

Casarett & Doull's Essentials of Toxicology, 2e >

Chapter 26. Toxic Effects of Terrestrial Animal Venoms and Poisons

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Key Points

- Venomous animals produce poison in a highly developed secretory gland or group of cells and can deliver their toxin during a biting or stinging act.
- Poisonous animals are those whose tissues, either in part or in their entirety, are toxic. Poisoning usually takes place through ingestion.
- The bioavailability of a venom is determined by its composition, molecular size, amount or concentration gradient, solubility, degree of ionization, and the rate of blood flow into that tissue as well as the properties of the engulfing surface itself.
- The distribution of most venom fractions is rather unequal, being affected by protein binding, variations in pH, and membrane permeability, among other factors.
- A venom may also be metabolized in several or many different tissues.
- Because of their protein composition, many toxins produce an antibody response; this response is essential in producing antisera.

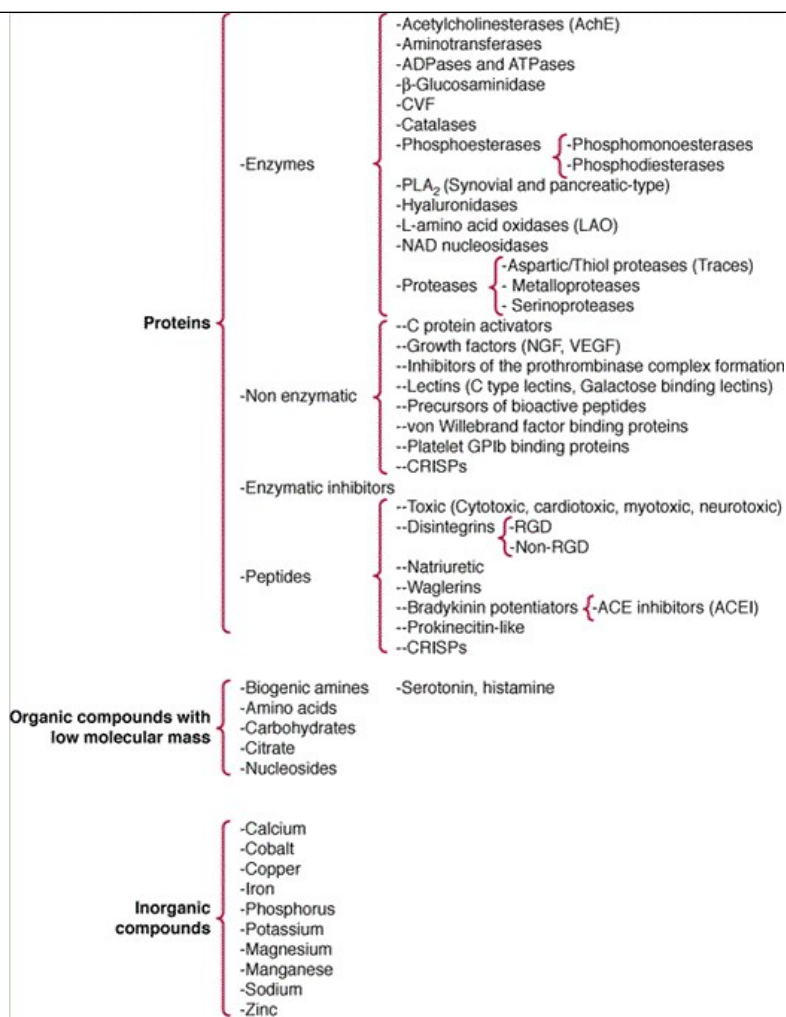
Toxic Effects of Terrestrial Animal Venoms and Poisons: Introduction

Venomous animals are capable of producing a poison in a highly developed exocrine gland or group of cells and they can deliver their toxin during a biting or stinging act. Poisonous animals have no mechanism or structure for the delivery of their poisons, and poisoning usually takes place through ingestion.

Properties of Animal Toxins

Venoms are very complex, containing polypeptides, high- and low-molecular-weight proteins, amines, lipids, steroids, glucosides, aminopolysaccharides, quinones, and free amino acids, as well as serotonin, histamine, and other substances. The complexity of snake venoms is illustrated in [Figure 26-1](#).

Figure 26-1



Source: Klaassen CD, Watkins JB, Casanett & Doull's Essentials of Toxicology, 2nd Edition: <http://www.accesspharmacy.com>
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Components of snake venoms. ACE = angiotensin-converting enzyme; CRISP = cysteine-rich secretory protein; CVF = cobra venom factor-like proteins; LAO = l-amino acid oxidase; PLA₂ = phospholipase A₂; RGD = arginine-glycine-aspartate. (Reprinted with permission from Ramos OHP, Selistre-de-Araujo HS: Snake venom metalloproteases—structure and function of catalytic and disintegrin domains. *Comp Biochem Physiol, Part C* 142:328–346, 2006. Copyright © Elsevier.)

Novel instrument developments have permitted researchers to tease out the complexity of natural venoms, thereby identifying the peptide and protein components of venom. Unfortunately, studying the chemistry, pharmacology, and toxicology of venoms requires isolating and dismantling the venoms and losing the synergy among multiple components. Nevertheless, advanced technology will permit peptide sequencing and the characterization of post-translational modifications, such as glycosylation, and the discovery of new pharmacophores.

Venom bioavailability is determined by its composition, molecular size, amount or concentration gradient, solubility, degree of ionization, and the rate of blood flow into that tissue as well as the properties of the engulfing surface itself. The venom can be absorbed by active or passive transport, facilitated diffusion, or even pinocytosis. It is then transmitted into the vascular bed, sometimes directly or sometimes through lymphatic channels. The lymph circulation not only carries surplus interstitial fluid produced by the venom, but also transports the larger molecular components and other particulates back to the bloodstream.

The site of action of venom is dependent on its diffusion and partitioning along the gradient between the plasma and the tissues where the components are deposited. Once the toxin reaches a particular site, its entry to that site is dependent on the rate of blood flow into that tissue, the mass of the structure, and the partition characteristics of the toxin between the blood and the particular tissue. Receptor sites appear to have highly variable degrees of sensitivity. With complex venoms, there may be several to many receptor sites. There is also considerable variability in the

sensitivity of those sites for the different components of a venom.

A venom may be metabolized in several or many different tissues. Some venom components are metabolized distant to the receptor site(s) and may never reach the primary receptor in a quantity sufficient to affect that site. The amount of toxin that tissues can metabolize without endangering the organisms may also vary. Organs or tissues may contain enzymes that catalyze a host of reactions, including deleterious ones. Once a venom component is metabolized or in some way altered, the end substance is excreted, principally through the kidneys. The intestines play a minor role. Excretion may be complicated by venom action on the kidneys.

Arthropods

The more than a million species of arthropods are generally divided into 25 orders. Medically, only about 10 orders are of significant importance. These include the arachnids (scorpions, spiders, whip scorpions, solpugids, mites, and ticks), the myriapods (centipedes and millipedes), the insects (water bugs, assassin bugs, and wheel bugs), beetles (blister beetles), Lepidoptera (butterflies, moths, and caterpillars), and Hymenoptera (ants, bees, and wasps). Most arthropods do not have fangs or stings long or strong enough to penetrate human skin.

The number of deaths from arthropod stings and bites is not known. However, deaths from scorpion stings exceed several thousand a year, whereas spider bites probably do not account for more than 200 deaths a year worldwide. A common problem faced by physicians in suspected spider bites relates to the differential diagnosis. The arthropods most frequently involved in misdiagnoses were ticks (including their embedded mouthparts), mites, bedbugs, fleas (infected flea bites), Lepidoptera insects, flies, vesicating beetles, water bugs, and various stinging Hymenoptera. Among the disease states that were confused with spider or arthropod bites or stings were erythema chronicum migrans, erythema nodosum, periarteritis nodosum, pyoderma gangrenosum, kerion cell-mediated response to a fungus, Stevens–Johnson syndrome, toxic epidermal necrolysis, herpes simplex, and purpura fulminans.

Any other arthropod may bite or sting and not eject venom. Some arthropod envenomations give rise to the symptoms and signs of an existing undiagnosed subclinical disease. In some cases, stings or bites may induce stress reactions that bring the unrecognized disease to the surface.

Arachnida

Scorpions

Of the more than 1000 species of scorpions, the stings of more than 75 can be considered of sufficient toxicity to warrant medical attention. Some of the more important scorpion species are noted in [Table 26–1](#). The dangerous bark scorpion, *Centruroides exilicauda*, is often found hiding under the loose bark of trees or in dead trees or logs, and may frequent human dwellings. Straw to yellowish-brown or reddish-brown in color, it is often easily distinguishable from other scorpions in the same habitat by its long, thin telson, or tail, and its thin pedipalps, or pincer-like claws.

Table 26–1 Location of some medically important scorpions.

Genus	Distribution
<i>Androctonus</i> species	North Africa, Middle East, Turkey
<i>Buthus</i> species	France and Spain to Middle East and North Africa, Mongolia, China
<i>Buthotus</i> species	Africa, Middle East, Central Asia
<i>Centruroides</i> species	North, Central, South America
<i>Heterometrus</i> species	Central and Southeast Asia
<i>Leiurus</i> species	North Africa, Middle East, Turkey
<i>Mesobuthus</i> species	Turkey, India
<i>Parabuthus</i> species	Southern Africa
<i>Tityus</i> species	Central and South America

Many scorpion venoms contain low-molecular-weight proteins, peptides, amino acids, nucleotides, and salts, among other components. The neurotoxic fractions are generally classified on the basis of their molecular size, the short-chain toxins being composed of 20 to 40 amino acid residues with three or four disulfide bonds and appear to affect potassium or chloride channels; the long-chain toxins have 58 to 76 amino acids with four disulfide bonds and affect mainly the sodium channels. Toxins can selectively bind to a specific channel of excitable cells, thus impairing the initial depolarization of the action potential in the affected nerve and muscle.

The symptoms and signs of scorpion envenomation differ considerably depending on the species. The sting of members of the family Vejovidae gives rise to localized pain, swelling, tenderness, and mild paresthesia. Systemic reactions are rare, although weakness, fever, and muscle fasciculations have been reported. Envenomations by some members of the genus *Centruroides* may or may not produce initial pain in children. However, the area becomes sensitive to touch, and merely pressing lightly over the injury will elicit an immediate retraction. The poisoned child becomes tense and restless and shows abnormal and random head and neck movements. Often the child will display roving eye movements. Tachycardia is usually evident within 45 min as well as some hypertension. Respiratory and heart rates are increased, and by 90 min the child may appear quite ill. Fasciculations may be seen over the face or large muscle masses, and the child may complain of generalized weakness and display some ataxia or motor weakness. Opisthotonos is not uncommon. The respiratory distress may proceed to respiratory paralysis. Excessive salivation may further impair respiratory function. Slurring of speech may be present, and convulsions may occur. If death does not occur, the child usually becomes asymptomatic within 36 to 48 h.

In adults the clinical picture is somewhat similar, but there are some differences. Almost all adults complain of immediate pain after the sting, regardless of the *Centruroides* species involved. Adults are tense and anxious, developing tachycardia, hypertension, and increased respirations. They may complain of difficulties in focusing and swallowing. In some cases, there is some general weakness and pain on moving the injured extremity. Ataxia and muscle incoordination may occur. Most adults are asymptomatic within 12 h but may complain of generalized weakness for 24 h or more.

Spiders

Of the 30,000 or so species, at least 200 have been implicated in significant bites on humans. Table 26–2 provides a short list of spiders, their toxins, and the targets of their toxins.

Table 26–2 Some significant spiders, their toxins, and the targets of the toxins.

Spider	Peptide	Target*
<i>Acanthoscurria gomesiana</i>	Gomesin	PLM
<i>Agelenopsis aperta</i>	ω -AfaI-IVA μ -Afatoxin 1–6	Ca^{2+} Na^+
<i>Grammostola spatula</i>	HaTx1,2 GsMTx2,4 GSTxSIA	K^+ MS Ca^{2+}
<i>Hadronyche versuta</i>	ω -ACTX-Hv1a ω -ACTX-Hv2a δ -ACTX-Hv1a	Ca^{2+} Ca^{2+} Na^+
<i>Heteroscodra maculata</i>	HmTx1,2	K^+
<i>Ornithoctonus huwena</i>	Huwentoxin I Huwentoxin IV	Ca^{2+} Na^+
<i>Psalmopoeus cambridgei</i>	PcTx1	ASIC
<i>Phrixotrichus auratus</i>	PaTx1,2	K^+
<i>Thrixopelma pruriens</i>	ProTxI, II	Na^+

*PLM = phospholipid membranes; Ca^{2+} , K^+ , and Na^+ = calcium, potassium, and sodium ion channels; MS = mechanosensitive ion channels; ASIC = acid-sensing ion channels.

Spider venoms are complex mixtures of low-molecular-weight components, including inorganic ions and salts, free acids, glucose-free amino acids, biogenic amines and neurotransmitters, and polypeptide toxins. [Table 26–3](#) lists local and systemic effect for known cases of major spider groups in Australia.

Table 26–3 Comparison of clinical effects of bites by some spiders of Australia.

Clinical Effects	<i>Lactrodectus</i> Redback Spiders	<i>Steatoda</i> Cupboard Spiders	Lamponidae White-tail Spiders	Mygalomorphae FWS, Mouse Spiders, Trapdoor Spiders
Severe pain (percent)	62	26	27	49
Duration of pain	36 h	6 h	5 min	60 min
Fang marks (percent)	6	17	17	58
Initial erythema	74	96	83	36
Swelling (percent)	7	9	8	13
Itchiness (percent)	38	48	44	0
Nausea, vomiting, headache, malaise (percent)	35	30	9	36
Distal limb bite (percent)	46	52	82	91

Agelenopsis Species (American Funnel Web Spiders)

These spiders contain three classes of agatoxins that target ion channels: (1) α -agatoxins appear to be use-dependent, noncompetitive antagonists of the glutamate receptor channels; (2) μ -agatoxins cause increased spontaneous release of neurotransmitter from presynaptic terminals and repetitive action potentials in motor neurons, and are specific for insect sodium channels; and (3) the four ω -agatoxins can be distinguished by sequence similarity and their spectrum of action against insect and vertebrate calcium channels.

Latrodectus Species (Widow Spiders)

Found throughout the world in all continents with temperate or tropical climates, these spiders are commonly known as the black widow, brown widow, or red-legged, hourglass, poison lady, deadly spider, red-bottom spider, T-spider, gray lady spider, and shoebutton spider. Although both male and female widow spiders are venomous, only the female has fangs large and strong enough to penetrate the human skin. Venom contains a family of proteins of about 1000 amino acid residues, latrotoxins. α -Latrotoxin is a presynaptic toxin that exerts its toxic effects on the vertebrate central nervous system, depolarizing neurons by increasing $[Ca^{2+}]$ and by stimulating exocytosis of neurotransmitters from nerve terminals.

Bites by the black widow are described as sharp and pinprick-like, followed by a dull, occasionally numbing pain in the affected extremity and by pain and cramps in one or several of the large muscle masses. Rarely is there any local skin reaction except during the first 60 min following the bite. Muscle fasciculations frequently can be seen within 30 min of the bite. Sweating is common, and the patient may complain of weakness and pain in the regional lymph nodes, which are often tender on palpation and occasionally enlarged; lymphadenitis is frequently observed. Pain in the low back, thighs, or abdomen is a common complaint, and rigidity of the abdominal muscles is seen in most cases in which envenomation has been severe. Severe paroxysmal muscle cramps may occur, and arthralgia has been reported. Hypertension is common, particularly in the elderly, after moderate to severe envenomations.

Loxosceles Species (Brown or Violin Spiders)

Variouly known in North America as the fiddle-back spider or the brown recluse, the abdomen of these spiders varies in color from grayish through orange and reddish-brown to blackish and is distinct from the pale yellow to reddish-brown background of the cephalothorax. Both males and females

are venomous.

Loxosceles venom may contain phospholipase, protease, esterase, collagenase, hyaluronidase, deoxyribonuclease, ribonuclease, dipeptides, dermonecrosis factors, and sphingomyelinase D.

The bite of this spider produces about the same degree of pain as does the sting of an ant. A local burning sensation may last for 30 to 60 min around the injury along with slight redness and minimal swelling. In more severe bites, pruritus over the area occurs, and the area becomes red, with a small blanched area surrounding the reddened bite site. Skin temperature usually is elevated over the lesion area. The reddened area enlarges and becomes purplish during the subsequent 1 to 8 h. Hemorrhages may develop throughout the area. A small bleb or vesicle, which forms at the bite site, increases in size until it ruptures and a pustule forms. The red hemorrhagic area continues to enlarge, as does the pustule. The whole area may become swollen and painful, and lymphadenopathy is common.

In serious bites, systemic effects include fever, malaise, stomach cramps, nausea, vomiting, jaundice, spleen enlargement, hemolysis, hematuria, and thrombocytopenia. Fatalities, while rare, are preceded by intravascular hemolysis, hemolytic anemia, thrombocytopenia, hemoglobinuria, and renal failure.

***Steatoda* Species**

These spiders are variously known as the false black widow, comb-footed, cobweb, or cupboard spiders. Bites by *S. grossa* or *S. fulva* have been followed by local pain, often severe; induration; pruritus; and occasional breakdown of tissue at the bite site.

***Cheiracanthium* Species (Running Spiders)**

C. puncturium, *C. inclusum*, *C. mildei*, *C. diversum*, and *C. japonicum* are common biting spiders. The abdomen is convex and egg-shaped and varies in color from yellow, green, or greenish-white to reddish-brown; the cephalothorax is usually slightly darker than the abdomen. The chelicerae are strong, and legs are long, hairy, and delicate. *Cheiracanthium* tends to be tenacious and sometimes must be removed from the bite area. The venom has a highly toxic 60 kDa protein and high concentrations of norepinephrine and serotonin.

The bite is sharp and painful, with the pain increasing during the first 30 to 45 min. A reddened wheal with a hyperemic border develops. Small petechiae may appear near the center of the wheal. Lymphadenitis and lymphadenopathy may develop. *C. japonicum* produces more severe effects that include severe local pain, nausea, vomiting, severe pruritus, headache, chest discomfort, and shock.

***Theraphosidae* Species (Tarantulas)**

Tarantulas feed on various vertebrate and invertebrate preys, which are captured after envenomation with venoms that act rapidly and irreversibly on the central and peripheral nervous systems. In humans, reported bites elicit mild-to-severe local pain, strong itching, and tenderness that may last for several hours. Edema, erythema, joint stiffness, swollen limbs, burning feelings, and cramps are common. In more severe cases, strong cramps and muscular spasms lasting up to several hours may be observed.

Ticks

Tick paralysis is caused by the saliva of at least 60 species of ticks of the families Ixodidae, Argasidae, and Nuttalliellidae. The tick bite involves insertion of cutting, tube-like mouthparts through the host's skin with anchoring so that the tick can feed for hours, days, or weeks. Saliva from the salivarium flows outward initially and the blood meal flows inward afterward. Saliva contains several active constituents including apyrase, kininase, glutathione peroxidase, an anticomplement protein, amine-binding proteins (that bind serotonin and histamine) and prostanoids. Ticks are known to transmit organisms causing Lyme disease, Rocky Mountain spotted fever, babesiosis, leptospirosis, Q fever, ehrlichiosis, typhus, tick-borne encephalitis, and others.

Tick bites are often not felt; the first evidence of envenomation may not appear until several days later, when small macules develop. The patient often complains of difficulty with gait, followed by paresis and eventually locomotor paresis and paralysis. Problems in speech and respiration may ensue and lead to respiratory paralysis if the tick is not removed. Removal of the tick usually results in a rapid and complete recovery, although regression of paralysis may resolve slowly.

The ticks that cause the paralysis in humans and domestic animals may be the same, and it is the length of the exposure to the feeding tick that determines the degree of poisoning. These comments are specific only for tick venom poisoning and not for allergic reactions, transmission of disease states, or other complications of tick bites.

Chilopoda (Centipedes)

These elongated, many-segmented brownish-yellow arthropods are found worldwide. The first pair of legs behind the head is modified into poison jaws. The venom is concentrated within the intracellular granules, discharged into vacuoles of the cytoplasm of the secretory cells, and moved by exocytosis into the lumen of the gland; from thence ducts carry the venom to the jaws.

The venoms of centipedes contain high-molecular-weight proteins, proteinases, esterases, 5-hydroxytryptamine, histamine, lipids, and polysaccharides. Such venom contains a heat-labile cardiotoxic protein of 60 kDa that produces changes associated with [acetylcholine](#) release. The bite produces immediate bleeding, redness, and swelling often lasting 24 h. Localized tissue changes and necrosis have been reported, and severe envenomations may cause nausea and vomiting, changes in heart rate, vertigo, and headache. In the most severe cases, there can be mental disturbances.

Diplopoda (Millipedes)

Ranging in length from 20 to 300 mm, these arthropods are cylindrical, wormlike creatures, mahogany to dark brown or black in color, bearing two pairs of jointed legs per segment. The lesions produced by millipedes consist of a burning or prickling sensation and development of a yellowish or brown-purple lesion; subsequently a blister containing serosanguineous fluid forms, which may rupture. Eye contact can cause acute conjunctivitis, periorbital edema, keratosis, and much pain.

Insecta

Heteroptera (True Bugs)

The clinically most important of the true bugs are the Reduviidae (the reduviids): the kissing bug, assassin bug, wheel bug, or cone-nose bug. The most commonly involved species appear to be *Triatoma protracta*, *T. rubida*, *T. magista*, *Reduvius personatus*, and *Arilus cristatus*. The venom of these bugs has apyrase activity and is fairly rich in protease properties. It inhibits collagen-induced platelet aggregation.

The bites of *Triatoma* species are definitely painful and give rise to erythema, pruritus, increased temperature in the bitten part, localized swelling, and—in those allergic to the saliva—systemic reactions such as nausea, vomiting, and angioedema. With some bites, the wound area will slough, leaving a depression.

The water bugs are water-dwelling true bugs of which at least three families, Belostomatidae, Naucordiae, and Notonectidae, are capable of biting and envenomating humans. Water bug saliva contains digestive enzymes, neurotoxic components, and hemolytic fractions. Water bug bites give rise to immediate pain, some localized swelling, and possibly induration and formation of a small papule.

There are some arthropods that are poisonous and the poison must come through their being crushed or eaten. These would include, among others, darkling beetles (stink bugs, *Eleodes*) and the blister beetles (*Epicauta*), from whom [cantharidin](#) is obtained.

Hymenoptera (Ants, Bees, Wasps, and Hornets)

Formicidae (Ants)

Most ants have stings, but those that lack them can spray a defensive secretion from the tip of the gaster, which is often placed in the wound of the bite. The clinically important stinging ants are the harvesting ants (*Pagonomyrmex*), fire ants (*Solenopsis*), and little fire ants (*Ochetomyrmex*). Harvester ants are large red, dark brown, or black ranging in size from 6 to 10 mm and have fringes of long hairs on the back of their heads.

Ant venoms vary considerably. The venoms of the Ponerinae, *Pseudomyrmex*, and Ecitoninae are proteinaceous in character. The Myrmecinae venoms

are a mixture of amines, enzymes and proteinaceous materials, histamine, [hyaluronidase](#), phospholipase A, and hemolysins, which hemolyze erythrocytes and mast cells. Formicinae ant venom contains about 60 percent formic acid. Fire ant venoms are poor in polypeptides and proteins, but are rich in alkaloids such as solenopsine. The sting of the fire ant gives rise to a painful burning sensation, after which a wheal and localized erythema develop, leading in a few hours to a clear vesicle. Within 12 to 24 h, the fluid becomes purulent and the lesion turns into a pustule. It may break down or become a crust or fibrotic nodule. In multiple stings there may be nausea, vomiting, vertigo, increased perspiration, respiratory difficulties, cyanosis, coma, and even death.

Apidae (Bees)

The commonest stinging bees are *Apis mellifera* and the Africanized bee, *Apis mellifera adansonii*. The venom contains biologically active peptides, such as melittin, apamine, phospholipase A₂ (PLA₂) and B, [hyaluronidase](#), histamine, [dopamine](#), mast cell-degranulating peptide, monosaccharides, and lipids. Bee stings typically produce immediate, sharp or burning pain, slight local erythema, and edema followed by itching. It is said that 50 stings can lead to respiratory dysfunction, intravascular hemolysis, hypertension, myocardial damage, hepatic changes, shock, and renal failure. With 100 or more stings, death can occur.

Vespidae (Wasps)

This family includes wasps and hornets. These venoms contain a high content of peptide, which include mastoparan in wasps and hornets and crabolin from hornet venom. Other peptides named waspkinins cause immediate pain, vasodilation, and increased vascular permeability leading to edema. These venoms also contain phospholipases and hyaluronidases, which contribute to the breakdown of membranes and connective tissue to facilitate diffusion of the venom.

Lepidoptera (Caterpillars, Moths, and Butterflies)

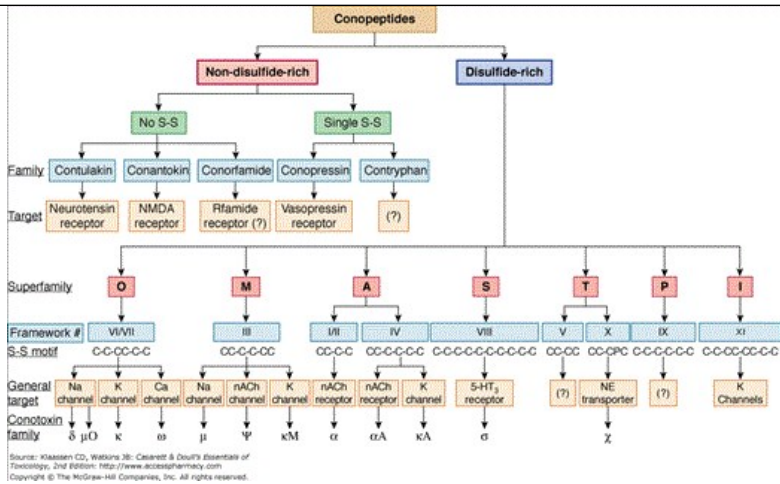
The urticating hairs, or setae, of caterpillars are attached to unicellular poison glands at the base of each hair. The toxic material contains aristolochic acids, cardenolides, histamine, and a fibrinolytic protein. After envenomation, coagulation defects such as prolonged prothrombin and partial thromboplastin times have been detected, and decreases in fibrinogen and plasminogen have been noted.

Stings of *Megalopygidae*, *Dioptidae*, *Automeris*, and *Hermileucinae* species of Lepidoptera give rise to a bleeding diathesis. In more severe cases, there is localized pain as well as papules (sometimes hemorrhagic) and hematomas; on occasion there may also be headache, nausea, vomiting, hematuria, lymphadenitis, and lymphadenopathy.

Mullosca (Cone Snails)

The genus *Conus* is a group of some 500 species of carnivorous predators found in marine habitats that use venom as a weapon for prey capture. There are probably over 100 different venom components per species ([Figure 26-2](#)). Components have become known as conotoxins, which may be rich in disulfide bonds, and conopeptides. After injection, conopeptides act synergistically to affect the targeted prey, often resulting in total inhibition of neuromuscular transmission. Various conotoxins inhibit presynaptic calcium channels that control neurotransmitter release, the postsynaptic neuromuscular nicotinic receptors, and the sodium channels involved in muscle action potential. Conotoxins also target ligand-gated ion channels that mediate fast synaptic transmission.

Figure 26-2



Organizational diagram for *Conus* peptides, indicating gene superfamilies, disulfide patterns, and known pharmacologic targets.

Only the superfamilies of the disulfide-rich peptides are shown. (Used with permission from Terlau H, Olivera BM: *Conus* venoms: a rich source of novel ion channel-targeted peptides. *PhysiolRev* 84:41–68, 2004.)

Reptiles

Lizards

The Gila monster (*Heloderma suspectum*) and the beaded lizards (*Heloderma horridum*) are far less dangerous than is generally believed. Their venom is transferred from venom glands in the lower jaw through ducts that discharge their contents near the base of the larger teeth of the lower jaw. The venom is then drawn up along grooves in the teeth by capillary action. The venom of this lizard has serotonin, amine oxidase, phospholipase A, a bradykinin-releasing substance, helodermin, gilatoxin, and low proteolytic as well as high-hyaluronidase activities. Helotherime, a 25-kDa protein, appears to inhibit calcium ion influx from the sarcoplasmic reticulum. The 35 amino acid peptide helodermin produces hypotension by activating potassium channels in vascular smooth muscle. The clinical presentation of a helodermatid bite can include pain, edema, hypotension, nausea, vomiting, weakness, and diaphoresis.

Snakes

Among the more than 2700 species of snakes, about 20 percent are considered to be venomous. Venomous snakes primarily belong to the following families: Viperidae (vipers), Elapidae, Atractaspidae, and Colubridae.

Snake Venoms

These venoms are complex mixtures: proteins and peptides, consisting of both enzymatic and nonenzymatic compounds, making up over 90 percent of the dry weight of the venom. Snake venoms also contain inorganic cations such as sodium, calcium, potassium, magnesium, and small amounts of zinc, iron, cobalt, manganese, and nickel. Some snake venoms also contain glycoproteins, lipids, and biogenic amines, such as histamine, serotonin, and neurotransmitters.

A simplistic classification of snake venoms would group toxin components as neurotoxins, coagulants, hemorrhagins, hemolytics, myotoxins, cytotoxins, and nephrotoxins. Neurotoxins produce neuromuscular paralysis ranging from dizziness to ptosis; to ophthalmoplegia, flaccid facial muscle paralysis, and inability to swallow; to paralysis of larger muscle groups; and finally to paralysis of respiratory muscles and asphyxiation. Coagulants may have initial procoagulant action that uses up clotting factors leading to bleeding. Coagulants may directly inhibit normal clotting at several places in the clotting cascade or via inhibition of platelet aggregation. In addition, some venom components may damage the endothelial lining of blood vessels leading to hemorrhage. Bite victims may show bleeding from nose or gums, the bite site, and in saliva, urine, and stools. Myotoxins can directly impact muscle contraction leading to paralysis or cause rhabdomyolysis or the breakdown of skeletal muscle. Myoglobinuria, or a dark brown urine, and hyperkalemia may be noted. Cytotoxic agents have proteolytic or necrotic properties leading to the breakdown of tissue. Typical signs

include massive swelling, pain, discoloration, blistering, bruising, and wound weeping. Sarafotoxins, which are found only in burrowing asps of Afro-Arabia, cause coronary artery constriction, reduced coronary blood flow, angina, and myocardial infarction. Finally, nephrotoxins can cause direct damage to kidney structures, leading to bleeding, damage to several parts of the nephron, tissue oxygen deprivation, and renal failure.

Enzymes

Snake venoms contain at least 26 enzymes, although no single snake venom contains all of them (Figure 26–1). Proteolytic enzymes, also known as peptide hydrolases, proteases, endopeptidases, peptidases, and proteinases, catalyze the breakdown of tissue proteins. Multiple proteolytic enzymes may be in a single venom. Metals are involved in the activity of certain proteases and phospholipases.

The crotalid venoms examined so far appear to be rich in proteolytic enzyme activity. Viperid venoms have lesser amounts, whereas elapid and sea snake venoms have little or no proteolytic activity. Venoms that are rich in proteinase activity are associated with marked tissue destruction.

Collagenase activity, a specific proteinase that digests collagen, has been demonstrated in the venoms of a number of species of crotalids and viperids. The venom of *Crotalus atrox* digests mesenteric collagen fibers but not other proteins.

Hyaluronidase catalyzes the cleavage of internal glycoside bonds in certain acid mucopolysaccharides, thereby decreasing the viscosity of connective tissues, thus allowing other fractions of venom to penetrate the tissues.

Arginine ester hydrolase is found in many crotalid and viperid venoms and some sea snake venoms but is lacking in elapid venoms with the possible exception of *Ophiophagus hannah*. Some crotalid venoms contain at least three chromatographically separable arginine ester hydrolases. The bradykinin-releasing and perhaps bradykinin-clotting activities of some crotalid venoms may be related to esterase activity.

Thrombin-like enzymes are found in significant amounts in the venoms of the Crotalidae and Viperidae, whereas those of Elapidae and Hydrophiidae contain little or none. The mechanism of fibrinogen clot formation by snake venom thrombin-like enzymes invokes the preferential release of fibrinopeptide A (or B); thrombin releases fibrinopeptides A and B. The proteolytic action of thrombin and thrombin-like snake venom enzymes is compared in Table 26–4 for several species (ancrod from *Calloselasma rhodostoma*, batroxobin from *Bothrops moojeni*, crotalase from *Crotalus adamanteus*, gabonase from *Bitis gabonica*, and venzyme from *Agkistrodon contortrix*).

Table 26–4 Comparison of **thrombin** and thrombin-like snake venom enzyme actions.

Enzymes	Action on Human Fibrinogen		Activation of Factor XIII	Prothrombin Fragment Cleavage	Platelet Aggregation and Release
	Fibrinopeptides Released	Chain Degradation			
Thrombin	A – B	α(A)	Yes	Yes	Yes
Thrombin-like enzymes	A ¹	α(A) ² or β(B) ³	No	Yes or no ⁴	No
<i>Agkistrodon c. contortrix</i> Venom	B	ND	Incomplete	ND	No
<i>Bitis gabonica</i> Venom	A + B	ND	Yes	ND	ND

¹Includes ancrod, batroxobin, crotalase, and the enzyme from *T. okinavensis*.

²Ancrod [batroxobin degrades α(A) chain of bovine but not human fibrinogen].

³Crotalase.

⁴Fragment I released by crotalase and *Agkistrodon contortrix* venom, but not by ancrod or batroxobin. ND = not determined.

PLA₂, which catalyzes the Ca²⁺-dependent hydrolysis of the 2-acyl ester bond producing free fatty acids and lysophospholipid, is widely distributed in the venoms of elapids, vipers, crotalids, sea snakes, atractaspids, and several colubrids. PLA₂ interact with other toxins in venom, often resulting in synergistic reactions. Although mammalian PLA₂s are nontoxic, the snake venom enzymes differ widely in their pharmacologic properties.

Phosphomonoesterase (phosphatase) is found in the venoms of all families of snakes except colubrids. It has the properties of an orthophosphoric monoester phosphohydrolase. There are two nonspecific phosphomonoesterases; many venoms contain both acid and alkaline phosphatases, whereas other venoms contain one or the other.

Phosphodiesterase, found in the venoms of all families of poisonous snakes, is an orthophosphoric diester phosphohydrolase that attacks DNA, RNA, and derivatives of arabinose.

There are other enzymes for which their toxicologic contribution to snake venoms is not understood. These include acetylcholinesterase, RNase, DNase, 5'-nucleotidase, nicotinamide adenine dinucleotide (NAD) nucleotidase, l-amino acid, and lactate dehydrogenase.

Polypeptides

More than 80 snake venom polypeptides are low-molecular-weight proteins and have toxic actions. Erabutoxin a, erabutoxin b, alpha-cobratoxin, crotactin, and crotamine are examples of neurotoxins. Disintegrins are short cysteine-rich polypeptides that exhibit affinities for many ligand receptors. The mycotoxins can induce skeletal muscle spasms and paralysis by altering sodium channel function.

Toxicology

In general, the venoms of rattlesnakes and other New World crotalids produce alterations in the resistances (and often the integrity) of blood vessels, changes in blood cells and blood coagulation mechanisms, direct or indirect changes in cardiac and pulmonary dynamics, and—with crotalids like *C. durissus terrificus* and *C. scutulatus*—serious alterations in the nervous system and changes in respiration. In humans, the course of the poisoning is determined by the kind and amount of venom injected; the site where it is deposited; the general health, size, and age of the patient; and the kind of

treatment. Death in humans may occur within less than 1 h or after several days, with most deaths occurring between 18 and 32 h. Hypotension or shock is the major clinical problem in North American crotalid bites.

Snakebite Treatment

The treatment of bites by venomous snakes is so highly specialized that almost every envenomation requires specific recommendations. However, three general principles for every bite should be kept in mind: (1) snake venom poisoning is a medical emergency requiring immediate attention and the exercise of considerable judgment; (2) the venom is a complex mixture of substances of which the proteins contribute the major deleterious properties, and the only adequate antidote is the use of specific or polyspecific antivenom; (3) not every bite by a venomous snake ends in an envenomation. In almost 1000 cases of crotalid bites, 24 percent did not end in a poisoning. The incidence with the bites of cobras and perhaps other elapids is probably higher.

Snake Venom Evolution

Considerable efforts are being expended to examine the complex process by which snake venom components are thought to have changed over the years. In general, the toxins from ancestral proteins that were constructed of dense networks of **cysteine** cross-linkages are considered among the most diverse today in terms of toxicologic insult.

Antivenom

Antivenoms have been produced against most medically important snake, spider, scorpion, and marine toxins. Animals immunized with venom develop various antibodies to the many antigens in venom. Antivenom consists of venom-specific antisera or antibodies concentrated from immune serum to the venom. Antisera contain neutralizing antibodies: one antigen (monospecific) or several antigens (polyspecific). The serum is harvested, partially or fully purified, and further processed before being administered to the patient. The antibodies bind to the venom molecules, rendering them ineffective.

Antivenoms are available in several forms: intact IgG antibodies or fragments of IgG such as F(ab)₂ and Fab. The molecular weight of the intact IgG is about 150,000, whereas that of Fab is approximately 50,000. IgG has a volume of distribution much smaller than that of Fab and is too large for renal excretion. The elimination half-life of IgG is approximately 50 h. Its ultimate fate is not known, but most IgG is probably taken up by the reticuloendothelial system and degraded with the antigen attached. Fab fragments have an elimination half-life of about 17 h, and undergo renal excretion.

All antivenom products are produced through the immunization of animals, which increases the possibility of hypersensitivity. The risks of anaphylaxis should always be considered when deciding whether to administer antivenom.

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