been isolated and characterized. Allergens are low-molecular-weight proteins or glycoproteins capable of eliciting a type I immediate hypersensitivity reaction (production of IgE antibodies). Allergens can be divided into those that exist in outdoor versus indoor environments. Pollens of trees, grasses, weeds, and certain fungi (e.g., *Alternaria* and *Cladosporium* spp.) usually provoke symptoms outdoors. Pollen-sensitive individuals typically experience seasonal rhinitis at predictable seasonal intervals when specific allergens are released. Fungi are ubiquitous and have less distinct seasons. Outdoor and indoor fungi thrive in moist and humid environments. In temperate climates, fungi counts rise in spring and peak in mid- to late summer. Indoor allergens include fungi, furred animals, cockroaches, and dust mites.

Pollens

Pollination in higher-order plants consists of transfer of the male gametophyte to the female gametophyte. In this process, pollen grains serve as vectors for male gametophytes. Of the different types of pollen-producing plants, flowering plants (e.g., trees, grasses, weeds) are the most important allergens. Flowering plants can be divided into those that rely on animal vectors (e.g., insects, or entomophilous) or the wind (i.e., anemophilous) for pollination. Typically, only anemophilous plants (including trees, grasses, and weeds) cause allergic symptoms.[124] Pollens of entomophilous plants do not achieve high airborne concentrations. In temperate climates, anemophilous pollination occurs at predictable seasonal intervals. Awareness of relevant local botany and pollination seasons allows prophylactic management of symptoms. Figures 67-2 and 67-3 list important pollen allergens and seasons.

In most temperate climates, tree pollination in spring marks the onset of allergy season. Grass pollen is a major cause of allergic rhinitis in sensitive individuals. In frost-free areas of the world, grass pollen may be present year-round. In temperate climates, grass pollination peaks in early summer. Unlike weed and tree pollen allergens, grass pollen allergens show extensive cross-reactivity among different species. Allergic individuals are typically sensitive to many species. In temperate climates, weeds typically generate pollen from end of summer through midfall.

Fungi

Numerous allergenic fungi are responsible for both seasonal and perennial symptoms. The three most important classes of allergic fungi are Zygomycetes (e.g., *Rhizopus, Mucor*), Basidiomycetes (e.g., rust, smut, *Ganoderma*), and Ascomycetes (e.g., *Cladosporium, Penicillium, Aspergillus, Alternaria, Epicoccum*). *Cladosporium* and *Alternaria* are the most abundant outdoor fungi and cause significant symptoms in sensitive individuals. Fungi grow best in warm, humid environments. Peak fungi season is typically midsummer to fall, with a marked reduction after first frost. Fungi levels may rise in spring, when decaying vegetation is uncovered by snow melt. Common outdoor sources of fungal growth are leaves, moist debris, and soil. Certain outdoor activities (e.g., raking, farming, mowing) significantly increase exposure.

Dust Mites

Dust mites are microscopic arachnids closely related to ticks and spiders. They feed on human epidermal scales and, like fungi, prefer a warm, humid environment. Dust mites are the most common indoor allergens and can cause significant perennial symptoms in sensitive individuals. Although exposure level and degree of rhinitis symptoms are poorly correlated, a dust level of 10 μg/g is considered a risk factor for acute asthma symptoms.[94] Common indoor sources of dust mite exposure include mattresses, pillows, blankets, upholstery, and stuffed toys. Dust mites can proliferate in sleeping bags stored in humid environments (e.g., damp basements).

Animals

Animals, especially cats, can be highly allergenic and in sensitized individuals can cause significant symptoms. Birds, rabbits,

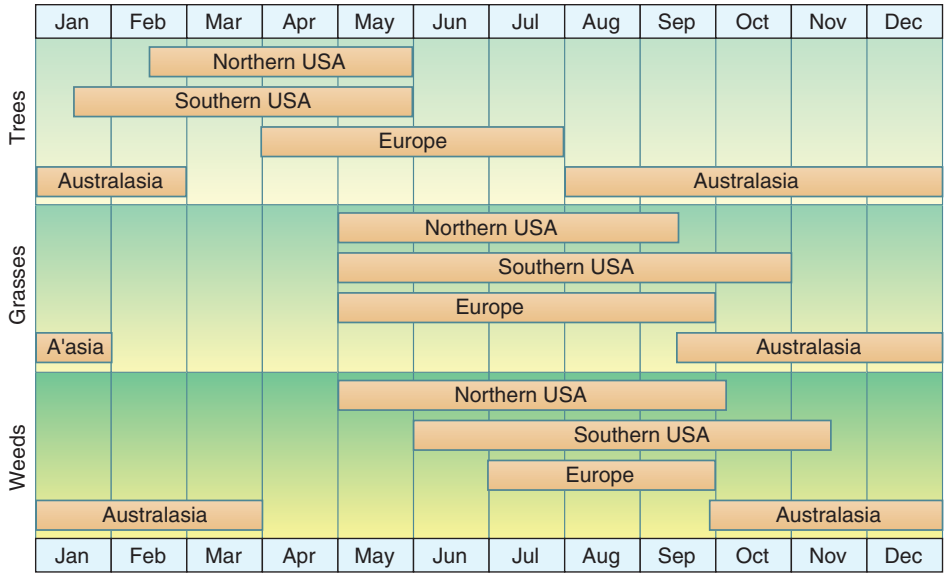

FIGURE 67-3 Pollen seasons in the United States, Europe, and Australasia. *(From Stewart GA, Peden DB, Thompson PJ, et al: Allergens and air pollutants. In Holgate ST, Church M, Broide D, editors:* Allergy, *4th ed, Edinburgh, 2012, Elsevier. Modified from Sicherer SH, Eggleston PA: Environmental allergens. In Lieberman P, editor:* Allergens in allergic diseases: Diagnosis and treatment, *Totowa, NJ, 2000, Humana Press.)*

hamsters, guinea pigs, rats, and mice are other potentially allergenic pets. Feline and canine allergens include products of their salivary and sebaceous glands. Cat allergens can remain for months after cat removal. Cockroach allergens are frequently encountered in heavily infested, crowded, or multifamily dwellings.

Outdoors, inhalation of insect related allergens (e.g., moths, locusts, beetles, flies) may cause allergic symptoms.

FUNCTIONS OF THE NOSE

Function of the nose (i.e., to warm, humidify, and filter air) depends on turbulent airflow enhanced by three bilaterally symmetric turbinates (superior, middle, and inferior). The neurovascular system modulates nasal mucosa function. Nasal blood supply is via the ophthalmic (branch of the internal carotid) and internal maxillary (branch of the external carotid) arteries. Neural innervations include sensory (via the trigeminal nerve, responsible for the sneezing reflex) and autonomic (parasympathetic and sympathetic) nervous systems. Nasal congestion is related to blood pooling in the cavernous sinusoids (located within the turbinates) and mucosal edema. Sinusoid pooling is controlled by the autonomic nervous system. Parasympathetic stimulation causes vasodilation by opening capillaries and closing postcapillary venule sphincters, causing the sinusoid reservoirs to fill. Conversely, sympathetic stimulation contracts capillaries and relaxes postcapillary venule sphincters, allowing reservoirs to empty.

Asymmetric cyclic swelling and shrinking of turbinates between the two sides of the nose is common. This nasal cycle, occurring over 1 to 4 hours, results from alternating sympathetic discharge. It is responsible for the alternating unilateral nasal blockage experienced by allergic rhinitis sufferers.[51]

Olfaction is another major nasal function. Olfactory structures are on the roof of the nasal cavity above the middle turbinate. Significant turbinate edema can lead to poor ventilation and the associated hyposmia common to allergic rhinitis patients.

CLINICAL EVALUATION

Allergic rhinitis was described in 1929: "The three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction and mucous discharge."[50] Allergic rhinitis symptoms range from intermittent and mild to incapacitating. The hallmark of allergic rhinitis is temporal correlation of symptoms with allergen exposure.[84] Common symptoms of allergic rhinitis (sneezing, nasal congestion, rhinorrhea, and pruritus of nose and eyes) are nonspecific. Itching and sneezing are the most distinctive complaints associated with allergic rhinitis.[85] Nasal congestion is more prominent in perennial than in seasonal rhinitis. In some patients, ocular symptoms predominate over nasal symptoms. Allergic rhinitis sufferers often experience priming effect (i.e., increased sensitivity to allergens after repeated exposure) and hyperresponsiveness to nonallergenic environmental stimuli (e.g., tobacco smoke, strong odors, pollutants, weather changes).[20]

Species-specific pollen production is predictable, so temporal correlation with symptoms is often helpful. Typically, tree pollen exposure causes symptoms in spring, grass and outdoor molds in summer, and weeds and outdoor molds in fall.[21] Ragweed sufferers characteristically start experiencing symptoms in late summer. In some regions, molds and pollens are perennial. In others, dust mites follow seasonal trends.[23,92] The terms *seasonal* and *perennial* may be inadequate to guide treatment decisions. The terms *intermittent* and *persistent* are more appropriate and better suited to guide diagnosis and treatment.[15]

In individuals with perennial rhinitis, it can be difficult to determine the responsible allergen(s). Upper respiratory tract diseases may mimic allergic rhinitis. Complications of allergic rhinitis include sinusitis, otitis media with effusion, and asthma flares.

Just as allergic symptoms may be vague, many physical signs are not exclusive to allergic rhinitis. Classically, nasal mucosa is pale blue and edematous, although this color is noted in only 60% of patients. Many individuals have erythematous mucosa.[31] In children, the "allergic salute" (upward nasal rubbing) and "allergic shiners" (dark, puffy circles under the eyes) may be present. Examine for septal deviation, polyps, and foreign bodies. Nasal discharge is usually clear to white. Discolored secretions are suggestive of chronic rhinosinusitis.[21] If congestion is profound, use of a topical decongestant (e.g., oxymetazoline) will improve visualization of the inside of the nose.

Allergic rhinitis is underdiagnosed and its severity underestimated.[81] Travel may unmask previously undiagnosed allergic rhinitis. Individuals may have acute worsening of symptoms during a wilderness sojourn (e.g., when traveling from winter to spring/summer) or can have marked improvement in symptoms (e.g., travel to high altitude, where offending allergens are decreased).

BOX 67-1 Differential Diagnosis of Rhinitis

Acute Rhinitis
Upper respiratory tract infection
Foreign body
Trauma

Chronic Rhinitis
Allergic
Nonallergic
- NARES (nonallergic rhinitis with eosinophilia syndrome)
- Chronic sinusitis
- Systemic diseases
  - Vasculitis
    - Wegener's granulomatosis
    - Churg-Strauss syndrome
  - Cystic fibrosis
  - Sarcoidosis
  - Hypothyroidism

Rhinitis medicamentosa
Medications
- Calcium channel clockers
- Angiotensin-converting enzyme (ACE) inhibitors
- β-Adrenergic blockers

Mechanical-anatomic obstruction
- Nasal polyps
- Foreign body
- Tumor
- Septal deviation
- Adenoid hypertrophy

Gustatory rhinitis
Atrophic rhinitis
Rhinitis of pregnancy
Cerebrospinal fluid leak
Vasomotor (idiopathic) rhinitis

Differential Diagnosis

To diagnose allergic rhinitis, the differential diagnosis of rhinitis must be considered (Box 67-1). Rhinitis can be classified as acute or chronic. The most common cause of acute rhinitis is a viral infection. Allergic rhinitis may be confused with viral rhinitis. Unlike the symptoms of allergic rhinitis, viral rhinitis symptoms typically persist less than 2 weeks, unless subsequent sinusitis develops. Nasal foreign body or trauma also can cause acute rhinitis. Unilateral symptoms suggest foreign body obstruction.

The differential diagnosis of chronic nonallergic rhinitis is broad. Nonallergic rhinitis with eosinophilia syndrome (NARES) is characterized by (1) symptoms similar to allergic rhinitis, (2) eosinophilia on nasal smear, and (3) a negative skin test.[57] Chronic rhinosinusitis, a potential complication of allergic rhinitis, typically causes nasal congestion, sinus pressure, postnasal drip, cough, and diminished senses of smell and taste. Symptoms of chronic rhinosinusitis are subtle and may require radiologic evaluation (e.g., computed tomography). Systemic diseases (e.g., vasculitis, cystic fibrosis) may cause chronic rhinitis. Rhinitis medicamentosa, usually secondary to overuse of topical α-adrenergic vasoconstrictors (e.g., oxymetazoline), is associated with profound nasal congestion due to rebound effects on withdrawal of the decongestant after prolonged (i.e., 5 to 7 days) topical use. Medications implicated in chronic rhinitis include nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blockers.

Examine for mechanical and anatomic abnormalities. Nasal polyps have a pearly, smooth, peeled-grape–like appearance and are often bilateral. Nasal polyps may be associated with chronic sinusitis, asthma, and aspirin sensitivity.[114] Unilateral symptoms should always heighten suspicion for a foreign body or tumor. Some degree of septal deviation is common, and unless symptoms are severe, treatment is unnecessary. In children, adenoid hypertrophy must be considered.

Gustatory rhinitis symptoms are caused by a cholinergic response to stimuli (e.g., eating, running, exposure to cold air). Atrophic rhinitis is a rare condition that manifests in older adults as a thick, bilateral, and odorous discharge with little nasal congestion.[43] Rhinitis of pregnancy should be considered if there is no previous history of rhinitis. In patients with clear rhinorrhea and history of central nervous system trauma, cerebrospinal fluid leak must be considered.

Vasomotor (idiopathic) rhinitis is a common cause of nonallergic rhinitis in adults. Although the term implies an etiology of vascular or neurologic dysfunction, the mechanism of vasomotor rhinitis is poorly understood. Symptoms of vasomotor rhinitis are frequently obstructive rather than secretory. Symptoms of nasal congestion and sinus pressure are more common than sneezing and rhinorrhea.[73] Individuals with vasomotor rhinitis typically experience perennial symptoms triggered by changes in weather, spicy foods, and irritants (e.g., smoke, strong scents, chemicals). It is a diagnosis of exclusion.

Allergy Testing

Allergy testing can guide allergen avoidance as well as provide a target for immunotherapy. Allergy testing can be performed by skin or radioallergosorbent testing (RAST). Skin testing is the more common and sensitive assay.[60] For skin testing, minute quantities of specific allergens are injected into the dermis. A positive response depends on allergen-specific release of histamine. In RAST, evidence of allergen-specific IgE is detected from patients' serum. Given its lesser sensitivity, greater cost, and longer turnaround time for results, RAST is typically reserved for patients whose skin tests might be difficult to interpret (e.g., patients with severe eczema or dermatographism).

TREATMENT

Treatment of allergic rhinitis begins with attempting to avoid offending allergens. Avoidance is often difficult. Allergens can be ubiquitous outdoors, as well as indoors if patients are unable to part from a beloved pet. Pharmacologic intervention is often necessary. Treatment should be individualized on the basis of symptoms, seasonal patterns, and presence of possible comorbid conditions. The best therapeutic agent effectively addresses both early- and late-phase reactions.[125] Medications available for allergic rhinitis treatment include histamine-1 (H_1-) antihistamines, decongestants, intranasal or oral glucocorticoids, anticholinergics, cromolyn sodium, and leukotriene receptor antagonists (LTRAs). Immunotherapy may be considered in moderately to highly sensitive individuals.

Avoidance

Although it may be difficult to avoid pollen, certain commonsense measures can decrease exposure. Outdoor activities should be limited or avoided on days when pollen counts are high. Pollen counts typically peak in late morning to midafternoon.[134] Limiting high-risk activities (e.g., leaf raking, lawn mowing, farming) can reduce exposure to outdoor fungi. Important indoor fungal control measures include dehumidification, proper ventilation, fungicide use in contaminated areas, and removal of substrate for fungal growth. Reduce dust mite exposure by covering mattresses and pillows with allergen-proof encasings, frequent washing of bedding in hot water, and removal (or treatment) of carpeting. A limited approach (e.g., using allergen-proof encasings without additional measures) may not be effective.[126] For symptoms related to animal allergens, remove the animal from the indoor environment. This option is often not exercised. If the pet stays in the home, bath it at regular intervals and keep it out of sleeping areas. High-efficiency particulate air (HEPA) filters remove animal allergens from the environment[25] but do not improve symptoms.[135]

Antihistamines and Decongestants

H_1-antihistamines are first-line therapy for treatment of allergic rhinitis.[99] They are most effective against seasonal rhinitis, in which sneezing, itching, rhinorrhea, and watery eyes are the most prominent symptoms. Only 33% to 50% of seasonal allergic rhinitis sufferers obtain complete relief with H_1-antihistamine therapy alone.[12] H_1-antihistamines have little effect on nasal congestion because histamine plays only a minor role in the pathophysiology

TABLE 67-1 Newer-Generation Antihistamines

Chemical Name	Trade Name	Dosage		
		Adult	Children (<12 Years)	Minimum Age
Cetirizine	Zyrtec	10 mg daily	2.5-10 mg daily	6 mo
Levocetirizine	Xyzal	5 mg daily	1.25-2.5 mg daily	6 mo
Loratadine	Claritin	10 mg daily	2.5-10 mg daily	2 yr
Desloratadine	Clarinex	5 mg daily	1.0-2.5 mg daily	6 mo
Fexofenadine	Allegra	60 mg bid to 180 mg daily	30 mg bid	2 yr
Azelastine	Astepro	2 sprays per nostril bid	1 spray per nostril bid	6 yr
Olopatadine	Patanase	2 sprays per nostril bid	1 spray per nostril bid	6 yr

bid, Twice daily.

of congestion. H_1-antihistamines are usually inadequate for treatment of perennial rhinitis, in which nasal congestion is often a predominant symptom.

H_1-antihistamines occupy H_1 receptors on cells and block histamine binding. Older- and newer-generation H_1-antihistamines are equally effective, but newer-generation (second- and third-generation) H_1-antihistamines are much less sedating and have fewer anticholinergic side effects. First-generation H_1-antihistamines (e.g., chlorpheniramine, diphenhydramine, brompheniramine, clemastine, hydroxyzine) are generally available over the counter (OTC), and although safe, can effect cognition[78] and impair driving performance.[88]

Newer-generation H_1-antihistamines are safe, effective, and well tolerated and do not have anticholinergic or anti–α-adrenergic activity[59] (Table 67-1). Most are given once daily. All are approved for use in children, and some (e.g., cetirizine, levocetirizine, desloratadine) are approved for patients as young as 6 months. Azelastine and olopatadine are safe and effective in relieving most allergic rhinitis symptoms and are the only H_1 receptor antagonists available as nasal spray formulations.[7,64] Although H_1-antihistamines have a relatively rapid onset of action, they are most effective if taken before exposure (e.g., before pollen season begins) or if used on a regular basis.

Given H_1-antihistamines' limited effect on nasal congestion, using a decongestant may be helpful. Decongestants act by stimulating α-adrenergic receptors and reduce blood flow to the sinusoids. Most oral formulations are short acting (4 to 6 hours) and available OTC. Pseudoephedrine is often used but of questionable efficacy.[53] Insomnia and irritability are the most common side effects. Individuals with hypertension, glaucoma, or cardiac arrhythmias should use oral decongestants only under a physician's supervision. Topical decongestants (e.g., oxymetazoline) have a prompt onset of action (within minutes) and provide rapid relief of symptoms. To decrease risk of rhinitis medicamentosa, topical decongestant use should be limited to no more than 3 to 5 days.

Intranasal Corticosteroids

Intranasal corticosteroids are the gold standard of treatment for allergic rhinitis. Intranasal corticosteroids are more effective than H_1-antihistamines and LTRAs,[131,133] control all symptoms of allergic rhinitis, and may improve allergic ocular symptoms.[8] Intranasal corticosteroids can be used as first-line therapy for patients with perennial rhinitis. Corticosteroids control protein synthesis by influencing gene transcription within the cell.[63] Corticosteroids have an inhibitory effect on late-phase reactions. Unlike their oral counterparts, intranasal corticosteroids also inhibit the early-phase reaction.[1]

Several preparations of intranasal corticosteroids are available (Table 67-2). Fluticasone and mometasone are potent and have negligible systemic effects.[110] Maximal benefit of nasal corticosteroids may not be realized until 1 to 3 weeks after initiation of therapy. For patients with seasonal rhinitis, start nasal corticosteroid therapy shortly before onset of pollen season. There is no role for regular use of oral corticosteroids in the treatment of allergic rhinitis. When symptoms are severe (e.g., during peak pollen season), a short course (3 to 5 days, without a rapid taper) of oral corticosteroids may be appropriate[21] and may facilitate delivery of nasal corticosteroids to nasal mucosa.

The most common side effects of intranasal corticosteroids are local irritation (10%) and bleeding (4% to 8%).[21] Side effects are higher during winter months because of drier conditions. Although rare, nasal septal perforation has been reported with use of intranasal corticosteroids.[112] If septal ulceration and crust formation are noted, treatment with saline spray should be instituted and corticosteroid therapy should be discontinued until the nasal mucosa has healed. Long-term studies have shown no evidence of mucosal atrophy associated with the use of intranasal corticosteroids.[18] Nasal corticosteroids are rapidly metabolized. Although hypothalamic-pituitary-adrenal axis suppression is rare, it is prudent to monitor growth of pediatric patients receiving intranasal corticosteroids.

Leukotriene Receptor Antagonists

Previously indicated only for asthma, LTRAs are now approved for use in allergic rhinitis. Cysteinyl leukotrienes are products of the arachidonic acid pathway and important mediators of allergic inflammatory effects. Leukotrienes cause vasodilation and nasal congestion. As antagonists, LTRAs can significantly reduce nasal congestion.[62] In addition, leukotrienes encourage mucus

TABLE 67-2 Intranasal Corticosteroids*

Generic Name	Trade Name	Recommended Dose (Each Nostril)	Amount Per Spray (mcg)	Minimum Age (Years)
Beclomethasone	Beconase AQ	1-2 sprays bid	42	6
Budesonide	Rhinocort Aqua	1-4 sprays daily	32	6
Flunisolide	Nasarel	2 sprays bid	29	6
Fluticasone propionate	Flonase	1-2 sprays daily	50	4
Fluticasone furoate	Veramyst	1-2 sprays daily	27.5	2
Mometasone	Nasonex	1-2 sprays daily	50	2
Triamcinolone	Nasacort AQ	1-2 sprays daily	55	2
Ciclesonide	Omnaris	1-2 sprays daily	50	6

bid, Twice daily.
*All preparations are aqueous based.

production, leading to rhinorrhea. Nasal lavage leukotriene levels are increased in patients with seasonal and perennial allergic rhinitis.[122] LTRAs block binding of cysteinyl leukotrienes to respiratory tract CYS-LT1 receptors.

Montelukast (LTRA) and loratadine (antihistamine) are equally effective in alleviating nasal symptoms.[91] Montelukast was significantly less effective than the nasal corticosteroid fluticasone propionate in relieving nasal symptoms.[74] The effectiveness of combining LTRAs and H_1-antihistamines is unclear. One study found that the combination of montelukast with loratadine was more effective than either agent alone. Other studies have refuted this finding.[82,86] For treatment of allergic rhinitis, LTRAs perform as well as H_1-antihistamines, but not as well as nasal corticosteroids.

Oral LTRAs include montelukast, pranlukast, zafirlukast, and zileuton. Only montelukast is approved for use in both allergic rhinitis and asthma. The recommended dosage of montelukast for adults and adolescents (≥15 years) is 10 mg at bedtime. Pediatric dosing is age dependent: 4 mg (6 months to 5 years) and 5 mg (6 to 14 years). Both are given at bedtime. LTRAs appear to be well tolerated. Liver toxicity has been reported with zafirlukast[103] and zileuton but not with montelukast.

Other Medications

Cromolyn sodium and nasal anticholinergic drugs are other treatments for allergic rhinitis. Cromolyn is believed to inhibit mast cell degranulation. It is much less potent than nasal corticosteroids but is very safe. As with H_1-antihistamines, cromolyn sodium is effective for relief of sneezing, itching, and rhinorrhea, but less so for nasal congestion.[21] For optimal effect, it requires regular use and frequent dosing (three to four times daily). Cromolyn may be used as a prophylactic treatment before exposure to a known allergen (e.g., visiting a person with a cat). In a similar circumstance, if rhinorrhea is the predominant allergic symptom, use of a nasal anticholinergic (e.g., ipratropium) may be beneficial and can reduce postnasal drip. The recommended dosage of ipratropium is 1 to 2 sprays in each nostril two to four times a day. Nasal dryness is the primary side effect of intranasal ipratropium.

Immunotherapy

Allergen immunotherapy seeks to achieve tolerance in a sensitized person by exposing the person to gradually increasing amounts of allergen. Traditionally administered subcutaneously, many allergen extract preparations can now be administered sublingually. Although the precise mechanism is unclear, immunotherapy leads to induction of allergen-specific IgG "blocking antibodies," decreases in allergen-specific IgE, modulation of mast cell or basophil function, and increases in suppressor T cells (CD8).[39]

In patients with allergic rhinitis, efficacy of immunotherapy has been well established.[33,76] Most individuals obtain a degree of relief and thus have better symptom control with less medication. Immunotherapy should be considered in patients who respond poorly to medical therapy, who experience significant medication side effects, or in whom allergen avoidance is not possible. Immunotherapy involves weekly exposure of allergens at escalating doses until a maintenance dose is reached, typically within 4 to 6 months. Maintenance can consist of one or more therapeutic exposures per month and can be influenced by the number of allergen sensitivities. Optimal duration of immunotherapy is not clear; recommendations are from 3 to 5 years.[22]

Approach to Treatment

Treatment of allergic rhinitis should be based on duration and severity of symptoms.[14] Mild or intermittent symptoms may be treated with oral H_1-antihistamine, intranasal H_1 blocker and/or decongestant, or LTRA. More severe or persistent symptoms may require treatment with intranasal glucocorticoids. Patients using intranasal glucocorticoids derive no additional benefit from oral antihistamines.[101,28] In contrast, if symptoms are inadequately controlled using intranasal glucocorticoids, adding intranasal H_1-antihistamines or ocular H_1-antihistamines (for ocular symptoms) can improve symptom relief.[49,66] Patients with severe symptoms may also benefit from a short course of systemic glucocorticoids. Ipratropium may be given for persistent rhinorrhea and an intranasal H_1-antihistamine for residual nasal congestion.[21] Immunotherapy should be considered in patients who fail to respond to the previous measures.

PREVENTION

Individuals with significant allergic rhinitis should obtain adequate supplies of appropriate medications (i.e., intranasal H_1-antihistamines, LTRAs, or intranasal glucocorticoids) before travel. If an unprepared traveler develops significant allergic rhinitis symptoms in the field, many general medical kits will only contain medications with less efficacy and more side effects (e.g., oral H_1-antihistamines and corticosteroids).

URTICARIA AND ANGIOEDEMA

Angioedema and urticaria often occur together, share a number of common etiologies, and have similar pathophysiology. Urticaria (i.e., hives) are intensely pruritic, erythematous, and plaque-like lesions caused by release of inflammatory mediators (e.g., histamine) by mast cells and basophils in the superficial dermis. Individual lesions resolve within 24 hours. Angioedema is caused by leakage of fluid in the deeper layers of the dermis and subcutaneous tissues. Angioedema presents as less well-defined, localized swelling in nondependent portions of the body. Angioedema and urticaria may be triggered through IgE-mediated allergic reactions or occur via nonallergenic pathways.

URTICARIA

Acute urticaria is defined as urticaria of less than 6 weeks' duration. Lesions vary in size from less than 1 cm (0.4 inch) to several centimeters. In severe reactions, the lesions may become confluent (Figure 67-4). The lifetime incidence of urticaria is about 20%. Urticaria may occur alone, with angioedema, or as part of an anaphylactic reaction. Common causes can include IgE-mediated allergic reactions to drugs or foods, infections, or direct activation of mast cells. Studies in children with acute urticaria have documented a high rate of infections as well as the concurrent use of antibiotics.[6]

IgE-mediated type I hypersensitivity reactions are the most common cause of acute urticaria and anaphylactic responses.

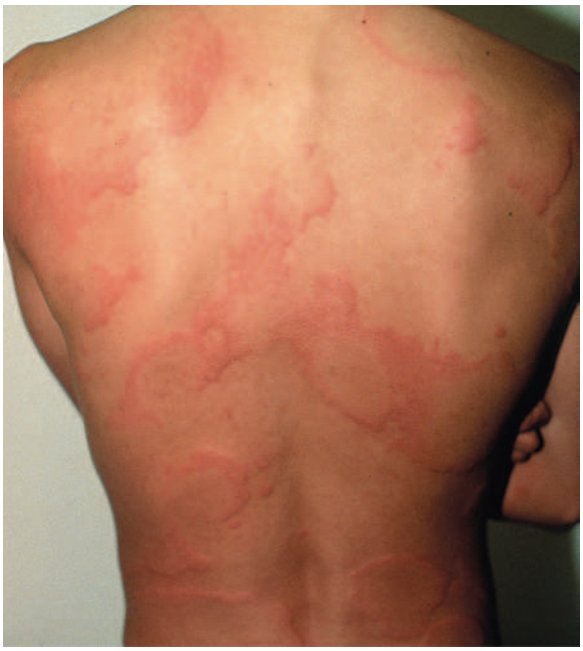

FIGURE 67-4 Urticaria. *(From Grattan CEH: Urticaria and angioedema. In Bolognia JL, Jorizzo JL, Schaffeer JV, editors:* Dermatology, *3rd ed, London, 2012, Saunders.)*

Type I reactions occur when an antigen binds to specific IgE antibodies attached to high-affinity IgE receptors on mast cells. Antigen binding causes cross-linking of adjacent IgE antibodies and leads to mast cell degranulation and histamine release. In children, foods such as peanuts, tree nuts, milk, soy, and eggs are common triggers. In adults, latex, shellfish, and fish are also culprits.[6,138] Insect envenomations (e.g., bee, wasp, hornet, fire ants) are a common environmental source. Urticarial reactions have been reported with most antibiotics; β-lactam antibiotics (e.g., penicillin, cephalosporins) are most common. Drug hypersensitivity reactions may be responsible for up to 20% of fatalities from anaphylaxis. IgG autoantibodies and immune complexes can also elicit non-IgE immune-related mast cell histamine release and present with urticaria. Plant-induced dermatitis is discussed in Chapter 64.

Urticaria can also result from direct mast cell degranulation induced by drugs, foods, contact allergens, or physical stimuli. Narcotics (e.g., morphine) often cause a reaction at the site of injection. Radiocontrast medium can cause nonallergic anaphylaxis (previously called anaphylactoid reactions) by a similar mechanism, with rash, hypotension, and respiratory compromise. Vancomycin is known for the generalized flushing called "red man syndrome," also mediated by direct mast cell stimulation.

Some foods and drugs can cause urticaria by IgE-mediated mast cell activation or through nonallergenic pathways. Children are more sensitive to nonallergic foods (e.g., tomatoes, strawberries). Nonselective NSAIDs are cyclooxygenase (COX)-1 inhibitors and may cause a reaction involving altered leukotriene metabolism. Even in NSAID-sensitive patients, selective COX-2 inhibitors typically do not induce urticaria.[138]

Reactions and skin lesions may also be caused by interaction of IgG antibodies with antigens such as drugs, viruses (e.g., infectious mononucleosis, hepatitis B), and bacteria to form complexes. These complexes aggregate in blood vessels and activate the complement cascade, generating anaphylatoxins that cause mast cells to degranulate and release histamine. Immune complex–mediated skin lesions may include purpura and urticarial vasculitis.[93] Lesions that resemble urticaria, but are painful and leave residual bruising, may be manifestations of urticarial vasculitis.

Physical urticaria is induced by mechanical stimuli, temperature alterations, or photoreactions. Dermographism is caused by mast cell histamine release induced by firm stroking of skin. Cholinergic urticaria results in fine, intensely pruritic lesions caused by heat exposure (e.g., exercise, warm temperature, hot bath). Cold-induced urticaria usually affects exposed skin but may cause dramatic anaphylaxis in susceptible individuals who dive into cold water. Urticaria of skin exposed to the sun has a broad differential diagnosis, including porphyria or photodermatitis caused by oral medications or topical contact.

Urticarial rashes can widely vary in severity, from acute, isolated pruritic rash to skin manifestation of life-threatening anaphylaxis. Angioedema can occur simultaneously and can be life threatening if it involves the airway.

Diagnosis of acute urticaria is based on history and physical examination. Routine laboratory work is not typically indicated unless other diagnoses are being considered. Acute generalized urticaria after exposure to a known or likely allergen may herald onset of anaphylaxis. Urticaria accompanied by signs or symptoms of involvement of other organ systems (e.g., hypotension, respiratory or gastrointestinal [GI] symptoms) is consistent with anaphylaxis. Immediate treatment with epinephrine is indicated. Patients with persistent urticaria, GI symptoms, and eosinophilia should be evaluated for parasitic GI infection. In a young child with an upper respiratory infection, acute urticaria is likely caused by an infectious stimulus. Unintentional weight loss and chronic urticaria not responsive to antihistamine therapy may be evidence of lymphoproliferative disease. Chronic urticaria in a patient with weight gain or other symptoms of thyroid suppression may indicate the need to test for antithyroid antibodies.

Treatment

Urticaria typically responds well to oral antihistamines. A short course of prednisone has been shown to decrease duration of symptoms.[93] High incidence of concurrent infection has resulted in less frequent glucocorticoid use in children. Treatment guidelines recommend a nonsedating (newer-generation) H_1-antihistamine in standard or double dose. A sedating H_1-antihistamine (e.g., diphenhydramine or hydroxyzine) may be used at bedtime to help with sleep. Some studies have shown additional improvement by adding an H_2-antihistamine (e.g., ranitidine or cimetidine).[72] Oral prednisone, 20 mg twice daily for 4 days, may be considered for adults with severe pruritus.[93] Box 67-2 lists treatment guidelines. Patients presenting with urticaria associated with anaphylaxis require treatment with epinephrine and intravenous (IV) fluids and careful observation for at least 6 hours. H_1-antihistamines and glucocorticoids are typically given to reduce the possibility of delayed or biphasic reactions, although only a benefit for skin manifestations has been proved.

BOX 67-2 Treatment of Acute Urticaria without Anaphylaxis

1. Administer nonsedating antihistamine such as fexofenadine, 180 mg daily (alternatives include loratadine and desloratadine).
2. Add sedating antihistamine such as diphenhydramine, 50 mg at bedtime, to help with itching and sleep.
3. Consider a short course of corticosteroids such as prednisone, 20 mg twice daily, for severe pruritus.
4. Addition of an H_2-antihistamine such as ranitidine, 150 mg twice daily, or famotidine, 20 mg twice daily, may be considered.
5. Any signs or symptoms of anaphylaxis mandate treatment according to anaphylaxis guidelines (see Boxes 67-6 and 67-7).

ANGIOEDEMA

Angioedema shares similar pathologic features with urticaria, but the postcapillary leakage in angioedema occurs in deeper layers of dermis and subcutaneous tissues, leading to swelling of face, lips, tongue, extremities, or genitalia (Figure 67-5).[102] Angioedema can be caused by mast cell release of mediators of vascular permeability (e.g., histamine, leukotrienes, prostaglandins). Familial, acquired, and ACE inhibitor–related angioedema are bradykinin mediated. Some episodes of angioedema are idiopathic.

Similar allergic and nonallergic factors that trigger mast cell–mediated urticaria can cause angioedema. Mast cell–mediated angioedema almost always presents with urticaria.[106] Direct mast

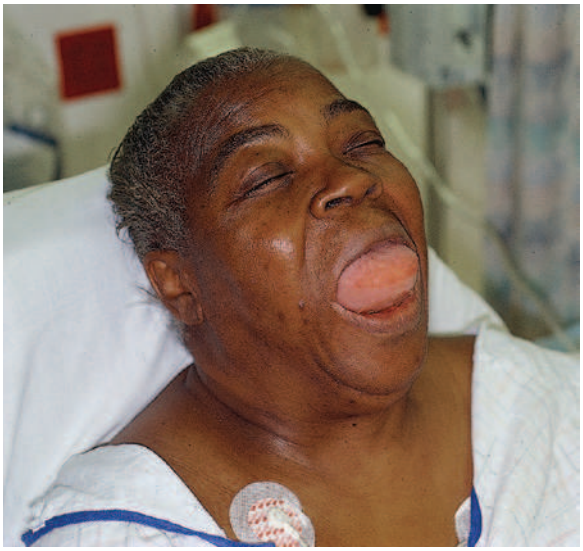

FIGURE 67-5 Angiotensin-converting enzyme (ACE) inhibitor–induced angioedema. *(From Roberts JR, Custalow CB, Thomsen TW, editors:* Roberts and Hedges' clinical procedures in emergency medicine, *6th ed, Philadelphia, 2014, Elsevier.)*

BOX 67-3 Treatment of Allergic Angioedema

1. If symptoms are mild and do not involve the airway:
   - Administer antihistamines such as diphenhydramine, 50 mg every 6 hours (other antihistamines acceptable).
   - Administer glucocorticoids such as prednisone, 20 to 40 mg twice daily for 5 to 7 days (dosing not established by trials).
2. Severe symptoms mandate treatment according to guidelines for anaphylaxis (see Boxes 67-6 and 67-7).

cell activation (e.g., by opiates or radiocontrast media) can cause angioedema. NSAIDs can precipitate urticaria and angioedema by various pathways involving prostaglandins and arachidonic acid metabolism.

In bradykinin-mediated angioedema, increased bradykinin levels cause increased vascular permeability. Patients may report a burning sensation. Pruritus and urticaria are usually absent. Hereditary angioedema (HAE) and acquired angioedema result from decreased levels of functional C1 esterase inhibitor, which increases bradykinin production. Onset of hereditary angioedema is usually during childhood. Late-onset acquired angioedema is associated with lymphoproliferative disorders. ACE inhibitors interfere with breakdown of bradykinin. ACE inhibitor angioedema accounts for 20% to 30% of angioedema. It typically affects soft tissues of the face and oral cavity (e.g., lips, tongue, soft palate, glottic structures). It can cause rapid onset of stridor, loss of airway patency, and death. Angioedema can also cause intestinal edema, with episodes of colicky pain, diarrhea, and vomiting.

Treatment

Identification of underlying etiology has therapeutic implications. Angioedema with urticaria is likely mast cell mediated and should be treated with antihistamines and glucocorticoids (Box 67-3). If there is any evidence of anaphylaxis (e.g., stridor, hoarseness, upper airway involvement, hypotension), epinephrine is indicated. Continuous airway monitoring is mandatory. In patients with airway edema, early endotracheal intubation is preferred. It may be a difficult intubation because airway anatomy can change rapidly and may be distorted by swelling.

Angioedema caused by excessive bradykinin is usually thought not to be responsive to antihistamines, glucocorticoids, and epinephrine. However, several small studies have shown benefit. Box 67-4 lists treatment recommendations. In one study, patients treated with antihistamines were extubated significantly sooner than were controls.[44] In angioedema with airway involvement, treatment with these medicines poses minimal risk and should be considered. Icatibant is a synthetic bradykinin B_2 receptor antagonist approved for treatment of HAE. A small case series of patients with ACE inhibitor–related angioedema treated with icatibant showed dramatic reduction in time to resolution of symptoms (4.4 vs. 33 hours) compared with a historical control group.[2] Icatibant should be considered for ACE inhibitor–related angioedema involving the airway. Availability may be limited because of cost (U.S. $8000 per dose). Fresh-frozen plasma contains ACE and is widely available; rapid improvement in symptoms after its administration is reported.[52] Patients with HAE should have a well-delineated plan of treatment for acute episodes. This may include home administration of medications and rapid transport to an emergency department for airway management and further medical treatment.

BOX 67-4 Treatment of Angioedema Caused by Bradykinin Excess

1. Discontinue drug if patient is taking an ACE inhibitor.
2. Initiate early airway management if patient has stridor or airway compromise.
3. Often, treat with corticosteroids and antihistamines because of concern about possible allergic etiology (doses as in Box 67-3).
4. If the airway is involved:
   - Consider treatment with icatibant, 30 mg subcutaneously, if available (off-label treatment supported by case series).
   - Consider treatment with fresh-frozen plasma as a second-line therapy (usual dose, 15 mL/kg)
5. Nebulized epinephrine (0.5 to 1.0 mL of 1:1000) may be considered to help relieve swelling in the oral and upper airway regions.

WILDERNESS CONSIDERATIONS

Potential for allergic reactions is not limited by geography. An expedition health care provider can prepare by reviewing medical histories and allergy lists to ensure medications are available in the field. Group medical kits typically include antihistamines, corticosteroids, and epinephrine to treat serious reactions. Patients with airway angioedema require close monitoring. The decision to evacuate a patient with angioedema to a higher level of care depends on acuity and severity of symptoms, medical provider experience, available resources, and options for timely evacuation under medical supervision. Physicians treating angioedema should anticipate the need for advanced airway management.

ANAPHYLAXIS

Anaphylaxis is a systemic, life-threatening allergic reaction that follows exposure to an allergen.[109] It is the most severe form of hypersensitivity reaction and involves multiple organ systems. Clinical manifestations may occur in skin, upper respiratory tract, lower respiratory tract, GI tract, and cardiovascular system. Anaphylaxis was first described in canine experiments involving sea anemone venom. Canine subjects experienced no ill effect from initial immunization, but died when later exposed to nonlethal doses of venom.[95]

Anaphylactic reactions should be described as either allergic or nonallergic. Allergic anaphylaxis describes reactions mediated by an immunologic mechanism (e.g., IgE, IgG, or immune complex complement related). Nonallergic anaphylaxis describes anaphylaxis from any nonimmunologic cause. "Anaphylactoid" has been used to describe severe, non–IgE-mediated allergic reactions. The term is no longer recommended;[17,116] *IgE-mediated allergic anaphylaxis* may be used when appropriate. Idiopathic anaphylaxis describes reactions in which no trigger can be identified[45,118] (Box 67-5).

ETIOLOGY

Foods are the most frequent cause of anaphylaxis.[136] Egg, cow's milk, wheat, soybean, peanut, tree nuts (e.g., hazelnut, walnut,

BOX 67-5 Classification of Anaphylaxis

IgE-Mediated Allergic Anaphylaxis
Food
Drugs (penicillin, cephalosporins, insulin, sometimes aspirin and other NSAIDs)
Insect stings and bites
Exercise (food dependent)
Other (exposure to antivenom or aquatic proteins)

Allergic Anaphylaxis (Not IgE Mediated)
Radiologic contrast material
Disturbances in arachidonic acid metabolism
Aspirin and other NSAIDs
Complement activation
Transfusion reactions
Other causes

Nonallergic Anaphylaxis
Direct stimulation of mast cells
Drugs (opiates, vancomycin)
Physical stimuli (e.g., heat or cold)
Exercise
Other causes

Idiopathic Anaphylaxis

IgE, Immunoglobulin E; *NSAIDs*, nonsteroidal antiinflammatory drugs.

cashew, almond), fish, and shellfish (e.g., shrimp, lobster, crab) account for more than 90% of all food-related anaphylactic reactions. In children, peanuts are the most frequent cause of food-induced anaphylaxis.[108] Individuals may accidentally ingest allergenic food when it is disguised by misleading labeling or contaminated during food preparation.

Drugs (e.g., antibiotics) may cause allergic and nonallergic anaphylaxis. Penicillin and its derivatives are most often implicated, with reactions occurring in one to five patients per 10,000 courses of treatment.[55] Opiates and vancomycin can directly degranulate mast cells and basophils. These reactions do not require prior sensitization. Aspirin and other NSAIDs can provoke IgE-mediated and non–IgE-mediated allergic reactions; they inhibit the COX pathway, increasing synthesis of lipoxygenase pathway products[68] (e.g., leukotrienes) that are important mediators of inflammation. In patients with asthma and chronic urticaria, this is the predominant mechanism for anaphylaxis.

Common outdoor causes of anaphylaxis are envenomation (e.g., Hymenoptera, i.e., bee sting), contact with aquatic proteins, and antivenom therapy (e.g., for snakebite). Estimated incidence of insect sting anaphylaxis is 0.3% to 3%.[104] Hymenoptera-related anaphylactic reactions are common in individuals younger than 20. These reactions are more likely to be fatal in older adults. Typically, children's reactions are milder (e.g., urticaria only) than those of adults. Individuals who experience a sting-related anaphylactic reaction have a 50% to 60% risk of anaphylaxis after subsequent insect stings.[104] Offending insects vary by geographic location. In the United States, yellow jackets cause most allergic reactions, whereas in Europe, honeybees and wasps cause the majority of insect sting–related reactions. Although rare, anaphylaxis can result from bites by certain insects, such as the kissing bug *Triatoma protracta*, the deerfly *Chrysops discalis*,[54] and ticks.[16]

Physical stimuli may provoke nonallergic anaphylactic reactions. In exercise-induced reactions, symptoms typically begin after 5 minutes of moderate to heavy exercise and resolve within 30 minutes to 4 hours after exercise cessation.[129] Approximately 50% of affected individuals are atopic, and most engage in regular vigorous exercise. A coinciding factor, such as ingestion of an allergenic food (e.g., shellfish)[75,89] or NSAID, may be necessary to induce this type of reaction. In cold-induced reactions, symptoms occur after exposure to a cold stimulus, such as being outside on a cold day, holding a cold object, or eating a cold food.

Recurrent anaphylaxis without identifiable cause is known as idiopathic anaphylaxis. Idiopathic anaphylaxis most often results in urticaria and/or angioedema, although all organ systems may be affected. Diagnosis of idiopathic anaphylaxis is one of exclusion. Patients who have frequent episodes are less likely to undergo remission. Acute treatment is identical to that for other forms of anaphylaxis. Long-term treatment may require regular use of oral corticosteroids.

In anaphylactic reactions caused by transfusion of blood products and immunoglobulins, complement activation plays a key role. Transfusion of incompatible blood type can cause cytotoxic anaphylactic reactions if complement-fixing antibodies to formed elements of blood (e.g., red cells, white cells, platelets) are present. In γ-globulin–related anaphylactic reactions, immune complex aggregation occurs when antigen-antibody complexes activate complement.

EPIDEMIOLOGY AND RISK FACTORS

Anaphylaxis affects 0.05% to 2% of the population, and its incidence is increasing.[70,128] Asthma is a risk factor for anaphylaxis.[42] Risk factors for death from anaphylaxis include severe asthma, cardiovascular disease, mastocytosis, and certain medications (e.g., β-blockers, ACE inhibitors).[98] Food, insect stings, and medications are the most common triggers for anaphylaxis. Frequently, no trigger is identified.[118,130]

Anaphylaxis is an infrequent occurrence in the outdoor setting. The National Outdoor Leadership School (NOLS) database recorded two cases of anaphylaxis and 149 cases of acute allergic reaction over 20 years (2.5 million participant-days).[111] There were no deaths.

PATHOPHYSIOLOGY

In anaphylaxis, clinical consequences of hypersensitivity are systemic. The primary event underlying anaphylactic episodes is degranulation of mast cells and basophils.[71] Histamine is the most important mediator and responsible for most of clinical manifestations. Important effects of histamine include vasodilation, increased vascular permeability, smooth muscle contraction, stimulation of nerve endings, and glandular secretion. Arachidonic acid metabolites (e.g., prostaglandins, thromboxane A_2, platelet-activating factor) are also released from mast cells and basophils, causing airway smooth muscle contraction, increased vascular permeability, goblet and mucosal gland secretion, and peripheral vasodilation. Platelet-activating factor also contracts smooth muscle and enhances vascular permeability. A late-phase reaction may occur many hours to days after the initial event.

CLINICAL PRESENTATION

Clinical manifestations of anaphylaxis may occur in various organs, including the skin (urticaria, angioedema, flushing), upper respiratory tract (rhinitis, stridor, hoarseness), lower respiratory tract (wheezing, bronchospasm, cough), GI tract (abdominal pain, diarrhea, vomiting), and cardiovascular system (tachycardia, hypotension, shock). Urticaria and angioedema are the most common manifestations, occurring in 83% to 90% of individuals with anaphylaxis.[61] The second most common manifestations are respiratory tract symptoms, followed by dizziness or syncope and GI symptoms. Cardiovascular collapse with shock can occur rapidly and without other antecedent symptoms. Table 67-3 presents the frequency of different signs and symptoms of anaphylaxis.

No single sign or symptom can be used to diagnose anaphylaxis. A standard definition of anaphylaxis has only recently been established. In 2005 an international symposium was convened by the U.S. National Institutes of Health (Allergy and Infectious Disease) and the Food Allergy and Anaphylaxis Network. This meeting created criteria to diagnose anaphylaxis (Box 67-6).[109]

Most anaphylactic reactions occur soon (within 5 minutes to 2 hours) after exposure to an inciting agent, but other patterns are possible. Protracted anaphylaxis can begin suddenly or gradually, but the clinical manifestations are prolonged, sometimes requiring hours or even days of resuscitation. Typically, abrupt

TABLE 67-3 Frequency of Signs and Symptoms in Patients with Anaphylaxis

Signs and Symptoms	Percentage of Cases
Cutaneous	>90
Urticaria (hives) and angioedema (localized swellings beneath the skin, most often on the lips and eyes)	85-90
Flush	45-55
Pruritus (itch) without rash	2-5
Respiratory	40-60
Dyspnea (shortness of breath), wheeze, cough	45-50
Upper airway angioedema (e.g., swelling in throat)	50-60
Rhinitis (runny nose, nasal congestion)	15-20
Dizziness, Syncope (Loss of Consciousness), Hypotension (Low Blood Pressure)	30-35
Abdominal	25-30
Nausea, vomiting, diarrhea, cramping pain	
Miscellaneous	
Headache	5-8
Substernal pain	4-6
Seizure	1-2

Based on a compilation of 1784 patients, reviewed in Lieberman P: Anaphylaxis and anaphylactoid reactions. In Middleton E et al, editors. *Allergy: Principles and practice*, 5th ed, St Louis, 1998, Mosby–Year Book, pp 1079-1092.

BOX 67-6 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

From Sampson HA et al: Second symposium on the definition and management of anaphylaxis, *J Allergy Clin Immunol* 117:391-397, 2006.
PEF, Peak expiratory flow; *BP,* blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg (1 month to 1 year old), less than 70 mm Hg + (2 × age) (1 to 10 years old), and less than 90 mm Hg (11 to 17 years old).

symptom onset is associated with increased symptom severity. Fatalities usually result from airway obstruction or cardiovascular collapse.[17]

DIAGNOSTIC TESTS

Plasma histamine and serum tryptase can help diagnose anaphylaxis. Both may be elevated during an acute episode. For best results, measure plasma histamine 10 to 60 minutes and serum tryptase 1 to 2 hours after symptom onset.[67]

TREATMENT

Anaphylaxis is a medical emergency. Treatment depends on severity and organ system(s) involved. For a mild allergic reaction limited to the skin (e.g., urticaria without anaphylaxis), antihistamines alone may be effective. Individuals with cutaneous reactions should be monitored closely for signs of respiratory or cardiovascular compromise. Clinical evidence of additional organ system involvement may require more aggressive measures (e.g., administration of fluids, bronchodilators, and epinephrine). Box 67-7 details acute management of anaphylaxis.

Epinephrine

Treatment for anaphylaxis is epinephrine. Epinephrine treats the primary symptoms of anaphylaxis: upper airway obstruction, lower airway obstruction, urticaria, angioedema, hypotension, and shock.[118] No randomized controlled trials of epinephrine in anaphylaxis have been published. Given that available evidence is compelling, it is unlikely a randomized controlled trial will ever be performed.[77,117] International evidence-based guidelines strongly recommend that epinephrine be given for anaphylaxis.[119]

Most fatalities result from delayed treatment.[36,96] If indicated, prompt administration of epinephrine is key. Intramuscular (IM) injection of epinephrine into the anterolateral thigh is preferred. This site provides faster absorption and higher plasma epinephrine levels than does subcutaneous administration or deltoid injection.[120,121] If reactions are life threatening or patients do not respond to IM epinephrine, IV epinephrine may be administered. IV epinephrine should be used with caution in persons older than 35 or with known coronary artery disease. Continuous epinephrine infusion is preferred to an IV bolus of epinephrine.[38,83] Bolus dosing of IV epinephrine should only be performed if the patient is in cardiac arrest.

Aerosolized aqueous epinephrine can prevent upper airway edema but is inadequate to abort systemic anaphylaxis.[26] Use of OTC epinephrine inhalation aerosol bronchodilators (e.g., Primatene Mist) is generally not recommended because they lack adrenergic specificity (i.e., are non–β_2 selective) and have extremely short half-life. These agents should also be used with caution in individuals with a history of coronary artery disease and arrhythmias.

BOX 67-7 Management of Anaphylaxis

General Measures

1. Place individual in supine position with feet elevated.
2. Establish and maintain airway.
3. Administer oxygen.
4. Place a venous tourniquet above the reaction site (e.g., insect sting or drug administration site) to decrease systemic absorption of antigen.
5. Obtain IV access and infuse normal saline (20 mL/kg over 10 minutes). Repeat as needed to achieve a systolic blood pressure of 90 mm Hg in an adult.

Epinephrine Use and Treatment of Hypotension

1. Administer aqueous epinephrine, 1:1000, 0.3 to 0.5 mL (0.3 to 0.5 mg) IM in the anterolateral thigh. Epinephrine dosage for children is 0.01 mL/kg. Repeat once or twice as necessary at 5- to 15-minute intervals to control signs and symptoms.
2. If the reaction is life threatening or if patient does not respond to IM epinephrine, administer epinephrine IV. Mix 0.1 mL (0.1 mg) of 1:1000 aqueous epinephrine in 10 mL of normal saline (final dilution, 1:100,000) and infuse over 10 minutes (10 mcg/min). If hypotension persists, a continuous epinephrine infusion may be started by adding 1 mL (1 mg) of 1:1000 epinephrine to 250 mL of normal saline, creating a concentration of 4 mcg/mL. Infuse this solution at a rate of 1 mcg/min (15 minidrops/min or 4 macrodrops/min, depending on the infusion set being used). Rate of infusion can be increased to 4 to 5 mcg/min if clinical response is inadequate. In children and infants, starting dosage is 0.1 mcg/kg/min, up to maximum of 1.5 mcg/kg/min.
3. If epinephrine and fluids are ineffective, an IV dopamine infusion should be initiated.
4. Norepinephrine, a potent vasopressor, can be used to treat severe hypotension that is unresponsive to administration of epinephrine, fluids, and dopamine.
5. Individuals taking a β-blocker medication may require treatment with glucagon (1 to 5 mg IV over 2 minutes). Continuous infusion of glucagon may be necessary.

Treatment of Bronchospasm

1. Administer a β_2-adrenergic agonist (e.g., albuterol, metaproterenol, pirbuterol, or terbutaline) via nebulization as required for bronchospasm that is not relieved by epinephrine.
2. Continuous nebulization may be required if bronchospasm persists.
3. Treatment with an anticholinergic (ipratropium) may be beneficial.

Antihistamines and Corticosteroids

1. Administer diphenhydramine, 25 to 50 mg (1 mg/kg in children), or chlorpheniramine, 10 to 20 mg (2.5 to 5 mg in children), IV over 3 minutes; IM or PO when the reaction is not severe. Addition of cimetidine, 300 mg, or ranitidine, 50 mg, IV over 5 minutes may be beneficial.
2. Most authorities advocate use of glucocorticoids to decrease likelihood of a late-phase reaction. Standard therapy includes hydrocortisone 200 to 300 mg or 125 to 250 mg methylprednisolone IV, or in milder cases, prednisone 30 to 60 mg orally.

IM, Intramuscular(ly); *IV,* intravenous(ly); *PO,* orally.

Epinephrine autoinjectors (e.g., EpiPen) are popular for their ease of use. Carrying epinephrine in ampule form with syringes and needles offers the benefit of multiple dosing. Smaller syringes, such as tuberculin or insulin syringes, can be used to avoid accidental overdose. Needle length should be sufficient to allow IM administration.[37]

Treatment of Hypotension

Place the patient in supine position to improve venous return. Sitting the patient upright may lead to death from decreased vascular tone.[97] If the supine position cannot be tolerated (e.g., because of respiratory distress or vomiting), the patient should be placed in semirecumbent or lateral decubitus position.

Patients with hypotension not rapidly responsive to epinephrine should be treated with IV fluids. Normal saline should be given in bolus doses of 20 mL/kg (1 to 2 L for an adult) over 10 minutes and repeated as necessary. Vasopressor drugs may be needed to treat hypotension if response to epinephrine and fluids is inadequate. Dopamine is often the initial drug of choice. Norepinephrine, a potent vasopressor, can be used to treat severe hypotension that is unresponsive to epinephrine, dopamine, and fluids. Glucagon may be necessary to treat refractory hypotension (e.g., patients taking β-adrenergic blockers) that is resistant to standard therapeutic regimens.[40,137] Atropine can be used to treat hypotension associated with bradycardia. Medical antishock trousers have been used successfully to treat refractory hypotension associated with anaphylaxis.[87]

β_2-Adrenergic Agonists

To treat severe wheezing, an aerosolized β_2-adrenergic agonist (e.g., albuterol) is recommended. Place in a nebulizer and administer as guided by symptom severity (intermittently or continuously). Nebulized anticholinergic agents (e.g., ipratropium) can also be used for treatment of bronchospasm.

Glucocorticoids

Limited evidence supports use of glucocorticoids in anaphylaxis. In a Cochrane Database systematic review, no studies met inclusion criteria for the review. Authors were unable to make recommendations for the use of glucocorticoids in the treatment of anaphylaxis.[19] Most authorities recommend glucocorticoids to decrease the likelihood of a late-phase reaction.[69]

Antihistamines

Limited evidence supports use of antihistamines in anaphylaxis. After treatment with epinephrine, antihistamines may be used to relieve itching and urticaria. Combining an H_1-antihistamine and an H_2-antihistamine may be more effective than administering an H_1-antihistamine alone.[72,107] Transient hypotension, bradycardia, and arrhythmias have been reported after rapid IV administration of cimetidine.

Biphasic Reactions

Recurrence of anaphylaxis after initial symptom resolution is known as a biphasic reaction. Biphasic reactions occur in up to 20% of patients, typically in the first 8 hours, but may occur several days later.[127] Prolonged monitoring has been recommended to monitor for biphasic anaphylactic reactions. Two large reviews of anaphylaxis found that less than 5% of patients had biphasic allergic reactions, of which 1% to 2.3% were deemed clinically important.[105] No deaths were reported.[46]

Medical Evacuation

The decision to transport patients to a higher level of care depends on skill and experience of medical providers, as well as available resources. If adequate supplies are available and care can be provided by a physician with experience in the management of anaphylaxis, patients with rapid and thorough response to initial treatment may not require evacuation. Local resources should include the ability to provide advanced airway management, IV access, and additional doses of medications, especially epinephrine and IV fluids. Every case of anaphylaxis deserves serious consideration of evacuation to a higher level of care. Special consideration should be given in cases of severe reaction, asthmatic patients, ingested allergen with possible continued absorption, and individuals with a previous history of biphasic reaction.[123] The Wilderness Medical Society's guidelines on use of epinephrine in wilderness settings state that "because of the life-threatening nature of anaphylaxis, as well as the possibility of a biphasic reaction, field victims of anaphylaxis should be evacuated if possible to definitive or hospital-based care."[37]

Sequelae and Aftercare

After resolution of symptoms, patients should continue a short course of oral antihistamines and glucocorticoids. Patients should be referred to an allergist or similarly qualified expert to identify precipitating agents so that preventive measures can be taken. Individuals with a history of anaphylaxis should carry at all times a device allowing self-injection of epinephrine. A medical information bracelet should be worn. Epinephrine autoinjectors, including multidose versions, require a prescription. Patients should obtain this immediately.

PREVENTION

Patients with drug allergies should avoid using new medicines in a wilderness setting. For instance, persons with a previous history of sulfa allergy should not start acetazolamide in the field to prevent acute mountain sickness. Although risk of cross-reactivity is low, it is prudent first to use this medicine in a suitable setting before moving to a remote high-altitude environment.[47]

Travelers with food allergies should be especially cautious with regard to food preparations. Individuals with peanut allergy need to consider regional differences in food preparation and the possibility of food contaminated with peanut-based products.

Medical providers should use latex-free gloves in anticipation of the possibility that they will be caring for persons with latex allergy.

Evaluation and treatment by an allergist or other appropriately trained medical provider is critical in patients with a history of allergic anaphylaxis. Immunotherapy can lead to substantial reductions in future episodes of anaphylaxis.[41,48]

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CHAPTER 68

Ethnobotany: Plant-Derived Medical Therapy

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The history of ethnobotany begins before the advent of written records. In all ancient civilizations, plants served as important elements of food, shelter, dyes, ornamentation, religious rituals, and medicines. The term *ethnobotany* refers to an individual culture's use of specific plants. Medicinal use of the plant kingdom has been termed *herbalism, plant medicine,* and *natural-based medicine* and is called *phytomedicine* in its current application. The word *herb* is broadly defined as a nonwoody plant that dies down to the ground after flowering. The most commonly used interpretation, however, is any plant used for medicinal therapy, nutritional value, food seasoning, or dyeing another substance.

The history of the discovery of the medicinal uses of plants by humans remains conjectural. Many scenarios probably occurred. Perhaps, in a prehistoric jungle of South America, a pool of water containing fallen plant material leached out some of the precious medicinal constituents of leaves, flowers, stems, and bark. Tannins, glycosides, sugars, and alkaloids from the bark were infused into the waters. Because of burning fever and severe dehydration, an extremely ill native drank from the pool, and his fever miraculously disappeared. The pond became known for its magical healing powers. If the water held bark from the cinchona tree, the native may have serendipitously discovered quinine.

Archaeologic evidence shows that prehistoric humans used plants extensively to treat physical ailments. Instinct and trial and error led to the realization that, for example, cinchona bark controlled intermittent fevers, animals fed ergotized grain aborted their fetuses, and the latex sap from the opium poppy could be eaten to alleviate pain. Innumerable medicinal plant traditions, some originating as far back as 2700 BC, remain intact. Ethnobotanically, the use of plant-based medicines in a particular culture represented much more than an individual's efforts to survive. Analyzing the methods and degrees of use of indigenous medicines reveals information about cultural philosophy, ingenuity, and sophistication. The Chinese developed an extensive and elaborate system for prescribing, classifying, and processing herbs that dates back to the third millennium BC. The formulas identified the specific effect of each herb and interactions with other herbs. Less tolerable herbs were blended with those that would counteract undesirable effects. Formulas were custom-blended, taking into account a victim's constitution and the stage of the disease. Some of the ancient knowledge from these writings is being used in contemporary herbal preparations commercially sold as "patent" (readily available in pill form) medicines.

Many native tribes of New Guinea, Indonesia, and the Amazon use single-herb formulations to treat almost all medical conditions, as they did thousands of years ago. In the West, written records dating to the Sumerians accurately describe medicinal uses of specific plants.[120] In the same period of about 3000 years ago, the first Asian written record, the Ben Tsao Gan Mu, was compiled by the Chinese. It listed more than 360 medicinal plants and their classifications, uses, contraindications, and methods of action as perceived at that time. Roman and Greek herbal remedies were described in the writings of Hippocrates and later in those of Galen, providing a pattern for development of the Western medical tradition. Hippocrates was an advocate of using a few simple plant preparations, along with fresh air, rest, and proper diet, to help the body's own "life force" eliminate problems. In contrast, Galen promoted use of direct intervention to correct the imbalances that cause disease, employing large doses of complicated mixtures that included animal, plant, and mineral ingredients.[134]

The earliest European compendium that listed the uses and properties of medicinal plants, *De Materia Medica,* was written by the Greek physician Dioscorides in the first century AD. He described about 600 plants, and his work remained the authoritative herbal medicinal resource into the 17th century.[45]

Herbalism was practiced in many different ways during and after the Middle Ages. There were learned traditional herbalists and lay practitioners, as well as wandering herbalists, who professed pagan animism or Christian superstitions that often were more influential in healing than were the herbs' properties. Little was added to the knowledge of herbalism during this period. After the Middle Ages and invention of the printing press in the 1400s, hundreds of herbal publications were compiled. Most early works were available only in Latin or Greek; it was not until the 15th through 17th centuries that the great age of herbalism was appreciated in English.[120]

Tides changed in European herbalism when a Swiss pharmacist-physician named Theophrastus Bombastus Von Hohenheim, better known as Paracelsus (1490 to 1541), introduced a new dimension. He advocated chemistry and chemical processing and used mineral salts, acids, and other preparations in medicinal therapies. This was a departure from the plant-based medicinal methods of the past. During the latter part of the 17th century, the predominance of plant medicines slowly eroded. In 1806, Freidrich Serturner, a small-town German pharmacist, became known for his efforts to isolate organic acids from plants in an attempt to find the active ingredient in opium. He discovered organic alkaloids, which became known as the first set of active plant constituents.[169] Because of their physiologic activity, the search for plant alkaloids continued into the 20th century.

Discoveries quickly followed. The bronchodilator and antitussive ephedrine, from the herb *Ephedra sinica,* was often used in Chinese medicinal formulas for bronchial asthma. Discovery of morphine led to creation of all the narcotic analgesics. The bark of the cinchona tree was found to contain quinine in 1819, which led to development of antimalarial drugs.

The traditional herbal extract from rhubarb (*Rheum* spp.) has several active compounds. These compounds mediate many of the pharmacologic effects, such as its purgative action (from sennosides); antibacterial, antifungal, and antitumor activities (from anthraquinones); antiinflammatory and analgesic activities; and improvements of lipid metabolism (from stilbenes). Treatment of leukemias from an extract of Madagascar periwinkle (*Catharanthus roseus*), known as vincristine, has been highly effective.[46]

Discoveries in the 19th and 20th centuries included atropine (from belladonna leaves, *Atropa belladonna*) in 1831, cocaine (from coca leaves, *Erythroxylum coca*) in 1860, ergotamine (from *Claviceps purpurea*) in 1918, and tubocurarine in 1935.[134]

European settlers brought herbal knowledge and their medicinal methods to the Americas. Because of the abundance and wide use of plants on the new continents, they also learned much from indigenous peoples. The colonists found that conditions afflicting them, such as malaria and scurvy, were treated effectively with herbs by the Native Americans.[136] In the 1700s, herbal medicine continued to have popular applications in lay circles, but was also investigated by the new medical establishment. Although creation of a small, elite group of learned professionals was thought to violate political and constitutional concepts of

the early American democratic movement, the practice of medicine was carried over from England and Scotland during pre-Revolutionary days. Before a professional medical class was established, most illness in America was treated within the family or extended-family network.

Many concepts were modified in the colonies between 1765, when the first medical school opened, and 1850, when more than 42 schools of medicine had been recognized. Inquiry into *Digitalis purpurea* (foxglove) by William Withering exemplified the change in perspective from anecdotal folk medicine to a critical examination for specific uses of botanicals from a biochemical point of view. During the early 1800s, the trend was to look at the efficacy of botanicals and their intrinsic value from a more scientific perspective.

Several developments delayed appreciation of herbalism by physicians in the colonies. For instance, Samuel Thomson promoted a system of herbal medicine by proselytizing about his patented method of herbal prescribing, which used many Native American herbs. A central theme in his approach was advocacy of self-prescribing based on the philosophies and herbal prescriptions found in his book, *New Guide to Health*. The right to sell "family franchises" for use of the Thomsonian method of healing was the basis of a widespread lay movement between 1822 and Thomson's death in 1843. Thomson adamantly believed that no professional medical class should exist and that democratic medicine was best practiced by laypersons within a Thomsonian "family unit."[43] Although his methods were considered crude and unscientific, he had more than 3 million faithful followers in 1839. Founded on ignorance, prejudice, and dogma, the Thomsonian school did little to help physicians accept European and American herbal medicines. European physicians in the Thomsonian movement wanted to separate themselves from lay practitioners by creating requirements and standards for the practice of Thomsonian medicine. Thomson was adamantly against this, but a decade after his death, the Thomsonian physicians formed the Eclectic School of Medicine, which attempted to unite "professional physicians," Thomsonianism, and traditional herbal medicine. Establishment of several Eclectic medical schools was a step toward validating herbal medicine, but failed to bring herbalism into the mainstream medical establishment. The founding of the American Medical Association and the Flexner Report on medical education in 1910 thoroughly established the modern pharmaceutical industry in the medical education system.[43]

Because of the availability of pure, active constituents from plant drugs and synthetic drugs that began to appear on the market toward the end of the 19th century, the prescribing habits of physicians began to change. The sensibility and predictability of administering exact doses were appealing. For example, the pure alkaloid of quinine, rather than a foul-tasting extract of cinchona bark containing variable percentages of quinine and other alkaloids with different physiologic properties, could be prescribed for malaria.

Many "crude drugs" were standardized for therapeutic activity. Digitalis, which still retains its status in the *United States Pharmacopeia* (USP), is one example. Of the 200 plant drugs officially listed in the USP in 1936, about 19% are still official today.[169] An estimated 25% of all prescriptions dispensed in community pharmacies between 1959 and 1980 contained ingredients extracted from higher plants. For a significant number of synthetic drugs, natural drug products continue to serve as either models or starting points for synthesis.

EVOLUTION OF PHYTOPHARMACEUTICALS

The drive toward patenting and ownership in the pharmaceutical industry has been a strong incentive to research and develop plant-based products. Because a plant cannot be patented, however, little U.S. effort has gone into developing herbal medicines during the past century. The principal active constituents of botanicals are investigated for their biologic activity, but in many cases, these are less effective than is the whole crude extract of an herb.[134]

One problem in development of the U.S. botanical pharmaceutical industry has been quality control. In addition, lack of standardization plagues plant-based products. Quality control and standardization of crude plant extracts for herbal medicines were virtually nonexistent until recently,[134] or we might be using more botanical medicines for common ailments. In Europe and Asia, where pharmaceutical firms have been producing standardized phytopharmaceuticals (plant-based standardized extracts) for decades, research and development have demonstrated that they make economic and medical sense. Europeans use phytopharmaceuticals as part of their mainstream medical practice. In hospitals, they are used primarily as adjuvant therapies. More than 70% of general practitioners in Germany prescribe phytopharmaceuticals, and the public health insurance system pays for most of these prescriptions. The total annual market for phytopharmaceuticals in Germany is $1.7 billion. Beginning in 1993, the licensing procedure for German physicians required knowledge of phytotherapy.[152]

Production and evaluation of botanical medicines have improved significantly in the past six decades. In crude plant evaluation, modern laboratory analysis can determine the percentage of active constituents, as well as solubility, specific gravity, melting point, optical rotation, and water content. Scientists detect resins, alkaloids, flavonoids, enzymes, essential oils, fats, carbohydrates, and protein content. They can precisely assay using liquid, high-pressure liquid, paper, and thin-layer chromatographies; spectrophotometry; atomic absorption; and magnetic resonance imaging. These methods improve predictability and therapeutic effectiveness of standardized crude botanical medicines, which are then evaluated for their efficacy in animal studies to determine pharmacologic potency, activity, and toxicity. U.S. and European companies have set strict quality control guidelines to ensure optimal yields of pharmacoactive constituents, with acceptable levels of impurities, pesticides, residual solvents, and heavy metals, and acceptable bacterial counts.

Specific cultivation and harvesting techniques affect the therapeutic value of a given herb, which is related to the amount of active constituents in a specific medicinal plant. Methods of packaging, storage, and transport can dramatically affect stability of active compounds. Extracts and concentrates are obtained by adding appropriate solvents to raw herbs, which draws out the active constituents. The most common method is *infusion,* which is analogous to a tea bag being steeped in hot water to make tea; in this case, water is the solvent. When the water is slowly evaporated, the concentrate contains the active constituents.

Pure ethanol is a solvent that is often used to concentrate active herbal constituents. Immersing a high-quality bulk or raw herb in pure ethanol for hours or days, depending on the herb and the part used, and then pressing the solids out, yields an herbal *tincture.* The alcoholic tincture is diluted with water to yield a 20% alcohol tincture. In another method, a 20% alcohol mixture is the solvent. *Fluid extracts* can be made by vacuum-distilling off some of the alcohol; this avoids elevating the temperature, which may affect some of the active constituents. Another concentration process, *solid extraction,* yields a solid or semisolid product that can then be powdered or granulated for administration.

Once an extract is produced, qualitative and quantitative analyses can be performed to assist in standardization. The percentage of known active constituents is assayed, to obtain predictable clinical results.

An herbal infusion is generally a better source of active compounds than is an air-dried or a sun-dried powdered herb (Figure 68-1), but its action may not be as strong as those of concentrates, such as tinctures, solid extracts, and fluid extracts. Potency of an extract can be defined by (1) percentage of active constituents or (2) concentration. Herbalists express concentration as an equivalency: a four-to-one extract is equivalent to or derived from four parts of the crude herb to yield one part extract. This is usually written as "4:1 solid extract." Longer shelf life, greater effectiveness, and higher concentration of active constituents make a more standardized (thus better) product than is the raw powdered herb; however, efficacy is difficult to compare.

FIGURE 68-1 **A,** *Calendula officinalis.* **B,** Calendula drying and dried in a jar. **C,** Calendula flower bud. (***A*** *and* ***B*** *courtesy Cascade Anderson Geller;* ***C*** *courtesy Jill Stansbury.)*

An example of a product that is standardized by the percentage concentration of pharmacoactive glycosides is *Ginkgo biloba* extract, marketed in Europe under the trade names Tanakan, Rokan, and Tebonin. It is typically standardized as 24% flavonoid glycoside. In experimental models, *G. biloba* extract has been shown to prevent metabolic and neuronal disturbances of cerebral ischemia and hypoxia.[101,115]

Quality control is addressed for many herbal products when the known clinical effectiveness can be attributed to a specific active constituent. Improved analytic methods and use of high-quality herbs (i.e., high in active constituents) help ensure standardization. In Europe, dosage is expressed in milligrams of active constituents, a system that favors consistency. The main difference between the infusion or extraction method, and chemical isolation or synthesis, is that the extracts still contain all the synergistic cofactors that enhance function of the active ingredient. This important aspect of herbal medicine is lost once the active constituent is removed from the whole plant.

HERBAL PREPARATIONS FOR CLINICAL AND WILDERNESS USE

Botanical preparations can be readily and accurately prescribed for travelers and wilderness enthusiasts who need medical help. Throughout the ages, botanicals have been useful adjunctive therapeutic agents. Knowing which preparations from the natural pharmacopeia can be used and how to use them engenders a sense of integration with the natural environment. Indigenous peoples who depend on the botanical world hold a vast amount of untapped knowledge. Wilderness enthusiasts should help preserve this understanding of the natural world and do what they can to save natural habitats. Further investigation into the plant kingdom for useful medicinal agents will aid in these efforts.

As for allopathic medicine, a word of caution is appropriate. Naturopathic remedies are sometimes offered as substitutes for more accepted Western medical remedies. The practitioner should always use the best and most proven remedy available. An example is treatment for spider bite, which is discussed from an allopathic perspective in Chapter 43, and mentioned briefly later in the discussion on a potential use for an activated charcoal poultice. The practitioner who selects any less commonly supported therapy should be aware of the science supporting the choice of therapy.

Herbal medicines can be prepared by decoction or infusion of bulk or raw herbs or by making an extract, a concentrate, or a tincture.

Infusions are prepared like a standard tea. The soft parts of plants—flowers, stems, and leaves—are placed in a warmed pot. Boiling water is poured over the herb, and the pot is covered to prevent beneficial essential oils from evaporating. The mixture infuses for approximately 10 minutes and then is strained. The supernatant can be used immediately or refrigerated in an airtight container for as long as 2 days. A standard adult dose of an herbal preparation is 28.3 g (1 oz) of dried herb in 473.2 mL (1 pint) of water, or 1 tbsp per cup. The amount is doubled if the herb is fresh.

Generally, it is best to take infusions hot by the cupful, three times daily for a chronic problem and up to every 1 or 2 hours during an acute illness. To make infusions palatable, many herbalists add licorice, aniseed, or honey. The hard or woody parts of plants, such as bark, seeds, roots, rhizomes, and nuts, have tough cell walls that must be broken down by longer heating before they impart their constituents to water. The herbs can be first broken into small pieces by chopping, crushing, or hammering.

Traditionally, a *decoction* was prepared in an earthen crock reserved especially for making herbal preparations. In the past, herbalists believed that some quality of the medicine was affected by the type of vessel or container in which the brew was prepared. Contemporary practitioners generally recommend use of stainless steel, ceramic, or enamel, and specifically discourage use of aluminum or other alloyed-metal pots. The herb is placed in the container and covered with cold water. The mixture is brought to a boil, covered, and simmered for 10 to 45 minutes, depending on the type and part of the herb being used. A decoction can be strained, flavored, or sweetened like an infusion and is consumed while hot.

Modern practitioners use the most efficient and predictable forms of specific herbal medicines. *Concentrates* in capsule form are most effective and easiest to administer. The standard herbal concentrate found in the marketplace is in a ratio of 4:1. Ease of administration and dosing and predictability of clinical effects have made this the industry standard. Herbal *tinctures* are extracted into a specific percentage of alcohol and can be mixed easily to make formulas tailored to personal circumstances. Formula prescribing is an art; a combination may be many times more effective than a single herb. Classic formulas for common ailments have been cataloged since the first herbal compendiums were recorded centuries ago. In this chapter, however, the focus is on single herbs and their specific uses, identification, and preparation.

HOMEOPATHIC USE OF BOTANICALS

Medical pioneer Samuel Hahnemann developed a radically different system of medicine nearly 200 years ago. Homeopathy is derived from the Greek words *homoios,* which means "similar," and *pathos,* which means "disease" or "suffering." The law of similars states that a substance that causes a set of symptoms in pharmacologic doses can be used as a cure for similar symptoms (even if the etiologic agent is different) if that substance is given in a homeopathic dilution. Most homeopathic remedies are prepared from plant, mineral, and animal products. In homeopathic medicine, there is a perfectly matched simillimum (the most effective medicine) if the predominant symptoms of a disease or illness match the symptoms produced when the substance is taken in large doses by a healthy individual. For example, the herb *Atropa belladonna,* which contains atropine, is poisonous.

In excessive doses, the herb causes death; in moderate doses, it creates hot, feverish states; and in tiny (homeopathic) doses, it can effectively treat certain types of fevers, viral syndromes, and inflammatory states.

A homeopathic dilution is created by taking a prepared tincture ("mother tincture") of a botanical or an extract from nonplant sources and diluting it in a sequential or serial method. The difference in a homeopathic dilution is in its methodology. To be effective, a homeopathic medicine must be successed (shaken or agitated) mechanically or manually a prescribed number of times between the serial dilutions. The succussion method originally discovered by Hahnemann is said to "dynamize" the medicine. The succussion method is purported to affect the water molecules, creating a "memory" that the water molecules store in a lattice formation. This is similar to the storage of information on a magnetic disk or tape, except the signature resonance pattern is created from interaction of the original tincture within the water's lattice structure. The dilution can range from a 1× potency, which is a decimal dilution of a given ingredient (one part mother tincture per nine parts solute), to a 1 cup (one part mother tincture to 99 parts solute), to an extremely dilute 200c (one part mother tincture per 99 parts solute, then serially diluted 200 times with one part of the subsequent solution, then diluted with 99 parts solute each of 200 times; thus, a 1:99 dilution each of 200 times). A high-potency dilution (serially diluted more than 30 times in the × [1:9 dilution each time] potencies and more than 12 times in c [1:99 dilution each time] potencies) would be taken much less frequently than would be a low-potency dilution.

To make a 30× homeopathic preparation of *Arnica montana,* 1 drop of the plant tincture is added to 9 drops of pure water, and the mixture is successed 50 to 100 times. Next, 1 drop from that solution would be added to 9 drops of pure water and again successed 50 to 100 times. This is repeated 30 times to yield the desired 30× homeopathic remedy. The number refers to the number of successions and the letter to the ratio of the mother tincture to pure water. Thus, a 30× remedy is a 1:9 dilution repeated 30 times.

The mechanisms by which homeopathy works have yet to be elucidated, even though it has been practiced effectively for several hundred years. In 1900, an estimated 15% of U.S. physicians were prescribing homeopathic remedies.[124] Recent studies have shown effective results in clinical trials using homeopathic medicines.[34,95,110] Mechanisms of action for many common pharmaceuticals also remain unknown. Many theories in medicine are still based largely on empirical observations rather than on theoretical understanding.

One herbal folk remedy for bruises, sprains, strains, and rheumatism in European and Native American medicine is topical application of the plant *Arnica montana* (leopard's bane). Consistent with the homeopathic principle, toxic quantities of the whole-plant extract of arnica produce the same set of symptoms that it is intended to cure when administered internally in a homeopathic dose or when the tincture or oil is applied topically to the affected area.

Arnica is contained in herbal and homeopathic doses in numerous ointments, salves, and poultices for the treatment of trauma resulting from localized sprains, strains, or contusions. Controlled studies in Germany have shown that effective products for sprains from athletic activity use an ointment that contains homeopathic arnica.[182]

TOPICAL APPLICATION

The earliest method of plant administration was topical application. Although many plants contain generalized moisture-enhancing properties, some were found to be particularly effective in ameliorating specific acute conditions when applied topically. Two methods are used to apply remedies to the skin. The *endermatic* method applies medicine on the skin without friction, as when applying a compress to the dermis and epidermis after an abrasion or laceration. The *epidermatic* method uses friction and is most effective with botanical oils, liniments, ointments, and medicated warm and cold friction rubs, primarily for subdermal contusions and trauma, to effect circulatory changes.[59]

Topical application of medicinal plants is useful for many conditions, including abrasions, lacerations, burns, insect bites, infections, rashes, and dermatoses. Other applications include contusions, varicosities, joint pain, inflammation, and musculotendinous aches, strains, and sprains.

Topical herbal remedies are applied with a poultice, compress, fomentation, or ointment. Probably the most common, the *poultice* is used to apply a remedy to a skin area with moist heat. A poultice is prepared by bruising or crushing the medicinal parts of the plant to a pulpy mass, then applying this to the affected area and covering it all with a moist heat source. If dried plants are used (or fresh plants if necessary), the materials are moistened by mixing with a hot, soft, adhesive substance such as moist flour or corn meal. A good way to apply a poultice is to spread the paste or pulp on a hot, wet cloth, which is wrapped around the affected area to help retain moisture and heat. The cloth is moistened with hot water as necessary. With irritant plants, such as those used in a mustard plaster, the paste is kept between two pieces of cloth to prevent direct contact with the skin. After the poultice is removed, the area is washed well with water to remove any residue. A poultice can be used to soothe, to irritate, or to draw impurities from the affected area, depending on which plants are applied.

A *fomentation* is a hot cloth soaked with an herbal infusion or decoction. Fomentations are generally less active than poultices. A cold compress is used for conditions that require an antiinflammatory cure. A cold, infusion- or decoction-soaked cloth is applied to an area and then removed when the body's circulation has warmed the cloth to body temperature. The botanicals' active constituents determine what actions the external applications will impart. For example, a poultice with an astringent herb, such as *Hamamelis* (witch hazel), has an entirely different effect from one made with a strong vasodilator and rubefacient, such as capsicum (cayenne pepper).

Ointments are another method of topical administration. Most ointments are made in a base of petroleum jelly, stable vegetable oils, beeswax, or a combination of these. The extract from the desired botanical is suspended within the base to create a stable solid product. Topical botanical products have the same function as do topical pharmaceutical ointments and are used to treat lacerations, abrasions, infections, and insect bites. Other uses for botanical topicals include hemostatic, antiinflammatory, antihistamine, rubefacient, analgesic, emollient, and circulatory stimulant actions. Herbal poultices, compresses, and ointments deliver their active compounds transdermally, as do pharmaceutical topical agents.

The first uses of most medicinal plants were probably topical. In contemporary herbology, many of these plants are also used internally. Whole plants containing more than one ingredient with biologic activity generally invoke synergistic action of several components to produce the therapeutic action. Thus, most botanicals have multiple applications for therapeutic purposes. Herbalists and homeopaths treat trauma of the skin, muscles, tendons, ligaments, and joint tissue with a topical agent in ointment or poultice form and give the same medicine internally in minute (homeopathic) doses to enhance the activity, as with concurrent use of arnica ointment and homeopathic arnica.

The major precaution in medical botany is to identify *toxicity*. Some of the most effective topical agents can be toxic if ingested. Most of these plants found in the wild could not be taken in sufficient doses to be fatal before causing gastrointestinal (GI) upset. A tincture, herbal concentrate, or powdered version of the plant, however, could have deadly potential and bypass obvious GI manifestations.

USE OF HERBAL MEDICINE IN THE WILDERNESS

Travelers in the wilderness can choose preprocessed herbal preparations or naturally available plants in the immediate vicinity. A surprisingly large number of minor medical conditions

encountered in an outdoor setting can be treated with plants in that location. North American recreational areas are home to medicinal plants that have been used by Native Americans for centuries. Recreationists in desert, alpine, and river environments can find medicinal plants in abundance. Almost all plants encountered during an alpine trek in North America have some medicinal property, as do many in tropical and subtropical regions.

Considerations for using herbal products in the wilderness are availability, ease of application, incidence of side effects, toxicity, spectrum of applicability, affordability, and effectiveness.

AVAILABILITY AND APPLICATION

If a condition can be improved by application of a local botanical growing in the immediate vicinity, the pharmacy is immediately available. Plants may be in season, plentiful, and easily harvested. Finding the appropriate plants can be challenging, however, depending on the location, the season, the traveler's familiarity with botanicals, and the type of medical condition. During mild seasons and at elevations conducive to plant growth in the continental United States, the chances of finding common plants are good. Otherwise, standardized commercial preparations of these herbs can be carried. These are packaged for long storage life, sanitary and convenient application, and standardization of active ingredients.

Hundreds of plants can be applied topically for a variety of conditions. Most of the readily available plants, even if properly identified, require some form of processing for the active constituents to be used fully. Furthermore, expertise in the field requires years of training by a knowledgeable botanist and herbalist. It also requires knowledge of plants' seasonal variations, ecologic niches, and precise identifications. However, a person who is neither a botanist nor a herbalist can gain basic understanding of a few plant medicines that have a wide spectrum of applicability and broad range of geographic distribution.

SIDE EFFECTS AND TOXICITY

The American Association of Poison Control Centers annually reports plant ingestion as a significant category of accidental poisoning. In 1997, 5.6% of U.S. poisonings came from plants and mushrooms. Of the substances that were involved in pediatric poisonings, plants were responsible for 7.4% of exposures.

Side effects or toxic reactions from botanicals are rare. Among the botanicals covered in this chapter, toxicity is not a major consideration, although anything can be toxic when used excessively or indiscriminately. Many toxic plants produce GI distress, vomiting, or diarrhea before they cause any severe neurologic or cardiorespiratory derangement. Often, toxic side effects are caused by one substance in a plant. When isolated, minute amounts of an alkaloid may be potentially dangerous, but when ingested in a form modified by other constituents, the altered drug effect allows tolerance of larger amounts of the toxic substance or substances.

As is true for any medication, medicinal plants should be applied appropriately, and doses for internal use should not exceed recommendations. Pregnancy and nursing may be contraindications. Doses for almost any herb can be found in numerous references.[134] Felter[59] stated that "as a rule, doses usually administered are far in excess of necessity and it is better to err on the side of insufficient dose and trust to nature, than to overdose to the present or future harm or danger of the patient." In general, for the self-harvested herbs presented in this chapter, the dry, crushed, herbal adult dose should be 1 tsp per cup or 8 oz of water; when the fresh herb is used, the amount should be twice that. Although no absolute law exists for administering medicines to children, Cowling's rule takes the child's age at the next birthday and divides by 24 to determine what fraction of the adult dose should be given.[59]

SPECTRUM OF APPLICABILITY

Most herbal medicines that have been catalogued and used historically are specifically indicated for one condition, although additional therapeutic effects have been noted over time. All the botanicals covered here have multiple uses. Comfrey (*Symphytum officinale*) may be used as a topical antiinflammatory agent; it also has constituents that are effective for GI conditions when taken internally. *Aloe vera* gel is an excellent topical agent for abrasions and burns; taken internally, the latex portion serves as an effective laxative. *Calendula officinalis* has antimicrobial properties that make it an effective topical dressing for mild infectious conditions, whereas internally it has antipyretic effects.[120]

AFFORDABILITY

If the herbalist collects plants and processes them personally, the cost is minimal. The purchase price of botanicals depends on the rarity and origin. Some exotic and rare botanicals from Asia and the Amazon rain forest demand a high price on the world market. *Panax ginseng* has long been regarded by Asian peoples as a prized herbal tonic and can cost hundreds of dollars per root, depending on the size, origin, and age. *Panax quinquefolius* (American ginseng), can cost as much as $52 per pound and was valued at $62 million as a cash crop in 1992.[19] Many exotic herbal and animal-derived medicines from China have prices as high as those of precious metals.

Most of the herbs produced in the continental United States and used for common ailments average 20¢ to 30¢ per dose (equivalent to 1 tsp of herbal tincture). Prices are not yet standardized. Quality control for production and supply and demand seem to dictate the cost of the mass-marketed herbal products. The best way to obtain a standardized product with a good quality-to-price ratio is to acquire the product from a botanical company that has been in business for at least 10 years and sells only to licensed health care practitioners.

NORTH AMERICAN PLANT MEDICINES

EPHEDRA (*Ephedra* species)

Description and Habitat

Common names for ephedra include Brigham Young weed, desert herb, Mormon tea, squaw tea, and teamsters' tea.

Ephedra spp. are shrubs with erect, straw-like branches found in desert or arid regions throughout the world and in the southwestern U.S. deserts. The Chinese ephedra called Ma Huang, *Ephedra sinica,* is found throughout Asia; *Ephedra distacha* is found throughout Europe; *Ephedra trifurca* or *Ephedra viridis* (desert tea) (Figure 68-2), *Ephedra nevadensis* (Mormon tea), and *Ephedra americana* (American ephedra) (Figure 68-3) are found in North America; and *Ephedra gerardiana* (Pakistani ephedra)

FIGURE 68-2 *Ephedra viridis. (Courtesy Cascade Anderson Geller.)*

FIGURE 68-3 *Ephedra americana. (Courtesy Jill Stansbury.)*

is found in Pakistan and India. The 0.6- to 2.1-m (2- to 7-foot) shrubs grow on dry, rocky, or sandy soils. The broom-like shrub has many jointed green stems with two or three small, scale-like leaves that grow at the joint of stems and branches (Figure 68-4).

Pharmacology

Ephedra is generally used for its alkaloid content, which tends to consist of ephedrine, pseudoephedrine, and norpseudoephedrine. The various species vary significantly in both alkaloid type and alkaloid content. In *E. sinica,* the total alkaloid content can be from 3.3% to 20%, with 40% to 90% being ephedrine and the remainder pseudoephedrine.[52] The North American varieties, such as Mormon tea (*E. nevadensis*), are reported to contain no ephedrine.

Ephedra's pharmacology centers on the actions of ephedrine. Ephedrine and pseudoephedrine are used widely in prescription and over-the-counter (OTC) drugs to treat asthma, hay fever, and rhinitis.[68]

The central nervous system (CNS) effects of ephedrine are similar to those of epinephrine but are much milder, and the duration of action is much longer. The cardiovascular effects are increased blood pressure, cardiac output, and heart rate. In addition, ephedrine increases brain, heart, and muscle blood flow while decreasing renal and intestinal circulation. Relaxation of bronchial, airway, and uterine smooth muscles also occurs.[68]

Pseudoephedrine has weaker CNS and cardiovascular system actions but has bronchial smooth muscle relaxation effects. Because it has fewer side effects, it is used more often than ephedrine for asthma.[68] Pseudoephedrine also demonstrates significant antiinflammatory activity.[81,102] Per 100 g, the dry leaf of ephedra is reported to contain 5 g protein, 5810 mg calcium, and 500 mg potassium.[52]

Native American and European Medicinal Uses

Ephedra has been used extensively in the West and in Asia for upper respiratory conditions such as asthma, bronchitis, and hay fever. It has also been used to treat edema, arthritis, fever, hypotension, and urticaria.[38] It is said to be valuable as a diuretic, febrifuge, and tonic.[120]

Navajo Indians applied the dried, crushed, long leaf of ephedra to syphilitic sores, and Hopi Indians drank a tea from the branches and twigs of a related species for the same condition.[176] Other tribes used the ground and roasted root for making bread.[52]

Mormon tea is a folk remedy for colds, gonorrhea, headache, nephritis, and syphilis. Mexicans mix the leaves with tobacco and smoke them for headaches.[52]

Modern Clinical and Wilderness Applications

Ephedra has proved to be an effective bronchodilator for treating mild to moderate asthma and hay fever. The common preparations include other herbs, such as licorice (*Glycyrrhiza glabra*) and grindelia (*Grindelia camporium*), that have antitussive and expectorant effects.

Ephedrine promotes weight loss.[134] Appetite suppression plays a role, but increased metabolic rate of adipose tissue is the main mechanism.[8] The weight reduction effects can be enhanced by up to 60% with addition of methylxanthine.[54]

In response to accumulating evidence of adverse effects related to *Ephedra*, the U.S. Food and Drug Administration (FDA) banned the sale of *Ephedra*-containing supplements on the retail market.

In the wilderness, specifically the desert, Mormon tea from the raw herb *E. nevadensis* or *E. viridis* can be useful for hay fever, mild asthma, bronchitis, or upper respiratory infection (URI). These species contain minimal amounts of ephedrine and principally contain pseudoephedrine; thus, they can be used without some of the unpleasant side effects of the Asian species. They can also be used for mild fevers associated with influenza or URI.

The shrubs are typically found growing on dry, rocky, or sandy slopes. The leaves can be picked fresh or sun-dried for 6 to 8 hours and can be prepared as a steeped tea or an infusion. Generally, the dose should be the equivalent volume of 1 tsp of dried, crushed stems per 8 oz of water, steeped for 10 minutes. The patient should not exceed a dose of this amount given six times daily. Once harvested, the leaves can be kept for an indefinite period for later use if stored in an airtight container.

Toxicity

According to Duke,[52] an infusion of ephedra produced "prompt and extensive contraction of uterine muscle when applied to smooth muscle strips of virgin guinea pig uteri." Ephedra may also elevate blood pressure. Frequent use may result in nervousness and restlessness. It should be used with caution if the patient has hypertension, heart disease, thyrotoxism, diabetes, or benign prostatic hypertrophy. Ephedra should not be used with antihypertensive or antidepressant medications.

FIGURE 68-4 Ephedra. *(Courtesy Jill Stansbury.)*

GOLDENSEAL (*Hydrastis canadensis*)

Description and Habitat

Hydrastis has a perennial root or rhizome that is tortuous, knotty, and creeping (Figure 68-5). The internal color is bright yellow, with numerous long fibers. The stem is erect, simple, herbaceous, and rounded, from 15 to 30 cm (6 to 12 inches) in height, becoming purplish and bearing two unequal terminal leaves. The leaves are alternately palmate with three to five lobes, hairy, dark green, and cordate at the base. The flowers, which are evident in early spring, are solitary, terminal, small, and white or rose colored.

The plant is a native of eastern North America and cultivated in Oregon and Washington. The parts used are the dried rhizome and roots.

Pharmacology

The alkaloids derived from *Hydrastis* are hydrastine (1.5% to 4%), berberine (0.5% to 6%), berberastine (2% to 3%), canadine, hydrastinine, and related compounds. Other constituents include meconin, chlorogenic acid, phytosterins, and resins.[134]

FIGURE 68-5 Goldenseal (*Hydrastis canadensis*).

Native American and European Medicinal Uses and Folklore

Native Americans used *Hydrastis* extensively as an herbal medicine and clothing dye. The Cherokee Indians used the roots as a wash for local inflammations, as a decoction for general debility and dyspepsia, and to improve appetite. The Iroquois Indians used a decoction of the root for whooping cough, diarrhea, liver trouble, fever, sour stomach, flatulence, pneumonia, and heart trouble.[129]

Early European uses date back to 1793. In *Collections for an Essay Towards a Materia Medica of the United States,* Benjamin Smith Barton noted that *Hydrastis* was useful as an eyewash for conjunctival inflammation and as a bitter tonic. In the pharmacy of the 19th century (1830), goldenseal was listed among the official remedies in the first revision of the New York edition of the USP. It was listed in the USP until 1926 and recognized in the *National Formulary* until 1955.[82]

Modern Clinical and Wilderness Applications

Goldenseal is among the top sellers in the American herbal medicine market. It is used as an antiseptic, hemostatic, diuretic, laxative, tonic, and antiinflammatory for inflammation of the mucous membranes. It has also been recommended for hemorrhoids, nasal congestion, sore mouth and gums, conjunctivitis, external wounds, sores, acne, and ringworm.[117]

Modern research into the active ingredients berberine and hydrastine has shown why some of the folk applications are effective. The most widely studied component is *berberine.* This isoquinoline alkaloid has demonstrated antibiotic, immunostimulatory, anticonvulsant, sedative, febrifugal, hypotensive, uterotonic, choleretic, and carminative (promoting elimination of intestinal gas) activities.[134] Berberine has broad-spectrum antibiotic activity. The antimicrobial activity has been demonstrated on protozoa, fungi, and bacteria, both in vitro and in vivo. Antimicrobial action has been noted against *Staphylococcus, Streptococcus, Chlamydia, Corynebacterium diphtheriae, Escherichia coli, Salmonella typhi, Vibrio cholerae, Pseudomonas, Shigella dysenteriae, Entamoeba histolytica, Trichomonas vaginalis, Neisseria gonorrhoeae, Neisseria meningitidis, Treponema pallidum, Giardia lamblia, Leishmania donovani,* and *Candida albicans.*[134] Berberine inhibits adherence of bacteria to host cells.[161]

Active ingredients in the crude botanical may be responsible for the wide-spectrum effectiveness of *Hydrastis.* The antifungal properties, for example, prevent overgrowth of *Candida,* which frequently occurs with use of other antibiotic therapies.

Other studies have shown the immunostimulatory activity of berberine-containing plants. Berberine increases blood flow through the spleen; improved circulation may augment immune function of this lymphoid organ.[147] Berberine also activates macrophages.[109] Historically, berberine-containing plants have been used as febrifuges, and in rat studies they have an antipyretic effect three times as potent as that of aspirin.[134]

Plants such as goldenseal are very effective in treating acute GI infections. In several clinical studies, berberine has successfully treated acute diarrhea caused by *E. coli, S. dysenteriae, Salmonella, Klebsiella, Giardia,* and *V. cholerae.*[14,41,49,75,100,148,153] Berberine-containing plants, in addition to having antimicrobial properties, influence the enterotoxins produced by offending pathogens.[28,162,163]

Gastrointestinal illness is a major concern of travelers to areas with questionable sanitation. Both waterborne and food-borne bacterial and protozoal infections are concerns for persons in wilderness and Third World environments. Some experts recommend using a berberine-containing botanical source prophylactically at least 1 week before a visit to questionable areas and for 1 week after return.[134]

Various eye complaints involving the conjunctivae and surrounding mucous membranes have been effectively treated with forms of berberine extract. Studies point to the effectiveness of berberine in treating infection caused by *Chlamydia trachomatis.* Clinical trials found that a 2% berberine solution compared favorably with sulfacetamide. Although the symptoms resolved more slowly with the berberine extract, the rate of relapse was much lower in the berberine-treated group.[10,130]

A standardized form of *H. canadensis* is beneficial for generalized digestive disorders (acute dysentery, gastritis) and for infective, congestive, and inflammatory states (sinusitis, pharyngitis, stomatitis) of mucous membranes. A typical dose depends on the source and method of the extract. For the previous conditions, the following doses, three times a day, are recommended: dried root or as infusion, 2 to 4 g; tincture (1:5), 6 to 12 mL (1.5 to 3 tsp); or solid extract (4:1 or 10% alkaloid content), 250 to 500 mg. *Hydrastis* can also be used as a wash or rinse for conjunctivitis, sinusitis, and pharyngitis. Eye drops, nasal lavage, and gargle are applied in a 5% preparation of a 1:5 tincture, or 1 to 2 tsp of powdered herb in 8 oz of water to create an infusion for application to inflamed mucous membranes. This can be repeated three times daily.

Toxicity

Berberine and berberine-containing plants are generally nontoxic. In recommended doses, berberine-containing plants have not been shown to be toxic in clinical trials. The median lethal dose (LD_{50}) of berberine sulfate in mice is approximately 25 mg/kg, and in dogs, intravenous (IV) doses up to 45 mg/kg do not produce lethal or gross toxic effects.[147] *Hydrastis* should not be used during pregnancy, and long-term ingestion may interfere with metabolism of B vitamins.

ARNICA (*Arnica montana*)

Description and Habitat

Arnica is a perennial plant generally found in mountainous areas of Canada, the northern United States, and Europe. The plant reaches a height of 30 to 60 cm (12 to 24 inches) and generally contains from one to nine large, daisy-like flower heads, which bloom during summer months (Figures 68-6 to 68-8).

Pharmacology

The flower is used both internally and externally for medicinal effects. The rootstock is used to make commercial preparations

FIGURE 68-6 *Arnica montana. (Courtesy Jill Stansbury.)*

FIGURE 68-7 *Arnica latifolia. (Copyright iStockphoto.com/SnowOwl Moon.)*

for tinctures and oils that are applied topically. The active constituents of the plant drug are flavonoids, volatile oils, and plant pigments (carotenoids).[177] Specific constituents include arnicine, formic acid, thymohydroquinone, lobelamine, and lobeline (piperidine alkaloid).[34]

Native American and European Medicinal Uses and Folklore

Catawba Indians administered the tea of arnica roots to treat back pain. In Europe, the flower heads have been used since the 16th century as an application for bruises and strains.[175] European arnica was included in the USP from the early 1800s until 1960 and recognized for its effects on the healing of bruises and sprains.

Specific instructions given in the *American Dispensory* in 1922 listed arnica as effective for "muscular soreness and pain from strain or overexertion; advanced stage of disease, with marked enfeeblement, weak circulation, and impaired spinal innervation; … tensive backache, as if bruised or strained; [and] … headache with tensive, bruised feeling and pain on movement."[59] Arnica in concentrated tincture form has been a popular, but not necessarily safe, medicine to treat inflammatory swellings and to relieve the soreness of myalgia and effects of bruises and contusions. Doses above the therapeutic range cause vagal inhibition when ingested and may cause toxicity if the concentrated tincture is applied topically. Therefore, the most common use has been fomentation of the flowers for topical application in the treatment of strains and sprains.

FIGURE 68-8 *Arnica montana. (Copyright iStockphoto.com/AGE photography.)*

Modern Clinical and Wilderness Applications

Contemporary use of *A. montana* is generally limited to topical commercially prepared ointments and salves, in conjunction with internal homeopathic (low dose) use for the same indications. Although its alkaloid (arnicine) and volatile oil (thymohydroquinone) are both relatively toxic, the actions of these constituents are extremely useful in resolving contusions and soft tissue injuries. Most ointments are found to contain a 1× homeopathic dilution of arnica tincture, which is about 4% by volume. Oral dosage is given in homeopathic potencies of 6× to 200c, depending on severity of the condition.

For application in the wilderness, most naturopathic first-aid kits include both ointment and the oral homeopathic forms of arnica. For direct use of the plant in treating minor sprains and strains, 2 tsp of the dried flower tops can be steeped in 1 cup of water for 10 minutes, and the infusion applied in a cold compress to the affected area. This should be repeated every 2 hours in addition to standard first-aid procedures. The infusion lasts 1 day if refrigerated and a few hours if not; therefore it is best to use a fresh infusion whenever possible. In addition, if available, the oral homeopathic preparation (30× to 200c) should be taken three times daily until swelling is reduced significantly. A topical ointment can be applied every 2 to 3 hours for this condition instead of the compress.

According to Weiss,[176] arnica is safe and effective for topical contusions and for stimulating granulation and epithelialization. A tablespoon of tincture is added to 500 mL of water, and the gauze compress is then placed on the wound. This stimulates local circulation and acts on peripheral vasculature. After granulation has occurred, ointments may be applied.

Toxicity

Arnica tincture or infusion can be toxic if the concentration is too high. Undiluted tincture should not be used internally or in compress form over an open wound. Vagus nerve inhibition is the primary toxic effect; GI irritation is also noted. Toxic reactions include gastric burning; nausea; vomiting; headache; decreased temperature; dyspnea; cardiovascular collapse; convulsions; motor, sensory, and vagal paralysis; and death.[34]

GARLIC (*Allium sativum*)

Description and Habitat

Garlic is a member of the lily family. It is a perennial plant cultivated worldwide (Figure 68-9). The garlic bulb is composed of individual cloves enclosed in a white skin. The medicinal herb is found in the bulb and is used either fresh or dehydrated. Garlic oil, which also has medicinal value, is obtained by steamed distillation of the crushed fresh bulbs.[117]

Pharmacology

The medicinal compounds in garlic generally contain sulfur and have been the subject of most research on garlic. Two primary compounds are an odorless chemical called alliin and the enzyme allinase, which begins a cascade of chemical reactions when the

FIGURE 68-9 Garlic blossom (*Allium* sp.). *(Courtesy Cascade Anderson Geller.)*

garlic clove is cut, crushed, or bruised. Alliin is converted to allicin, which is responsible for the characteristic odor of garlic. Allicin is strongly antibacterial and considered to be the major source of the antimicrobial effects of garlic. Breakdown products of allicin include diallyl sulfide, disulfide, and trisulfide. Heat speeds up the reaction, so cooked garlic and steamed distilled garlic oil contain little or no allicin. About 0.1% to 0.36% of the volatile oils in garlic is composed of sulfur-containing compounds (e.g., allicin, diallyl sulfide, diallyl trisulfide). These volatile oils are thought to be responsible for most of the pharmacologic properties of garlic. Other constituents of garlic include *S*-methyl-L-cysteine sulfoxide, protein (16.8% by dry weight), a high concentration of trace minerals (particularly selenium and germanium), vitamins, glucosinolates, and the enzymes allinase, peroxidase, and myrosinase.[134,142]

Native American and European Medicinal Uses and Folklore

Throughout history, garlic has played an important part in medicinal herbology. Clay garlic bulbs dating back to 3750 BC were found in Egypt. Preserved garlic bulbs were discovered in the tomb of Tutankhamen. An entire basket of these bulbs from the tomb of Kha at Thebes is in the Turin Egyptian museum. The Greek historian Herodotus recorded that an enormous amount of money was spent on garlic for the builders of the great pyramids. One of the earliest Sanskrit manuscripts, the Bower manuscript, devotes its entire first section to garlic, describing its legendary origins. It states that garlic keeps in order the three fluids and can cure thinness, weakness of digestion, lassitude, coughs, inflammation of the skin, piles, glandular swellings in the abdomen, splenic enlargement, indigestion, constipation, excessive urination, worms, wind in the body (rheumatism), leprosy, epilepsy, and paralysis.

Within the traditional medical circles of Greece and Rome, medieval Europe, and the Far East, similar claims may be found. Galen, Dioscorides, and Aristotle extolled garlic as an excellent medicine. Hippocrates recommended garlic as a diuretic; to regulate digestion; to treat bowel pains, inflammations, and infections; and to regulate menstruation. Early Chinese and European herbalists used garlic as a heating and drying agent, and therefore to prevent and cure diseases arising from cold, poisons, excesses of diet and drink, and sluggish metabolism.

In 1858, Pasteur noted garlic's antimicrobial properties. Albert Schweitzer used garlic in Africa to treat amebic dysentery. Garlic was also used as an antiseptic to prevent gangrene during both world wars.

Modern Clinical and Wilderness Applications

The pharmacologic effects of garlic are based on its activity as a hypoglycemic and hypolipemic regulating agent,* anticoagulant,† antihypertensive,[122,143] antimicrobial,[1,4,5,36,62,111,121,136,168] detoxifier of heavy metals,[3] and immune system modulator.[97]

Animal and human studies have substantiated that garlic lowers serum cholesterol and triglyceride levels and increases the amount of high-density lipoproteins. Dietary atherosclerosis was significantly reduced in rabbits fed garlic consistently for weeks; also, an extract of garlic and onions was more effective than clofibrate against hyperlipidemia and subsequent lipid deposition within the aorta.[24] After 4 months of feeding rabbits a high-cholesterol diet, the average lipid content in the aorta of the control animals rose from 5.95 to 13.75 mg/100 g dry weight. Animals taking clofibrate for 4 months had 7.95 mg, and garlic-fed animals 6.23 mg/100 g dry weight of lipid content in the aorta.[24] Other studies of experimental atherosclerosis in rabbits support these findings.[91,106] Decreased atheromatous lesions seem to be a consistent finding in rabbits fed high-cholesterol diets supplemented with garlic.

Of various sulfur-containing amino acids isolated from garlic, *S*-methylcysteine and *S*-allylcysteine exert the greatest antilipidemic effects.[89] Components of garlic can combine with the sulfhydryl group, the functional part of coenzyme A that is necessary for biosynthesis of fatty acids, cholesterol, triglycerides, and phospholipids. The lipid-lowering effect may best be attributed to inactivation of the sulfhydryl group.[9] In vitro and in vivo tests show reduced conversion of acetate into cholesterol by liver tissues.[39] Because sulfhydryl groups are involved at all levels of metabolic activity, the impact of garlic could be more extensive. Studies suggest that garlic may lower blood pressure by acting the same way as prostaglandin E_1, by decreasing peripheral vascular resistance.[138]

As a nutritional supplement, garlic is composed of magnesium, iron, copper, zinc, selenium, calcium, potassium chloride, germanium, sulfur compounds, amino acids, and vitamins A, B_1, and C. Garlic increases the body's capacity to assimilate thiamine by enhancing its absorption. Thiamine is a key part of the cocarboxylase enzyme system, which has beneficial effects on liver cells; this may explain why garlic offers prophylaxis against liver and gallbladder damage. In one study, garlic was shown to protect hepatocytes in tissue culture from the damage of carbon tetrachloride.[138]

Antioxidant activity has been attributed to garlic and garlic derivatives. The free radical scavenger action of garlic may be explained by its germanium, glutathione, selenium, and zinc content. The last three are key components of the antioxidant enzyme superoxide dismutase and glutathione peroxidase. Animal studies show that feeding garlic oil enhanced physical endurance in normal rats and also reduced the decrease in endurance induced by isoproterenol, a synthetic catecholamine that induces myocardial necrosis.[151]

Garlic inhibits platelet aggregation in animals; similar effects can be demonstrated in vitro and in vivo in humans.[47,157] Ajoene, an antiplatelet extract of garlic, was found to potentiate the antithrombotic effect of antiinflammatory drugs. Under fasting conditions, inhibition of platelet aggregation by garlic or its extracts is dose related.[159]

The garlic effect may be linked to inhibition of thromboxane synthesis or to altered properties of the plasma membrane. Methyl (2-propenyl) trisulfide, another component of garlic, is 10 times more potent as an inhibitor of platelet aggregation than is diallyl disulfide or trisulfide.[6] Thrombocyte aggregation inhibition is enhanced by two other compounds, 2-vinyl-1,3-dithiene and allyl-1,5-hexidienyl-trisulfide.[18]

Garlic and its juice or oil also enhance fibrinolysis.[26] In a double-blind, placebo-controlled trial, cycloallin, a component of garlic, was given to volunteers and patients after myocardial infarction and significantly increased fibrinolysis 1.5 hours later.[57] Chutani and Bordia[42] observed that the increase took place 6.5 to 12 hours after garlic intake. Daily garlic ingestion for 1 month generated a 72% to 85% increase in fibrinolysis in patients with ischemic heart disease.[146]

The pharmacologic versatility of garlic is best reflected by its antiviral, antifungal, antiprotozoan, antiparasitic, and antibacterial activities.[4,5,36,62,137,164,181] Laymen are credited with being the first to describe the scientific basis for medicinal use of garlic extract.[179]

*References 7, 9, 15, 23, 25, 29-31, 39, 40, 76, 89, 90, 93-95, 98, 99, 106, 107, 137.

†References 6, 22, 27, 28, 32, 66, 92, 121, 135, 149, 158.

Huddleson and colleagues[85] and Cavallito and Bailey[37] demonstrated in 1944 that garlic juice and allicin at low concentrations inhibited growth of *Staphylococcus, Streptococcus, Bacillus, Brucella,* and *Vibrio* species. Recent studies using serial dilutions and filter paper disk techniques have shown that fresh garlic, powdered garlic, and vacuum-dried preparations were effective antibiotic agents against many bacteria, including *Staphylococcus aureus,* α- and β-hemolytic *Streptococcus, E. coli, Proteus vulgaris, Salmonella enteritidis, Citrobacter,* and *Klebsiella pneumoniae.*[134] These studies compared the antimicrobial effects of antibiotics, including penicillin, streptomycin, chloramphenicol, erythromycin, and tetracycline, with those of garlic. Beside confirming garlic's well-known antibacterial effects, studies demonstrated its effectiveness in inhibiting growth of certain antibiotic-resistant bacteria.[1,56,154]

Garlic has also demonstrated significant antifungal activity against a wide range of fungi.[2,4,86,128,131,141,150,169] From a wilderness perspective, inhibition of fungi that can affect the skin (*Microsporum, Trichophyton, Epidermophyton,* and *Candida albicans*) can be significant. Garlic juice applied topically is an effective alternative in treating fungal skin diseases.[4] Garlic compares well with nystatin, gentian violet, and six other reputed antifungal agents used to treat *C. albicans*.[2,131,141,150]

Garlic has long been associated with prophylaxis against influenza virus. In vivo studies with mice revealed that garlic administration protected mice against intranasal inoculation with influenza viruses and enhanced reproduction of neutralizing antibodies after vaccine administration.[136] In vitro studies showed that garlic has antiviral activity against influenza B virus and herpes simplex virus type 1.[166] Preliminary studies revealed significant enhancement of natural killer (NK) cell activity in humans administered raw or cold, aged whole-clove garlic preparations daily for 3 weeks.[97] Antiviral activity of garlic in humans may result from the direct toxic effect on viruses and enhanced NK cell activity that destroys virus-infected cells.

Wilderness Medical Applications

Uses of garlic in the outdoor setting can be extensive. Its use as a food should be encouraged despite its odor, particularly in people with elevated cholesterol levels, heart disease, hypertension, diabetes, asthma, fungal infections, respiratory infections, and GI disorders (intestinal parasites, dysentery). A macerated garlic poultice and garlic slices serve as topical agents for fungal infections, ulcerated wounds, pyoderma, and other skin infections. The poultice can be used directly on the dermatologic problem, and as a suppository it can be used to treat vaginitis, particularly infections caused by *C. albicans*. For this application, one to two fresh-chopped cloves can be made into a poultice. This should be kept on the affected site for several hours and changed at least once every 6 hours with a fresh preparation. If the garlic causes epidermal irritation, its use is discontinued.

Prophylactic use during the flu season can reduce incidence of infection. Within the first 48 hours of onset of a flu or URI, one or two cloves can be consumed with a carbohydrate source to prevent stomach irritation. Alternatively, two or three oil-of-garlic capsules can be taken. For persons concerned about the social-segregating aspect, extracts that preserve the allicin content but remain odorless can be used.

Toxicity

For the vast majority of individuals, garlic is nontoxic at usual doses. However, some people develop allergic contact dermatitis or irritation of the digestive tract. Apparently, they are unable to detoxify allicin and other sulfur-containing components. Prolonged consumption of large amounts of raw garlic by rats results in anemia, weight loss, and failure to grow.[137]

GINGER (*Zingiber officinale*)

Description and Habitat

Ginger is an upright perennial herb with tuberous rhizomes, from which an aerial stem grows to 1.5 m (5 feet) in height. It is native to southern Asia, although it is cultivated in the tropics. Extracts and dried ginger are produced from dried unpeeled ginger; peeled ginger loses much of its essential oil content.[171]

FIGURE 68-10 Ginger (*Zingiber officinale*) flower. *(Courtesy Kevin Davison.)*

Pharmacology

Ginger is composed of a rich variety of nutrients and enzymes. The general composition is starch (50%); protein (9%); lipid (6% to 8%) composed of phosphatidic acid, lecithin, free fatty acids, and triglycerides; protease (up to 2.26%); volatile oils (1% to 4%), the principal components of which are three sesquiterpenes (bisabolene, zingiberene, zingiberol); vitamins, especially niacin and vitamin A; and resins.[171]

Native American and European Medicinal Use

Zingiber officinale is native to southern Asia and tropical Africa (Figures 68-10 and 68-11). Therefore, it did not have a role in the early herbal preparations of European and Native American herbal medicine.

Modern Clinical and Wilderness Applications

Clinical use of ginger for antiinflammatory action, cholesterol-lowering effects, and relief of dizziness and motion sickness is

FIGURE 68-11 Ginger plant with rootstock. *(Courtesy Kevin Davison.)*

noted in herbal texts.[59,61,72-74,108,133,155,159,160,171] A choleretic effect (promotion of bile flow to the gallbladder and small intestine) and conversion of cholesterol into bile acids are enhanced by ginger ingestion and may be responsible for its overall cholesterol-lowering effect.

An early Eclectic medical text listed ginger as a local stimulant, sialogogue, diaphoretic, and carminative.[59] Powdered ginger in a large quantity of cold water taken before sleep frequently "breaks up" a severe cold, and a hot infusion of ginger tea is a popular remedy for similar use to mitigate the pains of dysmenorrhea.[59] Ginger may relieve painful spasmodic contractions of the stomach and intestine. The antiinflammatory action of ginger is thought to be caused by potent inhibition of inflammatory compounds, such as prostaglandins and thromboxanes.[108] Ginger is also known to contain strong plant proteases such as bromelain, ficaine, and papain, which may explain some of its antiinflammatory action.[171]

Ginger has been used historically for major GI complaints. It is generally regarded as an excellent carminative (promoting elimination of intestinal gas) and intestinal spasmolytic.[134] One of the most noted uses of ginger in contemporary herbal medicine that applies to wilderness medicine is its action on the symptoms of motion sickness and seasickness.[72,73,133] Ginger is also a significant antiemetic. It has long been used for treatment of nausea and vomiting associated with pregnancy. The efficacy of ginger has been confirmed in hyperemesis gravidarum, a severe form of nausea and vomiting during pregnancy. Ginger root powder at a dose of 250 mg four times a day brought a significant reduction in both severity of nausea and number of attacks of vomiting during pregnancy.[61] To treat motion sickness and vertigo, two 500-mg capsules of powdered ginger root are eaten 20 to 30 minutes before the precipitating event. The same dose is used for the nausea of pregnancy during the acute attack. The raw ginger root can be grated using 1 tsp in 4 oz of water, steeped for 10 minutes, and taken every 30 minutes until the symptoms of motion sickness abate.

Toxicity

There appears to be no toxicity associated with ginger root ingestion.

COMFREY (*Symphytum officinale*)

Description and Habitat

Comfrey is a perennial herb with a stout spreading root that is divisible for propagation (Figure 68-12). Comfrey grows about 1 m (3.3 feet) high and has coarse, bristly, oblong, lanceolate leaves. The tubular flower can be purplish, blue, white, red, or yellow (see Figure 68-12, *A*). About 25 *Symphytum* species are described; they are indigenous to countries around the Mediterranean Sea and in northern Asia. Comfrey is typically found in moist meadows and other wet places in the United States and Europe.

Pharmacology

The chemical constituents of *S. officinale* roots include carbohydrate, predominantly sucrose; the amino acids serine and asparagine; the phenolic acids chlorogenic acid, caffeic acid, and *p*-coumaric acid; the alkaloids choline and allantoin; and the pyrrolizidine alkaloids viridiflorine, echinatine, heliosupine, symphytine, echimidine, and lasiocarpine.[172] The most concentrated (0.88% to 1.71%) alkaloid, allantoin, is generally credited with comfrey's beneficial effects.

Native American and European Medicinal Uses and Folklore

In Europe, comfrey is a common perennial grown in the garden for animal fodder. Russian comfrey is often promoted as a medicinal herb for use as a tonic. Comfrey is also cultivated in Japan as a green vegetable. A tonic made from comfrey has been used in American herbal medicine for hundreds of years.[113]

Comfrey has long been known as an external agent for rehabilitation of musculoskeletal and orthopedic injuries. Its former name, "bone knit," derives from the external use of poultices of

FIGURE 68-12 **A,** Comfrey (*Symphytum officinale*) flower. **B,** Comfrey (*Symphytum officinale*) leaf. (***A*** *courtesy Cascade Anderson Geller.)*

leaves and roots, which were believed to help heal burns, sprains, swellings, and bruises. Comfrey has been claimed to heal gastric ulcers and hemorrhoids, suppress bleeding, and relieve bronchial congestion and inflammation.[16] The healing action of a poultice derived from the roots and leaves is probably related to the presence of allantoin, an agent that promotes cell proliferation. The underground parts contain 0.6% to 1.3% allantoin and 4% to 6.5% tannin.[35,127] Comfrey extracts applied topically have been reported to heal wounds and bones in about one-half the normal time. In herbology, a general rule is that "if anything is broken, use comfrey."[180] Herbalists have also found that the allantoin concentration from a fluid extract of comfrey can increase the rate of wound healing of lacerations sufficiently to avoid the use of sutures.[178]

In European folklore, comfrey was regarded as an herb having unsurpassed ability to heal any injured or broken tissue. The mucilage (gelatinous mucopolysaccharide) of the comfrey root was named "the great cell proliferator," helping new flesh and bones to grow. Comfrey was one of the main herbs found in any poultice or fomentation. European herbalists considered comfrey exceptional for coughs and soothing inflamed tissues. Comfrey is effective for treating upper respiratory inflammation and has been used successfully to treat hemorrhagic conditions of the lungs.

Modern Clinical and Wilderness Applications

Comfrey lotions and salves containing 0.5% to 2.5% allantoin have been used for sprains, strains, and contusions. In the 1980s, comfrey became controversial because of potential hepatotoxicity. Members of the family Boraginaceae (*Heliotropium,*

Symphytum) contain a variety of related pyrrolizidine alkaloids reported to cause hepatotoxicity in animals. Although no hepatotoxic episodes from ingestion of comfrey have been reported in humans, the potential exists, so caution is advised when using comfrey for internal consumption.[113] Topical use of comfrey products as yet poses no concern for toxicity.

As a topical agent after acute trauma, such as musculoskeletal injuries, strains and sprains, or contusions, comfrey is an exceptional medicine.[17] A prepared gel of comfrey with a standardized allantoin concentration should be carried during travel or camping expeditions in the wilderness.

The raw herb can be used if the plant is nearby. The herb is readily identifiable, but should not be confused with foxglove (*Digitalis purpurea*), and should be used with caution when taken internally in its raw state. For use in a poultice or compress, the leaves may be picked damp, macerated, and applied topically for up to 24 hours.

Toxicity

Comfrey is not recommended for routine internal ingestion. Animal studies indicate that hepatic damage is an eventual outcome if the herb is consumed over a long period.

ALOE (*Aloe vera*)

Description and Habitat

The aloe is a perennial plant native to South and East Africa and is also cultivated in the West Indies and other tropical and temperate areas. The leaves, which emerge from a central rosette produced by a central fibrous root, are 30 to 60 cm (12 to 24 inches) long, narrow, fleshy, and light green with spiny teeth on the margins (Figure 68-13). Aloe is easily cultivated as a houseplant and can be grown in a sunny, warm spot with good drainage.

The genus *Aloe* comprises more than 300 species, which are members of the Liliaceae (lily) family. *Aloe* spp. are perennial succulents native to Africa. They are not cacti and should not be confused with American aloe, the century plant.

Pharmacology

Two important products are derived from aloe: a gel and latex. Aloe gel is a clear gelatinous material extracted from the mucilaginous cells found in the inner tissue of the leaf (see Figure 68-13). It is obtained by crushing the leaves and straining the mass repeatedly to remove cellular debris. The result is a clear gel, which is the product most frequently used in the health food and cosmetic industries. It is generally devoid of anthraquinone glycosides. A variety of compounds have been identified in *Aloe* spp., including polysaccharides, tannins, organic acids, enzymes, vitamins, minerals, saponins, and steroids.[113]

The bitter yellow latex of aloe contains cathartic anthraquinone glycosides, mostly barbaloin, as the active constituents. The concentrations of the glycosides vary with the type of aloe, ranging from 4% to 25% of aloe in concentration. The water-soluble fraction of aloe is called aloin and is a mixture of active glycosides. Cathartics have been derived from extracts of the latex and can create strong purgative effects by stimulating the large intestine.

FIGURE 68-13 *Aloe vera* with exposed latex gel. *(Courtesy Kevin Davison.)*

Native American and European Medicinal Uses and Folklore

Fresh *Aloe vera* gel is well known for its domestic medicinal values.[69,116,132,139] It has been dubbed the burn plant, first-aid plant, and medicine plant. When fresh, the gel relieves thermal burns and sunburns and promotes wound healing. It also has moisturizing and emollient properties. Because of these effects, aloe is widely used as a home remedy.

Aloin and other anthraquinone derivatives of aloe are extensively used as active ingredients in laxative preparations. Aloin is also used as an antiobesity preparation.[117] Aloe or aloin extracts are used in sunscreens and other cosmetic preparations, as well as in drugs for moisturizing, emollient, or wound-healing purposes.

In folk medicine, aloe is used for condylomas, warts, abnormal skin growths, and cancers of the lip, anus, breast, larynx, liver, nose, stomach, and uterus.[52] Folklore suggests that parts of the plants should be chewed to purify the blood. The pulp is said to possess wound-healing hormonal activities and "biogenic stimulators," and is used for intestinal ailments, sore throat, and ulcers. In India, aloe is used to treat piles and rectal fissures. Slukari hunters in Africa's Congo basin rubbed their bodies with the gel to eliminate the human scent, making them less likely to disturb prey. During epidemics of influenza, Lesotho natives take a public bath in an infusion of *Aloe latifolia*.[52]

Modern Clinical and Wilderness Applications

Although numerous claims have been made for aloe gel, its most common lay use is in the treatment of minor burns and skin irritations. In 1935, a report described the use of aloe in the treatment of radiation-induced dermatitis.[44] This study followed a 5-week course of topical applications of either the whole leaf or the leaf macerated into gel, resulting in complete wound healing after 4 months. In 1937, studies used a calamine- and lanolin-based aloe preparation to treat skin irritations resulting from burns, pruritus vulvae, and poison ivy. The results suggested that aloe stimulated tissue granulation and accelerated wound healing.[113]

Barnes[12] evaluated the effect of 5% aloe ointment on sandpaper-abraded fingertips and found the wound-healing rate was two to three times that of controls, as measured by decreased electrical potential of the wound. Other studies measured tensile strength of the healed surgical wounds of mice. Healing occurred within 9 days, an improvement over the results in control mice.[70]

Studies of antibacterial activity of aloe extracts have been attempted several times, yielding mixed results. In 1963, studies of the antibacterial effect of macerated *Aloe vera* gel found no activity against *Staphylococcus aureus* and *Escherichia coli*.[63] Other studies have determined that *Aloe chinensis* is effective against *S. aureus, E. coli,* and *Mycobacterium tuberculosis,* although *Aloe vera* showed no inhibitory effect.[71] The latex possesses in vitro activity against several pathogenic strains of bacteria, although the whole leaf minus the latex from the leaf epidermis and mesophyll of aloe showed no activity.[118] Two commercial preparations of aloe gel were found to exert antimicrobial activity against gram-negative and gram-positive bacteria and *C. albicans* when used in concentrations greater than 90%.[78]

The moisturizing effect of aloe may be beneficial for treatment of burns. The healing process may be related to mucopolysaccharides along with sulfur derivatives and nitrogen compounds in the gel, but this has not been well substantiated.[112] In attempts to document the antiinflammatory effects of aloe, a 1976 study found that *Aloe vera* had bradykinase activity in vitro, but this was not confirmed in vivo.[65]

Evidence for the internal use of aloe has been limited to studies involving mucous membrane tissue repair. Corneal ulcers treated with aloe extracts had more healing, less cellular reaction, and fewer signs of irritation than did control groups.[113] Topical application of *Aloe vera* gel after periodontal flap surgery reduced

postoperative pain more than did the saline control, and swelling of the treated tissue was less marked than with the control.[80]

Because of easy recognition and administration, use of the aloe plant in the wilderness environment is practical. The wild plant can yield an excellent preparation for dermal abrasions, cuts, and superficial wounds. A leaf cut from the base of a healthy plant can be conveniently carried. This allows the gel to remain intact, protected by the outer skin of the leaf. It can be squeezed from the inside through the cut portion directly onto superficial wounds with or without a gauze dressing. A standardized preparation of *Aloe vera* may be used as an antibacterial agent and emollient for superficial wounds or dermatitis.

In the event of constipation, the mixture of aloe gel and latex can be scraped or squeezed from the leaf cortex and ingested, 1 tbsp three times daily, or until a mild laxative effect is noted. A gel and latex mixture produces less cathartic effect than does latex alone. Because of the bitterness of the gel and latex, the mixture should be taken with food or a flavored beverage.

Toxicity

Because of its cathartic effects, oral aloe is not advised if gripping pain is associated with constipation. Aloe taken orally is contraindicated in pregnancy. Otherwise, aloe has no reported toxicity.

PLANTAIN (*Plantago major*)

Description and Habitat

The common broadleaf plantain is a familiar perennial "weed" found along roadsides and in meadowlands (Figure 68-14). Plantain belongs to the family Plantaginaceae, which contains more than 200 species, 25 to 30 of which have domestic use (Figures 68-14 to 68-16). *Plantago major* is a small weed with a rosette of ribbed leaves and small, projecting seed stalks. Its seeds, known as "psyllium seeds" in North America, resemble those of another species, *Plantago psyllium*. The leaves contain 84% water, 2.5% protein, 0.2% fat, and 14% carbohydrate; trace amounts of calcium, phosphorus, iron, sodium, and potassium; and beta-carotene, riboflavin, niacin, and ascorbic acid. Biochemically identified compounds include allantoin, adenine, baicalein, baicalin, benzoic acid, chlorogenic acid, choline, cinnamic acid, ferulic acid, L-fructose, fumaric acid, gentisic acid, D-glucose, *p*-hydroxybenzoic acid, indicain, lignoceric acid, neochlorogenic acid, oleanolic acid, plantagonine, planteose, saccharose, salicylic acid, scutellarein, sitosterol, sorbitol, stachyose, syringic acid, tyrosol, ursolic acid, vanillic acid, and D-xylose.[52]

Native American and European Medicinal Uses and Folklore

Historically, plantain has long been used for stings, bites, and irritations from venomous insects and reptiles. Folk medicine of the eastern United States suggests using crushed plantain leaves to stop the itching of poison ivy. It has also been reported to help relieve toothache. Ancient herbalists maintained that plantain had "refrigerant" (imparting a cooling sensation to the mucosa and allaying thirst), diuretic, and astringent properties. When the leaves are applied to a bleeding surface wound, hemorrhage lessens. In the highlands of Scotland, plantain is still called *slan-lus,* or "plant of healing."

In the United States, plantain has been known as "snake weed," from the belief that it is effective for bites from venomous creatures. Felter[59] noted that "the crushed leaves were very effective for the distressing symptoms caused by puncture by the horny appendages of larvae of *Lepidoptera* and the irritation produced by certain caterpillars, as well as the stings of insects and bites of spiders." In Native American folklore, the plant was

FIGURE 68-15 *Plantago laycedota. (Courtesy Jill Stansbury.)*

FIGURE 68-14 Plantain (*Plantago major*). *(Courtesy Cascade Anderson Geller.)*

FIGURE 68-16 *Plantago*—flowering plantain. *(Courtesy Jill Stansbury.)*

FIGURE 68-17 Chamomile (*Matricaria chamomilla*).

known as "white man's foot," in reference to its trait of growing in the settlements of white people. The Shoshoni Indians heated the leaves and applied them in a wet dressing for wounds.[177]

Modern Clinical and Wilderness Applications

Plantain is readily available in recreational areas of North America. This plant is extremely useful for various superficial wounds, abrasions, stings, and bites of mildly venomous insects. The constituents in the crushed leaves have an antihistaminic effect and anesthetic quality. In the event of a tooth fracture, a compress or poultice of 0.5 tsp of fresh leaves may be used on the tooth's exposed nerve root. Seeds of the plantago plant are useful for spastic colon, an effect that appears to be related to their mucilaginous properties. Psyllium seeds, known on the Asian continent as "flea seed husk," are often used as a bulk laxative. The seeds are collected from the stalk, and 2 tsp of fresh seeds in 4 oz of water are taken twice a day for mild constipation. Water should be ingested throughout the day to alleviate the condition and assist the laxative effect.

Because of its astringent quality, an infusion of the leaves is recommended to treat diarrhea. The preparer pours 1 pint of boiling water on 1 oz of the herb and leaves it in a warm place for 20 minutes. After straining and cooling, 0.5 cup is ingested three or four times a day.

Toxicity

No known toxicities are attributed to *Plantago*.

CHAMOMILE (*Matricaria chamomilla*)

Description and Habitat

Chamomile is a low-growing perennial with a hairy, prostrate branching stem (Figure 68-17). It blooms late in July through September and is found growing throughout North America and Europe. The name *chamomile* is derived from the Greek *chamos* (ground) and *melos* (apple), which refer to the plant's low growth and the apple-like scent of its fresh blooms.[156] The flower head is about 2.5 cm (1 inch) in diameter, has a conical receptacle, and is covered by yellow disk-like flowers surrounded by 10 or 20 white, down-curving ray flowers.

Pharmacology

The most important chemicals associated with chamomile are the volatile oils containing tiglic acid esters, chamazulene, farnesene, and α-bisabolol oxide. These volatile oils are destroyed if the herb is boiled.[157]

Native American and European Medicinal Uses and Folklore

A distinction should be made between the German and Roman species of chamomile, although they have been used interchangeably for centuries. German chamomile is preferred on the European continent, whereas Roman chamomile has been used widely in Great Britain. In the United States, German chamomile is much more widely consumed.[123]

German chamomile has a long tradition as a folk or domestic remedy. It has been used as an external compress or fomentation for gout, sciatica, inflammations, lumbago, rheumatism, and skin ailments. Infusions, decoctions, and tinctures have long been used internally to treat colic, convulsions, croup, diarrhea, fever, indigestion, insomnia, teething, toothaches, and bleeding or swollen gums. Historically, Roman chamomile was used similarly.[52,117] Chamomile is also a folk remedy for cancer.

Modern Clinical and Wilderness Applications

The principal biochemical constituent of chamomile is *chamazulene*. It is found in both species of chamomile and is reported to have antihistaminic properties.[58] Both histamine release and inhibition of histamine discharge have been considered mechanisms for the potential antiallergic action of chamazulene.

In Germany, chamomile products include tinctures, extracts, teas, and salves, widely used as antiinflammatory, antibacterial, antispasmodic, and sedative agents.[123] Studies have shown that chamazulene and α-bisabolol have antiinflammatory activity. Chamazulene may constitute as much as 5% of the essential oil. Other studies have shown that α-bisabolol has a protective effect against peptic ulcer, as well as antibacterial and antifungal effects. α-Bisabolol has reduced fever and shortened the healing time of skin burns in laboratory animals.[48] Most commercial European chamomile preparations have been standardized with regard to chamazulene and α-bisabolol content.[169]

According to Rudolph Weiss,[176] one action of chamomile is to reduce gastric motility and secretions, which would alleviate colic and painful spasm. About 20 flavones and flavonols, such as apigenin, are found in the aqueous portion of the distillation process. These are three times as effective at spasmolytic activity as is the opium alkaloid papaverine. Chamomile also has a significant calming effect and has traditionally had application as a mild sedative.

Chamomile is a good botanical to have on hand when traveling or camping. For infants experiencing restlessness and discomfort from teething, one-third of the adult dose may provide relief. For treatment of conditions (intestinal gas, colic, peptic ulcers) that may arise from excessive nervous tension, 2 tsp (or one standard teabag) of the flower tops can be added to a cup of boiling water and infused for 5 to 10 minutes; 2 to 3 cups may be taken over 30 minutes for acute intestinal colic.

ECHINACEA (*Echinacea* species)

Description and Habitat

Echinacea is a perennial herb native to the midwestern region of North America, from Saskatchewan to Texas (Figures 68-18 and 68-19). Species include *Echinacea angustifolia* and *Echinacea purpurea*. The plant produces a characteristic large, pale-purple flower and thick, hairy leaves and grows 60 to 90 cm (2 to 3 feet) high. The dried root is typically used for medicinal purposes.

FIGURE 68-18 Echinacea flower. *(Courtesy Jill Stansbury.)*

FIGURE 68-19 Echinacea (*Echinacea purpurea*).

Pharmacology

The compounds currently identified from *Echinacea* spp. are inulin, glucose, fructose, betaine, echinacin, echinacoside, 3-(*m*-trihydroxyphenyl) propionic acid, and nonspecific resins.[170]

Native American and European Medicinal Uses

This medicinal herb came to the attention of American herbalists in the late 1800s. Echinacea was originally used by the Indian tribes of Nebraska and the Sioux for treatment of snakebite and as an antiseptic and analgesic. Eclectic practitioners used it externally for the same purposes but used it internally to treat "bad blood" or any condition that manifested signs of local or systemic infection, whether bacterial or viral.

Modern Clinical and Wilderness Applications

Echinacea is probably the most common botanical used and known by the public, especially in relation to its immunomodulating effects. Many have empirically found that it can reduce symptoms and derail the onset of URIs and minor influenza episodes. However, an evaluation of *E. angustifolia* in experimental rhinovirus infections concluded that extracts of this plant's root, either alone or in combination, did not have clinically significant effects on infection with the virus or on the clinical illness that results from it.[167]

Echinacea is also a good systemic adjunct for treatment of any contusion or laceration. The polysaccharide component echinacin can maintain structure and integrity of the collagen matrix in connective tissue and ground substance, and it can accelerate wound healing experimentally.[134] Echinacin also has a cortisone-like effect, with intermediate stabilization of inflammation reactions. Inulin, a major component of echinacea, is a powerful activator of the immune system's alternative complement pathway. It may increase host defense mechanisms for neutralization of viruses, destruction of bacteria, and increased action of white blood cells (lymphocytes, neutrophils, monocytes, eosinophils) within areas of infection. Extracts of the root have been shown to possess interferon-like properties. As an immune stimulant early in infection, and for post-trauma rehabilitation, doses are taken orally three times daily: tincture (1:5), 30 to 60 drops, or solid extract (dry powdered extract, 6:1), 250 to 500 mg.

CALENDULA (*Calendula officinalis*)

Description and Habitat

Calendula, a member of the daisy and dandelion family, is found throughout Asia, North America, and Europe (see Figure 68-1). It is most often known as the pot marigold. The flower is generally used for production of a tincture.

Pharmacology

Calendula's chemical constituents include flavonoids, carotenes, saponin, resin, and volatile oils. The volatile oil content is responsible for localized increase in blood circulation and diaphoresis. The resin content is responsible for antimicrobial and antiinflammatory action of the topical application.

Native American and European Medicinal Uses

Native Americans apparently did not use calendula extensively; early European literature mentions only its medicinal role. Calendula, however, is one of the best topical applications for treatment and prevention of infection and skin irritation. Early American surgeons highly regarded its ability to treat and prevent postsurgical infections.

Modern Clinical and Wilderness Applications

A fluid or water extraction, or an oil infusion (prepared as a tincture but using vegetable oil instead of alcohol) of calendula should be used in the initial treatment of lacerations, abrasions, and scalds; immediately after any required debridement and cleaning of a wound; and for generalized inflammation of mucous membranes. It has shown its usefulness in dermatitis and in vaginal, sinus, ophthalmic, and middle and external ear infections. The choice of application mode (ointment, tincture, or fluid extract) depends on the wound. The succus (fluid extract) of the flower should be applied for irrigation of wounds and for ophthalmic uses.

GENTIAN, BITTER GENTIAN, YELLOW GENTIAN (*Gentiana* L. species)

Description and Habitat

More than 300 species of gentian are found throughout the world (Figure 68-20). It is especially common in mountainous regions of southern and central Europe, Eurasia, and western North America. All parts are used, but it is primarily the roots and rhizomes that are medicinal. Because of concern that overharvesting may endanger this genus, partial root/rhizome collection or leaf-only preparations are recommended.

Pharmacology

The yellow gentian is native to Europe and has been used as a digestive bitter, antiinflammatory, and aid to treating infection. Secoiridoids, γ-pyrones, and triterpenoids are among the most notable studied constituents. The bitter secoiridoid gentiopicroside (2% to 4% of the root) is known to have antibacterial and smooth muscle–relaxing effects consistent with gentian's traditional use as a digestive bitter, antibacterial, and antiarthralgic.[109,145]

Native American and European Medicinal Uses

Gentian has been used since ancient times. The genus is named after King Gentius, the king of Illyria (180 to 167 BC), and it was described by Dioscorides in *De Materia Medica*. Although gentian is native to Europe, it is generally considered one of the best stomach tonics worldwide. In Germany, it is approved by the Commission E for digestive disorders (loss of appetite, fullness, flatulence)

Traditionally, gentian has been used for chronic dyspepsia, indigestion, and poor digestive function. The root, rhizome, or cut herb is steeped and drunk 15 to 30 minutes before eating,

FIGURE 68-20 Gentian (*Gentiana lutea*).

especially in the evening. It stimulates appetite and disperses the "full" and "not hungry" sensation. It is very bitter.

Modern Clinical and Wilderness Applications

A tea of the leaf, root, or rhizome is most convenient and readily available in many areas at altitude or below tree line. Gentian can be very helpful for indigestion and digestive dysfunction brought about by poor food quality, weakness, and overexertion that impairs appetite. This tea can also be very helpful for fever or joint inflammation from infection, fatigue, and overuse. In Chinese herbal medicine, gentian is an essential component of Long dan xie gan wan, an excellent herbal formula for fever, viral infection, headache, iritis, cystitis, urethritis, genital herpes, and liver dysfunction.

DESERT PARSLEY, FERN-LEAFED LOMATIUM (*Lomatium dissectum,* Nutt.)

Description and Habitat

Lomatium, a perennial herb, is native to the western United States and grows predominantly at low to middle elevation in temperate to arid regions (Figure 68-21). The genus *Lomatium* contains more than 80 species, used more or less interchangeably. It is found on wooded or brushy rocky slopes, alpine meadow steppes, or dry hillsides. The root is drunk as an infusion, chewed, or pounded for topical application.

Pharmacology

The root extract has been shown to inhibit completely the cytopathic effects of rotaviruses in vitro.[126] The active constituent from *Lomatium suksdorfii,* suksdorfin, is related to coumarin and has been shown to strongly inhibit human immunodeficiency virus (HIV)-1.[114] This finding is consistent with its use as an antiinfective. Flavonoids and ichthyotoxic (fish-killing) tetronic acids have also been identified.[174]

Native American and European Medicinal Uses

Lomatium was highly revered by Native Americans and used for a wide variety of problems. It gained legendary status in the U.S. Southwest when Native Americans used it during the influenza pandemic of 1917. The Paiutes of Nevada treated sore throats with a decoction of the root. Many Native American groups considered *Lomatium* important for treatment of tuberculosis, asthma, and other lung diseases. It was also used internally and topically for venereal disease. Naturopathic physicians in the western United States have popularized use of *Lomatium* as an antiviral when the root extract is taken internally, for vaginitis when used as a douche, or as an oral rinse to treat periodontal disease.[13]

Modern Clinical and Wilderness Applications

Because of unconfirmed toxicity, it is probably best to avoid the tops of *Lomatium,* but the root is very helpful for URIs, viral illnesses, sore throats, mouth infections, and topical local infections. In the clinic, specific root isolates (with resins removed) are used; in naturopathic medicine, these are considered specific for herpes infections. These isolates are also thought to reduce the incidence of a benign hive-like rash that appears in individuals sensitive to *Lomatium.* A pioneer in naturopathic medicine, John Bastyr, said the appearance of the rash is a sign to decrease the dose, not discontinue the medicine.[13]

In the wilderness, *Lomatium* may be a significant aid in treating and preventing a wide variety of microbial and viral infections. It is easily prepared from fresh or recently dried root as a decoction.

FIGURE 68-21 Desert parsley or fern-leafed lomatium (*Lomatium dissectum,* Nutt).

FIGURE 68-22 Devil's club flower (*Oplopanax horridus*). *(Courtesy Jill Stansbury.)*

DEVIL'S CLUB (*Oplopanax horridus*)

Description and Habitat

Native to North America, *Oplopanax* is an erect, slightly spreading deciduous shrub present in moist but well-drained forested and riverbank ecosystems (Figures 68-22 and 68-23), from coastal Alaska to central Oregon, east to Idaho, Montana, northwestern Alberta, southwestern Yukon, and the Canadian Rockies, with a few populations near northern Lake Superior, the upper peninsula of Michigan, and Ontario. The stems, leaves, and petioles have a dense armor of needle-like yellow spines that can cause injury and irritation. Flowers are small, whitish, and numerous in compact terminal pyramidal clusters. Notably, *Oplopanax* is a member of Araliacea, which includes *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Aralia nudicauli* (sarsaparilla).

Pharmacology

The best-known constituents of devil's club include saponin triterpenoid glycosides, which have been described primarily in Japanese and Russian *Oplopanax*. There has been much discussion as to whether these saponins are similar to the ginsenosides

FIGURE 68-23 Devil's club (*Oplopanax horridus*). *(Courtesy Jill Stansbury.)*

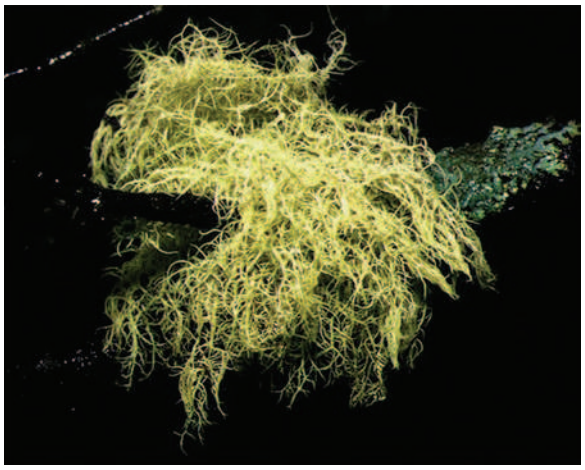

FIGURE 68-24 Old man's beard (*Usnea* sp.).

in *Panax* spp., consistent with devil's club traditional use among Native Americans as a tonic. Sterols, sesquiterpenes, and polyenes have been shown to have significant action against mycobacteria, fungi, and common bacteria such as *S. aureus, Bacillus subtilis, Pseudomonas aeruginosa, E. coli, and C. albicans*.[105] These findings are consistent with the primary historical use of devil's club internally and topically for all varieties of infection, including tuberculosis.

Native American and European Medicinal Uses

It is difficult to overstate the importance of this herb to the native peoples of North America. Devil's club is of extreme significance as a spiritual and shamanic herb, including purification and healing, protection against evil spirits, and gaining of supernatural powers, and as an emetic and purgative. Its primary uses as medicinal herb are for infections, fever, arthritis, respiratory ailments, bleeding after childbirth, pain, broken bones, digestive ailments, stomach complaints, and even dandruff and lice.

European medicinal use of *Oplopanax* is mostly in formulas for joint pain, arthritis (especially autoimmune arthritis), and rheumatism. The root is considered to be an effective expectorant and respiratory stimulant. Marketers have played up the adaptogenic potential of *Oplopanax,* calling it "Alaskan ginseng" or "Pacific ginseng." Commercial products also emphasize the root, whereas traditional uses and much of the research have focused on the inner bark of the stem.

Modern Clinical and Wilderness Uses

Modern clinical use is focused primarily on joint pain, osteoarthritis, and inflammatory arthritides. Devil's club is used in various formulas or as a single herb. It is often found as an antiinfective combination in combination with devil's claw (*Harpagophytum*), cat's claw (*Uncaria* spp.), or one of its western companions, chaparral (*Larrea tridentata*) and Oregon grape (*Berberis aquifolium*). Decoction of the inner bark of the stem is the primary method of preparation, but other parts, such as the inner bark (burned, and the ash used topically), whole stems, berries, leaves, and root, have all been used. In the wilderness, an infusion or decoction of the stem's inner bark is easily prepared and may help allay fatigue, ease joint or headache pain, or serve as an expectorant. In the practice of traditional medicine, devil's club appears to be "good for everything."

OLD MAN'S BEARD (*Usnea* species)

Description and Habitat

Usnea species are lichens (composed of fungi and algae in a stable symbiotic relationship) that are ubiquitous in old-growth forests of the U.S. Northwest (Figures 68-24 and 68-25). They can be seen hanging from shrubs or conifers, often lightly tethered to the tree bark, or lying on the forest floor, especially after a storm. It is difficult for anyone but an expert to distinguish between species of usneas, but they typically have a long, single, unbranched (or sparsely branched) central cord colored from white to yellow with an outer portion that is gray to pale green.

Native American and European Medicinal Uses

This plant has been used since ancient times in the Americas, Europe, and China. Native Americans saw *Usnea* as representing the male gender and the northerly direction and maintaining the "respiratory" system of the planet (namely the trees); they saw its human uses as secondary to this crucial function.[88] *Usnea* appears in the ancient Chinese herbal, the *Shennong Ben Cao Jing* (*Divine Farmer's Materia Medica,* ~200 BC), and it is classified as a phlegm-resolving herb. Among northwestern Native Americans, it has been used as bedding, as sanitary napkins, and to wipe slime when cleaning salmon. Most significantly, however, it is used as a wound dressing and bandage material,[173] because of not only its wispy soft form, but also its antibacterial properties. In Europe, it has been used predominantly as a topical medication, employing the active constituent usnic acid, present in many lichens, and as an antibiotic, antiinflammatory, and analgesic substance.[83] Since its isolation in 1844, usnic acid has been the most studied of lichen constituents and one of the few to be commercially available. In addition to bacterial inhibition of staphylococci, streptococci, pneumococci, and mycobacteria, usnic acid has been shown to have antiviral, antiprotozoal, and antiproliferative effects consistent with its traditional use.[87] Also present in *Usnea,* but less well studied than usnic acid, are the organic acids usnaric, thamnolic, lobaric, and stictinic.

Modern Clinical and Wilderness Uses

Although pure usnic acid has been used for weight loss in recent times, this use cannot be considered safe and has been associated with liver failure.[55] *Usnea* has been used in several formulas in modern-day China, usually paired with the seaweed *Laminaria* or *Sargassum* (or both) for treatment of thyroid cancer,[84] and in the treatment of bronchitis with profuse sputum.[50] Other current uses include lozenges for oral inflammation and many different salves and creams with antimicrobial and antiinflammatory action.

In the wilderness, *Usnea* is readily available in the regions mentioned earlier. It makes excellent bandages for wounds, superficial infections, and contact dermatitis. Most herbalists recommend collection from the ground so as not to disturb growth on shrubs or trees. Soft and wispy *Usnea* is applied directly to

FIGURE 68-25 *Usnea* sp. *(Courtesy Jill Stansbury.)*

the affected area and held in place by whatever means are available. Alternatively, dry *Usnea* may be powdered and sprinkled directly on wounds, affording antimicrobial wound protection.

FIRST-AID KIT OF NATURAL PRODUCTS

A natural products first-aid kit should contain a variety of products that are easy to obtain and replace and that have a wide spectrum of use, including herbs (Box 68-1), homeopathic preparations, and vitamin and enzyme supplements (Table 68-1).

HOMEOPATHIC MEDICINES

Homeopathy can be an excellent source of relief and treatment for emergencies and general first-aid situations. Homeopathic preparations include powders, tablets, tinctures, lotions, ointments, creams, and sprays. Advantages of homeopathy are ease of administration, lack of toxicity, rapid action, and small volume of material. Disadvantages are the degree of understanding and competence required to become an effective prescriber and the lack of readily available sources of each medicine at most North American pharmacies.

A kit made exclusively of homeopathic medicines can cover most first-aid emergency situations. For the acute, straightforward injury or malady without a complex set of symptoms, the correct simillimum and rapid amelioration of symptoms are not difficult to achieve. This section discusses a few indications for use of homeopathic medicines and the preparation most often used. Unless otherwise noted, a 6× to 12× potency in lactose pellet form should be given every 15 to 30 minutes immediately after the injury until noticeable improvement occurs. If no effect is noted after the first two doses, the medicine selection should be reconsidered.

The personal experience of one of the authors (KJD) exemplifies the relief that can be obtained from an acute injury with the appropriate homeopathic medicine:

I was bitten on the lip by a small centipede while sleeping. I instantly experienced swelling and intense burning pain. Local application of ice provided no relief. I chose the homeopathic medicine *Apis mellifica* in a 6c potency because the wound was shiny and felt hot, and the swelling was increasing. After sublingual ingestion of two pellets, I waited 1 to 2 minutes, still in excruciating pain with no change in symptoms. My next selection was cantharis in a 6c potency, because a key symptom for this remedy is extreme red and hot burning pain of the face. Less than 30 seconds after administration, the pain was almost undetectable. Total relief was obtained within a few minutes after being bitten. As an unintended control, I have had no homeopathic kit available after other centipede bites, and the pain generally lasted for hours and the residual swelling for days. Reactions from different centipedes can cause different sensations and symptoms, however, so cantharis may not work for all bites.

Proper selection of the simillimum or indicated homeopathic medicine requires the ability to note the subtle differences in the ways the patient responds to apparently similar traumatic or toxicologic influences. An appropriate homeopathic field guide that lists specific indications and differentiations for each homeopathic remedy should accompany any first-aid kit. It is essential to understand the specific homeopathic indications for each of the remedies (simillima) on hand. Otherwise, the chance of obtaining a successful outcome is small.

Practitioners and the homeopathic industry have realized the difficulty of single-remedy prescribing, which involves understanding and memorizing indications for every homeopathic medicine. Therefore, medicines have been developed that combine remedies to cover a large number of the symptoms and symptom characteristics that typically accompany most ailments. These medicines, known as *complex* or *combination* homeopathic preparations, can be very helpful for the new user.

BOX 68-1 Herbal Medicines Recommended for a First-Aid Kit

Aloe gel and powder capsules
Arnica ointment
Calendula gel, ointment, and tincture
Chamomile tincture
Comfrey gel or ointment
Echinacea tincture or freeze-dried powder capsules
Ephedra freeze-dried powder capsules
Goldenseal tincture or ointment
Hypericum ointment or tincture
Plantain tincture
Witch hazel fluid extract or tincture

SINGLE PREPARATIONS AND THEIR INDICATIONS

Aconite

Tincture of the whole plant with its root is derived when monkshood or wolfsbane (*Aconitum napellus*) begins to flower. Aconite is indicated for acute states of emotional disturbance, including anxiety and intense fear or pain. This is one of the key remedies that should be administered after an acute injury that has dazed, shocked, or frightened the patient. Persons who are fearful or restless, cannot tolerate being touched, and have pain followed by numbness and tingling sensations are most responsive to aconite. Those with sudden onset of fever, nausea, and vomiting and who exhibit symptoms of fear, restlessness, and anxiety may also benefit.

Apis

The original tincture is manufactured from the whole honeybee and from dilutions of its venom (*Apis mellifica*). Apis is used for insect stings, particularly from bees and related insects, when the wound is swollen, shiny, and hot to the touch. Treatable symptoms from other conditions are histamine reactions (resulting in facial flushing; puffiness or swelling around the mouth, face, and eyes), sunburn, hives, burns, and early stages of abscesses and frostbite. If symptoms include a stinging, burning, or swelling quality and subside by applying cold rather than heat, apis is the indicated remedy.[144]

Arnica

Tincture comes from the whole fresh plant, flowers, and dried roots of leopard's bane or Fallkraut (*Arnica montana*). Arnica is indicated for blunt traumatic wounds (resulting in both deep and superficial hematomas), contusions, swelling, and localized tenderness. It is also effective for sore muscles, as well as sprains, fractures, dislocations, and internal bleeding. We recommend taking a 6× to 30× potency every 15 minutes to 3 hours for the first few days after a severe injury. The more severe the injury, the more frequently the dose is taken for the first day. As symptom severity decreases, the medicine is taken less often. Arnica can be helpful in decreasing severity of symptoms and recovery time.

Arsenicum

Derived from arsenic trioxide, arsenicum is used for skin rashes (those that feel warm but are relieved by hot applications), hay fever, asthma (especially when accompanied by notable anxiety), diarrhea, vomiting, and gastroenteritis (especially from foodborne microbes).

Belladonna

Belladonna (*Atropa belladonna,* deadly nightshade) is a perennial herbaceous plant native to Europe, North Africa, western Asia, and some parts of Canada and the United States. The foliage and berries are extremely toxic, containing the tropane alkaloids scopolamine and hyoscyamine, which are used as pharmaceutical anticholinergics, including the drug atropine. Belladonna has been used throughout history as a poison administered orally or by arrow tips. Used in eye drops by women in the past to dilate their pupils and appear seductive, the name is translated as "beautiful woman." As a homeopathic preparation, belladonna

TABLE 68-1 Uses for Phytopharmaceuticals

Plant Medicines	Analgesic	Antibiotic	Antifungal	Antiinflammatory	Astringent	Antiseptic	Decongestant	Sedative
Aconitum napellus	—	—	—	—	—	—	—	Homeopathic internal
Apis mellifica	—	—	—	Homeopathic topical, internal	—	—	—	—
Arnica montana	Homeopathic internal Botanical topical	—	—	Homeopathic topical, internal	—	—	—	—
Arsenicum album	—	—	—	—	—	—	—	Homeopathic internal
Bromelain	—	—	—	Botanical internal	—	—	—	—
Calendula	—	—	Botanical internal, topical	Botanical topical	Botanical topical	Botanical topical	—	—
Chamomile	Botanical internal, topical	Botanical internal, topical	—	Botanical internal, topical	—	Botanical topical	Botanical internal	Botanical homeopathic internal
Comfrey	—	—	—	Botanical topical	—	—	—	—
Echinacea	Botanical internal, topical	Botanical internal, topical	Botanical internal, topical	Botanical internal	—	Botanic homeopathic topical	—	—
Ephedra	—	—	—	—	—	—	Botanical internal	—
Goldenseal	—	Botanical internal, topical	Botanical internal, topical	Botanical topical	Botanical internal, topical	Botanical topical	—	—
Hypericum	—	—	—	—	—	Homeopathic topical, internal	—	Homeopathic internal
Peppermint	—	—	—	—	—	—	Botanical internal, topical	—
Plantain	—	—	—	—	Botanical topical	Botanical topical	—	—
Rhus toxicodendron	—	—	—	Homeopathic topical, internal	Botanical topical	—	—	—
Witch hazel	—	—	—	—	Botanical topical	—	—	—

has a long history of use to treat various conditions, including motion sickness, headache, seizures, vertigo, pharyngitis, bronchitis, influenza, tonsillitis, sinusitis, epistaxis (nosebleed), inflammations, constipation, and cystitis.

Cockle

Indian cockle (*Cocculus indica*) is used to treat motion sickness, vertigo, nausea, and jet lag and to restore normal sleep cycle.

Hypericum

The tincture comes from the whole fresh plant and flowers of St John's wort (*Hypericum perforatum*). Indications include any pain that affects the peripheral or central nervous system and exhibits shooting pains that travel in a dermatomal pattern (e.g., sciatica). Wounds that affect nerve endings, such as injuries to fingers, toes, or teeth, are improved by hypericum. Pain from dental surgery, toothache, injury to the coccyx, and first- and second-degree dermal burns are other indications.

Ledum

Ledum is made from leaves and stems of the whole fresh plant of wild rosemary (*Ledum palustre*). Homeopathic indications include puncture wounds from small, sharp objects (e.g., nails, needles) and some mosquito bites when the injured area feels cold, swollen, and numb and the pain would be relieved by application of cold.

Poison Nut

From the seeds, blossoms, and bark of *Strychnos nux-vomica* (nux vomica, poison nut) come the highly poisonous, intensely bitter alkaloids strychnine and brucine. As a homeopathic preparation, nux vomica may be the most diversely useful remedy for common diseases. It should be considered during bouts of influenza and with associated GI symptoms of vomiting and diarrhea. Nux vomica is probably the most helpful remedy for hangover from ingestion of alcohol. Other indications include nausea, heartburn, headache, vertigo, GI cramping, colic, constipation, upset stomach, cystitis, allergic rhinitis, cough, asthma, sinusitis, pain, and stiffness.[20,21,60,104,140]

Rhus

The homeopathic preparation of *Rhus* comes from leaves and stems of the whole fresh plant of poison ivy. This is the remedy of choice for the urticaria caused by poison ivy exposure and is also helpful for some cases of poison oak. Other skin rashes that are red, weeping, blistered, and swollen with itching can be treated with *Rhus*. It is also effective for treatment of connective tissue irritations with swelling, stiffness, and tightness. *Rhus* is often used for overuse injuries (e.g., fasciitis, tendinitis) and some forms of arthritis, especially when the injured area feels better with warm applications and movement. Note that the name of this preparation may change, because *Toxicodendron* is now the correct name of the genus.

COMBINATION PREPARATIONS FOR ACUTE SPRAINS AND STRAINS

Homeopathy companies have created combination remedies for the general public that can be used without the need for in-depth understanding of homeopathic prescribing. These remedies are designed to cover a broad range of symptoms associated with acute ailments and trauma-induced medical conditions. They are sometimes touted to be effective for many disorders on the basis of empirical observations, rather than on the basis of randomized, blinded studies. Practitioners are advised to be aware of the possibility for unsubstantiated claims of clinical efficacy for these and any other medications marketed for profit.

Traumeel is a combination homeopathic formula that is effective for treatment of trauma and inflammatory changes affecting skin, connective tissue, and muscle.[67] The preparation comes in liquid, tablet, and ointment form. Traumeel includes remedies indicated for traumatic injuries (sprains, strains, contusions) and resulting pain, swelling, and ecchymoses. Many German studies have demonstrated its effectiveness.[33] Traumeel may be the primary homeopathic medicine chosen for the first-aid kit because of its wide range of applications and multiple delivery systems.

Inflamyar ointment is a uniquely formulated homeopathic medicine that combines eight ingredients to provide treatment of traumatic sports-related injuries, such as sprains, bruises, and muscle strains. This formula developed from a long tradition of German homeopathic salves also is available as a homeopathic tincture. It has been used with great success for immediate relief and resolution of bursitis, sciatica, and acute and chronic inflammation, as well as pain of rheumatic and arthritic conditions. After strenuous exercise, massaging Inflamyar into tender points will help prevent soreness the next day. Routine self-massage with Inflamyar into tender points has been shown to restore flexibility and elasticity to muscles, tendons, and ligaments.

Herbal Combination Formulas

In the tradition of Chinese herbal medicine, many formulas have been developed over the centuries to treat acute ailments. Many of these formulas were kept secret and reserved for the nobility and ruling class. As the field of Chinese herbology has become more accessible to the general population, some of the secret formulas have been mass-produced into convenient pill form, known as "patent medicines." Many are extremely useful for acute conditions.

Zheng Gu Shui ("Rectify Bones Liquid") trauma lotion is used for sprains, strains, and bruises. It is also indicated for back pain and arthritis pain. The herbs of which it is composed invigorate circulation, relieve pain, induce a pleasant warming feeling, and accelerate healing. This formula has long been a mainstay of martial artists, massage therapists, and Chinese herbalists. It should be applied to affected areas two to three times daily, keeping the liquid away from mucous membranes and open cuts. It accelerates resolution of bruises and connective tissue injuries, reducing swelling, pain, and inflammation. It is produced by Guangxi Yulin Pharmaceutical Factory, which is well known in China and has been honored with awards for quality and effectiveness. This product can be ordered through the Institute for Traditional Medicine (ITM; see Appendix at the end of this chapter) and from most Chinese herbal pharmacies.

NUTRITIONAL SUPPLEMENTS

For immune system support, antiinflammatory action, and pain relief, many natural products in the nutritional supplement category have proved to be effective agents.

Bromelain

Bromelain is a naturally occurring proteolytic enzyme found in pineapple that is used to reduce pain and swelling after sprains and strains of soft tissues. Ingested on an empty stomach, the complex proteases in bromelain are absorbed intact and have significant antiedema, antiinflammatory, and coagulation-inhibiting effects. Bromelain exhibits fibrinolytic activity and acts to inhibit fibrinogen synthesis, decreasing kininogen and bradykinins.[119] For treatment of injuries and postsurgical recovery, 125 to 400 mg is ingested three times daily at 30 minutes before or 90 minutes after a meal. Bromelain is nontoxic even at high doses and is generally prepared as 100-mg tablets.

Papain

As with bromelain, papain is a naturally occurring plant enzyme (from papaya fruit) that exhibits proteolytic activity. Papain is generally used externally to neutralize bee, ant, or wasp venom. It is available as commercial meat tenderizer (e.g., Adolph's) or in tablet form. After removal of the stinger, a thick paste is prepared from water and tenderizer (or five or six crushed tablets) and applied to the area as soon as possible.

A convenient form that contains bromelain, papain, and pancreas-derived proteolytic enzymes is the product Wobenzym. This product has had decades of use in addition to clinical trials to back its claims as an effective proteolytic antiinflammatory. Suggested use is three tablets three times a day or as directed by the practitioner. Wobenzym N is taken on an empty stomach at least 45 minutes before meals.

Vitamin C

Ascorbic acid has both wound-healing and antiinflammatory effects. Vitamin C is required for hydroxylation of proline and subsequently for synthesis of effective collagen. Studies have shown that the stress associated with injury and wound healing results in an increased need for vitamin C.[125] For acute trauma and acute upper respiratory allergy, vitamin C in larger doses (2 to 5 g/day in divided doses) has been claimed to reduce anaphylactic reactions and recovery time.[77] Therefore, for any traumatic event, high-dose vitamin C should be administered as part of the treatment.

Vitamin D_3

Classically known in deficiency to cause rickets, vitamin D_3 has demonstrated profound impact on the immune system. It has been stated that no other single nutrient supplement could save more health costs and provide more prevention. Vitamin D_3 is available in capsule or liquid form. Daily doses of 1000 to 5000 international units (IU) are recognized to support health and wellness, decrease susceptibility to multiple cancers, and enhance the glucose-insulin response, among other benefits. During travel, increased dosing may offer protection from communicable infections or may help clear upper respiratory conditions more quickly.

FOR ACUTE GASTROENTERITIS

Pill Curing (Kang Ning Wan, "Healthy Quiet Pill"), botanically called Coix Formula, consists of 16 herbal medicines that are collectively effective for relieving disturbances caused by motion sickness, food poisoning, overeating, excessive alcohol consumption (nausea, headache, vomiting), difficulty passing stool, loose stools, and GI cramping and pain. Coix Formula is currently produced in a convenient globule form. One or two capfuls of globules are swallowed with warm water every hour until symptoms improve. Relief should occur within 4 hours of administration. Pill Curing (or Culing) is also available as a Chinese patent (or prepared) medicine from ITM or from a Chinese herbal pharmacy. The package includes 10 vials; the usual dose is 1 to 2 vials, each containing multiple small pilules to be swallowed all at once. Relief is generally within hours. This is an all-purpose remedy claimed to be useful for everything from traveler's diarrhea, to hangover, to the common cold. Coix Formula is well known to provide relief from motion sickness, food poisoning, excessive eating, drinking alcohol, nausea, headache, vomiting, diarrhea, constipation, GI cramping, and generalized pain.

Diarrhea

While using botanicals or any other remedy for diarrhea, it is critical to continue to maintain adequate hydration through oral and IV means as necessary. The primary medical risk of common diarrhea still remains dehydration.

Travelers may use a pharmaceutical, such as loperamide, to limit or stop diarrhea. Botanicals may help to quiet the intestinal tract, although typically not as aggressively as do pharmaceutical agents. Most botanicals that help to relieve diarrhea contain the compounds tannin, pectin, and mucilage. Tannins have astringent action that decreases intestinal inflammation. Pectin is a soluble fiber that adds bulk to the stool and soothes the gut. Pectin is the "pectate" in the OTC antidiarrheal medicine Kaopectate. Mucilage soothes the digestive tract and adds bulk to the stool by absorbing water and decreasing swelling.

Agrimony (*Agrimonia eupatoria*) contains high amounts of tannin and is endorsed by the German Commission E for common diarrhea. Apple (*Malus domestica*) pulp is high in pectin, which is amphoteric, acting as a remedy for diarrhea and helping with constipation because of its action as a stool softener. Bilberry and blueberry (*Vaccinium* spp.) are rich in both pectin and tannins and thus offer relief for common diarrhea. Blackberry and raspberry (*Rubus* spp.) are also both high in tannins and may be effective in the treatment of diarrhea. Carob (*Ceratonia siliqua*) powder has been shown to reduce diarrhea duration by as much as 50% in children with bacterial or viral diarrhea.

Cooked carrots (*Daucus carota*) are good choices for adults or infants with diarrhea. Carrots soothe the digestive tract, decrease diarrhea, and provide vitamins and minerals often lost during sickness. Fenugreek (*Trigonella foenum-graecum*) seeds contain up to 50% mucilage. They swell in the gut to relieve diarrhea and also soften the stool, having amphoteric action like apple. Portions should be limited to avoid gut irritability that may be experienced with too large a dose.

Oak (*Quercus* spp.) in the form of a tea made from 2 tsp of dried oak bark is recommended by the German Commission E for treating diarrhea. Psyllium (*Plantago ovata*) is known for its use in relieving constipation; it also has a high mucilage content that makes it useful for treating diarrhea (amphoteric). Caution is advised with this botanical, as for many others; if allergic symptoms arise after its use, it should not be further used.

FOR ACUTE HEMORRHAGIC CONDITIONS

The product Yunnan Bai Yao ("Yunnan white medicine"), produced in the western Chinese province of Yunnan, has been used for centuries as a first-line approach to trauma that results in internal or external bleeding. It is prescribed in China for excessive menstrual cramps and bleeding, bleeding ulcers, trauma-induced swelling, bleeding wounds, and allergic reactions to insect bites. It comes in powder (4 g per bottle) and capsule (packets of 20) form and contains one red pellet that is to be ingested only for serious bleeding conditions. Dose is 1 to 2 capsules four times daily. The powder can be applied externally after the wound has been properly cleaned. This product is exclusively produced in China from a proprietary formula and can be obtained from most Chinese herbal pharmacies. Other botanicals recognized for anticoagulant properties include clove (*Syzygium aromaticum*) and helichrysum (*Helichrysum italicum*).[103] Each of these also is reported to offer antiseptic activity.

FOR DERMATOLOGIC CONDITIONS

SssstingStop Gel

The Boericke and Tafel SssstingStop gel is for temporary relief of itch, pain, and redness of nonpoisonous insect bites and stings from insects, including mosquitoes, bees, and wasps. It also soothes fever blisters and cold sores. According to Boericke and Tafel, the London School of Hygiene and Tropical Medicine conducted two clinical studies using mosquitoes not fed for 24 hours and human volunteers and reportedly proved that the medicines in SssstingStop provide dependable, effective relief.

SssstingStop combines three natural homeopathic medicines prepared from botanical sources and listed in the *Homeopathic Pharmacopoeia of the United States* (HPUS). It contains no hydrocortisone or other steroids, antihistamines, "-caine" anesthetics, or any synthetic medicines. It is applied to the affected skin area, with applications repeated as needed. Ingredients are *Echinacea angustifolia* (1×, 10%), *Ledum palustre* (1×, 10%), *Urtica dioica* (1×, 10%), and citronella and eucalyptus oils in a water-gel base.

Ching Wang Hun (or Jing Wan Hong) Burn Ointment

This rapid-acting analgesic and burn-healing salve is a remarkable herbal medicine. It is effective for chemical, thermal, electrical, radiation, and solar burns. It can also be used to decrease inflammation and stimulate regeneration of the skin and is used for contact dermatitis (poison oak, ivy, sumac), hemorrhoids, and infected skin. The ointment is applied liberally to the affected areas. Ideally, it is covered with a dressing to prevent accumulation of dirt and grime and to reduce the red stain that occurs if the ointment contacts clothing. It should be reapplied and the dressing changed once or twice a day. This ointment is made by one of the best-known manufacturers in China and can be ordered through ITM (see Appendix) and from most Chinese herbal pharmacies.

Other Skin Therapies

Other botanicals with applications for skin conditions should be considered for inclusion in the travel first-aid kit. As

previously noted, aloe (*Aloe vera*) has been used since ancient times to treat burns and other wounds and trauma. Arnica (*Arnica montana*) is well recognized for its efficacy to treat trauma, bruises, swelling, and other wounds. Comfrey (*Symphytum officinale*) has been used since ancient Greece for skin problems. Activated charcoal is indicated for a wide variety of poisonous plant and other topical dermatological conditions. In these cases, activated charcoal poultices may be applied topically.

FOR GENERAL HEALTH AND WELLNESS

It is always advisable to begin travel in a healthy condition, which should include pretravel preparations. Certain botanicals are useful to enhance the immune system and act as a general tonic. Teas, capsules, and powdered preparations that promote general health and wellness are available with multiple botanicals combined. These typically may include gingko biloba, American or Asian ginseng (*Panax quinquefolius* or *P. ginseng*), echinacea (*Echinacea* spp.), evening primrose (*Oenothera biennis*), garlic (*Allium sativum*), gotu kola (*Centella asiatica*), milk thistle (*Silybum marianum*), peppermint (*Mentha piperita*), purslane (*Portulaca oleracea*), thyme (*Thymus vulgaris*), chamomile (*Matricaria recutita*), and horsetail (*Equisetum arvense*). These and other botanical combinations provide antioxidant, antiaging, and antiinflammatory effects and may help promote better energy, clearer thinking, better mood, emotional stability, desirable enhanced hormone levels, and general immune support.

JET LAG AND TRAVEL FATIGUE[64]

St John's wort (*Hypericum perforatum*) is a common OTC remedy that is one of the most widely used botanicals in Europe. It contains the compound hypericum, which shows significant improvement for anxiety, depression, and feelings of worthlessness in clinical studies. Some studies have also shown beneficial effects to improve sleep quality. Once thought to be caused primarily by a monoamine oxidase (MAO) inhibitor effect, studies now indicate that additional influencing compounds are present, and that their combination yields the clinical result without side effects. *St John's wort is not advised during pregnancy.*

Lemon balm or Melissa (*Melissa officinalis*) is recommended by the German Commission E as a sedative and to soothe the stomach. Active compounds include terpenes, which are also found in juniper, ginger, basil, and clove, although none has a reputation as a bedtime herb comparable to lemon balm. Valerian root (*Valerian officinalis*), another botanical endorsed by the German Commission E for promotion of sleep, is usually taken as a tea, although capsules may be easier for travel. It has also been recommended for anxiety, restlessness, and nervousness. More than 80 OTC sleeping aids in the United Kingdom (UK) contain valerian root. The common hangover feeling often associated with prescription anxiety and sleep medications is not prevalent with this plant remedy.

Lavender (*Lavandula* spp.) is typically used in massage oil or diffused into the air to promote relaxation and rest, as well as to reduce irritability. Be aware, however, that some species of lavender, notably Spanish lavender, are actually stimulants. Passionflower (*Passiflora incarnata*) is a mild sedative and is included in more than 40 OTC sleep preparations in the UK. Despite extensive use worldwide for centuries to treat nervous tension, anxiety, and insomnia, the FDA has not approved this botanical remedy. Chamomile (*Matricaria recutita*) tea has been used as a bedtime beverage for centuries. The constituent chemical apigenin is one of the most effective sedative botanical compounds. Rooibos (*Aspalathus linearis*) is a shrubby African legume that is a favorite for bedtime tea among many South Africans. Its popularity has spread to the United States. In addition to promoting sleep, it is used to calm the digestive tract and reduce nervous tension.[53] Homeopathically, *Cocculus indicus* may be very useful for jet lag and to help restore the normal sleep/wake cycles in the new destination.

MOTION SICKNESS AND SEASICKNESS

Cocculus indicus and tabacum are two leading homeopathic remedies for motion sickness and seasickness. Ginger has been used traditionally for acute motion sickness as well as other causes of simple dyspepsia. As a quick and easy travel method, take ½ tsp of fresh ginger, finely dice it, and swallow it whole.

COUGH, COLD, AND FLU

The Great Plains Indians chewed echinacea, the mountain daisy or coneflower, for centuries to treat colds, flu, and other ailments (see earlier discussion). Naturopathic and integrative medical physicians encourage using echinacea for general immune support. Echinacea increases a chemical in the body called properdin, which activates the immune system[53] and is responsible for increasing defense against viruses and bacteria. Echinacea extracts have demonstrated antiviral activity against influenza, herpes, and other viruses.

Garlic (*Allium sativum*) contains the chemical allicin, one of the plant kingdom's most potent, broad-spectrum antibiotics. Ginger (*Zingiber officinale*) contains nearly a dozen antiviral compounds, including sesquiterpenes that have specific action against rhinoviruses. Other compounds include gingerols and shogaols, known to relieve pain and fever, suppress cough, and mildly sedate to encourage rest. Onion (*Allium cepa*) is closely related to garlic and has similar antiviral activities. Citrus fruits and other plants containing vitamin C are important as a part of the diet or as a supplement to reduce severity and duration of cold symptoms.[79] Amazonian fruit camu camu (*Myrciaria dubia*) has the world's highest vitamin C content, and other good sources include acerola, bell peppers, cantaloupe, and pineapple.

Elderberry (*Sambucus nigra*) is a herb containing two compounds that are active against influenza viruses. It also prevents the virus from invading respiratory tract cells. The patented drug Sambucol contains elderberry and has demonstrated antiviral activity in preliminary trials against Epstein-Barr virus, herpesvirus, and HIV. Forsythia (*Forsythia suspensa*) and honeysuckle (*Lonicera japonica*) are common Chinese traditional approaches to treating colds and influenza. Anise (*Pimpinella anisum*) is recognized by the German Commission E as an expectorant. In larger doses, anise has antiviral properties. Ephedra (*Ephedra sinica*) is known as Ma Huang in traditional Chinese medicine and has long been used as a potent decongestant. Ephedra's chemicals, ephedrine and pseudoephedrine, dilate bronchial airways. Caution is important because the compounds in ephedra may also lead to elevated blood pressure, insomnia, and agitation. The FDA has placed restrictions on their distribution because of occasional deaths, especially with overuse.

PAIN AND TRAUMA[64]

It is critically important that a competent health care provider provide a proper evaluation for the patient who presents with pain. A number of botanicals should be considered for treating pain.

As previously mentioned, aloe (*Aloe vera*) has been used since ancient times to treat burns and other wounds and trauma. Arnica (*Arnica montana*), or coneflower, is well recognized for its efficacy to treat trauma, bruises, swelling, and other wounds. Calendula (*Calendula officinalis*) reduces inflammation and promotes wound healing. Clove (*Syzygium aromaticus*) has been recognized for its usefulness for dental pain. Clove oil is applied directly to the gum and tooth involved. Evening primrose (*Oenothera biennis*) is rich in the amino acid tryptophan. Studies have demonstrated that tryptophan supplements are effective in relieving pain of acute and chronic conditions. Although the oil has been often recommended by some, much of the tryptophan is lost in the oil extraction process, so powdered seeds should be a better choice. Ginger (*Zingiber officinale*) is a highly effective pain reliever. Furthermore, ginger may be applied to painful areas topically, such as with hot ginger compresses for abdominal

cramps, headache, or joint pain. Kava kava (*Piper methysticum*) is a tropical herb that has demonstrated analgesic effectiveness comparable to aspirin. Chewing the leaves leads to mouth numbness, and therefore kava kava can be useful for dental pain, canker sores, and sore throat.

Peppermint (*Mentha piperita*) contains menthol, which has anesthetic effects. Because peppermint oil is typically very concentrated, mix a few drops in a tablespoon of coconut or olive oil to decrease the potential to irritate the skin. Never drink peppermint oil, because a small amount can be toxic. Red pepper (*Capsicum* spp.) has become a popular natural choice for pain therapy, both in OTC and pharmaceutical preparations. Pain-relieving compounds called salicylates, similar to salicins, are the botanical equivalent of aspirin. Additionally, the red peppers contain capsaicin, a compound that stimulates the body's natural endorphins and depletes the pain transmitter substance P. One should wash hands thoroughly after applying capsaicin-containing cream so as not to rub it accidentally into the eyes. It is best first to use a small portion on a limited skin area to determine that it will be tolerated and to be able to discontinue use promptly if it leads to skin irritation.

Turmeric (*Curcuma longa*) is found in curries and has long been a staple of South Asian cuisine. It has some of the most potent botanical antiinflammatory properties known. Turmeric has recently gained recognition and popularity. Willow bark (*Salix* spp.) contains salicin, from which aspirin was derived approximately 100 years ago. Willow may provide relief for a wide variety of pains. It should be avoided by persons who are allergic to aspirin compounds. Do not give willow or similar products to young children who have a viral syndrome, because of the risk of inducing Reye's syndrome.

FROSTBITE, HEAT EXHAUSTION, AND HEATSTROKE[64]

Ginkgo biloba should be considered as a botanical approach to managing frostbite or chilblains. Containing numerous compounds that include terpenes, flavones, proanthocyanidins, and ginkgolides, *Ginkgo* can improve arterial and venous circulation, especially in the brain, eyes, ears, and limbs. It may scavenge free radicals, perhaps the mechanism for its protective effect on vasculature. Common dosing is 50 mg up to three times daily.

Aloe (*Aloe vera*) is indicated for frostbite. Common oak (*Quercus rubor*) has astringent properties. It can be applied topically as a poultice of the leaves, bark, and acorns or as a tea or capsule. Lungwort (*Pulmonaria officinalis*), commonly known in French as "the cardia herb," has been recognized as being of benefit for frostbite. Black walnut (*Juglans nigra*) has been mentioned as a remedy for frostbite.

Sunstroke (heatstroke) and overheating may be addressed with a variety of botanicals to cool the body and help dispel excess heat. American ginseng (*Panax quinquefolius*) and Siberian ginseng (*Eleutherococcus senticosus*), both prepared as a tea, are noted for efficacy in heat exhaustion. Peppermint (*Mentha piperita*) should be considered as a cool forehead compress or used orally. Black mulberry *(Morus nigra*) may be beneficial, prepared as a tea. Passionflower (*Passiflora incarnata)* is also noted for clinical benefits to treat heatstroke and heat exhaustion.

ACTIVATED CHARCOAL FOR TRAVEL[64]*

Activated charcoal is an exciting natural remedy from the botanical world that is deceptively ordinary at first appearance. It possesses extraordinary properties that may help to clear toxins, fight microbial infections, and offer other significant health-producing effects.

Charcoal is the blackened residual of burning wood and other products, before complete consumption. For the purpose of medicinal care, hardwoods, coconut shells, and bones are the most common starting materials, and commercial medical- or food-grade charcoal is called *activated charcoal*. Activated charcoal is further processed by exposing the source material to gas or to oxygen or steam at extremely high temperatures, resulting in a carbonization or oxidation process that renders the material to be microporous, with pores measuring 1 micron in high-quality activated charcoal. Because of this microporosity, 1 g (¼ tbsp) has a surface area of 500 to 1500+ m^2, as determined by gas adsorption.

Activated charcoal is listed by the FDA as a Class I "safe and effective" agent to treat acute poisoning. It adsorbs gases, liquid, and dissolved solids by having them adhere within the microporous structure. This occurs due to the structural framework and resultant van der Waals forces.

Medicinal activated charcoal is available in powder, tablet, capsule, and even toothpaste form and can be used internally and topically for a diverse set of clinical conditions. In addition to adsorbing certain toxins, it can also adsorb and thereby inactivate bacteria, viruses, fungi, and parasites. Charcoal filters are used in many portable and industrial water-treatment devices and are readily available in lightweight, portable containers.

Plant and Other Poisons or Medications Neutralized by Activated Charcoal

Plant poisonings may be neutralized by activated charcoal (Box 68-2). Activated charcoal poultices may be applied topically for poison ivy or stinging nettle skin reactions or internally when these plants are internally consumed.[165a]

When the amount of poison consumed is unknown, a general rule is to administer 1 g of activated charcoal per kilogram of body weight, or about 0.5 g of activated charcoal per pound of body weight.

How to Make an Activated Charcoal Poultice

Activated charcoal poultices are easy to make and may provide benefit for many topical illnesses. For its simplest application, pure charcoal powder may be sprinkled on wounds, including skin ulcers, abrasions, lacerations, and decubitus ulcers. Activated charcoal may be applied with a gauze, muslin cloth, or paper towel underneath to provide a barrier between the activated charcoal powder and the topical surface. Using this technique, the poultice may also be applied over the closed eyelids for eye infections, on the ears for otitis, in the nose for hemostasis of epistaxis, and on the skin for ant bites, bee/wasp stings, scorpion stings, or spider bites,[21a,51] and for topical eruptions such as from poison ivy, oak, or sumac. In any circumstance where a practitioner uses a naturopathic remedy instead of or in addition to an accepted allopathic remedy for a potentially life-threatening situation, it must be done in full recognition of the quality of the science supporting the remedy.

It is imperative that the activated charcoal poultice be sufficiently moistened that the dressing remains moist for 10 to 12 hours. A dry poultice will not adsorb and neutralize the intended target. An excellent poultice may be made from equal parts of powdered or blended activated charcoal and ground flaxseed, or

BOX 68-2 Botanical Poisons Neutralized by Activated Charcoal

Alder
Autumn crocus
Azalea
Black nightshade
Bryony
Buckthorn berry
Christmas rose
Daphne
Deadly nightshade
Foxglove
Hemlock
Holly berry
Honeysuckle berry
Jerusalem cherry
Laburnum
Lily of the valley
Mistletoe
Monkshood
Oleander
Poison ivy
Poison oak
Poison sumac
Privet berry
Rhodendron
Savin juniper
Spindle tree berry
Thorn apple
Woody nightshade
Yew

*NOTE: Consultation with a competent health care professional is appropriate for all infectious illnesses. *Do not delay consultation* if you are using activated charcoal.

with therapeutic clay such as bentonite or zeolite. After changing the poultice, discard the used poultice.

Although a tattooing effect when applying charcoal on open wounds may be a concern, this does not generally seem to be an issue and should be minimized if the charcoal is placed with a barrier (e.g., moist gauze, muslin cloth, paper towel) against the wound surface.

ESSENTIAL OIL REMEDIES FOR TRAVEL[64]

Essential oils are natural aromatic compounds found in the seeds, bark, stems, roots, flowers, and other parts of plants. Potent and widely used botanical products, they are extracted through steam distillation and cold pressing. Essential oils provide many opportunities for maintaining health and wellness during travel. Highly fragrant, the aromatherapeutic uses are only a part of essential oil–rich benefits. Essential oils typically deliver quick and potent clinical effects because the oils are much more powerful and effective than the dry herbal products. Essential oils may be diffused, inhaled, placed in baths, applied topically, or taken internally for a variety of ailments. Essential oils are well absorbed but do not build up in the body; they are excreted after yielding their benefits.

Historically, cinnamon, frankincense, myrrh, and sandalwood were considered very valuable and at times were exchanged for gold along the ancient trade routes. French chemist René-Maurice Gattefossé is credited with rediscovering the benefits of essential oils in modern times, having treated a severely burned hand with pure lavender oil in 1937.* Dr. Jean Valnet, a contemporary of Gattefossé, successfully treated injured soldiers during World War II using therapeutic-grade essential oils. He continued his work with essential oils and became a renowned world leader in development of aromatherapy practices.

Manufacture of essential oils is a highly specialized process and requires large amounts of raw materials for distillation of the oils. For example, as many as 12,000 rose blossoms are required to distill 5 mL of essential rose oil; 100 pounds of plant material is required to produce 1 pound of lavender essential oil. Certain citrus oils are extracted by compression and others by using solvents, which are later removed from the final product.

Essential oils are thought to activate the brain's limbic system.† The odor of fragrant essences also stimulates various hormones and other metabolic processes. Olfactory responses to various fragrances have been documented extensively. The oils may be used individually or in complex blends, depending on user experience and desired benefits.

Many essential oils have antibacterial, antifungal, and antiviral properties. Essential oils that are best for cleaning include lemon, grapefruit, eucalyptus, peppermint, tea tree, lavender, and rosemary.

Thieves blend essential oil was developed based on the ingredients found in the "Four Thieves Vinegar" or "Marseilles Vinegar," which was used to protect against the plague in the 15th century; this essential oil blend was prepared by thieves and grave robbers who wanted protection from the plague and other ailments.[165] Diffusing Thieves blend of cinnamon, clove, eucalyptus, lemon, and rosemary oils can kill 99% of airborne bacteria in 12 minutes. This makes Thieves blend a consideration for airline and other similar crowded travel (Box 68-3).

Use of Essential Oils during Travel

Essential oils typically come as single or blended combinations in small bottles of 5 to 15 mL. Based on the particular clinical need, as highlighted next, one is able to choose an essential oil collection and use the drops in a diffuser or directly from the bottle to inhale, placed on the palmar wrists and areas of distress and rubbed in topically, or taken orally as a drop or in water. It is very important *only* to use the essential oils "neat" (no dilution) when so indicated and only to take those essential oils internally that are approved for this use. Some essential oils need to be diluted for either topical or oral use. The recommended amount of essential oil remedies and acceptable methods of use should be listed on the package or container.

Aromatic Uses. When diffused into the air, essential oils can be either stimulating or calming and soothing. Beyond their emotional benefits, diffusing essential oil can rid air of unwanted odors and some airborne pathogens. Oil diffusers with low or no heat are recommended to minimize any change in the chemical structure of the oil. Rosemary, lavender, peppermint, grapefruit, chamomile, lemon, and ylang ylang essential oils have been shown to calm the mind and emotions, as well as enhance memory and test performance. Clary sage oil helps with premenstrual syndrome (PMS). It should not be overused for this or any other purpose.

Topical Uses. Essential oils may be easily absorbed by the skin and may be safely applied topically to unbroken surfaces because of their microparticle composition. Essential oils often yield a prompt local benefit to the treated area. Chamomile specifically has been shown to decrease hives. Highly favored for massage and beauty therapies, essential oils have calming as well as restorative properties; furthermore, some are natural disinfectants. Topical essential oils should usually be blended with other oils, waxes, or alcohols. Citrus essential oils should not be applied when there will be direct sunlight exposure.

Essential oils that are generally regarded as safe to use undiluted on the skin include lavender, German chamomile, tea tree, sandalwood, and rose geranium. It is especially important only to use half-strength (or more dilute) oils on children and infants. Box 68-4 lists essential oils that are generally considered safe for infants and children.

BOX 68-3 Thieves Blend Essential Oil Properties

Cinnamon bark (*Cinnamonum verum*): Antiseptic, antiviral, antibacterial, antifungal, COX inhibitor (antiinflammatory), a strong oxygenator
Clove (*Syzygium aromaticum*): Antiseptic, antiviral, antifungal, COX inhibitor (antiinflammatory), one of the highest ORAC (Oxygen Radical Absorbance Capacity) values of any plant in the world*
Eucalyptus (*Eucalyptus radiata*): Antiinflammatory, antiseptic, antiviral, antibacterial, antifungal, supports respiratory system
Lemon (*Citrus limon*): Antiseptic, immune stimulating, purifying and uplifting
Rosemary (*Rosmarius officinalis*, CT cineol): Antiseptic, antiinfectious, reduces mental fatigue, eases anxiety

*www.orac-info-portal.de/download/ORAC_R2.pdf.

BOX 68-4 Essential Oils Generally Safe for Infants and Children

Bergamot (*Citrus bergamia*)*
Cedarwood (*Cedrus atlantica*)*
Chamomile, Roman (*Chamaemelum nobile*)
Cypress (*Cupressus sempervirens*)
Frankincense (*Boswellia carteri*)
Geranium (*Pelargonium graveolens*)
Ginger (*Zingiber officinale*)
Lavender (*Lavandula angustifolia*)
Lemon (*Citrus limon*)*
Mandarin (*Citrus reticulata*)*
Marjoram (*Origanum majorana*)
Melaleuca (tea tree) (*Melaleuca alternifolia*)
Orange (*Citrus aurantium*)*
Rose Otto (*Rosa damascena*)
Rosemary (*Rosmarinus officinalis*)*
Rosewood (*Aniba rosaeodora*)
Sandalwood (*Santalum album*)
Thyme (*Thumus vulgaris*, CT linalol)
Ylang ylang (*Cananga odorata*)

From www.abundanthealth4u.com/Essential_Oils_Care_for_Babies_and_Children_s/40.htm.
*Always use these in diluted form for infants and children.

*www.vanderbilt.edu/AnS/psychology/health_psychology/what_is_aromathery.html.

†www.yalescientific.org/2011/11/aromatherapy-exploring-olfaction/.

Internal Uses. Because of their microparticle composition, essential oils may be absorbed into the bloodstream from the skin for internal benefits. When used as dietary supplements, some essential oils have been shown to have powerful antioxidant properties, whereas others help support healthy antiinflammatory responses.[11] Although many essential oils are commonly regarded as safe for internal use, others should not be taken internally. *Only use essential oils internally if they have the appropriate dietary supplement facts on the label.*

It is highly recommended that only 100%-pure, therapeutic-grade essential oils be used in any manner, and all label warnings and instructions must be followed. CPTG (Certified Pure Therapeutic Grade) is the accepted standard for pure essential oils; the essential oils that carry this designation are guaranteed to be pure, natural, and free of synthetic compounds or contaminants. Essential oils should be stored in dark-colored bottles. Most remain potent for 5 to 10 years, whereas citrus essential oils retain potency for 1 to 2 years.

Common Essential Oil Remedies during Travel

Prevention. Using essential oils is a sound approach to maintaining health before and during travel. Because the oils are concentrated, the containers are small enough that a well-stocked travel kit does not require much space or weight in packing. Some of the most common essential oils to consider include lemon, grapefruit, eucalyptus, peppermint, tea tree (*Melaleuca*), lavender, and rosemary. One of the best essential oil combinations is the Thieves blend.[96]

Frankincense offers muscle relaxation and sedative support that may be very helpful to gain rest during travel. Likewise, lemon, orange, and valerian may be calming. Lemongrass is said to be a revitalizer. Patchouli is reported to be both a relaxant and a stimulant, as is ylang ylang. Other essential oils specifically reported as beneficial for jet lag and travel fatigue include eucalyptus, geranium, grapefruit, lavender, and peppermint.

Motion Sickness and Seasickness. Essential oils to consider for motion sickness include ginger, lavender, patchouli, and peppermint. With a few drops placed over the mastoid, at the base of the skull behind the ears, and also on the navel, relief may be quite rapid. When possible, a warm compress may be placed over the abdomen after applying the essential oil for further comfort. In addition, one may inhale the oils for 15 to 20 minutes or even place 1 to 2 drops on the tongue.

Cough, Cold, and Flu. Cough, colds, and flulike illnesses may often be cleared with the administration of essential oils by diffusion, orally, or topically. Many essential oils are antimicrobial and immune stimulants. Some also are mucolytic and anticatarrhal, reducing nasal congestion and thick mucus that often accompanying these ailments. Thieves blend can be used for all these conditions. Individual oils with antimicrobial benefits include blue tansy, citronella, clove, eucalyptus, frankincense, lemon, lemongrass, myrtle, patchouli, peppermint, rosemary, rosewood, and tea tree essential oils. Eucalyptus offers mucolytic and expectorant benefits, as do helichrysum, lemon, and myrtle.

Diarrhea, Dysentery, and Vomiting. Various essential oils calm the GI tract and may offer relief for episodes of diarrhea and vomiting, including fennel, lavender, nutmeg, patchouli, and peppermint. Nausea is covered in the section on motion sickness. Clove is known to protect the stomach. Lavender and valerian are antispasmodic and vermifuges (anthelmintics). Orange is an antispasmodic. Patchouli, peppermint, and rosemary are digestive aids. Essential oils should be considered for food poisoning; patchouli, peppermint, rosemary, tarragon, and the Thieves blend may be helpful. These may be taken as a few drops on the tongue or diluted in a small amount of water.

Pain and Trauma. Essential oils that have disinfectant properties include hyssop, oregano, tea tree, thyme, and Thieves blend. Helichrysum, rose otto, and geranium are known to help reduce bleeding, and clove, elemi, and myrrh should be considered for infected wounds. Essential oils that promote healing include Canadian hemlock, dorado azul, lavender, and tea tree. These may be used singly or blended and applied topically two to five times per day, diluting as indicated per essential oil used. Box 68-5 provides a recommended natural first-aid spray.

BOX 68-5 Essential Oils Natural First-Aid Spray

2 drops cypress
2 drops lavender
3 drops tea tree
Blend essential oils with ½ tsp of salt.
Add this blend to 8 oz of distilled water in a spray bottle.
Shake until dissolved.
Spray topically as indicated.

More than 60 different essential oils have been shown to have analgesic properties. Wintergreen essential oil contains 85% to 99% methyl salicylate. Peppermint, clove, and helichrysum should be considered to treat muscle pain. Dental pain may be treated with black pepper, clove, Idaho tansy, tea tree, and wintergreen. With these, one may apply the oil diluted 50:50 with water directly to the tooth and gum.

Box 68-6 lists essential oils that may be applied to insect bites and stings. Apply 1 to 2 drops directly on each bite or sting three to four times daily. In addition, various essential oils are excellent natural mosquito repellents (Box 68-6).

Frostbite. Conventional medical care is recommended, with integrative care to further promote healing. Essential oils may increase blood flow and provide gentle warming to frostbitten tissues. Essential oils to consider include helichrysum, peppermint, cypress, lavender, and marjoram. Apply 1 to 2 drops of the essential oil or blend topically to the affected areas and *very gently* massage the extremities to increase circulation and soothe the affected areas, followed by a mildly warm compress. Helichrysum is also known for nerve healing and regeneration. This approach may be repeated for a total of two or three treatments daily, even after the extremities are warmed, to provide relief and promote healing.

Heat Exhaustion and Heatstroke. After sunburn, lavender essential oil may be applied directly or in a 50:50 blend with water to promote a cooling sensation and healing of skin.

For heat exhaustion, remove clothing (if possible) and apply a cool, moist washcloth to the skin, adding peppermint essential oil for cooling sensation. Peppermint essential oil increases blood flow to the skin, perhaps helping the body to release heat more quickly and return to normal body temperature. Consider using peppermint mist in a spray bottle by adding 25 drops of peppermint essential oil to a 6-oz water bottle, and spray when feeling overheated.

Contraindications to Essential Oils on Travel

Essential oils should only be used during pregnancy under a competent physician's orders and care. Essential oils are *not* indicated for use in the eyes, ear canal, or open wounds. One may apply any natural oil, such as extra virgin, cold-pressed coconut oil or olive oil, to the affected area if redness or irritation develops while using essential oils topically.

BOX 68-6 Essential Oils for Insect Bites and Mosquito Repellent

Insect Bites/Stings
Basil
Eucalyptus
Lavender
Peppermint
Rosemary
Tea tree

Natural Mosquito Repellents
Basil
Blue cypress
Clove
Dorado azul
Eucalyptus globulus
Eucalyptus radiata
Geranium
Idaho tansy
Lavender
Lemon
Lemongrass
Peppermint
Thyme

INDICATIONS FOR BOTANICAL AND ESSENTIAL OIL REMEDIES

Boxes 68-7 and 68-8 list indications for botanical remedies and essential oil remedies, as used in the first-aid kit of natural products.

BOX 68-7 Botanical Remedies for Travel: Indications

Aloe vera gel, liquid, powder capsules: Promotes healing; burns, sunburn, abrasions, cuts, hives, frostbite, gastrointestinal distress, constipation
Anise: Mucolytic, expectorant, antiviral
Arnica ointment, capsules, tea, tincture: Disinfecting; wound healing; sprains, strains, bruises, dislocations, muscle pain, joint pain, bites, stings, sunburn
Calendula gel, ointment, tincture: Cuts, bruises, antiinflammatory, bites, stings, sunburn, antibacterial, antiviral, antifungal
Chamomile tincture: Relaxant, somnolent, antibacterial, antiviral, immune support, stings
Echinacea tincture or capsules: Immune support, cough, colds, flu, antibacterial, antiviral, antifungal, wound repair
Gingko biloba extracts, tinctures, capsules: Enhanced circulation, arrhythmias, altitude sickness, hangover, headache, frostbite, antioxidant, free radical scavenger, immune support
Hypericum* (St John's wort) capsule, ointment, tincture, tea: Jet lag, sedative, anxiolytic, antidepressant, bites, stings, scabies, bruises, cuts, burns, sunburn
Plantago capsule, tincture, tea: Diarrhea, constipation, burns, sunburn, bites, stings, poison ivy, laryngitis, pharyngitis, antibacterial, astringent
Valerian capsules, tincture, tea: Jet lag, sedative, antianxiety, arrhythmias, palpitations, improves circulation, lowers high blood pressure, improves cardiac output, gastrointestinal spasm
Coix Formula: Motion sickness, food poisoning, excessive eating and alcohol, nausea, headache, vomiting, diarrhea or constipation, gastrointestinal cramping, generalized pain
Zheng Gu Shui: Sprains, strains, bruises, muscle pain, arthritis pain

*Avoid in pregnancy, and use caution with sunlight.

BOX 68-8 Essential Oils: Indications*

Clove (*Syzygium aromaticum*): Antiinflammatory, antiseptic, antiviral, antibacterial, antifungal, antiinfectious, antiparasitic, antiaging, antioxidant, analgesic, anticoagulant, immune stimulant, anticonvulsant, disinfectant, stomach protectant, warming
Eucalyptus (*Eucalyptus globulus*): Antiviral, antibacterial, antifungal, antiaging, antiinfectious, antiinflammatory, antirheumatic, antiseptic, deodorant, insecticidal, mucolytic, expectorant
Frankincense (*Boswellia carterii*): Anticatarrhal, antidepressant, antiinfectious, antiseptic, expectorant, immune stimulant, muscle relaxant, sedative
Helichrysum (*Helichrysum italicum*): Antiviral, antiinflammatory, antispasmodic, expectorant, mucolytic, anesthetic, anticoagulant, anticatarrhal, antioxidant, liver stimulant/detoxifier, skin and nerve regenerator
Lavender (*Lavandula angustifolia*): Antifungal, analgesic, antiseptic, anticonvulsant, vasodilator, antispasmodic, antiinflammatory, vermifuge (anthelmintic)
Orange (*Citrus sinensis*): Antiseptic, antidepressant, antispasmodic, digestive aid, circulatory stimulant, sedative, tonic
Patchouli (*Pogostemon cablin*): Antiinflammatory, antifungal, antimicrobial, antiseptic, antitoxic, astringent, decongestant, deodorant, diuretic, insecticidal, stimulant, relaxant, digestive aid, tonic
Peppermint (*Mentha piperita*): Antiinflammatory, antiviral, antiparasitic, antibacterial, gallbladder, digestive stimulant, pain reliever, analgesic, antispasmodic
Rosemary (*Rosmarinus officinalis*): Antifungal, antibacterial, antiviral, antiparasitic, liver protecting, cardiotonic, digestive, detoxicant, anxiolytic
Tea tree (*Melaleuca alternifolia*): Antiviral, antibacterial, antifungal, antiparasitic, antiseptic, antiinflammatory, antioxidant, decongestant, immune stimulant, insecticidal, tissue regenerator
Ylang ylang (*Cananga odorata*): Antiinflammatory, antispasmodic, antiseptic, antidepressant, vasodilator, regulates heartbeat, antidiabetic, tonic, sedative

*For blended essential oils (Thieves blend), see Box 68-3.

Appendix

COMPANIES

BOIRON

Natural Home Health Care LeKit contains 36 single-remedy medicines in distinctive blue tubes, including the commercial flu remedy Oscillococcinum. The home kit also contains four external remedies: tinctures of calendula and hypericum, and ointments of arnica and calendula. Travel LeKit is a more compact collection of single remedies (22 multidose and 16 one-dose tubes) plus the flu remedy.

BIOLOGICAL HOMEOPATHIC INDUSTRIES (BHI)

BHI is the U.S. distributor of the German line of complex homeopathic remedies manufactured by Heel:
http://www.heel.com

BIORESOURCE INC.

BioResource Inc. is the U.S. distributor of quality German botanical and homeopathic medications such as Inflamyar ointment.
http://www.bioresourceinc.com

INSTITUTE FOR TRADITIONAL MEDICINE (ITM)

http://www.itmonline.org
ITM is a nonprofit resource for Chinese herbal medicines, patent formulas (prepared medicines), and professional herbal formulas for practitioners. Jintu is the nonprescription resource for the products listed here:
http://www.itmonline.org/jintu.

Website to access Wobenzym N and other products that are generally sold only to health care practitioners:
http://www.purepresciptions.com

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PRACTITIONERS

AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS

4435 Wisconsin Ave, NW, Suite 403
Washington, DC 20016
202-237-8150 telephone
866-538-2267 toll-free
202-237-8152 fax
http://www.naturopathic.org

HERBAL MEDICINES

HERB RESEARCH FOUNDATION

http://www.herbs.org

NUTRITIONAL PRODUCTS

CRANE HERB COMPANY

745 Falmouth Rd
Mashpee, MA 02649
800-227-4118
http://www.craneherb.com (registration required)

THORNE RESEARCH

25820 Highway 2 W
PO Box 25
Dover, ID 83825
800-228-1966
http://www.thorne.com

METAGENICS

100 Avenida La Pata
San Clemente, CA 92673
800-692-9400
http://www.metagenics.com

MOUNTAIN PEAK NUTRITIONALS

3310 SW Vista Dr
Portland, OR 97225
877-686-7325

VITAL NUTRIENTS

45 Kenneth Dooley Dr
Middletown, CT 06457
888-328-9992
http://www.vitalnutrients.net

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