Chapter 18

TOXINS FROM VENOMS AND POISONS

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INTRODUCTION

This chapter considers toxins that might be exploited as offensive biological weapons, or that may have medical relevance to deployed military personnel. The major characteristics of important toxin classes are summarized, and their medical effects are covered. Venom toxins are emphasized because little information is available about venomous animals in relation to military medicine. This chapter highlights selected plant, fungal, and animal toxins as examples of potent agents that target essential physiological processes, and it provides information that may facilitate recognition of types of envenoming or poisoning in an affected patient. This chapter also supports the perception that animal toxins are generally of low relevance to military applications, and contrarily, the relevant—but limited—nontactical importance of some plant and fungal toxins. This information is intended to increase awareness of the potential hazards posed by animal toxins that can be used for offensive applications on a small scale and also provide some important considerations about possible exposures to venomous and poisonous animals, plants, and mushrooms that might occur during military deployments.

The use in warfare of diverse animal-derived venoms, as well as the venomous animals themselves, has probably been contemplated for most of human history. The well-known mythical account of the second labor of Hercules slaying the malevolent nine-headed serpent, the Lernaean Hydra (Figure 18-1), featured him using venom-coated arrowheads to accomplish the deed. Some folklore scholars consider this to be the first description of the use of a bioweapon.[1] The practice may have been used in any of the ancient Greek Wars, and, as has been noted by numerous authors, the word toxic is derived from toxikon, Greek for poison arrow. This is one of the reasons why Findlay E Russell (1919–2012), in consultation with other founders of the International Society on Toxinology (IST), named the IST journal *Toxicon*. Circa 200 BCE, Hannibal reportedly used pottery containing venomous snakes to "bombard" opposing maritime vessels. The Roman Legion's assault on Hatra in 199 CE resulted in retaliation by civil forces that included the hurling of clay pots filled with scorpions over the walls.[1] Several Native American tribes (eg, Wishram, Yuma) used venom- or venom gland extract-coated arrowheads in warfare, and some such as the Achomawi and Karok used arrowheads dipped in rattlesnake organs or their extracts that they believed to be toxic.[2]

Historically, the offensive military use of venoms and their component toxins (all of natural origin) has been a rare and small-scaled occurrence. Venoms or venom-derived toxins have not generally been considered suitable for use as a mass offensive weapon; however, primarily fungal- or plant-derived toxins certainly have been weaponized (eg, ricin; see chapter 16). Using venoms as a weapon is also obviously distinct from the weaponization of toxins from bacteria.

However, many toxins found in animals, plants, and mushrooms are highly toxic—even lethal—to humans. These toxins, which can form the basis for developing tailored toxin derivatives for specific functions, are the subject of current intense research in the pharmaceutical industry. A well-known example is paclitaxel, a taxane initially derived from bark extract of the Western yew, *Taxus brevifolia*. Taxanes, such as paclitaxel, are potent cytotoxins that stabilize micro-

Figure 18-1. Hercules slaying the Lernaean Hydra. Illustration: Antonio del Pollaiolo, *Ercole e l'Idra e Ercole e Anteo*, Google Art Project. Wikimedia Commons, public domain. https://it.wikipedia.org/wiki/File:Antonio_del_Pollaiolo_-_Ercole_e_l%27Idra_e_Ercole_e_Anteo_-_Google_Art_Project.jpg.

tubule assembly, thereby disrupting physiological assembly/disassembly of microtubules in a guanosine triphosphate-independent manner.[3] These taxanes, which have a proven pharmacotherapeutic efficiency against a wide array of solid neoplasms, are a significant part of the chemotherapeutic armamentarium.

Several pharmacotherapeutics are derived from venom components, and some are in various stages of clinical trials. Two prominent examples are the entire class of antihypertensives: (1) the angiotensin-converting enzyme inhibitors (ACEIs) and (2) the parenteral insulin secretagogue exendin-4. Exendin-4 is a 39-amino acid peptide isolated from venom of the helodermatid lizard, the Gila monster (*Heloderma suspectum*), that has greater than 50% structural homology with glucagon-like peptide 1. Exendin-4 exhibits functional similarity with glucagon-like peptide 1, but has a longer half-life and biological stability. This peptide increases insulin secretion, accelerates gut emptying, and stimulates β-islet cell proliferation and survival, as well as other actions. It was tested as an antidiabetic agent and introduced as Byetta (Amylin Pharmaceuticals, San Diego, CA) in 2005.[4] Similarly, the ACEI arose from the study of bradykinin-potentiating oligopeptides present in several South American lance head pit vipers (eg, the jararaca, *Bothrops jararaca*, and others) in conjunction with study of the complex renin-angiotensin and kallikrein-kinin systems. Extensive investigation eventually resulted in teprotide, an early, parenterally administered ACEI, and eventually the first oral ACEI, Captopril (Par Pharmaceutical, Woodcliff Lake, NJ), was developed.[5] A broad variety of ACEIs have become among the three most frequently prescribed classes of antihypertensive medications in the United States and most of the world.

The potential threat posed by these toxins and their derivatives (as discussed further in the section on Relevance to Biological Warfare) relates mostly to their practicality for weaponization and delivery, rather than their inherent toxicity.

SOME DEFINITIONS: VENOMS, TOXINS, AND POISONS

Toxins are substances produced by living organisms (animals, plants, mushrooms, bacteria) that cause significant adverse effects when administered to another living organism, particularly those that offer the producing organism some advantage, either offensive or defensive.

Venoms are mixtures—often complex mixtures—of toxins produced in defined organs (usually venom glands) or organelles (eg, nematocysts/cnidocysts located in specialized cells and nematocytes/cnidocytes in jellyfish) that are delivered to the target organism usually using an evolved delivery system such as fangs or a stinging apparatus. Therefore, venom is delivered as an active process, and if sufficient (this may be minute in some cases) amounts are introduced into the target organism, it causes envenomation (also known as "envenoming"). Venom may be used defensively against predators (eg, stings from bees or venomous fish), but more commonly it is used offensively to assist in acquiring prey (eg, as by venomous snakes). Venom used offensively may be used to either kill or immobilize the prey, possibly aid digestion of the prey, or combine these functions, which may also be useful when venom is used defensively. The evolution of venom has been positively selected among a wide range of taxa, suggesting that it provides diverse organisms with selective advantages and fitness. The definition of venom from evolutionary, phylogenetic, and functional perspectives is actively debated.[6–10] The criteria defining the words venom and venomous and the related terminology may be subjected to interdisciplinary consensus in the future.[11]

Poisons are technically differentiated from venoms because they need to be ingested rather than injected (as venom is delivered) to induce their toxic effects. Animal, plant, or fungal toxins consist of individual or mixtures of toxins that are produced by the organism or, in some cases, by symbiotic bacteria (eg, the synthesis of tetrodotoxin by at least 18 microbial taxa, including *Vibrio* spp[12,13] and *Shewanella putrefaciens*[14]) that colonize the poisonous animal. These toxins are generally delivered in a passive and, in most cases, a defensive way to an organism attacking or trying to consume the toxin producer. Examples include tetrodotoxic fish that cause poisoning when eaten, some toads (eg, common African toad, *Amietophrynus regularis*) that exude toxins from parotid skin glands when mouthed by predators, and both poisonous plants and mushrooms when ingested. However, other animals such as several species of hedgehogs (eg, four-toed, spiny, or Cape hedgehog, *Atelerix albiventris pruneri*[15]) anoint their spines with toxic toad parotid secretions, and thereby can be considered to actively deter predators by exposing them to toad toxins via their spines. Therefore, in nature, poisoning by toxins is most often a passive process because the poison is introduced by the aggressor organism's actions. In terms of natural selection, it is often better to deter rather than kill a predator. When delivered at the typically delivered dose, the toxins in poisoning can often cause unpleasant but nonlethal effects. Clear exceptions exist when ingestion of only a tiny quantity of some of these poisonous organisms, because of their high lethal potency, can be fatal for humans.

NONWARFARE EPIDEMIOLOGY OF VENOM-INDUCED DISEASES AND RELATED TOXINS

Toxin-induced disease affects millions of humans every year. Detailed epidemiology is unavailable for any toxin-induced disease (other than selected microbial toxin diseases, and this information is often incomplete) at the global level, but more epidemiologic data may emerge for some key disease types, as a result of increasing international efforts directed at the improved management of regionally important venom diseases (eg, several snakebite initiatives). An approximate estimate of epidemiology for some principal groups is provided in Table 18-1.

Venomous Bites and Stings

Venomous animals include a vast array of organisms found in many phyla, from primitive to highly advanced, but certain groups have a particularly important impact on human health.

Venomous Snakes

Snakebite has the most significant impact on human health. Most regions contain some venomous species, but the rural tropics have a particularly high

TABLE 18-1

ESTIMATED HUMAN IMPACT OF ENVENOMING AND POISONING BY SOME PRINCIPAL GROUPS OF TOXIN-PRODUCING FAUNA AND FLORA*

	Estimated Annual Global Impact	
Organism Group	**Number of Cases**	**Number of Fatalities**
Venomous snakes	>2.5 million	>100,000
Scorpions	>1 million	>3,000
Spiders	>100,000	<100
Paralysis ticks	>1,000	<10
Insects†	>1 million	>1,000
Spiny venomous fish	>100,000	<10, likely close to zero‡
Stingrays	>100,000	<10§
Cone snails	<1,000	<10
Octopus (blue-ringed octopuses)	<100	<10
Jellyfish and related coelenterates	>1 million	<10¥
Fugu poisoning (tetrodotoxic fish)	Unknown	Unknown, likely >100
Ciguatera (ciguatoxic fish)	>20,000	Unknown, but few
Shellfish poisoning (several types)	Unknown	Unknown
Poisonous mushrooms	Unknown	Unknown, likely >100
Poisonous plants	Unknown	Unknown, possibly >1,000

*Data are based on most reliable published data, extrapolations of that data, or best guess estimates based on fragmented published data. The most reliable data are for snakebite and the annual global fatalities are probably underestimated. Most authorities consider published epidemiology data for envenoming as underestimates, and it is possible the estimated incidence given here is similarly an underestimate.
†Figures for insects include severe and fatal allergic reactions to venomous stings, which are responsible for the vast majority of medically significant cases.
‡No well-documented fatalities exist, and insufficient evidence for any approximations of possibly reliably reported semianecdotal cases.
§The handful of rare fatalities almost always results from intraperitoneal penetrative envenoming.
¥Almost all of the uncommon fatalities occur after envenoming by *Chironex fleckeri*, or one of several other chirodropid or charybdeid taxa that cause Irukandji syndrome (see Marine Envenoming in text).
Data sources: (1) Williams D, Gutiérrez JM, Harrison R, et al. The global snake bite initiative: an antidote for snake bite. *Lancet*. 2010;375:89–91. (2) Skinner MP, Brewer TD, Johnstone R, Fleming LE, Lewis RJ. Ciguatera fish poisoning in the Pacific Islands (1998 to 2008). *PLoS Negl Trop Dis*. 2011;5:e1416. doi:10.1371/journal.pntd.0001416. (3) Mebs D. *Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists*. Boca Raton, FL: CRC Press; 2002: 360. (4) Meier J, White J. (eds). *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. Boca Raton, FL: CRC Press; 1995. (5) Wang DZ. Neurotoxins from marine dinoflagellates: a brief review. *Mar Drugs*. 2008;11:349–371. (6) Noguchi T, Arawaka O. Tetrodotoxin-distribution and accumulation in aquatic organisms, and cases of human intoxication. *Mar Drugs*. 2008;6:220–242. (7) Warrell DA. Venomous bites, stings and poisoning. *Infect Dis Clin North Am*. 2012;26:207–223. (8) Personal observations of the authors.

burden of envenoming. The estimated global toll from snakebite remains a mixture of some quality evidence and projected speculation. Recent estimates suggest more than 2.5 million cases per year, with more than 1 million of these resulting in significant morbidity, approximately 400,000 cases requiring amputations, and more than 100,000 fatalities.[16] The economic impact likely is correspondingly enormous, but it has yet to be reliably quantified. Despite this impact, snakebite has generally been relegated to minor status in medical planning. The World Health Organization (WHO) briefly classified snakebite as one of three globally important "other neglected conditions" included under the recognized grouping of "neglected tropical diseases" that contains 17 infectious diseases responsible for a large proportion of morbidity and mortality in rural Third World regions.[17] However, in 2015, the WHO removed it from the list, and thus the considerable global impact of snakebite (especially among the world's most medically underserved communities) is no longer recognized (see http://www.who.int/gho/neglected_diseases/en/).

Scorpions, Spiders, and Other Arachnids

Scorpion stings are second, after snakebite in regards to medically significant occurrences, and probably affect more than 1 million humans each year, but with a low fatality rate (see Chippaux and Goyffon, 2010).

Spiderbite is also common, but with a few notable exceptions (widow spiders, *Latrodectus* spp, family *Theridiidae* [Figure 18-2]; recluse spiders, *Loxosceles* spp, family *Sicariidae* [Figure 18-3]; banana spiders, *Phoneutria* spp, family *Ctenidae*; Australian funnel-web spiders, *Atrax* spp [Figure 18-4]; and *Hadronyche* spp, family *Hexathelidae*), these are most commonly of minor medical significance (see www.toxinology.com). Tick envenoming causing paralysis is a problem in Australia, North America, and southern Africa, and possibly elsewhere, but reported cases are few, although rare fatalities have occurred (see Meier and White, 1995). The ticks involved are often members of

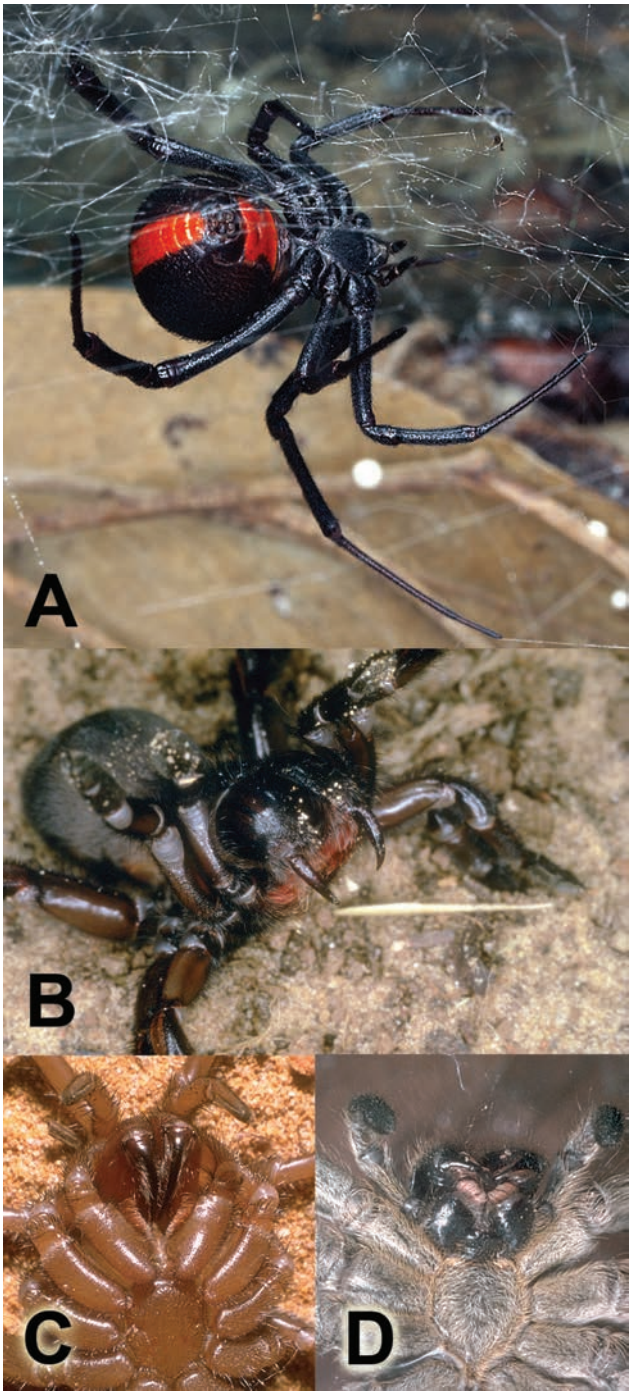


Figure 18-2. A medically important widow spider (*Latrodectus* spp) and comparison of the vertically deployed venom delivery apparatus of a mygalomorph spider and the horizontally deployed venom delivery apparatus of an araenomorph spider. (**A**) Red back widow spider (*Latrodectus hasselti*, *Theridiidae*). (**B**) Fangs of the mygalomorph, *Aganippe subtristis* (four-spotted trapdoor spider, female specimen, family Idiopidae). Note the vertical direction of the fang-bearing chelicerae traditionally termed paraxial, with the spider in an adopted defensive posture. (**C**) Fangs of the mygalomorph, *Aganippe subtristis*. The figure again illustrates the vertical direction of the fang-bearing chelicerae. (**D**) Fangs of the araenomorph, *Pediana* spp (a taxon of huntsman spider, family *Sparassidae*). The figure illustrates the horizontal deployment of the chelicerae-bearing fangs traditionally termed diaxial.
Photographs: Copyright © Julian White. In: White J. *A Clinician's Guide to Australian Venomous Bites and Stings*. Melbourne, Australia: Commonwealth Serum Laboratories; 2013: 300+ pp.

Figure 18-3. Brown recluse spider (*Loxosceles reclusa*). One of two genera (*Sicarius* and *Loxosceles*) belonging to the family *Sicaridae*, there are approximately 113 recognized taxa of *Loxosceles*. Several of these, including *L reclusa*, have inflicted medically significant bites that may occasionally cause a recurrent ulcer. In some parts of South America, several species may cause systemic envenoming (viscerocutaneous loxoscelism), an uncommon but potentially life threatening venom disease. There is antivenom available in several Latin American countries (eg, Brazil, Chile, Peru, Mexico), but treatment in the United States remains somewhat controversial with no quality evidence supporting the previous management (eg, surgical debridement, etc) of verified *L reclusa* bites. Meticulous wound management and possibly bariatric oxygen treatments are the most appropriate management methods. Recluse spider bites are among the most misdiagnosed presentations to emergency departments and outpatient/urgent care facilities, and diagnosis must be founded on verified identification of a spider or, in lieu of a specimen, with a well-supported history of a bite occurring within the range of recluse spiders (many suspected bites have occurred well outside any natural range or region in which the species has been accidentally introduced).
Photograph: Copyright © Julian White. In: White J. Venomous animals: clinical toxinology. *EXS.* 2010;100:233–291. In: Luch A (ed). *Molecular, Clinical and Environmental Toxicology*. Vol 2: *Clinical Toxicology*. Basel, Switzerland: Birkhäuser; 2010.

the family Ixodidae (hard-bodied ticks), particularly including members of the genera *Ixodes*, *Amblyomma*, *Dermacentor*, and the less common family *Argasidae*, notably the genus *Argas* (soft-bodied ticks, which so far have caused paralysis in animals only, not humans).

Insects

Insect sting envenoming causing toxin-induced disease of medical significance is uncommon, but allergic reactions to hymenopteran insect stings (eg, anaphylaxis from ants, bees, wasps, and hornets) are common and sometimes fatal. Retrospective studies have suggested that typically 40 to 100 deaths occur each year from hymenopteran sting anaphylaxis in the United States.[18] This amount is a significantly higher annual patient fatality rate than that of snakebite envenoming in the United States (typically between 5 and 8 patients).

Some bee venoms (eg, bumblebee, *Megabombus pennsylvanicus*; honey bee, *Apis mellifera*; Figure 18-5) contain mast cell degranulating peptide, a 22-amino acid cationic peptide that can directly trigger release of proanaphylactic mediators without prior sensitization.

One unusual example of a medically important insect venom is the Lepidopteran larvae (caterpillar) of the giant silkworm moth, *Lonomia obliqua* (family *Saturniidae*; Figure 18-6), whose spines contain several direct and indirect prothrombin activators, as well as several other toxins.[19] The sting of this caterpillar can cause a hemorrhagic diathesis, and fatalities have been documented.[34] Other Lepidopteran larvae have been implicated in human disease, at least some of which may involve local envenoming. Other terrestrial venomous animals cause few cases of human disease.

Marine Envenoming: Sea Snakes, Cnidarians, and Venomous Fish

Marine envenoming, such as jellyfish stings, are common, but few are medically significant. Significant types of marine envenoming include box jellyfish (eg, *Chironex fleckeri*, family *Chirodropidae*) stings (sometimes lethal); Irukandji jellyfish stings (resulting in a syndrome caused by several taxa of cnidarians, rarely lethal; see below under Excitatory Neurotoxins); and blue bottle (*Physalia* spp, family *Physaliidae*) stings (nonlethal envenoming, but occasional cases of potentially lethal allergic reactions). Sea snake (family Elapidae) bites can cause lethal envenoming, but are increasingly uncommon because of changes in fishing methods (eg, decreased manual removal of snakes from purse nets). Painful stings from venomous fish from several different families (eg, *Scorpaenidae*, *Trachinidae*, and *Tetrarogidae*), including many popular food and aquarium fishes as well as marine and fresh or brackish water stingrays, are common but generally unlikely to be lethal.

Some 200 species of stingrays, which belong to seven of nine families, can deliver venomous stings, or more accurately termed, penetrative envenoming. The most medically important stingrays belong to the following families:

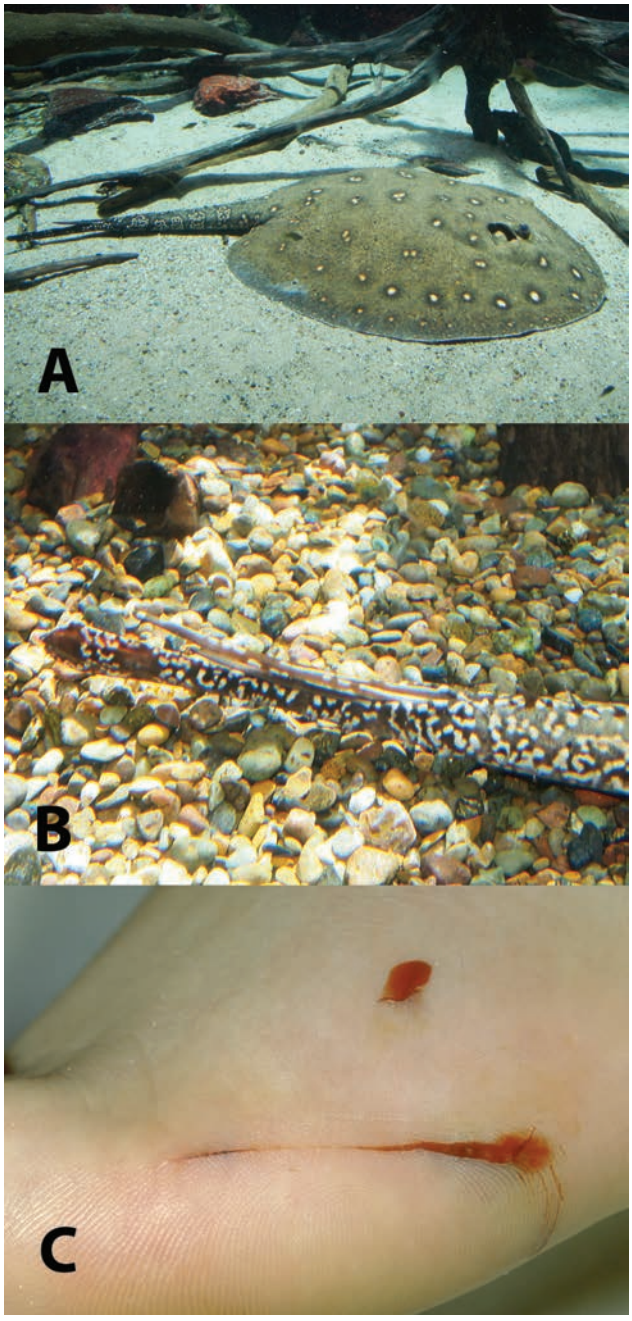
Figure 18-4. Sydney funnel-web spider (*Atrax robusta*). Approximately 13 fatalities have resulted from *A robusta* envenoming that clinically presents as a catecholamine storm produced by potent neuroexcitatory venom toxins.
Data source: White J. *A Clinician's Guide to Australian Venomous Bites and Stings*. Melbourne, Australia: Commonwealth Serum Laboratories; 2013.
Photograph: Copyright © Julian White. In: White J. *A Clinician's Guide to Australian Venomous Bites and Stings*. Melbourne, Australia: Commonwealth Serum Laboratories; 2013: 300+ pp.

- *Urolophidae* (stingarees),
- *Dasyatidae* (whiptail stingrays),
- *Hexatrygonidae* (sixgill stingrays),
- *Potamotrygonidae* (river stingrays), and
- *Plesiobatidae* (giant stingrays).

Stingrays, which are cartilaginous relatives of sharks (all in the class Elasmobranchii) and do not possess venom glands, deliver their stings using a serrated spine that is covered with mucosal secretions and venom-secreting cells (Figure 18-7A, B). The cells release the venom into the wound produced by the spine penetration (penetrative envenoming). The venom contains cytotoxic and vasculotoxic (including probably cardiotoxic) properties, and secondary infection from the wounds is common. Laceration of the lower extremities (especially the foot and ankle) is common (Figure 18-7C) with later clinical evolution of edema, cellulitis, and occasionally necrosis. Rare deep penetrative envenoming from giant species such as the Australian smooth stingray (*Dasyatis brevicauda*, family *Dasyatidae*) can be fatal if the thoracic cavity is pierced. In these uncommon cases, fatal effects usually result from physical trauma rather than envenoming, although, as mentioned previously, some experimental data have demonstrated cardiotoxicity of some stingray venoms (see Mebs, 2002 and Meier and White, 1995).[34,35] The well-known television personality Steve Irwin succumbed rapidly to the intracardiac

Figure 18-5. Honeybee (*Apis mellifera*). Stings from hymenopterans (especially bees and wasps) can cause life-threatening anaphylaxis in susceptible individuals. There are significantly more annual fatalities in the United States from hymenopteran sting-induced anaphylaxis than from snakebite envenoming.
Data sources: (1) Weinstein SA, Dart RC, Staples A, White J. Envenomations: an overview of clinical toxinology for the primary care physician. *Am Fam Physician*. 2009;80:793–802. (2) Weinstein SA, Warrell DA, White J, Keyler DE. *"Venomous" Bites from Non-venomous Snakes. A Critical Analysis of Risk and Management of "Colubrid" Snake Bites*. 1st ed. New York, NY: Elsevier; 2011.
Photograph: Copyright © Julian White. In: White J. *A Clinician's Guide to Australian Venomous Bites and Stings*. Melbourne, Australia: Commonwealth Serum Laboratories; 2013: 300+ pp.

Figure 18-6. Larvae of the giant silkworm moth (*Lonomia obliqua*). The larvae of this moth can inflict a life-threatening envenoming that features coagulopathy.
Photograph: Centro de Informações Toxicológicas de Santa Catarina, Brazil. Wikipedia Commons, public domain. http://www.cit.sc.gov.br.



penetration from a giant Australian stingray, and his death most likely resulted from cardiac tamponade, not envenoming.

Poisoning by Animals, Plants, and Mushrooms

Poisonings from ingestion of poisonous animals, especially marine animals, are common. These animals include the fugu puffer fish (eg, *Takifugu* spp, family *Tetraodontidae*); most species of fish that belong to the order Tetraodontiformes, which contain tetrodotoxin; ciguatoxic fish (numerous species, including many colorful diverse reef species and apex predators such as the great barracuda, *Sphyraena barracuda*); and several types of shellfish. In some Pacific island populations, ciguatera poisoning affects up to 1 in 5 people each year, and from 1973 to 2008 an estimated 500,000 people were affected by ciguatera poisoning.[20] Some types of marine poisoning carry a significant fatality rate, particularly the ingestion of sushi made with fugu (especially when including visceral organ meats), which equates with tetrodotoxin poisoning (see Mebs, 2002 and Meier and White, 1995).[34,35] Some types of shellfish poisoning also have a substantial risk of death (see Mebs, 2002).[34]

Poisoning from ingestion of poisonous plants and mushrooms, which is similarly common, is particularly frequent or important in some regions, notably parts of the tropics (poisonous plants) and in Europe and parts of North America (poisonous mushrooms). It can occur as a consequence of accidental circumstances (misidentification of the plant/mushroom) or as a deliberate act (eg, use of oleander [eg, *Thevetia peruviana*, family *Apocynaceae*] ingestion in suicides in the Indian subcontinent).[21,22] Some types of plant or mushroom poisoning carry a relatively high fatality rate, especially in delayed or late presentations; however, this may reflect regional trends because in some Western countries (eg, the United States), the case fatality rate for mushroom poisoning remains low.[23]

Figure 18-7. South American freshwater or river stingray (*Potamotrygon motoro*), venom apparatus and stingray penetrative envenoming. (**A**) Ocellate or peacock-eye river stingray (*Potamotrygon motoro*). This increasingly rare species is popular among home aquarists. It is capable of inflicting a sting that can cause moderate to severe local effects, including severe pain, and systemic effects including shock. (**B**) Stingray tail spine. Stingrays do not possess a venom gland; rather, their serrated tail spines have venom-containing cells that release their contents when physically disrupted. The spine also is coated with a mucous layer that may be colonized with several taxa of marine microorganisms and can predispose to serious local infection in an envenomed victim. (**C**) Stingray spine (species unidentified)-inflicted wound on foot. Wounds may result from directly stepping on a ray covered with sand, or from a glancing, slash-like wound. These wounds often require medical imaging in order to determine if any spine fragments remain imbedded in the wound, as well as meticulous wound care and prophylactic antibiotics.
Photographs: Copyright © Julian White. In: White J. *A Clinician's Guide to Australian Venomous Bites and Stings*. Melbourne, Australia: Commonwealth Serum Laboratories; 2013: 300+ pp.

Relevance to Biological Warfare

Venomous animals generally evolved to target prey or predators on an individual basis—not en masse—so they are not readily adapted to act as ideal weapons in human warfare. However, either using the native toxins or modifying those toxins to enhance a particular action and developing an artificial weaponization and delivery strategy is possible, but presents logistical challenges that would likely outweigh practicality in most cases.

Venoms contain some highly potent agents that can kill humans in small doses. In most cases the lethal outcome will not be instantaneous, but likely prolonged over several hours. Venoms are not ideal overall for biological warfare because of these delivery problems as well as the absorption/direct administration required in most examples to optimize their actions. Even for potent neurotoxins, such as paralytic or neuroexcitatory toxins, other equally or more potent chemicals are available that allow mass delivery. Also, most venom-derived toxins are susceptible to thermolability and varying degrees of denaturation through other environmental influences that can affect their potency. Some of them also exhibit nonmammalian prey target specificity, for example, some antagonize the acetylcholine receptors of lizards and birds. Thermostable toxins are found in a few venoms such as those of the venomous helodermatid lizards (*Heloderma* spp; see below) and the unusual peptide neurotoxins from temple or Wagler's pit viper (*Tropidolaemus wagleri*) venom.[24,25] Some of the specific factors influencing the use of biological toxins in biowarfare and preparedness against such a threat have been discussed by Osterbauer and Dobbs.[26]

Research into specific toxins, including their molecular modification, and possible xenogenic incorporation of toxin-encoding genes into potentially infectious microorganisms may allow substances to be developed with biological warfare potential. Several countries have explored the potential uses for such recombinant products. The ethics and realities of such research are beyond the scope of this chapter.

Similarly, toxins from poisonous animals, plants, and fungi may—in general—be unattractive as biological warfare agents, although ricin (from the castor bean plant, *Ricinus communis* [family *Euphorbiaceae*]) and the aflatoxins (from the molds, *Aspergillus* spp, family *Trichocomaceae*) are exceptions. Specifically excluded from this discussion is the casual/accidental interaction between combatants and venomous fauna on the battlefield or in otherwise deployed locations.

However, the risk posed by accidental envenoming, especially snakebite and scorpion sting, should not be overlooked in developing risk-mitigation strategies for any potential combat zone. Some authors have described the impact that venomous animals may have on field troops. Maretic[27] reported several accounts of mass envenoming of large numbers of troops by widow spiders, *Latrodectus* spp. These troops include the troops of Ludwig in Calabria in 866 CE who were "decimated" by spiders. Also, during the eve of the Battle of Loncomilla that occurred during the Chilean Revolution on the 8th of December 1851, soldiers bitten by *Latrodectus* spp were chloroformed so as not to "betray with their screams" the position of the army.[27]

However, the general concerns about risks posed by venomous animals to modern troops deployed in locales with several medically important venomous species have appeared to be disproportionate to the small number that are seriously or fatally envenomed. For example, Ellis[28] reported only three recorded snakebite-related deaths among British troops during World War II, and Minton and Minton[29] reported only one well-documented fatal snakebite inflicted on an American soldier during the Vietnam War. It is likely that such cases were underreported and the actual numbers of those less seriously envenomed are unknown. Although few figures account for envenomings among coalition troops in Operations Desert Shield or Desert Storm, the Persian Gulf War, or Operation Enduring Freedom in Afghanistan, there are a handful of documented cases. Two enlisted American military service personnel were among 17 snakebite victims treated at three US medical facilities in Afghanistan. Most of the patients in this series were local Afghans, and the identity of the envenoming snake species was unknown in 11 of 17 cases (65%).[30] There were no fatalities, and 10 of 17 patients (58%) received antivenom.[30]

However, in some circumstances, natural disasters may share some features with the effects of warfare on civilian populations. Envenoming can become a significant risk in certain disasters. The effects of massive flooding in Bangladesh are well studied because it is a frequent disaster event. Although drowning is the single most common reason for fatalities in floods by a substantial margin, snakebite is the second most common reason for fatalities and causes as many or more deaths than all other causes (except drowning) combined.[31] The diagnosis, first aid, medical treatment, and prevention of such accidental envenoming are major subjects beyond the scope of this chapter, although some basic recommendations are presented.

MAJOR TOXIN CLASSES AND THEIR CLINICAL EFFECTS

There are many ways of classifying toxins, including by taxonomic origin, chemical structure, molecular targets, and biological activity. For this chapter, a pathophysiologically based scheme is most relevant in considering the primary actions of venom toxins and possible clinical presentations that may occur as a result of their action.

Paralytic Neurotoxins

For venomous animals, paralysis is a biologically useful state to induce in either prey or predator. For some arthropods, paralyzing prey allows them to both overcome larger prey and provide a food store for leisurely later feeding, or for their offspring to feed on during their larval stage. For cone snails (*Conus* spp, family *Conidae*; Figure 18-8), the use of paralytic neurotoxic peptides delivered by ejection of a harpoon-like modified radula tooth allows this slow moving predator to capture and ingest fast moving prey (fish). For most cephalopods (eg, octopuses) and some squamate reptiles (eg, venomous snakes), the use of neurotoxins delivered respectively by beak or canaliculated fang (containing an internal lumen)/externally grooved modified maxillary teeth (Figure 18-9) allows safe subjugation and consumption of prey (eg, respectively, crabs, mammals) that otherwise might injure the octopus/snake.

Figure 18-8. Textile cone snail (*Conus textilis*). These gastropods are highly coveted by amateur conchologists for their beautiful shells. There are rare human deaths from stings delivered by these snails when they are handled. A modified tooth, the radula that closely resembles a miniature harpoon, delivers the venom into prey or an unfortunate human victim. This adaptation allows this slow-moving snail to capture fast moving fish. Various *Conus* species (>650 currently recognized) often favor specific prey such as fish or other gastropods (including other *Conus* spp).
Photograph: By Jan Delsing. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Conus_textile_010.jpg.

For poisonous animals, the effects of neurotoxins may either permanently deter potential predators or allow escape by the poisonous animal. The theoretical evolutionary value for poisonous plants and mushrooms is less clear, although it can be speculated that excessive foraging of these species may have occurred and endangered their survival. Perhaps these plants produce noxious and toxic substances to discourage their consumption. Also, these toxins may serve (or have served) other functions important to the physiological functions of the plant that are unrecognized. The costs of evolving such a biosynthetic capability may be a factor contributing to the less common occurrence of such toxins in these taxa.

The mechanism that causes paralysis is variable, but in most cases it involves direct toxin activity in the peripheral nervous system, rather than a central effect. The molecular variability in these toxins is considerable, but within particular venomous animal groups tends to be more homogenous and conserved. The best described examples are snake venom neurotoxins, many of which have been duplicated among different ophidian clades (Table 18-2).[32–35]

There are essentially four principal snake paralytic neurotoxin types of clinical significance (see Table 18-2). Most are polypeptides, some have multimeric structures that include one or more basic phospholipases A2 (PLA2) subunits, and a few unusual neurotoxins are small peptides. Within each type, some molecular variability exists, particularly among presynaptic neurotoxins, which are generally the most potent though slightly slower acting paralytic toxins. Postsynaptic neurotoxins generally fall within one of two classes that are commonly termed short and long chain, but these are now collectively classed as "three-finger-fold" toxins in reference to the three β-stranded loops extending from their central core that contain all four conserved disulfide bonds. These toxins most commonly have molecular masses ranging from 6 to 8 kDa (see Table 18-2). The other well-characterized toxins such as the fasciculins (a group of anticholinesterases that have the three-finger fold conformation) and dendrotoxins (neuronal voltage-gated potassium channel inhibitors; see Table 18-2) from mamba venoms act differently from each other, but are synergistic. All act at the neuromuscular junction (Figure 18-10).[32–35] The cited references offer more detailed reviews of these essential toxin classes.

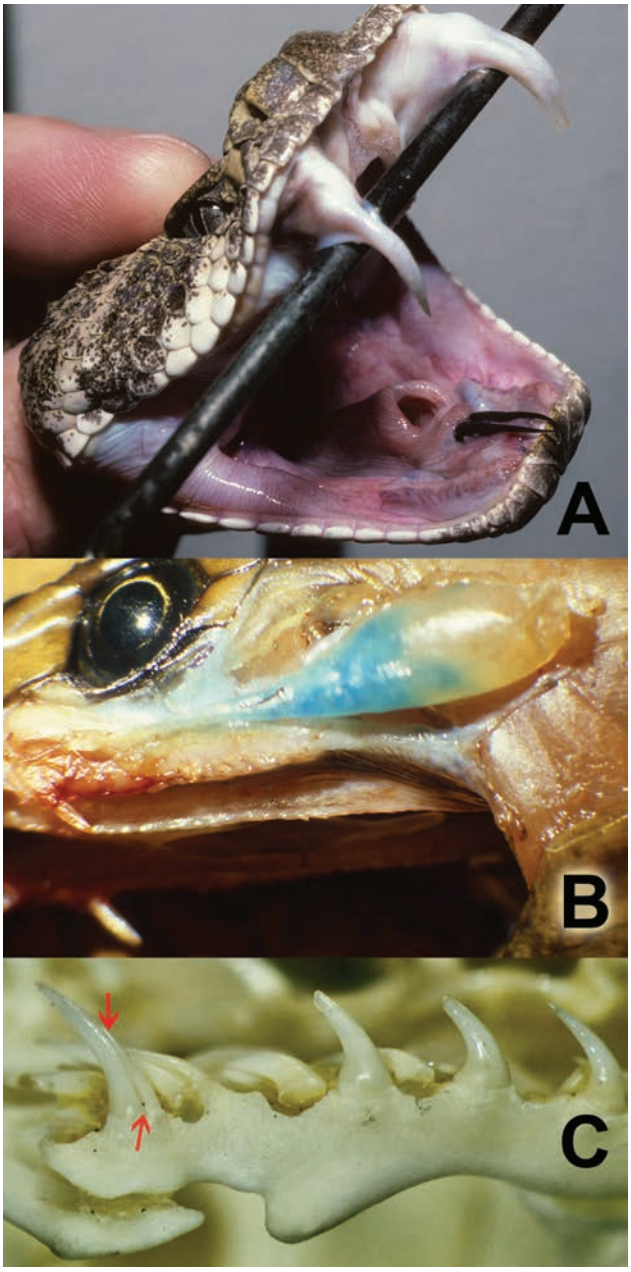


Figure 18-9. Representative venom delivery apparatuses found among some snakes. (**A**) Distensible fangs of a representative viperid, Western diamondback rattlesnake (*Crotalus atrox*). This dentitional arrangement has often been termed solenoglyphous. Elapids, viperids, and front-fanged lamprophiid snakes are collectively termed front-fanged colubroids. (**B**) Fixed fangs of a representative elapid, Eastern brown snake (*Pseudonaja textilis*). This dentitional arrangement has often been termed proteroglyphous. (**C**) The posterior grooved maxillary teeth of a non–front-fanged colubroid, the Mangrove or ringed cat eye snake (*Boiga dendrophila*). The maxillary is placed upside down to better illustrate the characteristics of the teeth. The deep external grooves conduct the venom from the low-pressure glands associated with the delivery apparatus. This dentitional arrangement that can include mid- or notably posterior maxillary teeth that may be enlarged and may also be grooved has been termed opisthoglyphous, or rear fanged with aglyphous referring to those non–front-fanged colubroids that have mid or posterior teeth that lack grooves and in some instances are also associated with a low pressure gland. These terms are not precisely accurate because the modified dentition may occur midway in the maxillary.
Photographs: (**A**) Copyright © Julian White. In: Brent J, Wallace KL, Burkhart KK, et al (eds). *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 1st ed. Philadelphia, PA: Mosby; 2005. (**B**) Copyright © Julian White. In: Covacebich J, Davie P, Pearn J (eds). *Toxic Plants and Animals: A Guide for Australia*. Brisbane, Australia: The Queensland Museum; 1987. (**C**) Copyright © Scott A Weinstein. In: Weinstein SA, Warrell DA, White J, Keyler DK. *"Venomous" Bites from Non-Venomous Snakes: A Critical Analysis of Risk and Management of "Colubrid" Snake Bites*. New York: Elsevier; 2011: 141.

Other neurotoxins, such as tetrodotoxin and saxitoxin, are nonproteinaceous and low molecular mass (often between 300 and 1,000 Da) toxins (the former is a guanidinium class toxin, the latter a polyether), and thus have different structures as well as mechanisms of action. These are mostly ion channel toxins that are very potent with notably low minimal concentrations required to affect biological activity.[36,37] Small amounts ingested (eg, through eating fugu fish [tetrodotoxin] or contaminated shellfish [eg, saxitoxins, yessotoxin]) can result in rapid complete paralysis, but the paralysis is usually of shorter duration, in comparison with snake venom neurotoxins.[33,38–40]

The biothreat potential of tetrodotoxin has been long recognized. It is included on the US Department of Health and Human Services' regulated select agent list and considered an agent "determined to have the potential to pose a severe threat to both human and animal health."[41,42]

Clinically, these paralytic neurotoxins cause grossly similar presentations, with progressive development of flaccid paralysis. In most cases a descending paralysis affecting cranial nerves occurs first (however, envenoming by paralytic tick species causes an ascending paralysis commencing with ataxia).[40,43–45] In a classic presentation after snakebite, the patient develops bilateral ptosis after one to several hours, which may progress to complete ophthalmoplegia and fixed dilated pupils if untreated, although even timely treatment does not always prevent this progression. Dysarthria, dysphagia, drooling, and loss of upper airway protection may occur, followed by limb muscle weakness, loss of deep tendon reflexes, diaphragmatic paralysis, and complete respiratory paralysis. Without intubation

TABLE 18-2

SOME PRINCIPAL PARALYTIC NEUROTOXIN TYPES

Toxin Class	Structure	Site of Action	Mode of Action	Source	Examples
Presynaptic neurotoxins	PLA2-based, mono- or multimeric	NMJ	Bind to surface membrane of terminal axon, modify SNAP proteins, enter the axon via synaptosomes, and then damage mitochondria and other cell structures, thus disrupting synaptosome production, thereby causing complete paralysis	Many elapid snakes (Australian elapids, coral snakes, kraits); a few vipers (South American rattlesnakes, a few North American rattlesnakes, some "old world" viperids, such as Russell's vipers)	Notexin (Australian tiger snake, *Notechis scutatus*); Mojave toxin (Mojave rattlesnake, *Crotalus scutulatus*); alpha-bungarotoxin (widespread in studied venoms from kraits, *Bungarus* spp)
Postsynaptic neurotoxins	Polypeptide, with variable number of disulfide bonds; variably termed, long-chain, short-chain, or three-finger-fold neurotoxins	NMJ	Bind to acetylcholine receptor on muscle end plate and cause reversible or irreversible block preventing activation of receptor	Many elapid snakes (Australian elapids, sea snakes, coral snakes, cobras, kraits) and some non–front-fanged colubroid snakes (NFFCs); studied NFFC toxins have so far been largely prey-specific	Long-chain or short-chain neurotoxins from banded water cobra (*Naja annulata*), black-necked spitting cobra (*N nigricollis*) and many others
Dendrotoxins	Polypeptides that are structurally homologous with Kunitz-type proteinase inhibitors	NMJ	Cause massive release of acetylcholine from terminal axons through activation of potassium channels, flooding the junctional space, and receptors	African mambas (*Dendroaspis* spp)	Eastern green mamba (*D angusticeps*)
Fasciculins	Three-finger-fold polypeptides	NMJ	Prevent regulated removal of acetylcholine from the junctional space, thereby overstimulating and inactivating receptors causing muscle fasciculation	African mambas (*Dendroaspis* spp)	Black mamba (*D polylepis*)
Tetrodotoxins	Steroidal alkaloid (Guanidinium class)	Na^+ channels in excitable nerve and muscle cells	Causes blockade of the voltage-gated sodium channels (NaV) in nerve and muscle cell membranes by binding to site 1 of the NaV α-subunit, thus blocking ion conduction and preventing the cells from activation, as well as inhibiting release of neurotransmitter	Blue-ringed octopus, puffer (fugu) fish, selected newts, toads, flatworms, and a diverse series of other animals; the toxin with the broadest phylogenetic distribution; probably produced in some species by symbiotic bacteria (eg, present in the beak-associated venom/salivary glands of blue-ringed octopuses and relatives)	Greater blue-ringed octopus (*Hapalochlaena lunulata*)

(**Table 18-2** *continues*)

Table 18-2 continued

Batrachotoxins, homobatrachotoxins	Steroidal alkaloid with oxazepine ring	Axolemma	Binds to site 2 of the NaV α-subunit, thereby increasing the permeability of the voltage-dependent sodium channel by prolonging the open state; this causes persistent activation and shifted voltage dependence; the toxin has approximately 10- to 12-fold greater experimental lethal potency than tetrodotoxin	Poison dart frogs (*Dendrobatidae*), pitohui birds (PNG); the dendrobatid frogs obtain these toxins from insect food sources (eg, coleopteran, hymenoptera, and others), and the toxin becomes absent in specimens maintained on nonindigenous insects in captivity	Yellow poison-dart frog (*Phyllobates terribilis*)
Saxitoxins, gonyautoxins; others	Purine derivatives (polyethers: the molecular structures classify into groups based on potency [most potent to least]; carbamates, decarbameyl, *N*-sulfacarbamyl, hydroxybenzoate)	Excitable cell membranes	Bind adjacent to the sodium channel, blocking the channel and preventing action potentials; like tetrodotoxin, saxitoxin exerts its activity by binding to site 1 of the NaV α-subunit	Selected shellfish (paralytic shellfish poisoning); toxins are produced by a wide variety of dinoflagellates and bioconcentrated in filter-feeding shellfish; some toxins may be produced in cyanobacteria and algal spp	Saxitoxin is produced by an indeterminate number of marine picoplankton, such as the dinoflagellates, *Gymnodinium*, *Alexandrium*, *Pyrodinium* and others; gonyautoxin is produced by some of the aforementioned species and others; these and other toxins have also been detected in cyanobacterial blooms in fresh water
Holocyclotoxins (HT-1)	Probably several isotoxins (HT-1, HT-2, HT-3, and possibly others); HT-1 is a basic polypeptide with a calculated molecular mass of 5.9 kDa	NMJ	Similar to snake venom presynaptic neurotoxins	Paralysis ticks in Australia, North America, and Southern Africa	Australian paralysis tick (*Ixodes holocyclus*)
Conopeptides	Broad array of peptides		A variety of mechanisms, depending on toxin; as an example, the μ-conotoxins bind to site 1 of the NaV α-subunit	Selected *Conus* spp cone snails; an indeterminate number of the >650 species produce these toxins; of those tested, many produce toxins that are prey-specific for either fish or invertebrates, including other molluscs; only a handful produce toxins that are medically significant in humans	Geographer or geography cone (*Conus geographicus*)

NMJ: neuromuscular junction; PLA2: phospholipase A2; PNG: Papua New Guinea; SNAP: synaptosomal-associated protein

Data sources: (1) Weinstein SA, Warrell DA, White J, Keyler DE. '*Venomous' Bites from Non-venomous Snakes. A Critical Analysis of Risk and Management Management of 'Colubrid' Snake Bites*. 1st ed. New York, NY: Elsevier; 2011. (2) Mebs D. *Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists*. Boca Raton, FL: CRC Press; 2002: 360. (3) Meier J, White J. (eds). *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. Boca Raton, FL: CRC Press; 1995. (4) Synthesized professional presentation materials (eg, lectures) of the authors.

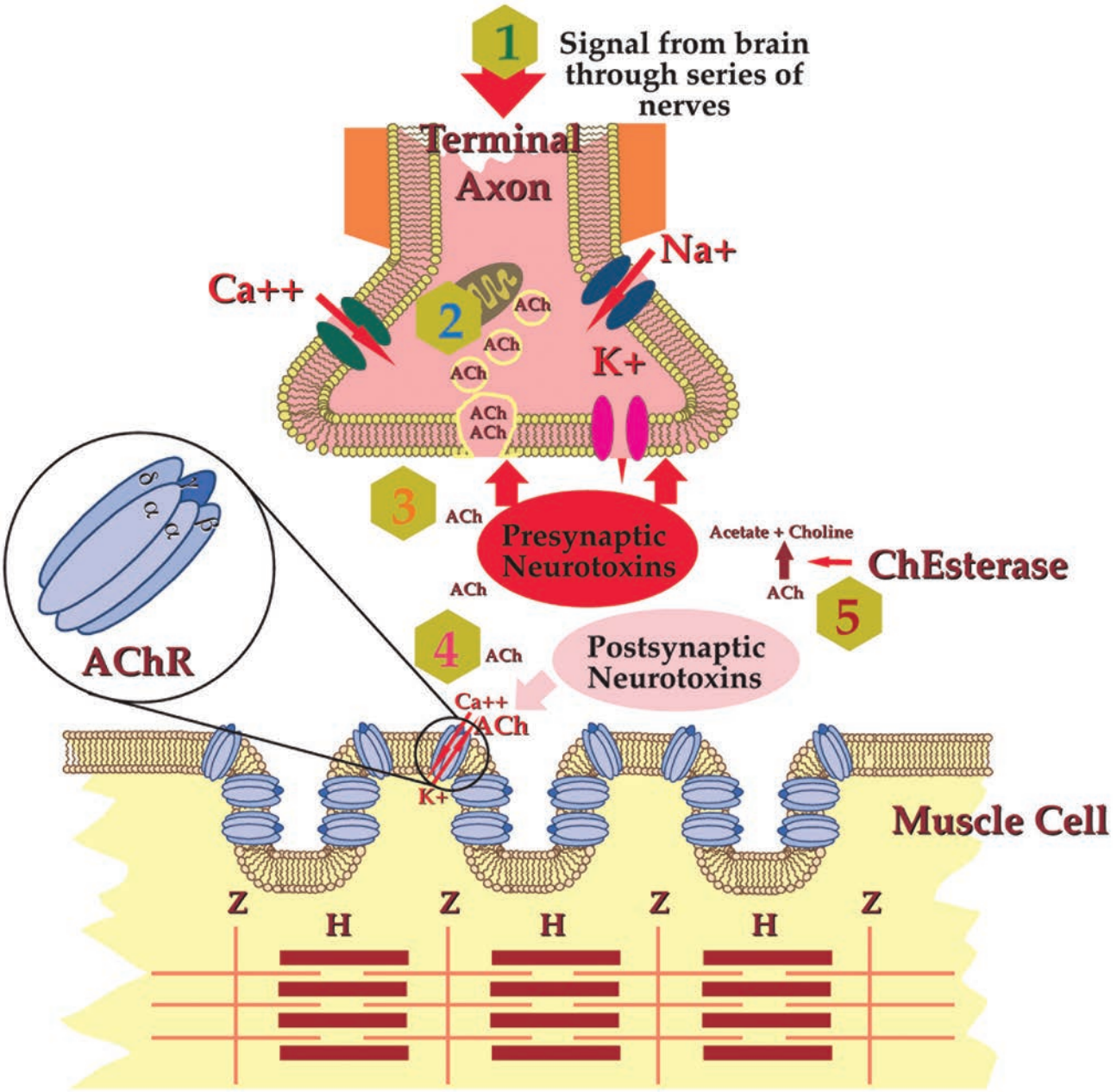


Figure 18-10. Sites of action of principal types of snake venom neurotoxins. Simplified overview of the general actions of phospholipase A2-multimeric presynaptic neurotoxins and postsynaptic neurotoxins. The *numbered steps* included in the figure indicate the following: (*1*) shows the initiation of translation of the electrical impulse into a biochemical release; (*2*) synaptic vesicles fuse with the axonal membrane thereby leading to exocytic discharge of acetylcholine (ACh); (*3*) discharged ACh enters the synaptic cleft; (*4*) the discharged ACh binds to motor end-plate receptors of the myocyte membrane leading to stimulation of contraction; and (*5*) the ACh at the motor end plate is then hydrolyzed by acetylcholinesterases, thus terminating the contractile stimulus. Note the site of respective site of actions of the presynaptic and postsynaptic neurotoxins. The investigation of presynaptic neurotoxin pharmacology has largely focused on the actions of several potent snake venom neurotoxins isolated from Australian or Asian elapids, as well as a few viperids (several species of rattlesnakes and viperine viperids). Some of the well-studied toxins—such as taipoxin, β-bungarotoxin, and crotoxin—ultimately inhibit ACh release at the neuromuscular junction, and in nerve-muscle preparations accomplish this in three phases: (1) an initial transient decrease/inhibition of evoked transmitter release that is promoted by Ca^{2+} (this phase has been absent in studies of some toxins, eg, notexin), (2) a facilitated transmitter release phase, and (3) the final phase that features a progressive fall in evoked

(**Figure 18-10** *continues*)

Figure 18-10 continued

release resulting in transmission failure and paralysis. Miniature end-plate potential frequency is similarly affected, although spontaneous release tends to occur at a low frequency after the failure of evoked neuromuscular transmission. However, spontaneous release amplitude does not change significantly, suggesting that synaptic vesicles do not fuse inside the axonal terminal and that the ACh-synaptosomal packaging mechanism is not impaired by the action of the studied species of these toxins. The phospholipase A2 subunit(s) in some of these toxins (eg, Mojave toxin) also have a degenerative effect on the motor end plate. There is still controversy about the specific enzymatic influence of phospholipase A2 subunits on the neurotoxicity and the initial phospholipid hydrolysis role in initiating the three-phase mechanism that ultimately results in paralysis, but the lysophospholipids produced by hydrolysis do alter the active zones of neuroexocytosis thereby making them less prone to membrane fusion with synaptic vesicles. Unlike the actions of several botulinum toxins (eg, botulinum toxins A and E) from *Clostridium botulinum* and tetanus toxin from *C tetani* that function as endopeptidases by cleaving integral proteins (eg, SNAP-25; other botulinum toxins cleave VAMP or SNAP-25 and syntaxin) of the presynaptic membrane, snake venom phospholipase A2-containing neurotoxins do not directly hydrolyze these SNARE proteins. Although other presynaptically acting neurotoxins, such as α-latrotoxin from the widow spider (*Latrodectus* spp) venoms function with a mechanism different from that of snake venom phospholipase A2 toxins, these different toxins still alter the axolemmal permeability and cause Ca^{2+} overload within the terminals and subsequent neuronal degeneration, a process that likely causes activation of the calcium-activated proteolytic activities of calpains. The increased Ca^{2+} permeability induced by α-latrotoxin occurs via toxin binding to its receptor(s) (eg, latrophilin) subsequently forming pores in the presynaptic membrane. The terminal is thus essentially flooded with Ca^{2+} and vesicle fusion is over-stimulated resulting in a massive release of neurotransmitter. Most snake venom postsynaptic neurotoxins bind to subunit interfaces in either muscle type (α-1) or neuronal type (α-7) nicotinic Ach receptors (AChR), thereby antagonizing neurotransmitter binding with resultant paralysis. The length of their primary sequence, long-chain and short-chain, has been commonly used to classify these toxins but recently all of these toxins have been renamed as three-finger-fold neurotoxins. The concave aspect of the three-dimensional structure of these toxins contains several amino acids that function as active sites for binding to respective AChR subunits. These toxins are widespread among elapid venoms and some are found in venoms of other snakes such as some colubrids and lamprophiids, as well as a few viperids (eg, *Daboia russelii*). Snake venom neurotoxicity should not be viewed as a result of the isolated action of discrete toxins such as those outlined above. For example, fasciculins and dendrotoxins from mamba (*Dendroaspis* spp) venoms can facilitate the subjugation of prey animals, as well as compound the clinical manifestations in envenomed patients. Fasciculins are reversible, selective acetylcholinesterase antagonists that cause an accumulation of acetylcholine at the neuromuscular junction thereby causing marked and prolonged fasciculations. Pita et al considered the potential use of fasciculins, as well as other anticholinesterase toxins, as biological warfare agents. Originally isolated from venom of the Eastern green mamba (*D angusticeps*), dendrotoxin is a 7-kDa polypeptide homologue of Kunitz-type serine protease inhibitors. However, unlike mammalian Kunitz-type inhibitors, the dendrotoxins are potent, selective blockers of voltage-dependent potassium channels. These toxins induce repetitive and sustained terminal neuronal firing, and have increasingly been used as molecular tools in ion channel neuropharmacology.

ChEsterase: cholinesterase; SNARE: soluble *N*-ethylmaleimide-sensitive factor activating protein receptor; VAMP: vesicle-associated membrane protein

Data sources: (1) Pungerčar J, Križaj I. Understanding the molecular mechanism underlying the presynaptic toxicity of secreted phospholipases A2. *Toxicon*. 2007;50:871–892. (2) Rossetto O, Montecucco C. Presynaptic neurotoxins with enzymatic activities. *Handb Exp Pharmacol*. 2008;184:129–170. (3) Duregotti E, Tedesco E, Montecucco C, Rigoni M. Calpains participate in nerve terminal degeneration induced by spider and snake presynaptic neurotoxins. *Toxicon*. 2013;64:20–28. (4) Davletov B, Ferrari E, Ushkaryov Y. Presynaptic neurotoxins: an expanding array of natural and modified molecules. *Cell Calcium*. 2012;52:234–240. (5) Teixeira-Clerc F, Ménez A, Kessler P. How do short neurotoxins bind to a muscular-type nicotinic acetylcholine receptor? *J Biol Chem*. 2002;277:25741–25747. (6) Harvey AL, Robertson B. Dendrotoxins: structure–activity relationships and effects on potassium ion channels. *Curr Med Chem*. 2004;11:3065–3072. (7) Pita R, Anadón A, Martínez-Larrañaga MR. Neurotoxins with anticholinesterase activity and their possible use as warfare agents. *Med Clin (Barcelona)*. 2003;121:511–517.

and mechanical ventilation, this condition is fatal. It may take many hours to reach this final, potentially fatal stage. With external respiratory support, most affected patients can be expected to survive.

If the paralysis is caused by presynaptic snake venom neurotoxins, then complete paralysis may extend to days and weeks (but rarely months) until the damaged terminal axons at the neuromuscular junction regenerate. Antivenom cannot reverse this process and is only effective if given early enough to neutralize the neurotoxins before they bind and enter the terminal axon.

If the paralysis is caused by only postsynaptic snake neurotoxins, then the blockade may sometimes be reversed by giving antivenom, or it can be moderated by increasing the supply of neurotransmitter

(acetylcholine) from the terminal axons. This can sometimes be accomplished by administering anticholinesterases (usually intravenous neostigmine) to partially overcome the receptor blockade.

For poisoning from the nonprotein neurotoxins such as tetrodotoxin, the patient is most often wholly reliant on mechanical ventilation that constitutes the only treatment during major paralysis. However, complete paralysis and the concomitant artificial ventilation may often last only a few hours. These toxins act rapidly and can cause complete respiratory paralysis within 20 to 60 minutes of toxin exposure; thus the onset of symptoms and signs is precipitous.

Excitatory Neurotoxins

Excitatory neurotoxins cause nonparalytic stimulation of the nervous system and may exert their effect on many or all parts of the peripheral nervous system, including the autonomic nervous system. These are the classic arthropod toxins found in selected scorpion and spider venoms. They also occur in some other venoms, such as Irukandji jellyfish venoms.

Most are potent and highly selective ion channel toxins, variously affecting sodium, potassium, and calcium channels and either activating or blocking these channels. For example, the δ-atracotoxins from *Atrax robusta* (Sydney funnel-web spider) venom interact with a specific voltage sensor transmembrane segment (S4) of α-subunit domain IV. The interaction of the δ-atracotoxins with S4 prevents the normal outward ionic movement, and associated conformational changes that are required for channel inactivation. This results in prolonged action potentials at autonomic or somatic synapses, which induces massive transmitter release.[46] Many excitatory toxins have become vital tools in unlocking the secrets of nerve signaling at the molecular level because of their specific mechanisms, and they are the subject of ongoing intensive research. Most are low molecular weight peptides (eg, the aforementioned δ-atracotoxins consist of 42 amino acids), and they have proved amenable to molecular manipulation/modification to enhance specific activities. These peptides are ideal as structural scaffolds for the production of unique new biologically active molecular species with highly specific targets or actions. Although of resultant great interest to the pharmaceutical industry, the problem of successful delivery of peptide therapeutics (or, potentially, offensive agents) remains an issue. This problem applies equally to the peptide toxins with different sites and modes of action, which also is the subject of pharmaceutical discovery research. For example, the diverse conopeptides are typically low molecular mass (<5 kDa) peptides that have complex pharmacology. More than a dozen classes of conotoxins exist, including:

- inhibitors or activators of voltage-gated sodium channels,
- nicotinic acetylcholine receptor inhibitors, and
- serotonergic 5-HT3 antagonists and many others.[47,48]

Some of these already have proven uses as pharmacotherapeutics. One conopeptide, ziconotide (Prialt, Jazz Pharmaceuticals, Dublin, Ireland), is already used as an alternative analgesic to treat moderate to severe refractory pain. Ziconotide, which is the only intrathecal nonopioid analgesic approved by the US Food and Drug Administration, binds to N-type calcium channels on primary nociceptive afferent neurons in the dorsal horn of the spinal cord.[49]

Some excitatory neurotoxins are larger polypeptides, and most of these, like the small pepide atracotoxins, stimulate neuroexocytosis. For example, the 110- to 140-kDa α-latrotoxins from widow spider (*Latrodectus* spp) venoms bind to several target proteins (eg, soluble *N*-ethylmaleimide-sensitive factor activating protein receptor [SNARE] proteins) in the neurolemma, and they cause calcium and sodium influx that results in massive neurotransmitter release.[50]

Clinically, these toxins cause symptoms and signs that reflect hyperexcitation of the nervous system, manifesting clinical effects, such as muscle fasciculations and spasms, tachycardia, paraesthesia, and more.[34,35,43,51] The pharmacology of these toxins may have broad similarities across many taxa of venomous animals, although with sometimes distinctive specific effects in particular groups.

Of the approximately 1,800 species of scorpions, only about 30 to 35 taxa are known to be dangerously venomous to humans. Most of these medically important species belong to the family *Buthidae*, and are widely distributed globally. The venom delivery apparatus (sting, the aculeus) is located at the end of the telson and delivers a bolus of venom. Many scorpions typically insert the sting into prey with protracted penetration. Stings delivered to potential predators or unfortunate humans can be relatively brief, but still may cause life-threatening effects, especially in children.

Medically dangerous buthid scorpions (Figure 18-11) often have numerous neurotoxic isotoxins present in their venoms. Some scorpion venoms contain long-chain polypeptide neurotoxins that act by stabilizing the open conformation of voltage-dependent sodium channels, thereby causing continuous and prolonged

Figure 18-11. The medically important scorpion, *Androctonus australis* (thick or fat-tailed scorpion, family *Buthidae*), is one of the most toxic species studied. This species is extensively distributed from Asia through the Middle East and northern Africa.
Photograph: Copyright © Julian White. In: White J. Venomous animals: clinical toxinology. *EXS*. 2010;100:233–291. In: Luch A (ed). *Molecular, Clinical and Environmental Toxicology*. Vol 2: *Clinical Toxicology*. Basel, Switzerland: Birkhäuser; 2010.

firing of the somatic, sympathetic, and parasympathetic neurons. The repetitive firing results in autonomic and neuromuscular hyperexcitation. Many of these toxins also stimulate neuroexocytosis. Well over 100 α-neurotoxins have been characterized from various scorpion venoms and have often been classified as toxic to mammals, insects, or both.[52] Interestingly, computational analyses of structure–function have suggested that scorpion α-toxins possess modular organization, and individual modules interact with different parts of their target sodium channels.[53] Most of these toxins have molecular mass around 65 kDa, share a common βαββ organization, contain four disulfide bridges, and primarily bind to site 3 of the voltage-gated sodium channel, thereby delaying inactivation; whereas other scorpion venom toxins (β-toxins) shift the membrane potential dependence of channel activation by binding to site 4.[54]

Some of the short polypeptide neurotoxins present in the same venoms simultaneously antagonize potassium channels. Most of these consist of 23 to 64 amino acids with molecular mass less than 4 kDa, and these structurally constrained polypeptides adhere to either the inhibitor cysteine knot or disulfide-directed β-hairpin folding motif.[55,56] The first structurally elucidated bound toxin-potassium channel complex contains the well-studied potassium channel-binding toxin charybdotoxin, isolated from venom of the Israeli yellow scorpion, *Leiurus quinquestriatus hebraeus*.[57] This imaginatively named distinctive toxin has specificity for a single site on the external end of big potassium channels, a form of Ca^{2+}-dependent, voltage-dependent K^+ channel that facilitates the passive flow of a relatively large current of potassium ions.[58,59] (The toxin was named after Charybdis, the daughter of Poseidon, who was transformed into a marine behemoth by Zeus. The whirlpools produced by the mythic Charybdis were analogized with the figuratively turbulent external face of the big potassium channel.[58,59] Other medically important scorpions often have been named with similar mythological flair. The toxic South American scorpion, *Tityus serrulatus* [Brazilian yellow scorpion, family *Buthidae*] derives its genus name from the giant, Tityus, who, according to Greek mythology, was banished to Hades by Zeus because of the former's attempt to rape his bride, the goddess Leto, a female Titan.) Charybdotoxin essentially "plugs" the channel closed, thereby antagonizing the flow of potassium current. Na^+ channel and K^+ channel toxins in scorpion venoms function synergistically, causing persistent depolarization of autonomic nerves and resulting in the massive release of autonomic neurotransmitters.[60]

Although the actual frequency and case morbidity/mortality rates of scorpion stings are unknown, at least several thousand fatalities occur per year. A recent global estimate suggested 1.2 million scorpion stings occur annually, with about 3,250 deaths (case fatality rate around 0.27%).[61] The hallmark features of envenoming are instant and severe local pain at the sting site, followed by rapid onset (usually within 15 to 60 minutes) of systemic envenoming that may include generalized pain, cardiac dysfunction, profuse sweating, labile blood pressure (hypertension or hypotension), and pulmonary edema. After envenoming by some members of the genus *Centruroides* spp (Central America, southwestern United States, and Mexico), bizarre signs such as rotational nystagmus may be seen in children. The cardiac dysfunction or pulmonary edema may prove fatal, especially in children.

Envenoming by Australian funnel-web spiders (*Atrax* spp and *Hadronyche* spp) produces a similar pattern of rapid hyperexcitation, starting with perioral parasthesiae and tongue fasciculation. These initial effects can progress in minutes to include hypertension, excessive sweating, salivation, lacrimation, tachycardia, pulmonary edema, hypoxia, coma, and death. If the envenomed victim survives this stage, they may develop progressive muscle fasciculation, bradycardia, hypotension, and terminal cardiac collapse. The envenoming syndrome has been likened to a catecholamine storm.

Figure 18-12. Brazilian banana spider (*Phoneutria nigriventer*). A medically important South American species of aeranomorph.
Photograph: Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Wandering_spider.jpg.

Widow spiders (family *Theridiidae*, genus *Latrodectus*; approximately 31 species, including well-known species such as black widows [*Latrodectus mactans*] and red-backed spiders [*Latrodectus hasselti*; see Figure 18-2]) cause less rapid or severe envenoming, with initial bite site pain, and sometimes with local sweating and piloerection. Regional pain and sweating that progresses in severe cases to generalized pain, sweating, hypertension, nausea, and malaise may follow. This syndrome (latrodectism) is unpleasant and may last many hours to days, but is rarely fatal. Brazilian banana spiders (family *Ctenidae*, genus *Phoneutria*; approximately eight species; Figure 18-12) cause similar clinical effects (phoneutrism), but with more prominent local pain; additionally, envenomation in young males may result in priapism.

Australian Irukandji jellyfish (several genera of the class Cubozoa) may also cause a catecholamine storm-like envenoming. Irukandji syndrome is named for the Aboriginal clan in Cairns, Queensland, Australia, where this type of envenoming was first noted. The agent responsible for these cases remained elusive for years and eventually was determined to be a single cubozoan species, the chirodropid, *Carukia barnesi*, named for Dr Jack Barnes, who in 1964 first associated this jellyfish species with the syndrome. It is now clear that at least two species of chirodropid [*C barnesi*, *Malo kingi*], one or more species of cubozoan carybdeid [*Carybdea* spp], and probably several others are responsible for these serious envenomings. The victim initially experiences minor local sting effects and then a delayed (usually 20 to 40 minutes) onset of systemic envenoming with severe muscle spasm pain (especially in the back), sweating, nausea, and hypertension that can fluctuate and recur over hours. In severe cases, cardiac dysfunction and pulmonary edema can occur, and although deaths have occurred, they are rare (see Table 18-2). Still, any patient presenting with a significant Irukandji envenoming should have continuous cardiac monitoring.

Antivenoms are available for some medically important scorpion species and, despite some controversy, the majority of evidence indicates that these are effective and lifesaving if administered intravenously at the earliest opportunity. Some information has suggested that glucocorticoids might improve outcomes in some severe scorpion envenoming cases. However, these suggestions have largely been based on low quality evidence, and a recent Tunisian case-control study found no benefit.[62,63]

Antivenom against Australian funnel-web spiders is highly effective and can be lifesaving. Antivenom for widow spider bites is used routinely in Australia, where most clinical practice suggests it is effective, or at least more effective than alternative therapies. Elsewhere, its use is often reserved only for the most severe cases, mostly due to largely overrated fears of side effects that are actually uncommon.

A similar situation exists for *Phoneutria* bites, where local pain relief, including local anesthesia, is used in preference to antivenom, except in children and the most severely envenomed. No antivenom for Irukandji stings exists, and treatment is supportive and includes use of opioid analgesia to help alleviate the severe systemic pain associated with serious Irukandji envenoming.

Myotoxins

Myotoxins are mostly systemic in action and commonly are PLA2, but some myotoxins, such as the 42 amino acid basic polypeptide crotamine, appear to have focused action on muscle groups in the lower extremities. Crotamine, which is found in selected North American rattlesnake venoms, probably aids prey capture by causing rear limb dysfunction, that inhibits locomotor ability (eg, prevention of lengthy prey travel post-envenoming). Hypothetically, it may decrease the metabolic cost of trailing envenomed prey (eg, following bite-release, an envenomed prey animal may not expire for a few minutes and have time to flee from the site of the encounter with the snake). Locally acting myotoxins cause cellular damage around the bite site, but the systemically acting myotoxins, particularly PLA2, selectively target

skeletal muscle and can cause extensive and severe muscle damage. Although binding may occur early, once venom has reached and then exited the circulation, a delay occurs before onset of clinical detection of pathology. Therefore, significant myolytic effects may occur before clinical indicators for treating myolysis, which has led some researchers to suggest that early intervention with antivenom is justified to prevent myolysis in some cases of bites inflicted by species known to produce serious myolytic effects.[64] This remains to be studied, as no current evidence supports this approach.

The systemic myotoxins bind to the skeletal muscle cells and cause progressive and severe damage to the cells. Experimental animals injected with purified myotoxic PLA2 often exhibit skeletal muscle changes characterized by dissolution of actin and myosin filaments, disruption of Z-band material, dilation of the sarcoplasmic reticulum, and swelling and disruption of mitochondria, as well as disorganization of the T-tubule system.[65–68] However, if the basement membrane is preserved, some muscle regeneration can occur that may commence 24+ hours postbite, but may require weeks to complete. It is thought that the PLA2 enzymatic action is a crucial component in their toxicity, but chemical modification of specific residues (eg, Asp49, Lys49, and others) in the primary sequence of some of these enzymes has suggested that some PLA2 species may have a pharmacologically active domain discrete from the catalytic functional site.[69] Clearly, cellular binding to the target cells is an essential first step, as the myotoxic PLA2 species do not cause widespread cellular injury and specifically target muscle cells.

Figure 18-14. Australian eastern brown snake (*Pseudonaja textilis*). The most medically important snake in Australia; its range encompasses a large proportion of Australia and southeastern Papua New Guinea. Its venom contains potent procoagulants and a presynaptic neurotoxin (textilotoxin) with the highest experimental lethal potency of any snake venom toxin isolated to date. Fortunately, many bites inflicted on human victims are dry, meaning no venom is injected. Photograph: Copyright © Julian White. In: Brent J, Wallace KL, Burkhart KK, et al (eds). *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 1st ed. Philadelphia, PA: Mosby; 2005.

Figure 18-13. Australian common tiger snake (*Notechis scutatus*). One of the world's most venomous snakes, its venom contains potent presynaptic neurotoxins, myotoxins, and procoagulants.
Photograph: Copyright © Julian White. In: White J. *A Clinician's Guide to Australian Venomous Bites and Stings*. Melbourne, Australia: Commonwealth Serum Laboratories; 2013: 300 pp.

PLA2 myotoxins or multimeric toxins containing PLA2 subunits (many with myolytic activity; see Table 18-2 for representative examples) are found principally in snake venoms, notably selected Australian elapid venoms (eg, notexin [common tiger snake, *Notechis scutatus*; Figure 18-13], textilotoxin [Eastern brown snake, *Pseudonaja textilis*; Figure 18-14], taipoxin [coastal taipan (*Oxyuranus scutellatus*)]), sea snake venoms [eg, myotoxin VI5 (beaked sea snake, *Hydrophis* [*Enhydrina*] *schistosus*[70]], PLA2-H1 [blue-banded or annulated sea snake, *Hydrophis cyanocinctus*]), and some krait venoms (eg, β-bungarotoxin found in several species [eg, *Bungarus candidus*; Figure 18-15]). They are also found in several rattlesnake (family *Viperidae*, subfamily *Crotalinae*) venoms (eg, crotoxin, found in venoms of several taxa of tropical rattlesnakes, including *C durissus* spp, and others such as Mojave toxin and its isotoxins in venom of the Mojave rattlesnake, *C scutulatus*, tiger rattlesnake, *C tigris* [Figure 18-16], timber or canebrake rattlesnake, *C horridus* and others), as well as some Russell's viper (family *Viperidae*, subfamily *Viperinae*) venoms (eg, possibly, VRV-PL4 [*D russelii*; Figure 18-17]).

Figure 18-15. Malayan or blue krait (*Bungarus candidus*), Thailand. A semi-fossorial species that ranges in Malaysia, parts of Southeast Asia, and Indonesia. Studied *Bungarus* spp have venoms containing highly potent presynaptic neurotoxins (bungarotoxins), postsynaptic neurotoxins, and other components, including some with cardiotoxic properties.
Photograph: Copyright © Julian White. In: Brent J, Wallace KL, Burkhart KK, et al (eds). *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 1st ed. Philadelphia, PA: Mosby; 2005.

Figure 18-16. Tiger rattlesnake (*Crotalus tigris*). This distinctive rattlesnake has venom that contains the crotoxin homologue, Mojave toxin, a potent presynaptic heterodimeric neurotoxin. There are only a few documented bites by this taxon, all of which were medically insignificant. However, any rattlesnake species with venom that contains Mojave toxin, crotoxin or related isotoxins (eg, horridus toxin, or canebrake toxin found in venom of some geographic populations of the timber rattlesnake, *C horridus*) must be considered capable of delivering a potentially fatal envenomation.
Photograph: Copyright © Julian White. In: White J, Dart RC. *Snakebite: A Brief Medical Guide*. Denver, CO: Rocky Mountain Poison & Drug Center; 2008.

Clinically, systemic myotoxicity presents several to many hours postbite as muscle pain, muscle weakness, myoglobinuria, and gross elevation of plasma creatine phosphokinase and often-raised hepatic enzymes (eg, alanine transaminase, alkaline phosphatase, aspartate aminotransferase). In some cases, a notable creatine phosphokinase elevation may be observed before muscle discomfort.

It is important to note that some snake species often considered as purely neurotoxic may inflict bites that can cause mixed neurotoxicity and rhabdomyolysis akin to that seen in some Australian elapid envenoming by coastal taipans, tiger snakes, and others. For example, bites from greater black kraits (*Bungarus niger*) and Malayan kraits (*Bungarus candidus*; see Figure 18-15) have respectively caused mixed neurotoxicity and myotoxicity in Bangladesh[71] and myotoxicity, cardiovascular instability, neurotoxicity, and hyponaetremia in southern Vietnam.[72] Thus, due to unpredictable venom variability, as well as clinical response to variable venom components, it is essential not to view a given species as solely "neurotoxic" or "hemotoxic," because the venom-induced disease may notably vary. Treatment is with early intravenous administration of antivenom and supportive treatment, especially to ensure good renal output with aggressive fluid resuscitation (as in any recommendation for clinical

Figure 18-17. Russell's viper (*Daboia russelii*), Bannerghatta, India. Along with the saw-scaled vipers (*Echis* spp) and several species of cobras (*Naja* spp), *D russelii* and *D siamensis* (Eastern Russell's viper) are the species most important in the global envenoming burden. The snakes have a wide distribution and are plentiful; they constitute a public health problem particularly among rural communities in the Indian subcontinent, as well as parts of Southeast Asia. Envenoming from *D russelii* from different geographic populations can result in several differing clinical syndromes including hypogonadism, one of the consequences of pituitary hemorrhagic infarct (Sheehan's syndrome) resulting in panhypopituitarism. Another member of the genus, *D palaestinae* (Palestine viper) is medically significant in the Middle East. Its venom has been studied as a source of several classes of pharmacotherapeutics, including analgesics.
Photograph: Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/Daboia_russelii#/media/File:Russellsviper_sal.jpg.

management, approaches such as aggressive fluid resuscitation must be applied in the setting of risk/benefit with consideration for the patient's possible preexisting comorbidities, such as congestive heart failure or other volume overload states).

With major myolysis, secondary renal failure is a risk and can contribute to severe and sometimes fatal hyperkalemic cardiac toxicity. Alkalinization of urine is sometimes recommended, but is unproven to provide any added benefit in snakebite myolysis, as well as in most other presentations (eg, serotonergic syndrome, crush injuries) featuring acute myoglobinuria capable of producing nephropathy.

Myolysis can also follow some other envenomings, including massive bee stings and ingestion of certain mushrooms (eg, family *Tricholomataceae*, *Tricholoma* [*flavovirens*] *equestre*, yellow knight mushroom).[73] Studies of some venomous fish have reported myotoxicity in the murine model,[74] but, to date, there are no well-documented clinical cases of fish stings having caused myotoxicity.

Hemostasis-Active Toxins

The complex human hemostatic system is a common target of venoms, particularly snake venoms, that may cause a wide variety of clinical effects most commonly associated with an increased bleeding tendency. When combined with the action of proteolytic hemorrhagins, some cause severe hemorrhagic diathesis, a pathological state that could hypothetically be viewed as inducing terror in some individuals or populations. Thus, although impractical as tactically deployed bioweapon agents, some of these toxins could conceivably be used offensively on a small scale. An overview of the major toxin groups involved is shown in Table 18-3.

Venoms cause activation or inhibition of the clotting system by several different mechanisms and at many possible target points (Figure 18-18). Some venoms contain multiple toxins affecting hemostasis that may be synergistic, independent, or counteracting (see Figure 18-18).

In most cases, this type of envenoming (most accurately termed coagulopathic, not hemotoxic) causes an increased bleeding tendency, often by either hydrolyzing clotting protein (fibrinogenases) or by activating normal systems of clot formation and dissolution (procoagulants). These activities are most widely represented in viperid snake venoms, and a prominent example is that of ecarin, the prothrombin-converting metalloprotease (and closely related toxins) found in saw-scaled viper (*Echis* spp; Figure 18-19) venoms (a group A prothrombin activator). Ecarin plays an important role in the clinical laboratory by providing a meizothrombin generation test allowing for the precise quantification of direct thrombin inhibitors. Russell's viper (*Daboia russelii*) venom is a pivotal reagent in laboratory medicine because it contains a phospholipid and Ca^{2+}-dependent potent activator of factor X that forms a complex with prothrombin and thereby converts fibrinogen to fibrin. This mechanism facilitates the diagnosis of phospholipid antibodies including lupus anticoagulant, because in these states the antibodies bind to the essential venom co-factor phospholipid and thus inhibit the venom-induced factor X activation and prolong the clotting time.

Some Australian elapids also have potent procoagulant venoms. A number of the procoagulants present in these venoms, such as those found in the common tiger snake and Eastern brown snake, have structures homologous to human clotting factors Xa (group D prothrombin activator) or Va and Xa combined (group C prothrombin activator). Other animals, such as the venomous lizards *Heloderma suspectum* (Gila monster) and *Heloderma horridum* (beaded lizard), have venoms that contain procoagulant toxins and other hemostasis-active toxins, such as the *H horridum* venom acidic PLA2 that inhibits thromboxane-induced platelet aggregation.[75] As mentioned previously, caterpillars of the Brazilian *saturniid* moth, *Lonomia*, have irritating hairs that contain toxins with powerful procoagulant effects. Envenoming by a caterpillar may seem far-fetched, but it is not to be taken lightly because *Lonomia* stings can produce fatal disseminated intravascular coagulopathy in humans. A few animals, such as the Martinique lancehead viper or fer-de-lance *Bothrops lanceolatus*, have prothrombotic venom, and envenoming can lead to deep venous thrombosis, pulmonary emboli, cerebral infarction, and related thrombotic events.

Clinically, toxins promoting increased bleeding tendency may cause few initial or early symptoms. In many cases, almost all circulating fibrinogen can be consumed without apparent bleeding until or unless bleeding is induced through injury or a medical procedure such as venipuncture. In the former case, a fall with relatively mild cranial trauma can result in catastrophic intracranial bleeding that may occur minutes to hours later.

To detect abnormalities at the earliest opportunity after a potentially coagulopathic bite or sting, serial laboratory assessment of clotting function is essential. Careful serial laboratory testing is a cornerstone of management because early provision of antivenom and other potential treatments (eg, replacement therapy; see next paragraph) can limit the possible cardiovascular effects induced by the venom disease. There is ongoing controversy over the role of antivenom in

TABLE 18-3

MAJOR VENOM TOXIN GROUPS AFFECTING HUMAN HEMOSTASIS

Toxin Type	Effect	Examples
Procoagulants	Factor V activating Factor X activating Factor IX activating Factor II (prothrombin) activating: Group A Group B Group C Group D Fibrinogen clotting	RVV-V (Factor V-activating serine protease from venom of the Russell's viper, *Daboia russelii*) Contortrixobin (Factor V activating serine protease from venom of the copperhead, *Agkistrodon contortrix*) RVV-X (metalloproteinase disintegrin activator of Factor X from venom of the Russell's viper) TSV-FIX-BP (C-type lection-activating Factor IX from venom of Stejneger's green tree viper, *Trimeresurus stejnegeri*) Ecarin (cofactor-independent metalloproteinase Group A prothrombin activator from venom of the saw-scaled viper, *Echis carinatus*) Carinactivase (Ca^{2+}-dependent metalloproteinase Group B prothrombin activator from venom of the saw-scaled viper) Oscutarin (Ca^{2+}- and phospholipid-dependent serine protease Group C prothrombin activator from venom of the coastal taipan, *Oxyuranus scutellatus*) Notecarin (Ca^{2+}-, phospholipid, and Factor Va-dependent serine protease Group D prothrombin activator from venom of the common tiger snake, *Notechis scutatus*)
Anticoagulants	Protein C activating Factor IX/X activating protein Thrombin inhibitor Phospholipase A2	ACC-C (protein C-activating serine protease from venom of the copperhead, *Agkistrodon controtrix*) Bothrojaracin (C-type lectin thrombin inhibitor from venom of the jararaca, *Bothrops jararaca*) CM-IV (anticoagulant PLA2 from venom of the African black-necked spitting cobra, *Naja nigricollis*)
Fibrinolytic	Fibrin(ogen) degradation Plasminogen activation	Ancrod (fibrinogenolytic enzyme from venom of Malayan pit viper, *Calloselasma rhodostoma*) Neuwiedase (α-chain fibrinogenase [metalloproteinase] from venom of the jararaca pintada, *Bothrops neuwiedi*) Brevinase (β-chain fibrinogenase (serine protease) from venom of the mamushi, *Gloydius blomhoffi*) TSV-PA (plasminogen-activating serine protease from venom of Stejnegers green tree viper, *Trimeresurus stejnegeri*)
Vessel wall interactive	Hemorrhagins	Echistatin (RGD disintegrin from venom of the saw-scaled viper, *Echis sochureki*)
Platelet activity	Platelet aggregation inducers Platelet activation inhibitors	Botrocetin (platelet agglutination with VWF from venom of the jararaca) Convulxin (C-type lectin platelet aggregation, from venom of the South American rattlesnake, *Crotalus durissus terrificus*) Jararhagin (RGD disintegrin snake venom metalloproteinase that causes inhibition of platelet aggregation, from venom of the jararaca) Echicetin (C-type lectin platelet aggregation inhibitor from venom of the saw-scaled viper)
Plasma protein activators	Serine protease inhibitors	Proteinase I and II (inhibition of serine protease inhibitors from venom of the eastern diamondback rattlesnake, *Crotalus adamanteus*)

RGD: arginine-glycine-aspartic acid, a peptide motif found in this group of snake venom metalloproteinases; vWF: Von Willebrand Factor
Data sources: (1) Mebs D. *Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists*. Boca Raton, FL: CRC Press; 2002: 360. (2) Meier J, White J (eds). *Handbook of Clinical Toxicology of Animal Venoms and Poisons*. Boca Raton, FL: CRC Press; 1995. (3) Mackessy SP (ed). *Handbook of Venoms and Toxins of Reptiles*. Boca Raton, FL: CRC Press, Taylor & Francis; 2010: 528 pp. (4) Synthesized information included in lectures and presentations of the authors.

treating snakebite-induced coagulopathy in Australia, but most authorities consider timely administration of antivenom as the optimal treatment. Outside Australia, antivenom remains the evidence-based treatment for snakebite coagulopathy, either for increased bleeding (eg, from bites by the saw-scaled vipers, *Echis* spp) or for increased clotting (eg, from bites by the Martinique lancehead viper or fer-de-lance *B lanceolatus*).

The role of blood clotting products (eg, fresh frozen plasma and cryoprecipitate) replacement remains controversial, and when antivenom is available, it should be used in preference to and before such blood products if the clinical circumstances (eg, severe depletion with notable bleeding risk) suggest the need for replacement. For patients with major bleeding, despite adequate antivenom, blood products may have a place as adjunctive treatment depending on clinical need. Anticoagulant drugs such as heparin and warfarin are not useful in treating snakebite coagulopathy, probably intensify bleeding, and are positively contraindicated.

Hemorrhagic and Hemolytic Toxins

Some snakes have venom toxins that actively damage blood vessels and other tissues, thereby promoting bleeding. When combined with pro- and/or anticoagulant toxins, the actions are synergistic and potentially cause extensive bleeding or tissue injury, particularly around the bite site. These toxins are often also called hemotoxins, but are more accurately termed vasculotoxins because of their direct effects on the microvasculature.

Most hemorrhagic toxins are metalloproteinase enzymes, usually with a zinc moiety. However, some are comprised of peptide complexes, such as the synergistically hemorrhagic PLA2-peptide complex (DR-HC-1), characterized from *D russelii* venom.[76] The larger venom metalloproteinases have additional domains carboxy to the zinc-binding domain. Some metalloproteinases, termed class P-II by many investigators, contain domains that are further processed and give rise to free domains such as disintegrins.[77–79] Class P-III metalloproteinases have disintegrin-like and cysteine-rich domains, whereas class P-IV is similar to P-III, but its metalloproteinases have additional lectin-like domains. Homologs of the venom P-III structures (ADAMs: A Disintegrin-Like And Metalloproteinase-containing protein) have been identified in a variety of mammalian sources and tissues[77] and possess myriad activities, including participation in essential cellular functions such as angiogenesis regulation, inflammation, matrix protein processing, and many others.[80] However, particular focus has been directed toward those that occur in reptile venoms and mammalian reproductive tissues (the reprolysins, or M12 metalloproteinase subfamily[79]). The angiogenic inhibitor and cell adhesion molecule regulation functions have attracted scrutiny of some of the venom disintegrins as potential antineoplastic agents.[81] In addition, tissue inhibitors of metalloproteinases not only regulate proteinases in mammalian systems, but also have signal-transduction roles that continue to be characterized.[82] This is a fertile and promising area of research, and full consideration of their structure-function is beyond the scope of this chapter.

The proteolytic actions of these toxins damage the endothelium/basement membrane of cells comprising the microvasculature. Some crotaline viperids such as the Western diamondback rattlesnake have venoms that contain several different isoforms (eg, atrolysins) of these toxins. Some hemorrhagins have a shared disintegrin domain (a 13-amino acid loop containing specific sequences of arginine, glycine, and aspartic acid, or RGD in abbreviated nomenclature) that facilitates binding to platelet receptor gIIb/IIIa. These toxins have attracted more attention than most snake venom hemorrhagins because of their use in integrin function studies[83] and for their roles as structure-function scaffolds for pharmacotherapeutics (especially for the development of antithrombotics and as antineoplastics). One of these peptides, barbourin, has been characterized from venom of the dusky pygmy rattlesnake (*Sistrurus miliarius barbouri*).

Clinically, these hemorrhagins contribute to rapid and potentially severe local tissue effects such as blistering, bleeding, and necrosis, which are mostly associated with significant local pain and sometimes major fluid shifts from the circulation into local tissues. This latter effect can result in profound hypovolemic shock. Although some characterized hemorrhagins, such as the 50 kDa nonproteolytic hemorrhagin from venom of *Atractaspis engaddensis* (Israeli or oasis mole viper or burrowing asp), exhibit dose-related hemorrhagic activity, others such as the atrolysins mentioned previously may induce dose-independent hemorrhage in vivo as a result of the combined activities of this rhexic hemorrhagin and other venom components, such as the 30 kDa antagonist that binds to platelet glycoprotein receptor Ib. In this instance, the inhibition of platelet adhesion probably acts synergistically with the hemorrhagins and other anticoagulant toxins, thereby increasing the hemorrhagic effect to a greater extent than that accomplished by any of the single components alone.

The role of antivenom in treating effects of hemorrhagins is controversial, although most authorities recommend using antivenom therapy for prohemorrhagic envenomings. However, the molecular size and steric hindrance posed by antibodies present in

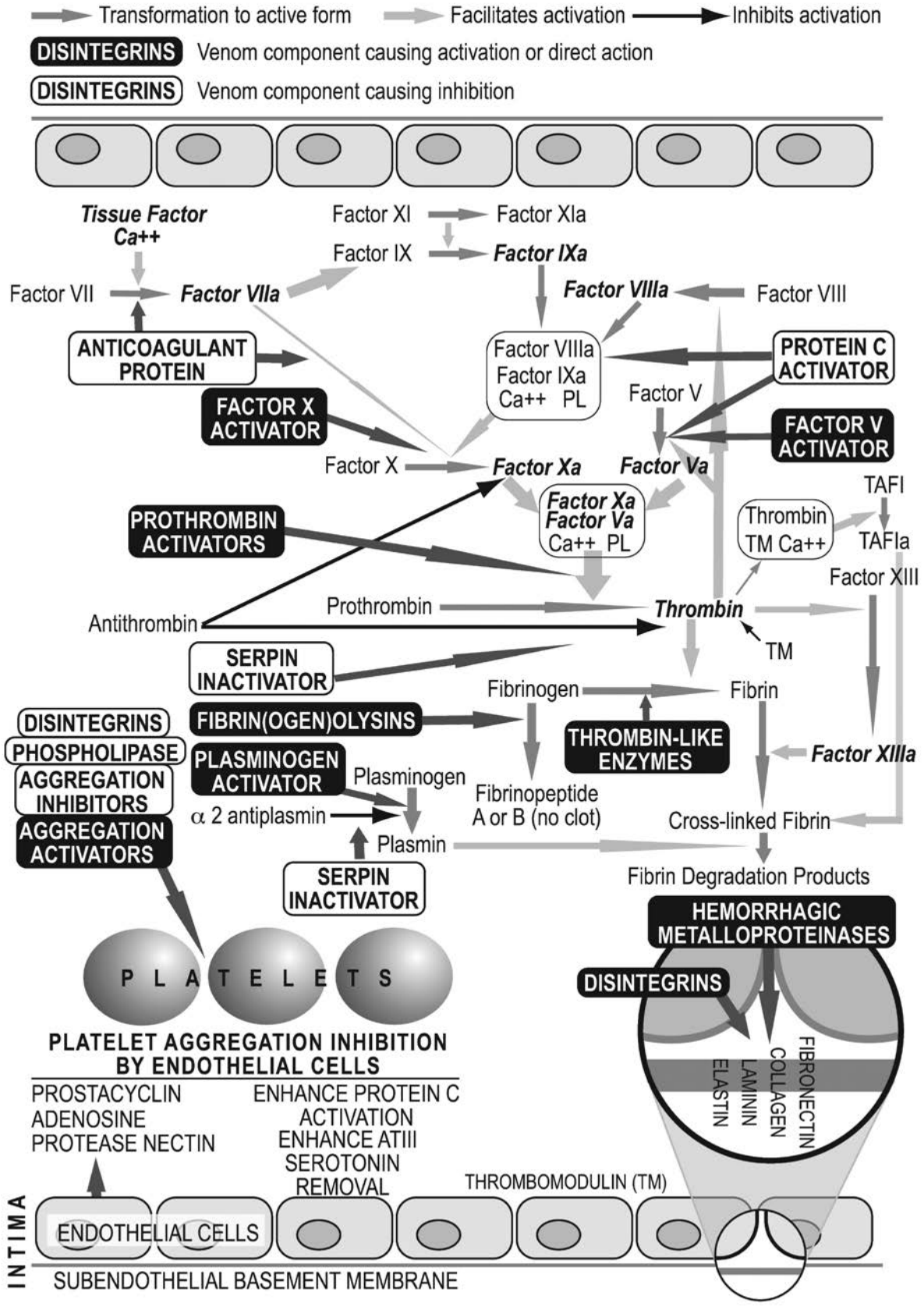

Transformation to active form
Facilitates activation
Inhibits activation
DISINTEGRINS
Venom component causing activation or direct action
DISINTEGRINS
Venom component causing inhibition
Tissue Factor
Ca++
Factor XI
Factor XIa
Factor IX
Factor IXa
Factor VII
Factor VIIa
Factor VIIIa
Factor VIII
ANTICOAGULANT PROTEIN
Factor VIIIa
Factor IXa
Ca++ PL
PROTEIN C ACTIVATOR
Factor V
FACTOR X ACTIVATOR
FACTOR V ACTIVATOR
Factor X
Factor Xa
Factor Va
Factor Xa
Factor Va
Ca++ PL
TAFI
PROTHROMBIN ACTIVATORS
Thrombin
TM Ca++
TAFIa
Factor XIII
Antithrombin
Prothrombin
Thrombin
TM
SERPIN INACTIVATOR
Fibrinogen
Fibrin
DISINTEGRINS
FIBRIN(OGEN)OLYSINS
THROMBIN-LIKE ENZYMES
Factor XIIIa
PHOSPHOLIPASE
PLASMINOGEN ACTIVATOR
Plasminogen
AGGREGATION INHIBITORS
Fibrinopeptide A or B (no clot)
α 2 antiplasmin
Cross-linked Fibrin
AGGREGATION ACTIVATORS
Plasmin
SERPIN INACTIVATOR
Fibrin Degradation Products
HEMORRHAGIC METALLOPROTEINASES
DISINTEGRINS
PLATELETS
FIBRONECTIN
COLLAGEN
LAMININ
ELASTIN
PLATELET AGGREGATION INHIBITION BY ENDOTHELIAL CELLS
PROSTACYCLIN
ADENOSINE
PROTEASE NECTIN
ENHANCE PROTEIN C ACTIVATION
ENHANCE ATIII
SEROTONIN REMOVAL
THROMBOMODULIN (TM)
INTIMA
ENDOTHELIAL CELLS
SUBENDOTHELIAL BASEMENT MEMBRANE

Figure 18-18. Diagrammatic representation of the human hemostasis system, with examples of where venoms may interact to activate or inhibit the clotting process. The diagram only represents some key elements of hemostasis, not every component currently known and similarly, only some common examples of toxin effects, not an exhaustive listing of all known toxin interaction sites. The diagram concentrates particularly on the coagulation cascade elements, whereby various triggers in normal hemostasis activate top levels of the cascade, resulting in progressive activation downstream until common pathways are reached. Principal among the latter are activation of procoagulant enzymes (mostly serine proteases), such as factor VIII to FVIIIa, factor X to FXa, factor V to FVa, with FXa and FVa forming the prothrombinase complex that then activates the final enzymatic step, prothrombin (factor II) to thrombin (FIIa). It is thrombin that then converts the clotting protein, fibrinogen, to fibrin, so that fibrin molecules can be cross-linked by factor XIIIa, to form a stable fibrin clot. Normally this clot formation occurs inside a protective platelet plug environment, at the site of blood leakage from a damaged blood vessel. The damaged edges (endothelial cells) of the blood vessel are a potent stimulus to activation of the hemostasis system. The fibrin blood clot then provides a semipermanent plug to prevent further blood leakage from the damaged blood vessel, allowing time (6–10 days) for the endothelium to repair and effect a permanent repair of the damage, at which time the fibrin clot is no longer required and is broken down by plasmin (activated form of plasminogen). There are a number of promoters and inhibitors of each step in this complex multistep process, each designed to ensure clots only form where needed and are dissolved once no longer needed. Each and every step in the process, including promoters and inhibitors, is a potential target for venom toxins. In addition, if the process is activated freely in blood, rather than in a protected platelet plug environment, some normal controls are bypassed, allowing rapid progression from procoagulant activation, through conversion of fibrinogen to fibrin, and then degradation of fibrin strands and cross-linked fibrin by plasmin. This process can potentially cause rapid consumption of all circulating or available fibrinogen, rendering the patient unable to form blood clots, so at risk of major bleeding. In one sense this is a profound form of anticoagulation, but it is achieved by aggressive stimulation of clotting, hence is usually termed a *procoagulant defibrination coagulopathy* (referred to as VICC by a few authors). This consumptive coagulopathy can be initiated by a variety of venom toxins, particularly the calcium-independent procoagulants (Groups A and B) found in saw-scaled viper (*Echis* spp) venoms, and the calcium-dependent procoagulants (Groups C and D) found in many Australian Elapid snake venoms (eg, *Pseudonaja* spp, *Oxyuranus* spp, *Notechis* spp, *Tropidechis carinatus*, *Hoplocephalus* spp). These latter procoagulants mimic closely the normal clotting factors, thus have extensive homology with either FXa, or the FVa–FXa (prothrombinase) complex. It can be speculated that these toxins were developed from recruitment of normal clotting factor genes. Once this process is activated there can be massive consumption of clotting factors, especially fibrinogen, but also FII, FV, FVIII, and FX among others, and while antivenom may, at least for some venoms, switch off the process, it cannot instantly restore depleted fibrinogen and other factor levels, so several hours may pass before protective levels are reached. Although giving factor replacement therapy (fresh frozen plasma, cryoprecipitate, or whole blood) may speed return to normal levels, if neutralization of venom toxins is incomplete, such replacement therapy can instead add fuel to the coagulopathy fire, potentially worsening the clinical picture. In contrast, phospholipase A2-based anticoagulant toxins (eg, from *Pseudechis* spp) merely inhibit portions of the hemostasis pathways without causing consumption of clotting factors, so that antivenom can almost instantly reverse this effect.
PL: phospholipid; TAFI: thrombin-activatable fibrinolysis inhibitor; VICC: venom-induced consumption coagulopathy

antivenom (usually whole IgG or the F(ab')^2 portion of IgG) may not easily leave the circulation to penetrate the areas being damaged by hemorrhagins. Drugs to directly target the enzymatic action of these toxins have been explored as adjunctive therapy and continue to attract study to identify possible alternative therapeutic agents.

In cases of hemorrhagic snakebite, it is essential to monitor for shock and ensure adequate intravenous hydration. The damaged bite area may appear markedly swollen and with poor vascular return, with concomitant pain, possibly suggesting an underlying compartment syndrome. Although snakebites may rarely cause compartment syndrome, most snakebite patients do not have definitive evidence of compartment syndrome. In addition, the clinical criteria defining compartment syndrome varies among surgical specialties (eg, orthopedics and vascular surgery), facilities, and individual physicians and surgeons. In facilities lacking intracompartmental measurement catheter systems, clinically experienced use of basic Doppler ultrasound may help clinical interpretation. Conversely, hospitals equipped with magnetic resonance imaging or multidetector computed tomographic arteriography could provide additional means to assess complicated cases, but the latter method would be positively contraindicated in any patient with coagulopathy.

Fasciotomy is the standard treatment for compartment syndrome, but when used injudiciously for snakebite it can accelerate blood loss and shock, and cause severe permanent tissue injury. Fasciotomy should only be performed in snakebite if there is direct pressure measurement confirmation of compartment syndrome with clinical correlation and then only after any coagulopathy has been treated. Several patients of

Figure 18-19. Northeast African saw-scaled or carpet viper (*Echis pyrimidum*). There are approximately 11 current recognized species of *Echis*. Several *Echis* spp cause a large proportion of the world's human envenoming burden, and are among the three most medically important venomous snakes. Conversely, *E carinatus* venom has yielded components important in laboratory medicine (eg, the metalloprotease prothrombin activator, ecarin), as well as a platelet aggregation inhibitor (tirofiban, marketed as Aggrastat) that reversibly binds to platelet GPIIb/IIIa receptors.
GP: glycoprotein
Photograph: Copyright © Julian White. In: Brent J, Wallace KL, Burkhart KK, et al (eds). *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 1st ed. Philadelphia, PA: Mosby; 2005.

snakebite-induced, verified compartment syndrome have also been treated successfully by purely medical methods (eg, hyperbaric oxygen therapy and cautious use of mannitol, the latter contraindicated in cases featuring hypovolemia).

Cardiotoxins

True cardiotoxins that cause direct cardiac effects in humans are uncommon. Some examples include the following:

- the 2.5 kDa endothelin homologues, the sarafotoxins from some venoms of the mole vipers or burrowing asps (*Atractaspis* spp; these are not vipers at all, but instead they are front-fanged members of the subfamily *Atractaspinae* of the African family *Lamprophiidae*),
- bufotoxins from toad (eg, the marine toad, *Rhinella marina Linnaeus* 1758, formerly *Bufo marinus*) parotid gland secretions, and
- the oleandrins from oleander plants (*Nerium oleander* [oleander; Figure 18-20] and *Cascabela* (*Thevetia*) *peruviana* [yellow oleander or lucky nut; Figure 18-21]).

The cardiac glycosides of both of the latter plants produce effects similar to digoxin by binding to and inactivating the Na^+/K^+-ATPase pump on the cytoplasmic

Figure 18-20. Oleander (*Nerium oleander*) and yellow oleander or lucky nut (*Cascabella* [*Thevetia*] *peruviana*). These attractive and popular ornamental plants contain digoxin-like toxins that inactivate the Na^+/K^+-ATPase pump on the cytoplasmic membrane of myocardiocytes. Concentrations of the toxins present in the plant vary according to plant component (eg, seeds, leaves, etc), but ingestion of small amounts is potentially fatal. (**A**) Oleander (*Nerium oleander*). (**B**) Yellow oleander or lucky nut (*Cascabella [Thevetia] peruviana*).
Photographs: Courtesy of Julian White.

Figure 18-21. Indo-Chinese spitting cobra (*Naja siamensis*). This cobra is medically important throughout its range in Southeast Asia (Thailand, Lao, southern Vietnam and Cambodia), but its congener, *N kaouthia* (the monocellate, or monocled cobra) is responsible for a large proportion of snakebite mortality and morbidity throughout its extensive range in Southeast Asia and the Indian subcontinent. Envenoming commonly features serious local effects including desquamation, cellulitis and necrosis, and can include systemic neurotoxicity, as well as rare direct cardiotoxicity. Predominance of local envenoming or neurotoxicity is variable due to marked population venom variance, and some populations can inflict envenoming with mixed clinical presentation of local effects and neurotoxicity. In addition, *N siamensis* and probably several populations of *N kaouthia* can forcibly eject ("spit") venom through modified fangs that contain an anteriorly oriented orifice. The venom is targeted at the head of the recipient, and often enters the eyes causing venom ophthalmia. Agrarian-based rural communities may be seriously impacted by these snakes, as well as by *Echis* spp and *Daboia* spp, because farmers working sustenance crops often are the victims of envenomings by these species and, when not fatal, the common disabling sequelae can threaten their livelihood.
Data source: Chu ER, Weinstein SA, White J, Warrell DA. Venom ophthalmia caused by venoms of spitting elapids and other snakes: report of ten cases with review of epidemiology, clinical features, pathophysiology, and management. *Toxicon*. 2010;56:259–272.
Photograph: Copyright © Julian White. In: Brent J, Wallace KL, Burkhart KK, et al (eds). *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 1st ed. Philadelphia, PA: Mosby; 2005.

membrane of cardiac cells.[22] As a result, intracellular Na^+ concentration increases, which affects the Na^+/Ca^{2+} exchange channels, resulting in an increase in intracellular Ca^{2+} that leads to a positive inotropic effect. The increase of intracellular Ca^{2+} ions also raises the resting membrane potential of the cell, leading to increasing rates of spontaneous cellular depolarization and myocardial automaticity.[84] Inhibition of the Na^+/K^+-ATPase pump affects the intracellular movement of K^+ leading to hyperkalemia.[84,85]

A few reports show dysrhythmias/cardiotoxicity after cobra bites (especially the monocellate or monocled cobra, *Naja kaouthia*), and some of these probably are caused by the direct effects of cardiotoxin (also known as direct lytic factor due to its weakly hemolytic and other cytotoxic properties). Similar effects may be caused by secondary complications that might be more likely in victims with cardiovascular comorbidities (see Figure 18-21).[86,87]

Secondary cardiac effects are more common, such as the severe and sometimes lethal hyperkalaemia, secondary to severe myolysis that can follow secondary renal failure, which in some cases probably results from myoglobinuric nephropathy. The myolysis causes massive release of intracellular potassium into the circulation, which is controlled by kidney excretion, but with renal failure this normal kidney function is impaired or ceases, and potassium levels in blood subsequently rise to toxic levels. Some scorpion venom toxins cause neuroexcitation that can result in secondary cardiac dysfunction, sometimes with output failure, arrhythmias, and cardiogenic pulmonary edema. Cardiac arrhythmias and arrest may also be indirectly caused by hyperkalemia resulting from the cytotoxicity caused by high doses of toxins from box jellyfish (eg, the Australian box jellyfish or sea wasp, *Chironex fleckeri*) and the closely related multiple taxa (eg, *C barnesi* and *M kingi*) that cause Irukandji syndrome. The clinical effects of cardiotoxins depend on the toxin and its mechanisms of action.

Antidotes may be available for some "true," or more accurately, directly acting cardiotoxins. For digoxin-like toxins (such as bufonid toad poisoning or ingestion of oleander plants), cardiac effects can sometimes be reversed using anti-digoxin Fab' (digoxin fragment antibodies, or antigen-binding fragments). In one case of possible cobra envenoming-induced cardiotoxicity, antivenom administration appeared to correct ventricular bigeminy, possibly a result of the neutralization of toxin effects, or an improvement of other venom effects, thereby alleviating the secondary effects of envenoming.[87] For box jellyfish, although antivenom can neutralize the toxins, the indirect cardiovascular effects can develop so rapidly that, under experimental conditions using rodents, even giving antivenom together with the toxin does not prevent death. Nevertheless, prevailing opinion currently supports provision of high dose antivenom in cardiac collapse caused by box jellyfish stings, combined with aggressive cardiac resuscitation.

Nephrotoxins

Few direct animal venom or plant-derived nephrotoxins are currently known. Examples include toxins from Russell's viper venom and from several mushroom taxa: *Cortinarius* spp mushrooms (sometimes called cortinars or webcaps), *Amanita smithiana* (Smith's amanita or Lepidella), *Amanita proxima* (near neighbor amidella), and others.[88] The former contains toxins (eg, a 7 kDa basic cytotoxin) that damage the tubular epithelium, while the latter contains orellanines (eg, 3,3′-4,4′-tetrahydroxy-2,2′-bipyridyl-*N*,*N*′-dioxide from *C orellanus*) that induce delayed renal tubular necrosis, which leads to renal failure.

Most renal pathology associated with venom, plant, or fungal toxins is secondary. In snakebite, it may follow coagulopathy and bleeding, myolysis, hemolytic anemia, or a period of hypotension/shock. Venoms causing major hemolysis are associated with renal failure, as seen after massive multiple hymenopteran stings such as those inflicted by bees or vespid wasps, as well as after some snakebites. Recluse spider bites may also cause hemolysis as part of widespread tissue injury (viscerocutaneous loxoscelism), with associated multiple organ involvement, including renal failure.

The nature of the kidney injury depends on the toxin mechanism or that of the secondary effects. In snakebites, the injury is often due to acute tubular necrosis, from which full recovery after a period of hemodialysis is possible. However, cases of bilateral renal cortical necrosis are reported, where renal recovery occurs far less frequently.[35] Renal dysfunction secondary to hemolysis is similarly likely to be transient, but renal pathology following orellanine mushroom poisoning is permanent in some cases.

Treatment for possible impending nephrotoxicity is firstly preventative, by ensuring adequate cardiovascular function and hydration. Renal output must be carefully monitored, and hydration appropriately adjusted, sometimes with the addition of diuretics. For envenoming where antivenom is available, early neutralization of venom may help prevent or moderate renal damage, but in some snakebites a microangiopathic hemolytic anemia (with secondary renal damage) can occur despite early and adequate antivenom treatment. The biomedical basis of this phenomenon is not well characterized.

Once significant renal failure has developed, dialysis—preferably hemodialysis—is the key to management. In many developing countries renal dialysis facilities are uncommon and because of their unavailability, some envenomed patients who may have otherwise survived die from renal failure. However, some severe patients may be poorly responsive to dialysis and have fatal outcomes despite aggressive treatment.

Necrotoxins

Necrotoxins are major components in some venoms, such as those of the recluse spiders (family *Sicariidae*, *Loxosceles* spp) and the Iranian scorpion, *Hemiscorpius lepturus* (family *Hemiscorpiidae*; this species does not have a generally used common name, but the genus is sometimes collectively called the Asian thin-tailed scorpions); while cytotoxic and hemorrhagic toxins in some snake venoms may cause similarly direct injury and necrosis around the bite site. Although several species of *Hemiscorpius* are found in Iran, Pakistan, Yemen, and Iraq, *H lepturus* occurs only in Iran and is the only known medically important taxon in the genus. There are no available data regarding the possible medical significance of other species, and these should be treated as dangerous until proven otherwise.

Recluse spider (*Loxosceles* spp) venoms contain sphingomyelinase D that initiates neutrophil recruitment and thereby ultimately stimulates neutrophil-induced cell lysis at the bite site. This destructive neutrophil response has been linked to locally elevated levels of complement such as C5a. Interestingly, sphingomyelinase D from *Loxosceles* spp venom also activates target cellular matrix proteases that cleave the C5a receptor, thereby initiating a protective mechanism against the elevated levels of C5a.[89] The sphingomyelinases also alter the morphology of target cell membranes by transforming sphingomyelin into ceramide-1-phosphate. However, there are many gaps in the characterization of the precise pathophysiological mechanisms of some necrotoxins such as sphingomyelinase. Further elucidation of these mechanisms could provide information important to characterization of regulatory mechanisms governing local complement levels and autoimmune cellular responses in a variety of pathological states.

Clinically, local necrosis is often painful and obvious from an early stage, but recluse spider bites may be painless with few visible clinical manifestations in the first 12 to 24 hours, followed by the development of a classic "target" lesion (necrosing blue-black central skin, with surrounding pallor and an outer ring of erythematous reaction). This lesion can evolve over several days into epidermal necrosis that may be painful, and local blistering occasionally occurs. Necrosis following selected snakebites is usually painful and often accompanied by blistering, either centrally or at the margins of the evolving demarcated necrotic focus.

H lepturus is a particularly medically important species in Iran.[90] It is the only scorpion species known to commonly cause hemoglobinuric nephropathy and subsequent renal failure. In a series of *H lepturus* envenomings involving children younger than 10 years, Afzali and Pezeshki[91] reported that 8% had a

fatal outcome and 2.2% succumbed to renal failure. Stings from this species also cause local edema and hemorrhagic effects.

Treatment of toxin-induced necrosis is controversial. Early debridement of necrotic tissue may sometimes help, but for recluse spider bite it may actually increase the necrotic area. For this reason, current opinion discourages debridement, but delayed debridement may be necessary.[92] Some patients have been treated with hyperbaric oxygen and other modalities, but have not resulted in consistent benefit, and thus cannot be generally endorsed without further supporting evidence.[92] Secondary infection can occur and may either accelerate the necrosis, or even be the more important contributor to the necrotic process. Therefore, careful infection control is important, including appropriate antibiotics, as determined by anaerobic and aerobic culture, sensitivity determination, and regional trends in antibiotic resistance.

Other Toxins

There are many lesser toxins that are either of minor clinical importance in humans, poorly understood, or clinically significant but uncommonly to rarely encountered. For example, the giant tropical and desert centipedes, particularly of the genus *Scolopendra* (class Chilopoda, family *Scolopendridae*), are semi-fossorial and often nocturnal, and are not frequently encountered. These fast-moving active predators can inflict a painful sting with a pair of modified front legs often called maxillipedes, or forcipules (with the tarsungulum being the fang-like business end[93]) that are associated with pressurized venom glands (Figure 18-22). Although of generally minor importance, stings from several species have caused mild to moderate local effects (eg, pain [sometimes severe], edema, secondary infection and necrosis, pruritis), as well as uncommon systemic effects (eg, nausea, headache), some of which may also be due to autonomic responses to pain or anxiety. There are a few anecdotal reports of fatalities, and *Scolopendra subspinipes* has been viewed as a species of potentially greater medical importance in some rural Southeast Asian communities. An *S subspinipes* reportedly inflicted a fatal sting in a child in the Philippines.[94] These isolated reports require careful assessment and further documentation before assigning a defined hazard index for the species. However, the possible medical importance for giant centipedes may be underestimated in some regions, and rare deaths result from secondary complications of centipede stings (eg, necrotizing fasciitis).[95]

Several taxa and strains of the mold *Aspergillus* spp (family *Trichocomaceae*) produce difuranocoumarin derivatives, the aflatoxins, which are synthesized by a polyketide pathway. Interestingly, this fungal genus can be subjectively viewed as one that possibly contains the greatest contrasting mix of species because some provide respective benefits to humans (eg, utilization of *A niger* in the fermentation industry for citric acid synthesis[96]), yet others (eg, *A flavus*) are among the most medically hazardous, especially due to their toxins' carcinogenicity. The most studied aflatoxins (B1, B2, G1, G2) were named as a result of their blue or green fluorescence under ultraviolet light and their thin-layer chromatographic mobility properties.[96] These toxins are acutely toxic in sufficient doses and are also potent carcinogens.

Figure 18-22. The venom delivery apparatus of a scolopendrid centipede. The fang-like structures located on each side of the head are modified legs (maxillipedes or forcipules) that deliver venom into grasped prey or a potential predator. Thus, centipedes deliver venom through stinging, rather than via a bite.
Photograph: By Fritz Geller-Grim. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Scolopendra_fg02.JPG.

An accumulating body of interdisciplinary information suggests that interspecies variability in response to aflatoxins probably results from multifactorial influences including variability in the cytochrome P450 system that converts aflatoxins to the reactive, DNA adduct-forming, and protein-binding 8,9-epoxide forms.[97] Clinical signs of acute aflatoxicosis include hypolipidemia, hepatic steatosis, and necrosis.[98] Etzel[99] estimated the human LD_{50} (derived from murine data) of ingested aflatoxin B1 in liquid medium as 0.15 to 0.30 mg/kg. The longer term, carcinogenic consequences of aflatoxin exposure are a result of toxin binding to both

TABLE 18-4

PRINCIPAL TYPES OF MUSHROOM POISONING

Mushroom Clinical Group*	Principal Toxin(s)	Major Effect
Group 1 — Amatoxic mushrooms, notably *Amanita phalloides* (death cap) and related spp, as well as several other taxa (eg, *Lepiota* spp; Figure T1)	Amatoxins	Delayed-onset cytotoxicity via inhibition of RNA polymerases II that arrest transcription resulting in cellular (especially hepatocellular) destruction

Figure T1. *Lepiota* spp (*Agaricaceae*), Outer Banks, Nags Hags Head Woods, North Carolina. Some taxa of these gilled mushrooms (eg, *L helveola*) contain amatoxins and ingestion of several species including *L helveola* has caused fatalities. Photograph: By Jason Hollinger. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Lepiota_(4503849093).jpg.

Figure T2. Fly agaric (*Amanita muscaria*), Ulm, southern Germany. Typically not fatal, ingestion of these mushrooms can produce agitation, elation, disorientation, depersonalization, manic excitement, visual misperceptions (rather than true hallucinations), confusion; the syndrome can be mistaken for alcohol intoxication. There can be ataxia, incoordination, dizziness, mydriasis, myoclonus, muscle fasciculation/tremors, hyporeflexia, coma, and in severe poisoning, especially in children, convulsions. Ingestion of the congener, *A phalloides*, can be fatal, and there are a substantial number of well documented life-threatening and fatal cases.
Photograph: By Holger Krisp. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Amanita-muscaria-fliegenpilz-b.jpg.

Group 2 — Gyrometrin-containing mushrooms, notably *Gyromitra* spp	Gyrometrin (hydrolyzed to monomethyl hydrazine)	Delayed-onset cytotoxicity; cellular destruction
Group 3 – Coprine-containing mushrooms (various)	Coprine (*N*-5,1-hydroxycyclopropyl-L-glutamine)	Rapid autonomic effects, only in association with co-ingestion of alcohol (disulfarim-mimetic)
Group 4 – Muscarinic mushrooms, notably *Inocybe* spp, *Clitocybe* spp, *Mycena* spp	Muscarine (2,5-anhydro-1,4,6-trideoxy-6-(trimethylammonio)-D-ribo-hexitol)	Rapid-onset neuroexcitatory effects (parasympathetic stimulation; classically sweating, salivation, and lachrymation)
Group 5 — Ibotenic mushrooms, notably *Amanita muscaria* (Figure T2) and *Amanita pantherina*	Ibotenic acid, muscimol	Rapid onset of central nervous system effects, including agitation, elation, disorientation, mania, and visual misperceptions

(**Table 18-4** *continues*)

Table 18-4 continued

Group 6 — Hallucinogenic mushrooms, notably spp of *Psilocybe*, *Conocybe*, *Gymnopilus*, *Panaeolus*, and others	Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine; *note*: purchased hallucinogenic mushrooms may be laced with LSD and related substances)	Rapid onset of central nervous system effects including illusions (visual, auditory, or tactile), most commonly euphoric (but potentially sinister)
Group 7 — Gastrointestinal irritants, many species	Diverse array of toxins	Rapid onset (1–3 h) of gastrointestinal effects (vomiting, diarrhea, or abdominal pain)
Group 8 — Orellanine (nephrotoxic) mushrooms, notably *Cortinarius* spp	Orellanine (2,2′-bipyridine-3,3′,4,4′-tetrol-1,1′-dioxide)	Delayed-onset cytotoxicity; renal failure often occurs days after ingestion
Group 9 — Nephrotoxic mushrooms, notably *Amanita smithiana* and *A pseudoporphyria*	Aminohexadienoic acid	Delayed-onset cytotoxicity; renal failure with prerenal symptoms occurring 0.5–12 h later
Group 10 — Primary myolytic mushrooms, notably *Tricholoma equestre*	Unknown (*note*: these are normally edible mushrooms)	Delayed-onset myolysis due to unknown mechanism or association
Group 11 — Myolytic mushrooms, notably *Russula subnigricans*	Unknown	Rapid-onset myolysis
Group 12 — Pain-inducing mushrooms, notably *Clitocybe acromelalga*	Acromelic acid (several toxins; eg, acromelic acids A and B; all are heteroaromatics)	Rapid onset of rash, edema, and digit-tip pain (allodynia)

*The groupings listed here are based on the type of clinical presentation, rather than toxin type or mushroom species. Some groups may have many mushrooms, while others may have only a single species known to cause the specific clinical syndrome. From a clinical perspective, patients frequently ingest mushrooms of multiple species and potentially from multiple groups; thus, the clinical picture in any given patient may be a mixture of effects from a variety of mushroom groups. Clinical cognizance is especially important in relation to potentially lethal groups, particularly Group 1 amatoxic mushrooms, when coingested with other mushrooms causing gastrointestinal disturbance, as this may lead to a mixed clinical picture initially suggestive of poisoning by nonlethal Group 7 species.
Data source: (1) White J, Weinstein SA, De Haro L, et al. Mushroom poisoning: a proposed new clinical classification. *Clin Toxicol*. 2017 (under review).

DNA and RNA, which cause inhibition of replication, transcription, and protein synthesis; protein binding can also cause enzyme inactivation.[100]

Although it may seem unlikely that carcinogenic toxins might be used as biological warfare agents, significant evidence indicates that aflatoxins from *A flavus* and *A parasiticus* were a significant part of Iraqi bioweapons development during the 1980s[100] and were loaded into warheads and stockpiled.[101–103] Several possible reasons for their selection as potential offensive agents have been considered including obvious stimulation of fear and terror, and simple exploitation of favored or available resources.[97] However, consideration must be given to the possibility of intended infliction of longer term serious health effects on a given population (eg, as the initial Iraqi intent may have been directed against the Kurds in northern Iraq), a potential form of generational genocide. Thus, these toxins remain of concern on a relatively small scale because they are impractical as tactical weapons.[104]

Several filamentous fungi, particularly of the genus *Fusarium* (family *Nectriaceae*), produce tricothecenes such as T-2 and deoxynivalenol (vomitoxin), which are potent eukaryotic protein synthesis inhibitors and may disrupt initiation, elongation, and/or termination. There are several groups of these toxins including the nonmacrocyclic group (which contains an ester-ether bridge between C-4 and C-15 instead of a macrocyclic ester), which is further subclassified into structurally based groups, A and B.[96] T-2 is a potent immunotoxin, which binds to the 60S ribosomal subunit and subsequently inhibits elongation; it also inhibits protein synthesis induction.[105,106] Ingestion of T-2 toxin causes severe gastrointestinal distress including nausea, profuse diarrhea, vomiting, distention, and pain; those affected may also present with dizziness, chills, and other flu-like symptoms. T-2 toxins damage labile cells such as those in the gastrointestinal tract; they cause degeneration and necrosis of the lymphoid tissues and the surface and crypt epithelium of the gastrointestinal mucosa,[104] as well as induction of thymic lymphocytic apoptosis.[106] In humans T-2 toxin can induce apoptosis in megakaryocyte progenitors, and affected animals exhibit a notable loss of cell-mediated immunity.[104,107] Due to the acute effects caused by T-2 and its natural

TABLE 18-5

SELECTED PRINCIPAL TYPES OF PLANT POISONING

Plant Clinical Group	Principal Toxin(s)	Major Effects
CYTOTOXIC PLANTS		
Ricinus communis (castor bean, castor oil plant; Figure T3)	Ricin is a heterodimeric subunit protein that belongs to the ribosome inactivating protein family. One subunit (B chain) is a lectin and the other (A chain) is responsible for most of the toxicity.	Cytotoxic, inhibits protein synthesis by catalytic (via *N*-glycosidase) depurination of the 28S RNA, thereby arresting translation. The toxin can potentially cause lethal multiorgan failure, but most cases of simple ingestion (eg, raw ingestion of intact or slightly disrupted seeds) cause nonlethal gastrointestinal effects only.
Colchicum autumnale (autumn crocus, meadow saffron; Figure T4)	Colchicine (antimitotic; mitotic spindle poison)	Concentrates in polymorphonuclear leukocytes and inhibits microtubule assembly. Abdominal pain, vomiting, diarrhea, paralysis, convulsions, hypovolemic shock, respiratory failure, bone marrow failure.
Abrus precatorius (jequirty pea)	Abrin (also a ribosome inactivating protein)	Concentrates in polymorphonuclear leukocytes and inhibits microtubule assembly. Abdominal pain, vomiting, diarrhea, paralysis, convulsions, hypovolemic shock, respiratory failure, and bone marrow failure.

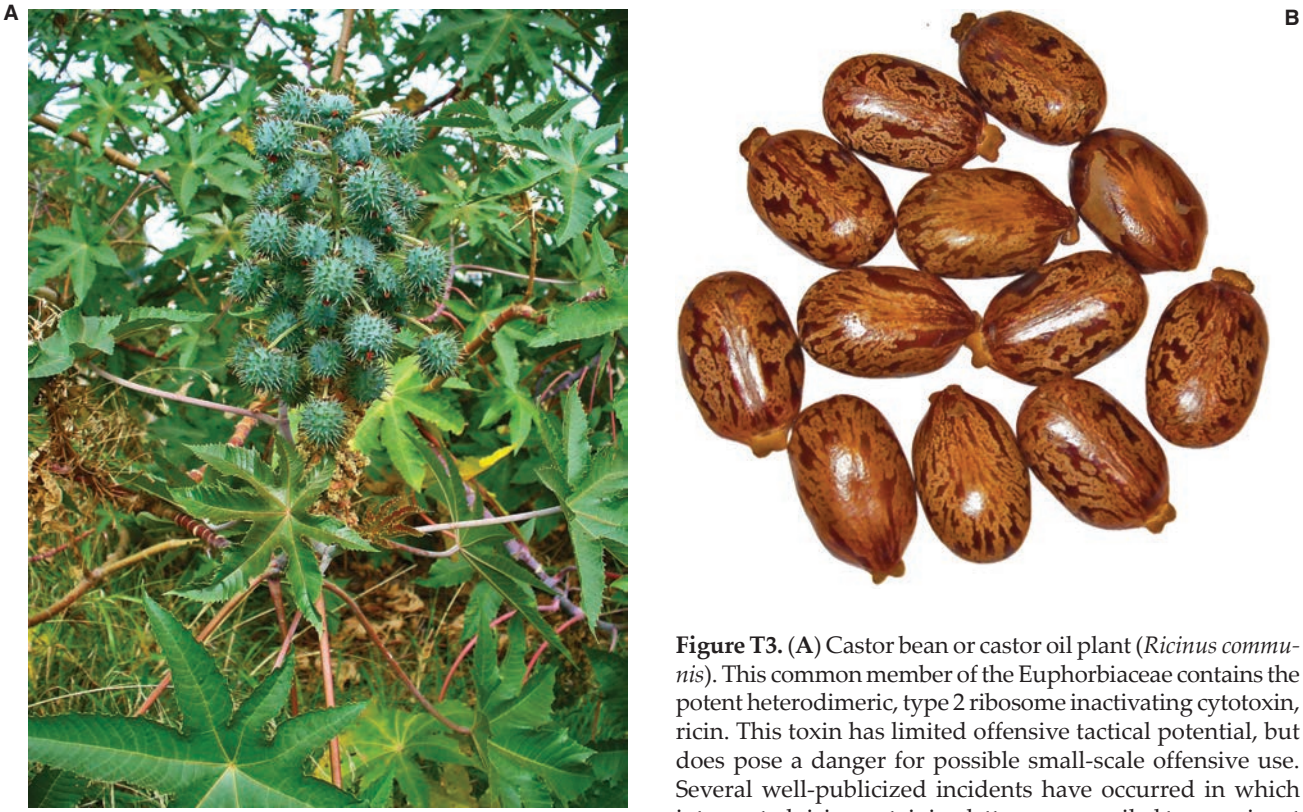


Figure T3. (**A**) Castor bean or castor oil plant (*Ricinus communis*). This common member of the Euphorbiaceae contains the potent heterodimeric, type 2 ribosome inactivating cytotoxin, ricin. This toxin has limited offensive tactical potential, but does pose a danger for possible small-scale offensive use. Several well-publicized incidents have occurred in which intercepted ricin-containing letters were mailed to prominent public figures, including the former Mayor of New York City, Michael Bloomberg, and President Barack Obama. This toxin has been used in several well-known perpetrated or attempted assassinations. (**B**) Castor bean (*Ricinus communis*) seeds. Photographs: By H Zell. Wikipedia Commons, public domain. (**A**) https://commons.wikimedia.org/wiki/Ricinus_communis#/media/File:Ricinus_communis_005.JPG. (**B**) https://commons.wikimedia.org/wiki/File:Ricinus_communis_008.JPG.

(**Table 18-5** *continues*)

Table 18-5 continued

Symphytum officinale (comfrey) and others	Pyrrolizidine alkaloids	Cyotoxic, toxic mechanisms uncertain, causes multiorgan damage, especially jaundice secondary to fibrosing hepatic venoocclusive disease.
Mentha pelugium (pennyroyal)	Pelugone	Cytotoxic, causing potentially fatal hepatotoxicity.

Figure T4. Autumn crocus or meadow saffron (*Colchicum autumnale*). This genus *Colchicaceae* contains more than 160 taxa. *Colchicum autumnale* is one of the species that contains the cytotoxic alkaloid, cochicine, an important pharmacotherapeutic especially used in the treatment of gout. Colchicine is a potent mitotic spindle poison, and has been suspected in several cases of intentional poisoning, but has no significant tactical potential.
Photograph: By Meneerke Bloem. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Colchicum_autumnale_clump_02.jpg.

Figure T5. Purple foxglove (*Digitalis purpurea*). The genus *Digitalis* contains approximately 20 species of perennials, shrubs and biennials. The leaves of some of these such as *D purpurea* contains the steroid, digoxin, the extract of which is used to produce digitalis and other related medications that are centrally important in the management of congestive heart failure and several dysrhythmias. Its mechanism of action targets the Na^+/K^+-ATPase pump on the cytoplasmic membrane of myocardiocytes (see Table 18-5), and acts as a positive inotrope. Its discovery is attributed to the Scottish physician, Dr William Withering, who reportedly obtained an early herbal mixture containing *Digitalis* spp from a gypsy, which led to his noting its effective therapeutic uses. Although it has no tactical potential, it has been used as a poison targeting individuals.
Photograph: Courtesy of Julian White.

(**Table 18-5** *continues*)

Table 18-5 continued

CYANOGENIC PLANTS		
Prunus spp (apricot, almond, peach, plum, apple, etc); hydrangea; cassava and others	Amygdaline	Metabolized to form hydrocyanic acid, causes metabolic failure, potentially lethal.
CARDIOTOXIC PLANTS		
Nerium oleander, Thevetia peruviana (oleanders; see Figure 18-20)	Cardiac glycosides (digitalis-like; oleandrin, nerium, thevetin, etc)	Cause digoxin-type cardiotoxicity by binding to and inactivating the Na^+/K^+-ATPase pump on the cytoplasmic membrane of myocardiocytes. As a result, the intracellular Na^+ concentration increases, and this affects the Na^+/Ca^{2+} exchange channels, thereby resulting in an increased intracellular Ca^{2+}. This causes a positive inotropic effect and also raises the resting membrane potential of the cell, leading to increasing rates of spontaneous cellular depolarization and myocardial automaticity. These effects can cause potentially lethal dysrhythmias, conduction anomalies, hyperkalemia, and death.
Carissa spectabilis (wintersweet)	Digoxin-like toxin	Cause digoxin-type cardiotoxicity by binding to and inactivating the Na^+/K^+-ATPase pump on the cytoplasmic membrane of myocardiocytes. As a result, the intracellular Na^+ concentration increases, and this affects the Na^+/Ca^{2+} exchange channels, thereby resulting in an increased intracellular Ca^{2+}. This causes a positive inotropic effect and also raises the resting membrane potential of the cell, leading to increasing rates of spontaneous cellular depolarization and myocardial automaticity. These effects can cause potentially lethal dysrhythmias, conduction anomalies, hyperkalemia, and death.
Digitalis purpurea, *D lantana* (foxglove) (Figure T5)	Digoxin	Cause digoxin-type cardiotoxicity by binding to and inactivating the Na^+/K^+-ATPase pump on the cytoplasmic membrane of myocardiocytes. As a result, the intracellular Na^+ concentration increases, and this affects the Na^+/Ca^{2+} exchange channels, thereby resulting in an increased intracellular Ca^{2+}. This causes a positive inotropic effect and also raises the resting membrane potential of the cell, leading to increasing rates of spontaneous cellular depolarization and myocardial automaticity. These effects can cause potentially lethal dysrhythmias, conduction anomalies, hyperkalemia, and death.
Convallaria majalis (lily of the valley)	Convallatoxin (cardiac glycoside)	As for other cardiac glycosides, but less potent.
Taxus breviffolia, T baccata (yew tree) (Figure T6)	Taxines (alkaloids derived from esterified diterpenes)	Cardiotoxins affecting cardiomyocytes by antagonizing sodium and calcium channels. These can potentially cause cardiac failure, but raw ingestions of plants are rarely lethal. The effects of isolated toxin ingestion are poorly documented, but probably carry a high risk of fatal outcome.
Veratrum spp (hellebore)	Veratridines (steroid alkaloids)	Act as agonists of the NaV and have neurotoxic and cardiotoxic effects. These toxins most commonly cause hypotension and bradycardia.

(**Table 18-5** *continues*)

Table 18-5 continued

Figure T6. Pacific Yew tree (*Taxus brevifolia*), Wenatchee Mountains, Wenatchee National Forest, Washington. The genus *Taxus* contains approximately seven species of monoecious or dioecious trees and shrubs. *Taxus* extracts have been long recognized as poisons, and the component alkaloids, the taxines, are potent cardiotoxins that antagonize cardiomyocyte ion channels (see Table 18-5). The yew tree also contains the diterpenes, the taxanes, which function as mitotic inhibitors. The very important chemotherapeutic agents, paclitaxel and docetaxel, are particularly used to treat a wide variety of solid neoplasms.
Photograph: By Walter Siegmund. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:PacificYew_7790.jpg.

Figure T7. Angel's trumpet (*Brugsmansia* spp). The genus *Brugsmansia* consists of about seven Solanaceae taxa that feature large flowers with notably strong aroma. Ingestion of parts of these plants causes a classic anticholinergic syndrome, including delirium, hallucinations, tachycardia, blurred vision, dry mucosa, and seizures. Serious poisoning can result in death.
Photograph: Courtesy of Julian White.

Figure T8. Belladonna, deadly nightshade (*Atropa belladonna*). Another genus in the family *Solanaceae*, and the source for several very important tropane alkaloids used as pharmacotherapeutics: atropine, scopolamine, and hyoscyamine. The genus is named for Atropos, one of the three female deities who supervised fate, the Three Fates, and was the one who cut the thread of life. This is a worthy appellation, because these plants also can cause a potentially fatal classic anticholinergic syndrome as noted for Brugsmansia (see Figure T7 caption and Table 18-5).
Photograph: By Rüdiger Kratz. Wikipedia Commons, public domain. https://commons.wikimedia.org/wiki/File:Atropa-bella-donna_Staude_102_b.jpg.

(**Table 18-5** *continues*)

Table 18-5 continued

ANTICHOLINERGIC PLANTS		
Brugmansia spp (angel's trumpet) (Figure T7), *Datura* spp (jimsonweed), *Atropa belladonna* (deadly nightshade) (Figure T8), *Hyoscamus niger* (henbane), *Mandragora officinarum* (mandrake), and others	Anticholinergics (scopolamine, atropine, hyoscyamine, etc)	Classic anticholinergic toxidrome (delirium, hallucinations, pupillary dilatation, blurred vision, dry skin/mucosa, hyperthermia, flushed skin, tachycardia, hypertension, potentially urinary retention, coma, convulsions, and death).
NEUROTOXIC PLANTS		
Nicotiana spp (tobacco tree)	Nicotine (bicyclic alkaloid; structurally resembles acetylcholine, the ligand for the receptor to which it binds)	Binds with the nicotinic acetylcholine receptor and causes excitation with tremor, tachycardia, sweating, convulsions, gastrointestinal effects, then depressant effects including coma, paralysis, bradycardia, and cardiovascular collapse; potentially fatal.
Conium maculatum (poison hemlock)	Coniine (piperidine alkaloid)	Causes nicotine-like effects (see nicotine, above).
Aconitum spp (aconite)	Aconitine (aconitum alkaloid)	Acts as an agonist of tetrodotoxin-sensitive NaV; causes excitation, widespread paresthesia, muscle weakness, hypotension, cardiac arrhythmias, gastrointestinal effects (vomiting, diarrhea, abdominal pain), sweating, lacrimation, confusion, headache, and death.
Cicuta spp (water hemlock)	Cicutoxin (a C17-conjugated polyacetylene)	Noncompetitively antagonizes γ-aminobutyric acid (GABA) receptors thereby cause unregulated central nervous system neuronal depolarization. Delayed onset of oral mucosal pain (oral ingestion), abdominal pain, vomiting, coma, frothing at the mouth, convulsions, and death.
Laburnum anagyroides (*Laburnum*; *Faboideae*)	Cytisine (tricyclic quinolizidine alkaloid)	Acts as a partial agonist of nicotinic acetylcholine receptors containing specific combinations of the α4 and β2 subunits. Delayed-onset salivation, sweating, vomiting, delirium, excitation, convulsions, respiratory paralysis, and death.
Solanum spp (nightshades, bittersweet, Jerusalem cherry, potato; Solanaceae)	Solanine and related glycoalkaloids	Function as reversible inhibitors of human plasma cholinesterase, and may also be cytotoxic. Poisoning may include vomiting, diarrhea, dilated pupils, drowsiness, cholinesterase inhibition, respiratory failure, and death.
Cannabis sativa (marijuana)	Cannabinoids (tetrahydrocannabinol)	Depression or excitation, tremors, hallucinations, and aberrant behavior.
Cycads (number of taxa belonging primarily to *Cycadaceae* and *Zamiaceae*)	Cycasin (a nitrogen-containing methylazoglucoside)	In mammals, cycasin undergoes modification (cleavage) in vivo and forms methylazoxymethanol resulting in acute intoxication. It is probably teratogenic and is a tumor initiator in experimental rodents. It has been strongly implicated as a cause of Pacific parkinsonism dementia/amyotrophic lateral sclerosis complex.
NEPHROTOXIC PLANTS		
Rheum rhaponticum (rhubarb; *Polygonaceae*)	Oxalates	Soluble oxalates cause local irritation/corrosion and potential renal damage related to the excretion of the oxalate crystals.

(**Table 18-5** *continues*)

Table 18-5 continued

GASTROINTESTINAL IRRITANTS		
Juniperus sabina (juniper; *Cupresaceae*)	Diterpenics (communic acids; *J communis* also contains isocupressic acid, an abortificant)	Ingestion of oils, berries, and other parts of the plant can cause vomiting and diarrhea.
Wisteria spp (wisteria; *Fabaceae*)	Wisterin (glycoside most commonly reported from seeds and pods)	Reports suggest that ingestion causes gastroenteritis that may be severe, particularly in children.
Melia azedarach (white cedar; *Meliaceae*)	Limonoids (oxygenated, modified triterpenes) and other triterpenoids	Ingestion of the fruits can cause gastrointestinal effects, coma, and convulsions; potentially fatal in severe cases.
LOCAL IRRITANTS		
Rheum rhaponticum (rhubarb, *Polygonaceae*), *Dieffenbachia* spp (dumbcane, *Araceae*), *Zantedeschia aethiopica* (arum lily, *Araceae*), *Philodendron* spp (*Araceae*), and other oxalate-containing plants	Oxalate salts	Oxalate crystals released when plant (especially parts that contain high concentrations such as Rheum leaves) is chewed, causing local pain and edema; may cause dermal irritation in some individuals.
Euphorbia spp (poinsettia, candelabra cactus, etc, *Euphorbiaceae*)	Phorbol esters (tigliane diterpenes)	Contact with sap causes intense local irritation to mucosal membranes and the eye; some authors have reported potentially blinding effects. These compounds mimic the action of diacylglycerol; thereby may activate protein kinase C and function as tumor promoters.
Toxicodendron spp (poison ivy, poison sumac, and poison oak; *Anacardiaceae*), *Metopium* spp (poisonwood, *Anacardiaceae*)	Urushiols (3-substituted catechols)	Contact with the plant, including the intact leaves causes local skin irritation. Some species (eg, *T verniciflua*, *Melanorrhea usitata*) containing urushiol or related irritants are sometimes used in the preparation of furniture varnish and may present an occupational irritant hazard.

LSD: lysergic acid diethylamide; NaV: voltage-gated sodium channel
Data sources: (1) Brent J, Wallace KL, Burkhart KK, et al (eds). *Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient*. 1st ed. Philadelphia, PA: Elsevier-Mosby; 2005: 1,690 pp. (2) Riet-Correa F, Psister J, Schild AL, Wierenga TL (eds). *Poisoning by Plants, Mycotoxins and Related Toxins*. Oxfordshire, England: CABI; 2011: 660 pp. (3) Information synthesized from lectures presented by the authors.

occurrence in rice, it remains an agent that attracts concern about possible offensive use. However, as noted in regard to aflatoxins, such reasonable concern should be balanced with their impracticality for tactical applications.

The toxins in cytotoxic mushrooms, particularly the potent transcription inhibitors, the bycyclic heterogeneous octapeptide amatoxins, are clinically important because they regularly cause fatal poisoning after accidental ingestion. Cytotoxic mushrooms include the death cap (*Amanita phalloides*) and other gilled mushrooms that may closely resemble edible species such as some *Lepiota* spp (Table 18-4 and Figure T1). Amatoxin acts by inhibiting DNA-dependent RNA polymerase II, thereby stimulating hepatocellular acute death and apoptosis. Amanita poisoning is characterized by delayed—typically 8 to 12 hours—severe gastrointestinal effects, followed by apparent recovery; 2 to 4 days later, progressive onset of liver failure occurs, which can be fatal. Early recognition of the risk, timely charcoal decontamination when possible, and treatment with silibinin, penicillin G, or D-penicillamine may reduce the severity of liver damage, but after closure of the early treatment window, patients with major liver failure can only be managed with liver transplant. However, transplants can be either medically impractical because the patient is already too ill or a transplantable liver is unavailable.

The hallucinogens (eg, alkaloids such as mescaline, indole alkaloids such as psilocybin) and other nonlethal toxins found in some mushrooms (eg, *Psilocybe* spp, "magic mushrooms") or cactus (eg, the spineless cactus, *Lophophora williamsii*, peyote) cause characteristic clinical effects (see Table 18-4). Treatment varies with the toxin type, but is most commonly symptomatic and supportive. Some *Psilocybe* spp are sold for recreational purposes in Amsterdam, and thus are legally available in quantity.

There is a vast array of poisonous plants. A particularly well-studied example of a potent plant-derived cytotoxin is ricin, the seed-derived heterodimeric, type 2 ribosome-inactivation protein from *Ricinus communis* (castor bean or oil plant, Euphorbiaceae; Table 18-5 and Figures T3A, B)[108]. Ricin contains A and B polypeptide chains with molecular masses of 32 and 34 kDa, respectively, that are covalently linked via a single disulphide bond. The lectin-binding properties associated with the B chain aids entry into the target cell, which leads to endocytic vesicle internalization, thereby facilitating its retrograde transport through the Golgi and endoplasmic reticulum. It enters the cytosol, where the A-chain re-natures and then inactivates ribosomes.[107] The ribosomal inactivation is effective because one molecule of A chain can inactivate 1,777 ribosomes per minute,[109] and is enzymatically accomplished because the A chain is a highly active N-glycosidase responsible for selectively deadenylating the first adenine in a GAGA sequence in the α-sarcin/ricin loop of 28S rRNA.[107,110] Removal of this adenine prevents mammalian elongation factor-2 from binding to the ribosome,[111] thus blocking protein synthesis and activating apoptotic pathways.[112] Ricin poisoning can lead to fulminant multiorgan failure and death. Bozza et al (2013) list at least seven incidents involving potential terrorist actions or assassinations (planned or completed) involving ricin.[109] Therefore, although having limited offensive military potential, ricin still poses a significant danger for possible small-scale offensive use.

Other plant toxins could conceivably be used in a limited offensive manner like ricin. Selected principal types of plant poisoning are shown in Table 18-5.

CONCLUSIONS AND DIRECTIONS FOR RESEARCH

Only a relatively small minority of natural toxins (especially animal-derived) have been thoroughly characterized, and the clinical effects and management of this limited group are similarly well understood. Most venomous and poisonous organisms have yet to be subjected to any toxinologic research, so their possible risk to humans is unknown. Unfortunately, limited public and private funding is available for most toxinological investigations.

There is limited potential for offensive military applicability of venom toxins because of their physical and biochemical characteristics (eg, unpredictable stability of some purified toxins), as well as limitations on practical use per routes of administration, and even marked species-specificity of some toxins. The experimental lethal potencies of some venom toxins are notable and far greater than that of cyanide (eg, the presynaptic neurotoxin textilotoxin, from venom of the Australian Eastern brown snake [murine ip LD_{50} 1 μg/kg] is approximately 3,000-fold more potent than that for oral ingestion of sodium cyanide by nonfasted rats [3 mg/kg]).[113] However, bacterial toxins such as botulinum toxins a–g (murine LD_{50} 1–2 ng/kg; toxin d does not have affinity for human tissues)[114,115] or readily dispersible organophosphate nerve agents such as the cholinesterase inhibitor sarin (methylphosphonofluoridic acid L-methylethyl ester; acute toxicity [LCt_{50}] in resting humans estimated to occur with inhalation of 70 mg–min/m^3 aerosolized agent)[116] are far more concerning as offensive biological weapons. This concern is largely because of their toxicity and potential practical application per mass delivery or population exposure. Furthermore, although textilotoxin is the snake venom toxin with the highest experimental (murine) lethal potency, few patients envenomed by *Pseudonaja* spp whose venoms contain this toxin present with—or develop—paralytic features. In contrast, very low doses of either botulinum toxins or sarin produce severe neurotoxicity in humans with a high risk of lethal outcome.

However, some plant toxins (eg, ricin), as well as fungal toxins (eg, aflatoxins such as aflatoxin B1, and the trichothecenes T-2 toxin and deoxynivalenol), have either been offensively used in a small scale (in political assassinations), or have been suspected of being deployed against small populations (eg, suspected yellow rain in Southeast Asia and Afghanistan).[104] They remain a threat as a biological weapon, as does the possible small scale offensive application potential of tetrodotoxin.

Even for well-known causes of envenoming or poisoning, major gaps in knowledge exist, and optimized (or unambiguous) evidence-based treatment strategies have not been developed. Where antidotes such as antivenom are available, they may not be optimal in design and function, and no viable antivenoms can counter the effects of the venoms from many medically important venomous animals.

An important starting point for toxinology research is to understand the epidemiology of envenoming and poisoning so realistic risk profiles can be generated. Such data are often scant and fragmentary, or of questionable validity. Major methodological hurdles exist in collecting valid and useful epidemiologic data on toxin-induced diseases, not least because even the taxonomy of some of the fauna and flora of concern remains incomplete or uncertain. These problems are compounded by the tendency in developing nations—particularly in rural populations—for patients to be treated outside the health system, mostly by native healers, witch doctors, or shamans. Thus, even where government data on presentations for envenoming and poisoning are available, they may represent only a small minority of the actual percentage of the population affected by venomous or poisonous animals, fungi, and plants. Therefore, it is necessary to conduct detailed community-based surveys such as the Million Death Study of snakebite mortality in India,[117] in addition to garnering prospective hospital-based statistics.

Once important risk organisms are identified, a targeted toxin identification process is required if the toxins have not been previously elucidated. This process may require complex fractionation of the venom or poison to locate relevant toxins, including test systems to identify important potential activities. Sometimes a global "fishing" approach may be required, as used in the discovery of the huge diversity of action of cone snail toxins, where systematic injection of each individual toxin into test mice revealed a complex array of precisely acting toxins. This facilitated a detailed examination of individual toxins to understand how they exerted their often highly specific action in the central nervous system. Both in vitro and in vivo experimentation are usually required to understand the potential clinical effects of a given toxin and the mechanistic basis of its pathophysiological effects.

Recognizing the risks associated with a venomous or poisonous species and then identifying the medically important toxins opens the door to development of specific treatments. These treatments may be either pharmacologic antidotes to specific toxin actions, or antibody-based antidotes such as antiserums, developed to neutralize either specific toxins (eg, cardiotoxins such as oleandrin that are neutralized by anti-digoxin antibodies) or antivenoms developed against mixtures of toxins present in venoms. Efforts to standardize and optimize production of antivenoms have recently been discussed in detail in a World Health Organization publication, which is essential reading for those undertaking antivenom production.[118]

Biomedical research identifying animal and plant-derived toxins of medical importance and their biological activities should be elevated to a significantly greater level of priority. It is also essential that the evidence-based assessment of medical management of envenoming and other toxin-based diseases and emergencies should be recognized as a significant public health problem among a large proportion of the world's population.[119-121] The World Health Organization recently removed snakebite from its previous inclusion as an "other neglected tropical disease." Thus, the unknown and undoubtedly substantial, as well as underestimated, human cost of envenoming in many economically disadvantaged nations remains very much "neglected." The likelihood of military deployments in some of these regions adds to the importance of carefully assessing and addressing the risks of venom diseases and poisoning syndromes, and this is where the military importance of venomous animals and their venoms, as well as poisonous organisms and plants, are most relevant.

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