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# Venomous animals: clinical toxinology

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*Abstract.* Venomous animals occur in numerous phyla and present a great diversity of taxa, toxins, targets, clinical effects and outcomes. Venomous snakes are the most medically significant group globally and may injure >1.25 million humans annually, with up to 100 000 deaths and many more cases with long-term disability. Scorpion sting is the next most important cause of envenoming, but significant morbidity and even deaths occur following envenoming with a wide range of other venomous animals, including spiders, ticks, jellyfish, marine snails, octopuses and fish. Clinical effects vary with species and venom type, including local effects (pain, swelling, sweating, blistering, bleeding, necrosis), general effects (headache, vomiting, abdominal pain, hypertension, hypotension, cardiac arrhythmias and arrest, convulsions, collapse, shock) and specific systemic effects (paralytic neurotoxicity, neuroexcitatory neurotoxicity, myotoxicity, interference with coagulation, haemorrhagic activity, renal toxicity, cardiac toxicity). First aid varies with organism and envenoming type, but few effective first aid methods are recommended, while many inappropriate or frankly dangerous methods are in widespread use. For snakebite, immobilisation of the bitten limb, then the whole patient is the universal method, although pressure immobilisation bandaging is recommended for bites by non-necrotic or haemorrhagic species. Hot water immersion is the most universal method for painful marine stings. Medical treatment includes both general and specific measures, with antivenom being the principal tool in the latter category. However, antivenom is available only for a limited range of species, not for all dangerous species, is in short supply in some areas of highest need, and in many cases, is supported by historical precedent rather than modern controlled trials.

## Introduction

Venom appears to have been a success story in evolution because venomous animals are found in such a range of taxa, but the success is muted since most animals remain non-venomous. Logically it follows that venom is not the answer to all life's challenges, so how does it benefit those animals that produce it? Venom appears to have two main functions; prey acquisition and processing, and defence against predators. The value mix between these two competing functions varies between animal groups, but for those venomous animals most likely to cause venomous harm to humans, notably snakes, scorpions, spiders, and jellyfish, prey acquisition seems to predominate. The honey bee, *Apis mellifera*, is the obvious exception, as the sting, with attached venom gland, is purely defensive, having no role in prey acquisition, but here it is not venom toxicity that affects humans, but venom allergy. So vast is the range and diversity of venomous life on earth that a single chapter cannot cover more than some key elements and groups, a caveat that readers should be cognisant of.

## Epidemiology

For most venomous animals for much of the world, detailed statistics on the number of humans bitten or stung, envenomed, or killed each year are unavailable. Published data are replete with conjecture, estimates, or guesstimates, with variable validity. It is clear, however, that certain taxa of venomous animals cause significant morbidity and mortality amongst humans. Top of this list are venomous snakes, with current estimates of >2.5 million cases and around 100 000 deaths per year [1]. Subsequent analysis has indicated that these estimates are likely on the high side, with low estimates nearer 1.2 million cases and 20 000 deaths annually [2] (Tab. 1). These figures hide the huge toll of morbidity after snakebite, which affects far more cases than fatal outcomes, and often results in long-term suffering, and social and economic loss [3]. That the snakebite toll is greatest in the rural tropics of the developing world [4], where poverty, poor education and under-resourced health systems combine to minimise effective care, is an ongoing tragedy of human existence, made worse by the effects of natural disasters [5].

After snakebite, scorpion stings likely account for many medically significant cases and incidence has been estimated as >1.2 million cases each year [6]. Mexico alone documents >200 000 cases requiring hospital care annually [6, 7]. In some regions scorpion stings are more frequent than snakebites; North Africa is an example. Deaths are increasingly uncommon, perhaps as a result of antivenom use plus higher standards of hospital care, but children remain at risk [6–8].

Spiderbite is undoubtedly common [9], as are spiders [10], but most bites are medically trivial and nearly all medically significant bites can be ascribed to just a few groups of spiders: widow spiders (*Latrodectus*), recluse spiders (*Loxosceles*), banana spiders (*Phoneutria*) and Australian funnel-web spiders (*Atrax*, *Hadronyche*) [9, 11–13]. Deaths are rare.

Table 1. Summary of most recent published data on snakebite epidemiology globally [2]

| Region | Envenoming | | Deaths | |
|---|---|---|---|---|
| | Low estimate | High estimate | Low estimate | High estimate |
| Asia | 237 379 | 1 184 550 | 15 385 | 57 636 |
| Australasia | 1099 | 1260 | 2 | 4 |
| Caribbean | 1098 | 8039 | 107 | 1161 |
| Europe | 3961 | 9902 | 48 | 128 |
| Latin America | 80 329 | 129 084 | 540 | 2298 |
| North Africa and Middle East | 3017 | 80 191 | 43 | 78 |
| North America | 2683 | 3858 | 5 | 7 |
| Oceania | 361 | 4635 | 227 | 516 |
| Sub-Saharan Africa | 90 622 | 419 639 | 3529 | 32 117 |
| Total | 420 549 | 1 841 158 | 19 886 | 93 945 |

Jellyfish encompass a vast range of species that share a common stinging mechanism, the cnidocil or nematocyst, an individual stinging cell that both makes and delivers venom [14, 15]. These cells can be numbered in the millions in the tentacles of large jellyfish, but while most species can induce local discomfort in humans, few can cause medically significant envenoming and almost none, lethal stings [14–16]. The clear exception, the Australo-Pacific box jellyfish (e.g., *Chironex fleckeri*), still occasionally kills humans, but in tiny numbers, almost unmeasurable compared to snakebite [14–18]. However, this threat has resulted in modified human behaviour in some at-risk regions, with consequent drops in rates of envenoming cases [19].

Stinging fish also will affect large numbers of humans, but while pain, however brief, can be severe, life is rarely at risk [15, 20].

## Venomous animals: Taxonomy

Venomous animals are represented in 6 phyla, across 20 subphyla or classes, including multiple vertebrate taxa [21]. A detailed discussion of the taxonomy of venomous animals is beyond the scope of this chapter.

## Venoms: A clinical overview

Venom can be defined as compounds or mixtures of toxins that are deleterious to another organism at a certain dosage [22]. Most venoms contain an array of toxins, usually with a diversity of actions. A single toxin can have multiple actions. For any single species of venomous animal, there will be a degree of variability in the composition of venom between individuals and even a single individual may have slight variations in venom composition over time [23–26]. Such variability can be seasonal or ontogenetic. The range of actions of toxins contained in a venom can reflect the variable types of prey that must be acquired, but may also reflect natural and rapid experimentation within populations of venomous animals [24, 25]. With such an array of toxins available, it might be expected that many would combine to cause toxicity in humans, but experience has shown that often clinical effects of significance can be attributed to just a few distinct toxins, or classes of toxins and it is these that are discussed further [27–29]. Venom classification is therefore considered below in terms of clinical effects in humans.

### *Neurotoxins*

#### *Paralysis*

Paralytic neurotoxins are a recurring theme amongst venomous animals, being present in such diverse taxa as snakes, ticks, jellyfish, cone snails and octo-

Table 2. Major venomous animal groups commonly associated with neurotoxic paralysis [163]

| Type of animal | Examples | Type of neurotoxin[#] |
|---|---|---|
| Elapid snakes | Kraits | Pre- and postsynaptic |
| | Coral snakes | Postsynaptic |
| | Mambas | Dendrotoxins and fasciculins |
| | Cobras (some) | Postsynaptic |
| | King cobra | Postsynaptic |
| | Selected Australian snakes; tiger snakes, taipans, rough scaled snake, death adders, copperheads | Pre- and postsynaptic |
| | Sea snakes | Postsynaptic |
| Viperid snakes | Mohave rattlesnake (some) | Presynaptic |
| | Neotropical rattlesnakes | Presynaptic |
| | Sri Lankan Russell's viper | Postsynaptic |
| Ticks | Paralysis ticks, *Ixodes* and *Dermacentor* spp. | Presynaptic |
| Cone shells | Variety of *Conus* spp. | Conotoxins |
| Octopusses | Blue ringed octopuses, *Hapalochlaena* spp. | Tetrodotoxin |

[#] Definite, predominate or most likely major site of action/type of toxin in humans.

puses (Tab. 2). They are well characterised in snakes, where their primary site of action is the neuromuscular junction (Fig. 1), causing progressive flaccid paralysis, although the precise mechanism of action varies between toxins, often with multiple toxin types represented in a single venom [27–29]. The mode of action can be of great clinical relevance, affecting response to antivenom therapy. A number of other taxa possess paralytic neurotoxins, also causing flaccid paralysis, but their site and mode of action differ, again with clinical implications centred on duration of paralysis.

*Excitation*

Amongst invertebrate venomous animals, neuroexcitatory toxins predominate, especially amongst arthropods, but also amongst some marine animals, notably a few jellyfish species [21, 30]. The structure and mode of action varies amongst these toxins, but the prime clinical effect is generally similar, with rapid, sometimes extreme excitation of portions of the nervous system, most commonly autonomic stimulation resulting in a "catecholamine storm" effect, which can be rapidly lethal [31].

*Myotoxins*

Activated myotoxins induce myolysis and fall into two broad groups: the locally acting type and the systemically acting type, with the latter, in particular, able to cause potentially devastating and lethal effects as a result of secondary renal

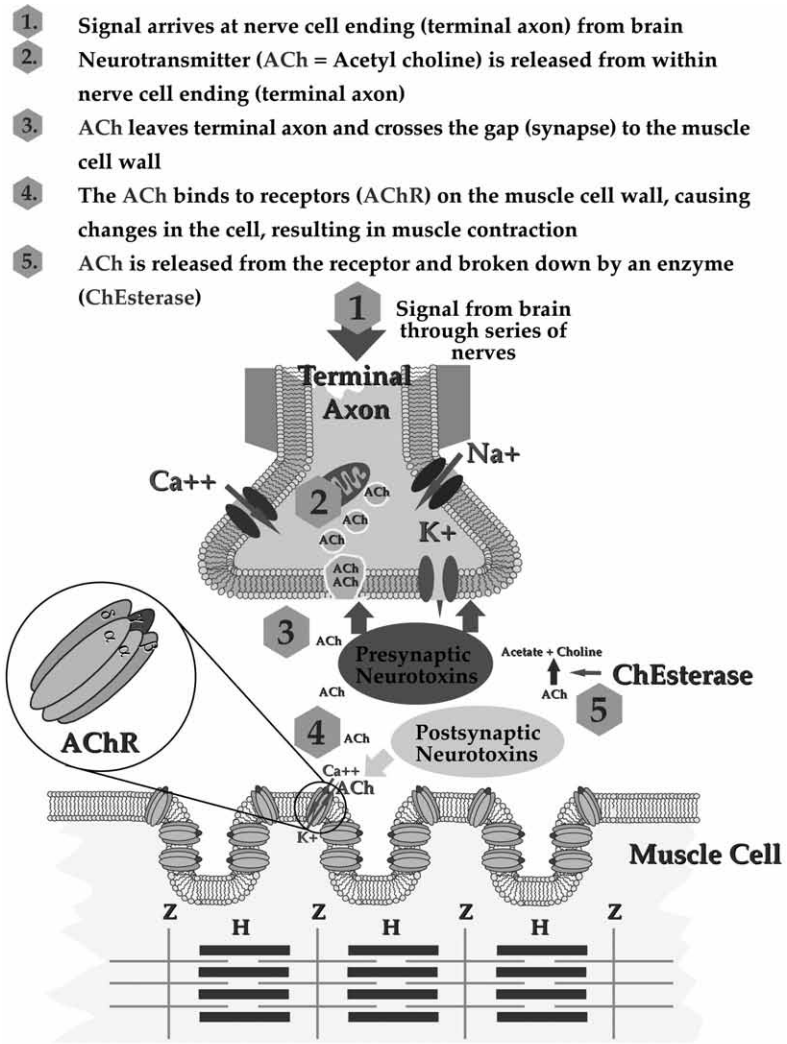


Figure 1. Diagrammatic representation of the site of action of principal neuromuscular junction paralytic neurotoxins (original photo/illustration copyright © Julian White).

failure, hyperkalaemia and cardiotoxicity [21, 28]. In most cases myotoxins are modified phospholipase $A_2$ ($PLA_2$) toxins, sometimes closely related to presynaptic neurotoxins [27]. In some cases a single toxin, such as notexin from Australian tiger snake (*Notechis scutatus*) venom, possesses both myotoxic and presynaptic neurotoxic activity, residing in separate portions of the molecule [27, 32]. Most venom myotoxins are found in snake venoms, although only in a minority of species, but myotoxic activity does occasionally occur with envenoming by other animals, including widow spider bites and mass hymenopteran stings [33–39].

## *Blood toxins*

### *Coagulants and related toxins*

Snakes have evolved a wide array of toxins to attack the complex haemostatic system (Fig. 2), and in many cases a variety of distinctly different toxins, with different targets, may coexist within a single venom [40, 41] (Tabs 3 and 4). However, more often a particular toxin will predominate in clinical effects on haemostasis. In the majority of species, this predominant activity will be procoagulant, most often causing either clotting through activation of thrombin, or direct attack on fibrinogen. While in the laboratory this may result in rapid plasma clotting, in an *in vivo* setting, like an envenomed human, the effects may be rather different, such as rapid consumption of all fibrinogen, causing hypocoagulability and a tendency to bleed [28, 40–45]. Thus, while these toxins may be characterised as potent clotting agents, their clinical effect may seem quite the opposite, effectively anticoagulating the blood through consumption of fibrinogen. There are exceptions to this, notably the potent clotting toxins in two Caribbean pit-viper venoms, which clinically cause extensive thrombosis, sometimes lethal [46–50]. Snakes are not the only venomous animals to specifically target haemostasis; a South American caterpillar with venom-tipped "hairs" can also cause severe procoagulant coagulopathy and fibrinogen depletion [51, 52]. Coagulopathy is also reported following stings by a few scorpion species, but is less well defined [53–55].

### *Anticoagulants*

In addition to the secondary anticoagulant effects of some procoagulant toxins, some snake venoms contain potent true anticoagulant toxins that work by

Table 3. Summary of common target points for venoms interfering with the human haemostatic system [163]

| Class of toxin | Specific activity |
|---|---|
| Procoagulant | Factor V activating<br>Factor X activating<br>Factor IX activating<br>Prothrombin activating<br>Fibrinogen clotting |
| Anticoagulant | Protein C activating<br>Factor IX/X activating<br>Thrombin inhibitor<br>$PLA_2$ |
| Fibrinolytic | Fibrin(ogen) degradation<br>Plasminogen activation |
| Vessel wall interactive | Haemorrhagins |
| Platelet activity | Platelet aggregation inducers<br>Platelet aggregation inhibitors |
| Plasma protein activator | SERPIN inhibitors |

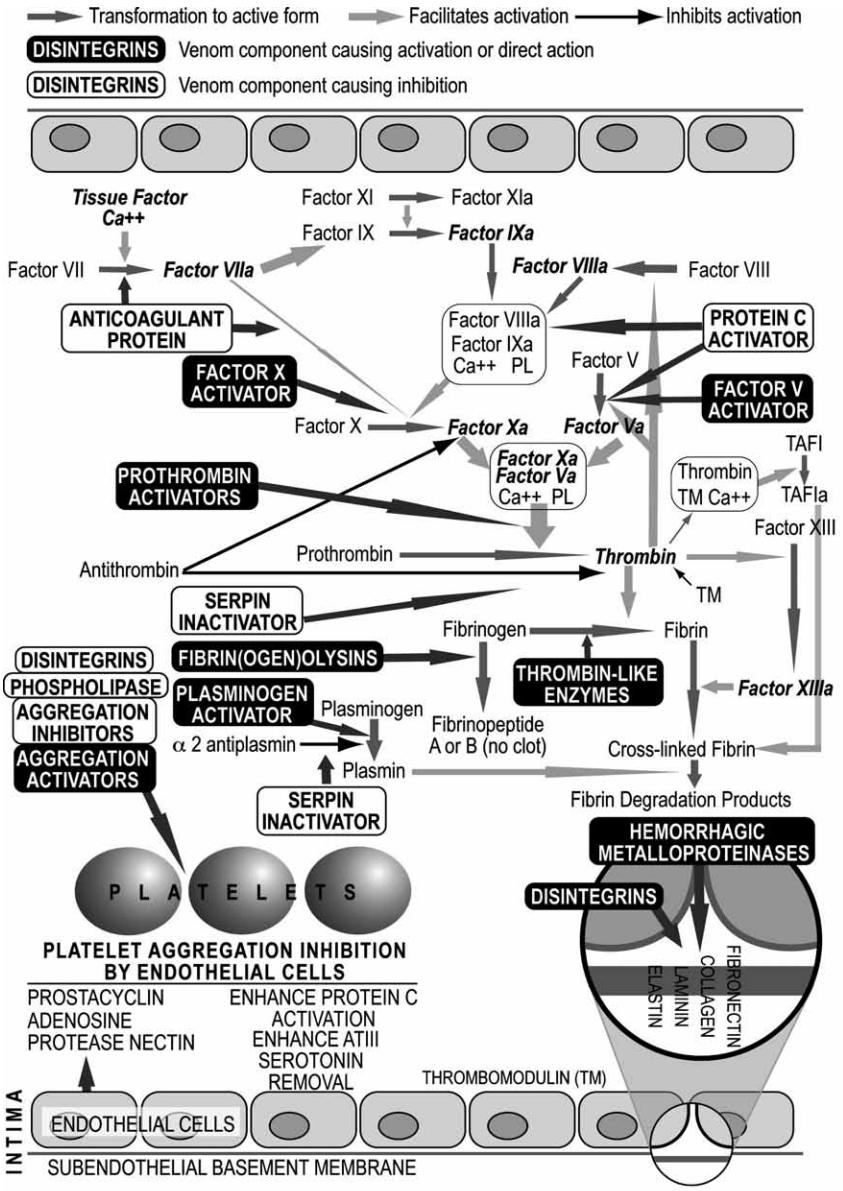


Figure 2. Diagrammatic representation of the human haemostatic pathways within blood vessels and some common targets where venom toxins can interfere with this process (original photo/illustration copyright © Julian White).

inhibiting the haemostatic process (Tabs 3 and 4) [40, 41]. This type of coagulopathy is largely restricted to a minority of snake species and, in most cases, causes less severe clinical problems than procoagulants [41, 56, 57].

Table 4. Major venomous animal groups likely to cause primary coagulopathy

| Type of animal | Examples | Type of venom action |
|---|---|---|
| Colubrid snakes | Boomslang, vine snake | Procoagulant |
| | Yamakagashi, red necked keelback | Procoagulant |
| Elapid snakes | Selected Australian snakes; tiger snakes, rough scaled snake, taipans, brown snakes, broad headed snakes | Procoagulant |
| | Selected Australian snakes; mulga snakes, Collett's snake, black snakes, Papuan black snake | Anticoagulant |
| Viperid snakes | Saw scaled or carpet vipers | Procoagulant, disintegrins, haemorrhagins |
| | Gaboon vipers and puff adders | Procoagulant, antiplatelet, disintegrins, haemorrhagins |
| | Russell's vipers | Procoagulant, haemorrhagins |
| | Malayan pit viper | Procoagulant, antiplatelet, haemorrhagins |
| | North American rattlesnakes | Procoagulant, fibrinolytic, antiplatelet, disintegrins, haemorrhagins |
| | North American copperheads | Procoagulant, anticoagulant, fibrinolytic, disintegrins |
| | South American pit vipers (selected *Bothrops* spp.) | Procoagulant, Anticoagulant, fibrinolytic, disintegrins, haemorrhagins |
| | Asian green pit vipers (selected *Trimeresurus* spp.) | Anticoagulant, fibrinolytic, antiplatelet, disintegrins, haemorrhagins |
| | EuroAsian vipers (selected *Vipera* spp.) | Procoagulant, disintegrins, haemorrhagins, |
| Insects | Latin American caterpillars, *Lonomia* spp. | Procoagulant |

### *Haemorrhagins*

Synergy between diverse toxins can often result in more devastating effects on prey, or humans, and this is clearly the case with haemorrhagins, found in a number of snake venoms, mostly based on a metalloproteinase toxin that directly damages tissue, especially vascular tissue (Tabs 3 and 4) [40, 41, 58–61]. This direct damage promoting bleeding sites when combined with procoagulants that defibrinate, so preventing thrombotic repair of bleeding sites, which can lead to very severe clinical effects, especially locally around the bite site.

### *Nephrotoxins*

Few primary nephrotoxins have been reported from venoms [62, 63], but secondary renal damage is very much a clinical problem with many snakebites,

and without renal supportive therapy, such as dialysis, can prove lethal [64–72]. Secondary renal damage can occur through a variety of venom-mediated mechanisms, including coagulopathy, myolysis and hypotension [27, 29]. A particular syndrome, microangiopathic haemolytic anaemia (MAHA), can occur after envenoming by some snake species, and is characterised by intravascular haemolysis, thrombocytopenia and renal failure, but the precise causative mechanisms in envenoming remain to be elucidated [71, 73].

### *Necrotoxins*

Local tissue injury following bites or stings is a common theme across many taxa, including snakes, spiders, scorpions (but only a very few species), centipedes and some marine animals such as the box jellyfish (*Chironex fleckeri*) and some of its relatives, and some stingrays [3, 11, 12, 18, 19, 21, 29, 45, 74–79]. The mechanism of injury is incompletely understood in most cases, although specific necrotoxins, such as sphingomyelinase D (from recluse spiders, *Loxosceles* spp.), are known [80–84], and the role of myotoxic $PLA_2$ in snake venom indicates a prime role in local tissue injury [81], while hyaluronidases are implicated in other venoms [85]. In many cases it is likely that local tissue necrosis is mediated by a complex interplay between several toxin effects and natural defence mechanisms within the victim.

### *Other toxins*

In addition to the specific toxins and effects listed above, most venoms have a number of other, less well understood components, the clinical significance of which is usually unknown. This group, which may include the bulk of all toxin types, includes many low molecular weight toxins, including peptides. The latter are of increasing interest as potential templates for new pharmaceuticals, but undoubtedly some have significant clinical actions. Also within this group can be included a very diverse and important mix of toxins originating in cone snails (Coniidae; *Conus* spp. and some related hunting marine snails). Broadly classified as “conotoxins”, these highly potent toxins are diverse in pharmacological effects and are already proving a rich area for new drug development [86].

## Envenoming: A management overview

Envenoming will vary in severity, depending on the relative toxicity of the venom involved, the amount of venom actually delivered, the size of the victim, any pre-existing medical conditions, and environmental/social considerations [21, 28, 29]. It follows that even for a highly dangerous species, such as

an Australian taipan snake (*Oxyuranus scutellatus*), the degree of envenoming and risk to life is not constant; while most cases may develop life threatening envenoming, often quite rapidly, there will still be some cases who never develop significant envenoming. Predicting which course each case will take, in the early stages, may be difficult to impossible, so it is a general rule that any case of definite or likely bite/sting by a medically significant venomous animal should be managed initially as a high priority medical emergency. Inevitably, a number of cases, perhaps the majority in some geographic regions, will ultimately prove to be only minor, with minimal or no envenoming. This is not a justification for assigning a low initial priority to bite/sting cases who seem apparently well on presentation. Envenoming can develop quickly, but can also be delayed in onset, yet still potentially lethal. Health professionals, except in a few situations, are unlikely to see or treat large numbers of bite/sting cases, so maintaining knowledge and skill can be problematic. It follows that in most situations, consultation with a doctor who is an expert in clinical toxinology is advisable, if optimal patient outcomes are to be ensured.

### *First aid*

Pre-hospital care can, quite literally, be the difference between life and death in cases of envenoming, particularly for those species causing rapid severe effects such as respiratory paralysis and cardiotoxicity. There are few research-proven first aid methods for envenoming, yet many methods are used or recommended, most of which have either no benefit, or more commonly, cause actual harm [87–106]. Appropriate envenoming first aid should follow three principles; (1) do no harm, (2) immobilise venom to prevent it reaching target sites, and (3) support vital functions (airway, breathing, circulation) [107]. The last of these, supporting vital functions, if adopted universally, would likely save life in many cases of envenoming. It is often overlooked, but the importance of ensuring airway patency, respiration and circulation cannot be overemphasised. Avoiding causing harm is a vital principle, also generally overlooked. Table 5 lists well-known first aid methods that cause actual harm in envenoming and should not be used. Table 6 lists those few first aid methods shown to have value in envenoming.

### *Approach to management*

As outlined earlier, two principles should guide care of the definitely or potentially envenomed patient: (1) all cases should be initially managed as potentially severe, and (2) expert advice should be sought at the earliest opportunity [107]. Locating expert advice will vary between countries, but in most cases, a major poisons information centre may be a reasonable first choice.

Table 5. Harmful or ineffective first aid methods that should not be used; only some prominent methods are listed

| Method | Problems |
|---|---|
| Tourniquet | Direct pressure injury under narrow band tourniquet<br>Severe pain<br>Ischaemic limb damage (may include loss of limb)<br>Potential for massive envenoming on release |
| Patent suction devices | Local tissue injury<br>Increased local necrosis<br>Painful<br>Only minor venom removal<br>No proven benefit in reducing envenoming |
| Local scarification, wound excision, amputation | Local tissue injury<br>Painful<br>May increase rate of envenoming<br>May introduce local infection<br>Can cause significant bleeding and blood loss<br>No proven benefit in reducing envenoming |
| Electric shock | Dangerous<br>No proven benefit in reducing envenoming |
| Chemical application | Potential toxicity<br>No proven benefit in reducing envenoming |
| Snake stone | No proven benefit in reducing envenoming |
| Traditional healers | No proven benefit in reducing envenoming<br>Cause potentially lethal delays in seeking definitive care |

Consultant clinical toxinologists are currently a rare commodity within health systems, but this may improve over time, as training courses output more graduates.

The first priority when assessing a case of bite/sting with definite or potential envenoming, is to ensure vital systems functioning (airway, breathing, circulation). One must be aware of the possibility that coagulopathy may be present or develop, and physical interventions, such as i.v. line insertion, should be chosen with care to avoid causing uncontrollable bleeding problems. In the presence of coagulopathy, certain i.v. sites (subclavian, jugular, femoral) and actions (e.g., i.m. injections, fasciotomy, tracheostomy) are hazardous and should be avoided if at all possible. The second priority is establishing a working diagnosis, from which more definitive care, including antivenom therapy, will follow where indicated and available.

### *Diagnosis of envenoming*

Diagnosis is a crucial early step in managing envenoming [28, 107]. Two parts of diagnosis can be discerned: (1) determining the cause of envenoming, from which more specific treatment can follow, and (2) determining the extent of

Table 6. First aid methods considered effective or possibly effective and not harmful

| Method | Useful for |
|---|---|
| Immobilisation of bitten limb and whole patient | All snakebites and other causes of systemic envenoming |
| Australian pressure immobilisation bandage technique | All non-necrotic or haemorrhagic snakebites, including all Australian snakes, kraits, coral snakes, king cobra, sea snakes, mambas, selected cobras, South American rattlesnakes; Australian funnel-web spiders;<br>Possibly (not proven experimentally or by clinical trial): Buthid scorpions, cone shells, blue ringed octopus |
| Cardio-pulmonary resuscitation | Any bite/sting causing impaired cardiac or respiratory function |
| Removal of attached organism | Any bite/sting, to prevent ongoing envenoming; specifically important to remove bee sting/venom gland, paralysis tick, Helodermatid lizard |
| Hot water (to 45 °C; care to avoid hotter water and thermal injury) | All venomous fish stings, stingray injuries, jellyfish stings (not yet proven for box jellyfish stings) |
| Direct wound care/staunching bleeding | Injuries affecting major blood vessels, such as some stingray injuries |
| Copious fluid irrigation of the eye | All cases with venom in the eye, particularly spitting cobras |
| Removal of rings, other constricting objects from limbs, especially digits | May reduce the chance of local swelling causing ischaemic damage |
| Reassurance | Calming the patient and keeping them still may reduce the rate of onset of envenoming and development of anxiety-related symptoms |
| Retrieval of the envenoming animal | If the culprit has been killed or captured and can be safely transported with the patient, do so, as this will assist in accurate diagnosis;<br>CAVEAT: Do not waste time or risk further bites/stings to kill/capture the culprit |

envenoming, including severity, progression, systems affected, and evident complications, which will guide the degree and nature of any therapeutic response. All three elements of the diagnostic process, history, examination, and laboratory tests, play a role, but the extent to which each may contribute varies with the venomous animal concerned. For many species, laboratory tests may add little to diagnosis and history will be crucial. However, the history may give no early clue to diagnosis, particularly when the presentation is symptom-driven, perhaps without any suggestion of a bite/sting occurring or being causative. Thus, in unexplained cases of coagulopathy, paralysis, neuroexcitation, myolysis, renal failure, collapse, convulsions, or local tissue injury, envenoming may sometimes be an important differential diagnosis needing consideration and exclusion.

*History*

Ideally, a toxinological history will answer some or all of the following questions: (1) is a bite/sting a likely diagnosis, (2) do the circumstances (including a description of the assailant, if available) and geographic location of the bite/sting indicate likely assailants, (3) does the patient have any symptomatology suggestive of envenoming, local or systemic, and does the pattern of symptoms indicate likely assailants, (4) are there any patient-related factors that might influence diagnosis, severity of envenoming, or outcome, and (5) is the patient in need of treatment urgently, or likely to need treatment later?

The key areas for questioning are shown in Table 7, but these are designed to fit all common situations, while in the real world, the list of possible assailants will likely be narrower and so the range of questions required will be less. Often the key diagnostic features emerge early and allow a more directed approach to confirm the likely assailant and therapeutic response required. However, some caution is required, because any venomous animal can, on occasion, cause an atypical presentation.

*Examination*

Examination is directed towards finding evidence that a bite/sting has occurred, and if any local or systemic envenoming effects are present. Where the history has not clearly identified a likely assailant, examination findings may help to narrow diagnostic possibilities. Key areas for examination are shown in Table 8. As for history, this list is designed to cover many common possibilities and in the real world, a more directed examination is often possible. Again, caution is required, to ensure no key signs are missed because early assumptions are made about the likely culprit.

*Laboratory tests*

Specific testing for evidence of envenoming is only applicable for some animals, mostly snakes, while no lab tests are routinely indicated for bites/stings by many non-snake venomous animals. Key lab tests are shown in Table 9, and as with history and examination, selection of which tests to request, if any, will be determined by the circumstances in each case, particularly the possible assailants to be considered.

*Urgent care*

The acutely and significantly envenomed patient presents an urgent case requiring prompt, accurate assessment and directed treatment. The patient presenting in extremis will require immediate life supportive care, then best-guess diagnosis of the likely culprit(s) and urgent specific treatment to cover these animals, followed by more considered assessment and treatment, once the acute emergency is controlled. In such a situation, it may still be possible to rapidly ascertain key diagnostic features, such as presence of coagulopathy, paralysis, myo-

Table 7. Important points in a toxinological history

| Area of questioning | Relevance |
|---|---|
| Circumstances of bite/sting | May indicate likely degree of envenoming (brief glancing attack *versus* chewing bite/prolonged sting), but even glancing bite can sometimes cause severe envenoming; May indicate likely culprit |
| Geographic location | Can narrow range of possible culprits |
| Description of animal | Can help determine likely culprit, but beware colour variability, especially in snakes |
| Number of bites/stings | Multiple bites/stings may cause increased envenoming |
| Immediate symptoms | May indicate possible culprit; May indicate likely severity |
| First aid, including timing | May influence onset of envenoming symptoms and signs |
| Onset and nature of any symptoms<br>Specifically enquire about symptoms of:<br>• Paralysis (drooping/heavy eyelids, slurred speech, drooling, difficulty walking, moving limbs, holding head up, breathing, swallowing)<br>• Myolysis (muscle weakness, pain, tenderness, red to black urine)<br>• Coagulopathy (bleeding gums, haematemesis, haematuria, melaena, sudden bruising)<br>• Renal damage (altered urine output, thirst)<br>• Cardiotoxicity (palpitations, collapse)<br>• Necrotoxicity (bite/sting site pain, blistering, bleeding, darkened or blue-black skin, eschar formation)<br>• Neuroexcitatory envenoming (increased sweating, salivation, lacrimation, piloerection, respiratory distress with frothing (pulmonary oedema), fasciculation of muscles, including tongue, nystagmus)<br>• Non-specific (headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, collapse, convulsions, metallic taste in mouth) | Can determine pattern and severity of envenoming, which can indicate likely identity of culprit and requirement for treatment |
| Medications | May identify medications that might interact with envenoming or skew interpretation of lab tests (e.g., warfarin and coagulopathy) |
| Past history | May identify pre-existing conditions of relevance to envenoming |
| Allergies | Particularly important to determine if there is a potential allergy to any treatment, such as antivenom, OR if the symptoms could be more related to allergy than envenoming |

Table 8. Key points in the toxinological examination

| Area of examination | Relevance |
|---|---|
| Bite/sting site | Is there evidence of multiple bites/stings, ongoing bleeding (coagulopathy), bruising (coagulopathy), blistering/bleb formation (necrosis), increased sweating (neuroexcitatory envenoming), major swelling (fluid shifts, impending shock), significant mechanical trauma (stingray), attached tentacle (jellyfish) or stinger (honey bee)? |
| Bitten/stung region/limb | Is there evidence of venom spread (lymphadenopathy or tenderness, lymphangitic tracking) or regional envenoming (spreading blistering/blebs, ecchymosis, increased sweating)? |
| Critical systems (cardiac, respiratory) | Is there hyper/hypotension, brady/tachycardia, cardiac arrhythmia, cyanosis/respiratory distress, use of accessory muscles? What is Glascow coma score (GCS)? |
| Neurological systems | Is there evidence of paralytic neurotoxicity (cranial nerve signs like ptosis, ophthalmoplegia, fixed dilated pupils, drooling, dysarthria, dysphagia, altered taste/smell, limb muscle weakness, reduced or absent deep tendon reflexes)? |
| | Is there evidence of neuroexcitatory envenoming (increased local, regional, or generalised sweating, piloerection, increased salivation, lacrimation, muscle fasciculation, including tongue, pulmonary oedema)? |
| Haemostasis systems | Is there evidence of increased bleeding (oozing from bite site, i.v. sites, gums, elsewhere, bruising, CNS signs of intracranial bleeding) OR of thrombotic problems (deep vein thrombosis, pulmonary embolus, stroke)? |

lysis, or neuroexcitation, which will guide the therapeutic response. The same rapid assessment techniques can be utilised to effectively triage cases with less life threatening features. Observation of the patient's face can often show if they are in significant pain (grimace), if they have any early developing paralytic features (ptosis, loss of facial tone, partial ophthalmoplegia; Fig. 3), or neuroexcitatory features (increased sweating, lacrimation), or coagulopathy (bleeding bite site, gums; Fig. 4), while a simple check of any i.v. insertion or sampling sites will reveal evidence of coagulopathy (continued ooze, bleeding, extending bruising), and a check of the bite/sting site will reveal if there is rapidly advancing swelling, or early tissue injury features (ecchymotic blistering, marked dark skin colouration, especially if clear demarcating edges; Fig. 5), or early neuroexcitation (increased local sweating, piloerection). If major neuroexcitatory envenoming is a likely diagnosis, chest auscultation (for signs of pulmonary oedema) is required. Except where pulmonary oedema is a significant risk, most envenomed patients will benefit from early i.v. fluid load.

Table 9. Key laboratory investigations to consider in a case of definite or suspected envenoming. The actual choice of tests will be determined partly by the type of organism and the clinical setting

| Test | Relevance | Relevant fauna |
|---|---|---|
| Whole blood clotting time (WBCT) | If substantially prolonged and/or with weak clot, can indicate coagulopathy (NOTE: always use glass vessel, do control) | Most snakebites, Brazilian *Lonomia* caterpillars, Iranian *Hemiscorpius* and *Nebo* scorpions, recluse spiders |
| 20-minute WBCT (is blood clotted at 20 minutes?) | Simple derivative of WBCT, validated for some snakebites | As above |
| Coagulation studies<br>• INR/prothrombin time<br>• aPPT/PTTK<br>• d-dimer/XDP/FDP<br>• fibrinogen | Definitive assessment of coagulopathy; d-dimer may be most sensitive early measure of developing coagulopathy | As above |
| Complete blood examination<br>• platelets<br>• haemoglobin (Hb)<br>• blood film for evidence of haemolysis<br>• white cell and absolute lymphocyte count<br>• reticulocytes (if haemolysis) | Important in assessing if there is haemolysis, MAHA, or isolated thrombocytopenia. Early absolute lymphopenia can be another marker for envenoming | As above, plus other fauna that may cause haemolysis, including severe jellyfish stings, massive hymenopteran multiple stings |
| Blood chemistry, especially<br>• renal function<br>• creatine kinase (CK, for myolysis)<br>• electrolytes (particularly $K^+$)<br>• bilirubin (if haemolysis)<br>• glucose (if scorpion sting)<br>• liver function tests (LFTs; if haemolysis, myolysis, or if pancreatitis is suspected after scorpion sting) | Each parameter specific for particular envenoming/complication, such as renal damage, myolysis, haemolysis, hyperkalaemia | Most snakebites, any major systemic envenoming/collapse, envenoming where haemolysis suspected, such as mass hymenopteran stings |
| Arterial blood gases | Principally assessing oxygenation, if respiratory compromise, such as in neurotoxic paralysis | Any bite/sting where respiratory failure/paralysis possible, including selected snakebites, Australian funnel-web spider, scorpion, paralysis tick, cone shell, blue ringed octopus, Irukandji jellyfish envenoming |
| Bite site wound swabs<br>• venom detection (Australia)<br>• culture and sensitivity | In Australian snakebites, for venom detection; everywhere, if wound is infected | Australian snakes; any infected wound |

### *Specific treatment: Antivenom*

In general, the only specific treatment for envenoming is antivenom and this is only available for some venomous animals.

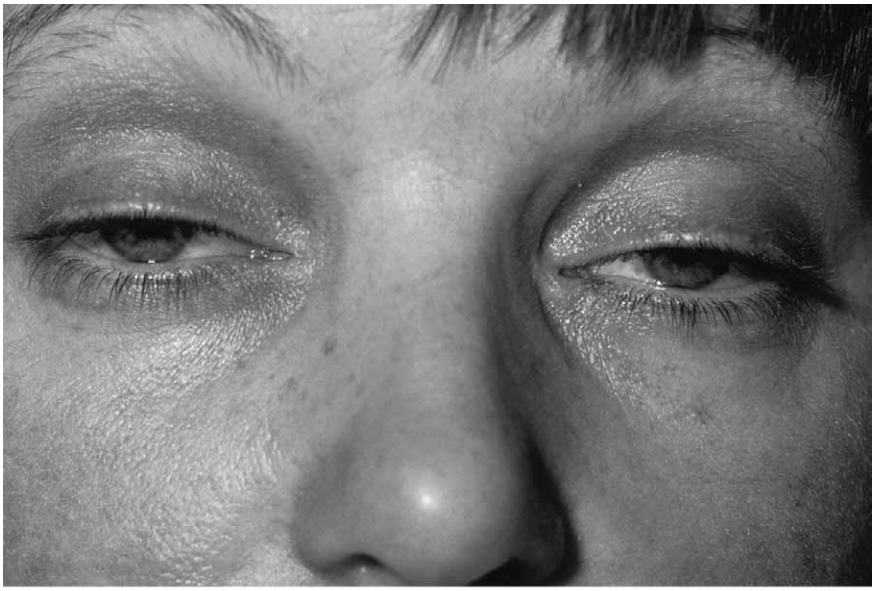

Figure 3. Ptosis, often the first sign of developing neurotoxic envenoming (*Notechis scutatus* bite) (original photo/illustration copyright © Julian White).

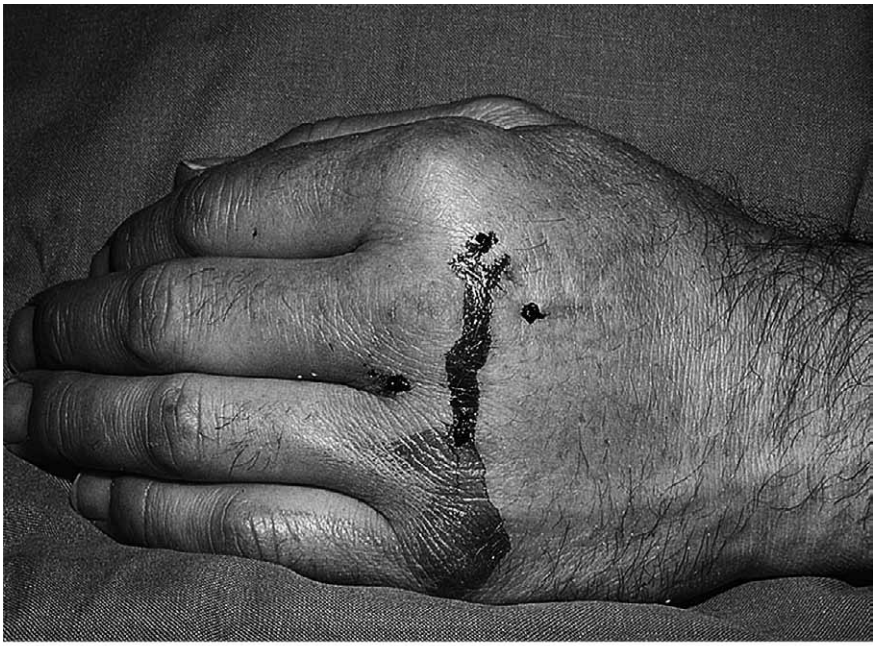

Figure 4. Persistent blood oozing from bite area, often indicative of coagulopathy (*Pseudechis* spp. bite) (original photo/illustration copyright © Julian White).

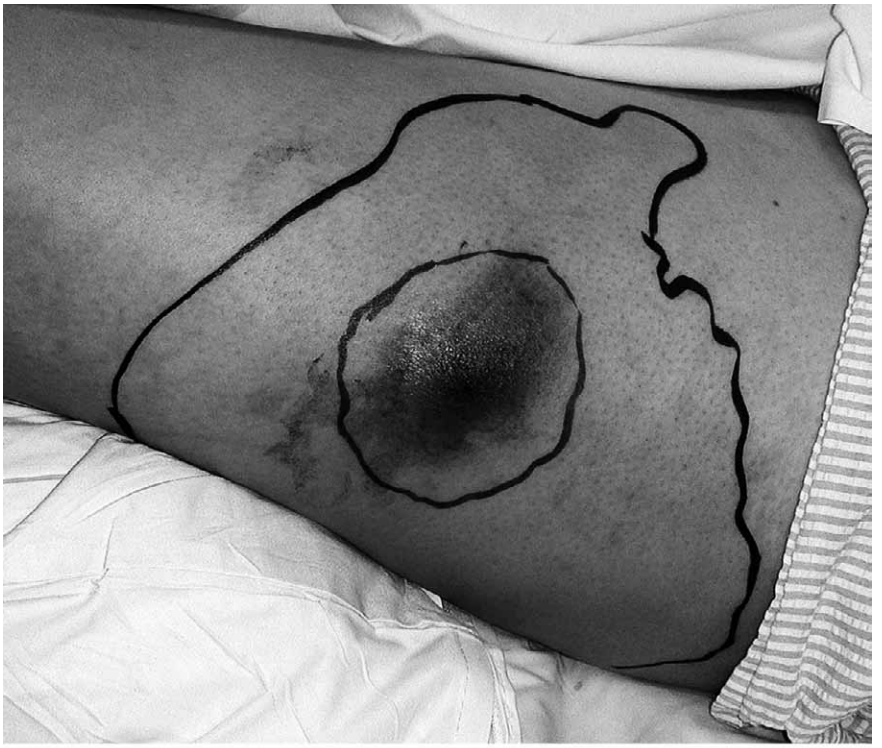

Figure 5. Demarcating area of tissue injury, indicative of an area likely of developing necrosis (*Pseudechis australis* bite) (original photo/illustration copyright © Julian White).

The era of antivenom therapy for envenoming dates back to the work of Calmette and others, in the final years of the 19th century [108]. Antivenom is essentially antibody raised against whole venom(s) or venom fractions in a domesticated animal (horse, sheep, goat, rabbit) and works by binding to toxins, either at the active site (so rendering them inactive), or elsewhere (allowing clearance) [109, 110]. It follows that a given antivenom contains neutralising antibody against only those venoms used in the immunising mix, so utility in treating envenoming by other species is dependent on sufficient antigenic similarities between venoms [111, 112]. For some venoms, there is considerable similarity with venoms from other, usually related, species. This provides cross-specific protection, therefore a particular antivenom may be effective in treating envenoming by a number of different species. However, such cross-specific protection is not a universal, or even particularly common, finding. As a rule, then, antivenom used in treatment should be proven as specific for a particular species, or group of species [110].

There are a variety of ways of producing antivenom, although all currently in use start by hyperimmunising an animal [109, 110, 112]. Nearly all antiven-

oms are based on mammalian IgG antibody, most commonly equine (horse). The IgG can be refined in a number of ways to eliminate contaminants from plasma that can stimulate adverse reactions. IgG can be further fractionated to yield fractions of IgG, each with distinct properties, advantages and disadvantages. Whole IgG and $Fab_2$ antivenoms have a prolonged half life, compared to Fab antivenoms, so they maintain clinically useful blood levels over several days, important in neutralising late-released venom from a depot at the bite site, but their larger size limits extravascular spread. Fab antivenoms have better extravascular penetration, but at the cost of short half life, measured in hours, usually necessitating repeat doses or continuous infusion [113–115]. Few Fab antivenoms are available, the principle ones being for North American pit viper bite (CroFab®) and European adder bite (Viperatab®), but early experience with these affinity-column-refined ovine (sheep) antivenoms shows they are relatively safe and effective, but commonly require repeat dosing to counter short half life [113–118]. In North America, an issue of recurrence of coagulopathy has raised questions about effectiveness, since this recurrence is sometimes resistant to further antivenom doses. However, examination of case experience with the previous equine whole IgG antivenom shows recurrence was also an issue and other factors may be at play [114]. Arguments have been mounted that whole IgG antivenoms are the most effective, but traditional manufacture has been associated with high levels of adverse effects [119–122]. As a consequence, many producers have moved to $Fab_2$ antivenoms, which are as effective, but generally have been considered to have a better adverse effect profile, a view now questioned [119–122]. However, development of caprylic acid treatment of whole IgG antivenoms is claimed to produce a product with high efficacy and a good adverse effect profile, with a further advantage of lower production cost [123–126]. This may swing antivenom production back towards predominantly whole IgG product.

Horses are by far the predominant host animal for antivenom production [109–112, 127–129]. They are relatively easy to manage, provide large plasma volumes with regular venesection or plasma pheresis, are comparatively safe as vectors of disease transmission, and production techniques are well established [130, 131]. However, equine antivenoms, especially whole IgG, have been associated with sometimes very high levels of adverse effects [132]. Because of this, a few producers have explored other animals, notably sheep [113, 115–117, 133]. Ovine antivenoms are now produced by two major producers and have proved safe but, because of an increased risk of disease transmission, particularly viral and prion disease, sheep are only practical in the few countries with certified safe flocks [131]. If new processing steps that can guarantee removal of infectious agents are developed, this may make ovine antivenoms more widespread, but the use of caprylic acid purification of whole IgG equine antivenoms may render such ovine antivenom developments unnecessary. Goats have also been used in the past and one producer currently uses rabbits for a low output specialised antivenom [134]. Current research is investigating camels, as these may be easier than horses in some regions,

such as Africa, and camelid IgG can be more readily fractionated into really small molecular size antivenoms that may open up possibilities for combined systemic and local use [135, 136]. This work is purely experimental and it is at present not known if it will translate to commercial production. Another different approach using hens to produce egg-based IgY antivenoms has also been explored, but a number of problems, including widespread major immunity to such a product, with the potential for severe adverse reactions, appears at this time to make commercial IgY antivenoms unlikely [137–140]. The development of genetically engineered antivenom production, using recombinant methods, is at an early stage of development, with no commercial products available as yet, although research is progressing, both into recombinant production of immunising toxins, and complete recombinant production of specific antivenom [141–144].

*Antivenom theory*

Antivenom works by binding specifically to venom toxins and rendering them inert and/or speeding clearance from the circulation [109, 112, 145]. To be effective, antivenom must rapidly bind and inactivate/remove all circulating venom from the circulation, and as far as possible, the rest of the body. This requires primary intravascular distribution, which is why antivenom should, in most cases, be given only i.v., not used locally or as an i.m. injection. There are a few antivenoms for which i.m. injection is advocated or has shown favourable results [134, 145–158] with some evidence that it is effective, although this is controversial in light of recent studies [158–162]. However, these are for organisms with more slowly developing and, in general, non-lethal envenomings.

The prime requirement for antivenom is therefore i.v. administration of an initial dose expected to fully neutralise all circulating venom. Except for Fab antivenoms, most or all of the antivenom will remain in the circulation, yet for many venoms, key components will exit the circulation to reach their extravascular targets, such as the neuromuscular junction or skeletal muscle. Toxins acting on the haemostatic system and haemorrhagins act within the intravascular system, so are readily accessible to antivenom. Concentration gradients between extravascular and intravascular venom levels are likely to draw extravascular venom back into the circulation, for neutralisation, as intravascular venom levels fall with neutralisation by antivenom. This mechanism requires high levels of antivenom, compared to venom, explaining the clinical requirement for adequate antivenom doses initially. Antivenom administered i.m. will be slow to reach high intravascular concentrations [160, 162], so will be far less efficacious, particularly for rapid, acute, severe envenoming, as caused by many snake species. Similarly, locally injected antivenom is unlikely to reach significant blood levels, so will be ineffective against circulating and distributed venom. Therefore, even if low molecular weight antivenoms are developed for local injection, there will still be a critical need for simultaneous i.v. administration.

*What is antivenom effective for?*

Antivenom is an effective antidote against venom components that are specifically covered as antigens for a given antivenom [163]. This implies that antivenom must be specific for the type of venomous animal involved, or have proven cross protection for that animal. It also implies antivenom must be able to access the venom. This may be difficult for locally sequestered venom, such as in the bitten limb. It follows that in general, antivenom is far more effective at neutralising systemic effects than local effects, except for low molecular weight antivenoms (Fab), which more readily reach extravascular sites. However, antivenom cannot repair injured tissue, it can only bind to venom with appropriate antigenic matching. Therefore, some venom effects that involve damage to target tissue, such as presynaptic neurotoxicity (terminal axonal damage), myotoxicity (damage to muscle cells), renal toxicity (direct or indirect renal damage) and secondary damage from coagulopathy, are not reversible with antivenom therapy. For this reason it is important to detect systemic envenoming at the earliest opportunity and commence appropriate antivenom therapy, before such tissue damage is extensive. Equally, this explains why late antivenom therapy to remedy such tissue injury is ineffective and generally not warranted. A caveat is that continuing venom absorption from the bite site, causing ongoing envenoming, requires maintenance of adequate antivenom levels, which may warrant repeat dosing, even for whole IgG or $Fab_2$ antivenoms. Clinically, this seems applicable for continuing myolysis. A list of clinical effects and their responsiveness to antivenom is given in Table 10.

The indications for administering antivenom in a case of envenoming are, to some extent, specific for each type of venomous animal, and discussing requirements for each species or antivenom is beyond the scope of this chapter. There are, however, some broad principles that apply in many circumstances. Firstly, antivenom should only be given if there is evidence of significant envenoming, either systemic, or in some settings, local. It is rarely justified giving antivenom to a patient who exhibits no evidence of envenoming. Bites/stings by nearly all venomous animals have a significant and variable rate of "dry bites", where bite/sting marks may be present, but insufficient venom is injected to cause medically significant envenoming effects. Just because a bite/sting is from a highly dangerous species does not mean significant envenoming will develop. Secondly, in most settings, antivenom should be given as soon as there is evidence of systemic envenoming developing. There are exceptions, particularly for those venomous animals that cause predominantly local effects, but not necrosis, and/or non-specific systemic effects with a low likelihood of threat to life (e.g., headache, nausea, vomiting, diarrhoea, abdominal pain, dizziness). Systemic effects that are virtually always worrying will usually indicate the need for antivenom (Tab. 11).

*Choosing an antivenom*

The ideal antivenom will be safe and efficacious at neutralising target venoms. In regions where polyvalent antivenoms predominate, covering all major med-

Table 10. Key clinical envenoming effects and their responsiveness to antivenom

| Toxin activity type | Clinical effects and responsiveness to antivenom |
|---|---|
| Paralytic neurotoxin<br>• Presynaptic<br>• Postsynaptic<br>• Anticholinesterase | Flaccid paralysis<br>• Resistant to late antivenom therapy<br>• Often reversal with antivenom therapy<br>• Muscle fasciculation |
| Excitatory neurotoxin | Often causes "catecholamine storm", massive stimulation of autonomic nervous system; can be very responsive to antivenom, but in some cases (some scorpions) must be given early to be effective |
| Myotoxin | Systemic skeletal muscle damage; may respond to antivenom, but damage pre-antivenom will remain, causing symptoms and lab test changes (mainly elevated creatine kinase, CK) |
| Haemostatic system toxins | Interfere with normal haemostasis, causing either bleeding or thrombosis; often respond to antivenom, as only effective treatment, but not effective for all venoms |
| Haemorrhagins | Damage vascular wall, causing bleeding; role of antivenom uncertain, may be helpful |
| Nephrotoxins | Direct renal damage; value of late antivenom uncertain |
| Cardiotoxins | Direct cardiotoxicity; role of antivenom uncertain, controversial |
| Necrotoxins | Direct tissue injury at the bite site/bitten limb; antivenom, given early, may be of some value, but overall results are not encouraging |
| Non-specific systemic effects (headache, vomiting etc.) | Often indirectly mediated; antivenom often very effective at controlling symptoms |

Table 11. Indicators for antivenom. Note only some indicators will be theoretically applicable for any particular species of venomous animal [191]

| Indicators |
|---|
| Any degree of developing or progressing neurotoxic paralysis |
| Any significant disturbance of haemostasis (except pure secondary disseminated intravascular coagulation, DIC) |
| Any degree of significant myolysis |
| Acute renal damage |
| Acute haemolysis |
| Prolonged collapse or convulsions in confirmed envenoming |
| Major and progressive local swelling |
| Developing necrosis (except if presenting days later) |

ically important species of snakes, there is no absolute need to determine the type of snake in choosing an antivenom. However, in this setting, knowledge of the type of snake may allow better prediction of likely progress, complications and prognosis, all valuable for the patient and the therapeutic process.

In regions where there is a choice of several different antivenoms, without one that covers all possible snakes in the region, there is an absolute need to determine the type of snake with a sufficient level of confidence to allow choice of an appropriate antivenom. There are several possible methods for determining the type of snake. All have advantages and risks and wherever possible, combination of several methods is preferred, to assure better accuracy of the result. Venom detection has been used as an experimental technique for many years [164–175]. In Australia and New Guinea there is a unique commercial snake venom detection kit (SVDK), designed specifically to determine the most appropriate antivenom to use [176–185]. While certainly useful, it is not useful in every case and suffers from both false-positive and false-negative results, the likelihood of which are increased with certain test sample choices. This SVDK was not designed to act as a diagnostic screen for snakebite and should not be used as such. It is possible that similar snake venom detection systems may be developed for other regions for which no single universal polyvalent snake antivenom is available.

Given the problems of identifying the snake, if a polyvalent antivenom is not available, why would producers choose to make monovalent or limited polyvalent antivenoms instead of full polyvalent antivenoms? One reason is the practical mechanics of antivenom production. If the range of snakes to be covered is large, and cross protection between species limited, there may be more different venoms required than is practical, both from an immunising and vial size perspective. Inevitably a polyvalent antivenom, covering a number of species, will generally be of higher volume than specific or monovalent antivenoms for each species. That higher volume may translate into higher costs or lower costs (reduced range of products required), but will inevitably result in a higher risk for the patient, because a higher volume of antivenom must be injected, only some of which is actually therapeutically useful (the antibody fraction against the particular snake involved in envenoming that patient). Delayed (type III) hypersensitivity reactions (serum sickness) can occur with any antivenom, but are more common with high volume antivenoms such as polyvalents [109, 117, 121, 136, 139, 148, 152, 160, 163, 186–190]. Therefore, for the patient, to reduce adverse effects and, in some cases, cost, a specific or monovalent antivenom is a better choice, providing the identity of the snake can be reliably determined. Australia and New Guinea have both specific/monovalent and a polyvalent antivenom against regional snakes. The SVDK allows preferential use of specific/monovalent antivenoms, rather than polyvalent antivenom, in most cases, which reduces rates of adverse effects and cost to the health system. Another option in parts of Australia, where the range of important venomous snakes is limited, is to use a mixture of two specific/monovalent antivenoms to cover possible species, where identity of the snake is not assured [134]. A similar approach is possible in some other regions.

For each region, clear delineation of the envenoming profile for each important species can provide the basis for diagnostic algorithms, as used in Australia

(Fig. 6), which can assist in determining the species involved and is a useful confirmatory procedure, even if venom detection is available [134, 191].

While the discussion above has been directed to antivenoms against venomous snakes, the principles apply to all antivenoms. However, for most other venomous animals, if an antivenom exists, it is a specific/monovalent product, because the range of species required to be covered in any region often does not warrant a polyvalent antivenom. There are exceptions to this, such as polyvalent anti-scorpion and/or anti-spider antivenoms, particularly in parts of South America, North Africa and the Middle East [127–130]. Advising on specific choice methods for antivenoms in each region is beyond the scope of this chapter.

*Administering antivenom*

As discussed earlier, in most settings, acute and rapidly severe envenoming mandates i.v. administration of antivenom to ensure rapid, therapeutically adequate blood levels. For those few antivenoms where the producer recommends an i.m. route, the clinician treating the patient should determine if this is advisable in the individual circumstances, if necessary in consultation with an expert (e.g., through a poisons centre or a clinical toxinology service).

The method of i.v. administration will be dictated by several factors: (1) the volume of the antivenom at the selected dose, (2) the size of the patient, (3) pre-existing health problems for the patient, (4) the availability of i.v. administration equipment, such as sterile i.v. giving sets, i.v. fluids, i.v. pumps etc. High-volume antivenoms in small children may pose fluid overload issues, exacerbated by the common practice of diluting antivenom in an i.v. carrier solution, up to 1:10, such as normal saline or Hartman's solution. In general, where practical, such dilution and administration through a giving set is advantageous, because it allows precise control of rate of infusion and may make adjustments for adverse reactions easier. There are other methods which are also validated, particularly direct slow i.v. injection of antivenom at the bedside, easiest if the total volume is not high [191]. This approach has several advantages; it requires less equipment, so is generally easier and cheaper, particularly in less well resourced health systems, and it forces the doctor, who must give the injection, to be present at the bedside throughout administration. This makes it far more likely that any adverse reaction will be detected early and the injection stopped and the reaction promptly treated. With diluted i.v. infusions there is a risk that staff will start the infusion and then be occupied with other duties or patients, potentially missing early signs of reactions and so missing the opportunity to treat early, when treatment will likely be more effective. In a well-managed hospital setting such risks can be avoided and it is the author's practice, in most cases, to give antivenom by diluted i.v. infusion.

Selection of the dose of antivenom is beyond the scope of this chapter, because it will vary between antivenoms, organisms causing envenoming, and degree of envenoming. There is one important principle that is universal; dose is not determined by patient size, therefore children receive the same dose as

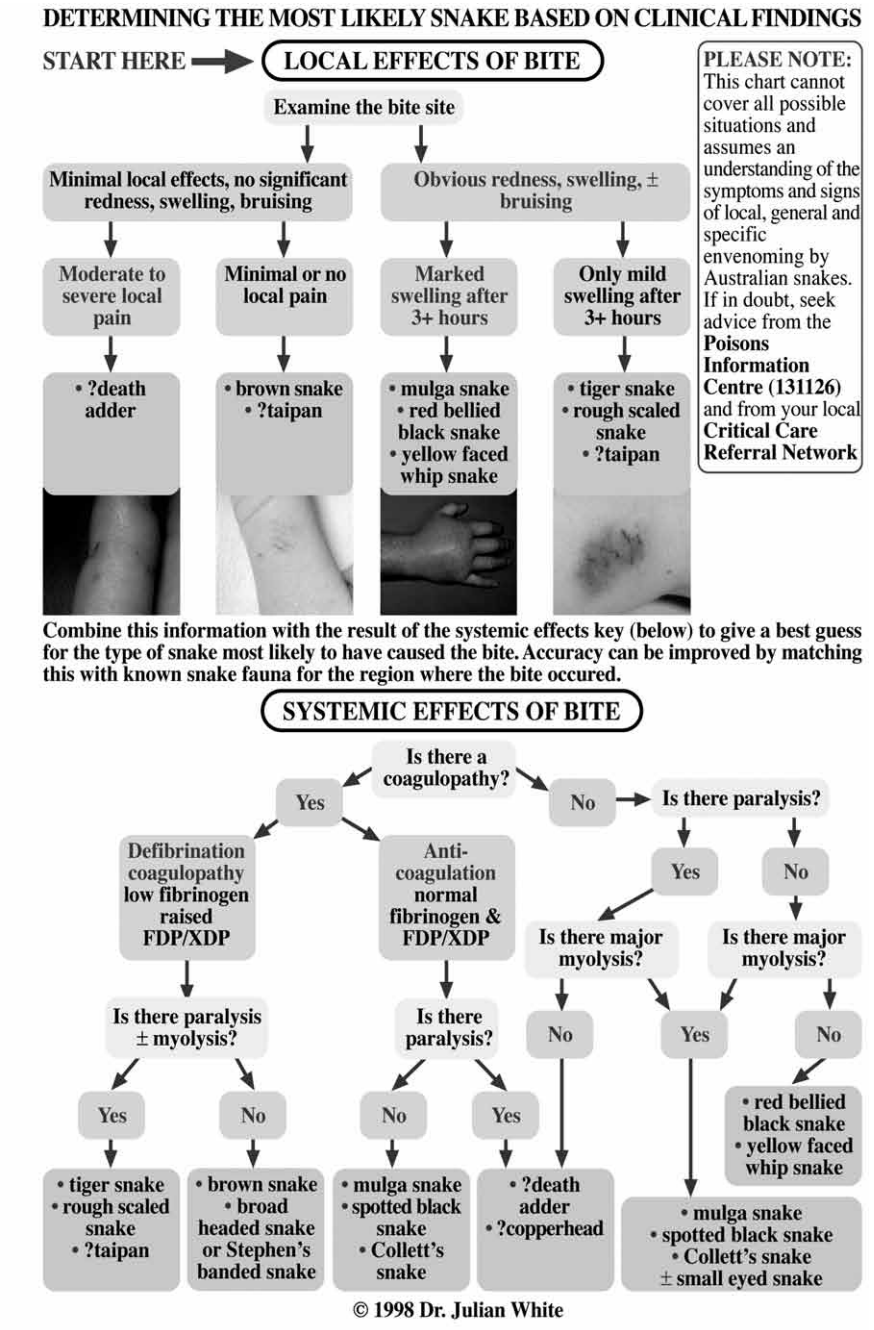


Figure 6. Diagnostic algorithms for Australian snakebite; an example of what may be possible if detailed profiling of envenoming by snake species is undertaken in a given geographic region (original photo/illustration copyright © Julian White).

adults. There is no paediatric dose for antivenom. Doses should never be reduced because the patient is a child.

*Adverse reactions*

All antivenoms are, by definition, foreign antigens when they are administered and all have the potential for adverse reactions, both early and late [134, 163, 191, 192]. The more highly purified the antivenom, in general, the lower the rate of reactions, but as noted earlier, whole IgG antivenoms purified with caprylic acid, may enjoy comparatively low reaction rates, especially compared with simple whole IgG antivenoms.

The causes of adverse reactions to antivenom are multiple, but contaminating components in the antivenom are of great importance and may include pyrogens from bacterial or other contamination, other plasma components as contaminants, such as albumin, Fc components of fractionated IgG, and elements of equine plasma that cause allergic responses [109, 119, 121, 136, 191, 192]. In addition, prior exposure to the antivenom or the host animal used in immunising may stimulate an allergic response, even IgE production in rare cases. Modern production methods should exclude contamination with live bacteria or viruses, but prions are harder to exclude, hence the requirement, particularly applicable to ovine antivenoms, that the host animal is from a flock/herd certified free of prion disease [131, 132].

The principle early reactions, in order of frequency and severity, are an erythematous rash, by itself of little consequence, rigors indicative of a pyrogenic reaction, and least common, a significant systemic allergic reaction, often characterised as “anaphylaxis”, although true IgE involvement occurs only in the minority of cases, with complement activation by the antivenom being a more common aetiology. The principle delayed reaction is serum sickness and this is partly dependent on the volume of antivenom administered; the higher the volume, the greater the risk.

For early reactions, other than simple rash, the first response should be to stop the antivenom infusion. If there is a major systemic allergic reaction, classic treatment for anaphylaxis is warranted, including adrenaline (epinephrine), i.v. fluids, resuscitation, as indicated. Detailed discussion of the management of anaphylaxis is beyond the scope of this chapter and readers are referred to current published reviews on this topic [193]. Once the reaction is controlled, antivenom infusion can be cautiously restarted, sometimes requiring titration of rate against blood pressure response and i.v. diluted adrenaline infusion [134]. The development of an anaphylactic reaction to antivenom is not a justification for abandoning antivenom therapy in that patient. If antivenom has been commenced on sound clinical grounds, because of major or life threatening envenoming, those grounds remain valid. Nevertheless, it is prudent to re-evaluate the extent/severity of envenoming before committing to restarting antivenom.

For late reactions, notably serum sickness, the patient will often have been discharged prior to onset, so it is essential that all patients receiving antivenom, whatever the type, amount, or route, be informed of the possibility of serum

sickness and presenting symptoms, to maximise the probability they will promptly return for treatment. A detailed discussion of management for serum sickness is beyond the scope of this chapter, but oral corticosteroids such as prednisolone, and oral antihistamines are generally the mainstays of treatment. Some doctors advise a short (about 5–7 days) course of oral corticosteroids after administration of antivenom, to reduce the likelihood of serum sickness. This is not a clinical trial-proven therapy, but logically may be of some benefit.

There is a considerable amount of literature on use of prophylaxis prior to antivenom, in an attempt to reduce the rate of adverse reactions. Several key points have emerged. Firstly, sensitivity testing prior to antivenom is a non-predictive and dangerous procedure, which should never be undertaken, even though some antivenom producers still recommend it [163, 191]. Secondly, there is no convincing evidence that antihistamines or steroids such as hydrocortisone prevent adverse reactions [163, 194]. There is highly conflicting evidence that subcutaneous adrenaline may be useful, but most recent studies and advice from leading authorities is that adrenaline as premedication for antivenom is inappropriate [163, 195].

### *Other antidotes*

Antivenoms are only available to cover some of the more dangerous venomous animals. Even where antivenom is available, there may be other treatments that can be effective as ancillary care, although not as a replacement for antivenom.

For neurotoxic paralysis caused by purely post-synaptic neurotoxins, anticholinesterases are theoretically attractive and have shown efficacy for envenoming by some species. By reducing the rate of acetylcholine destruction within the neuromuscular junction (Fig. 1), it is sometimes possible to overwhelm the effect of the toxin in blocking the muscle end-plate acetylcholine receptor, thus reducing the extent of paralytic features. In selected cases this may be enough to wean the patient off the need for ventilatory respiratory support, but frequent re-dosing is usually required. This ancillary treatment has been successful in treating paralysis following bites by Philippines cobras (*Naja philippinensis*), death adders (*Acanthophis* spp.) and sea snakes (New Caledonia; species not certain) and is likely applicable to a wider range of snakes [196–199]. However, recent research indicates at least some death adders also have pre-synaptic neurotoxins in their venom, which may explain cases refractory to both antivenom and anticholinesterase treatment.

For scorpion stings causing neuroexcitatory envenoming, some clinicians report that prazosin is highly effective [200–206]. Experimental studies also indicate prazosin may be effective in countering Irukandji jellyfish (*Carukia barnesi*) envenoming, in cases with significant cardiac involvement [207, 208]. In both these settings there is a form of “catecholamine storm”. However, the cardiovascular collapse caused by severe box jellyfish (*Chironex fleckeri*) envenoming is not responsive to prazosin [209, 210].

*General treatment*

For most cases with significant envenoming it is a reasonable and common practice to give an initial i.v. fluid load (crystalloids), the degree of loading being tempered by patient factors such as presumed degree of dehydration (if any), patient age, size and pre-existing infirmity (such as cardiac disease) [134]. Particularly in children it is important not to overload with fluid.

Analgesia will depend on both the type of envenoming and patient factors [107]. Many envenomings will not result in significant pain, so routine analgesia is not required and where indicated, oral analgesia should be used before considering parenteral analgesia. In all cases, it is best to avoid narcotic analgesia that may cause respiratory depression [107, 163, 211]. However, some forms of envenoming are routinely associated with severe pain, requiring prompt and vigorous analgesia, such as use of i.v. fentanyl for Irukandji stings [212], or regional nerve blocks for intransigent pain from stingray or venomous spined fish wounds [20, 213]. In some cases, antivenom will be the most effective "analgesic", such as in widow spider bites and stonefish stings [9, 20, 134, 152, 214].

Most envenoming cases do not develop significant secondary infection, so routine antibiotic use is generally not warranted [9, 191]. As the organisms involved in those cases that do become infected are highly variable, wherever possible culture and sensitivity should be performed prior to commencing initial antibiotic therapy, often with broad spectrum cover. Some envenomings, notably some snakebites in South America by *Bothrops jararaca*, *B. jararacusu* and related species can develop significant local sepsis and abscess formation, so routine antibiotic therapy may be appropriate in such bites, although is not always effective [215–219].

All bites and stings are potential sources for tetanus [191, 220, 221] and it is important to ensure current tetanus immunisation status, but care should be taken when giving i.m. tetanus immunisation updates in the presence of active coagulopathy, as caused by many snake species [191, 222–224]; the coagulopathy must first be under control.

Major local limb swelling is a common sequelae of envenoming by many snake species [163, 191, 225, 226]. In the past it has been assumed by some doctors that compartment syndrome would commonly occur, so fasciotomies were frequently performed. This invariably resulted in damaging scarring, which often progressed to long-term functional disability. It is now clear that true compartment syndrome is an infrequent complication of such local snake envenoming and fasciotomy should only be performed in cases where two criteria are met: (1) there is confirmation of compartment syndrome by direct measurement of intracompartmental pressure, and (2) any coagulopathy associated with envenoming has been reversed [163, 191, 225, 226].

Debriding necrotic wounds, should in most cases be done in the first few days, except for loxoscelism (recluse spider bites), where early debridement may spread venom and extend the area of necrosis [9, 227–229]. In these cases

it is advisable to wait until the area of necrosis has stabilised. For deep penetrating wounds, such as with some stingray injuries, after debriding damaged and necrotic tissue, it is important to allow wounds to heal by secondary intention [230].

## Specific groups of venomous animals

In the following accounts, only selected groups or representatives are discussed, as the vast array of venomous animals is too great to cover in a chapter such as this. Similarly, the range of possible data sources is immense, so readers are referred to a few key texts [15, 22, 27–29, 127–130, 134, 163, 191, 211] and a website (www.toxinology.com), rather than listing many hundreds of further references for individual species or species groups in the remaining portion of this chapter.

### *Venomous snakes*

As discussed earlier, venomous snakes represent the single most important venomous animal group from a medical perspective, accounting for more mortality and serious morbidity than all other groups combined. Amongst the snakes, the majority of species fall into the four broad families containing venomous species [1–3, 163], but true venomous species represent only a minority of the snake fauna, and species dangerous to humans an even smaller proportion.

#### *Colubrid snakes (Colubridae)*

Family Colubridae comprises a diverse assemblage of over 1850 snake species, with some recent taxonomic work indicating that the family could be split into an array of further families [231, 232]. The majority of colubrid snakes are considered technically "non-venomous" and lack distinct venom apparatus or fangs [233]. However, it is clear that many other colubrid snakes can produce toxic oral secretions that some authors argue constitutes venom, a view possibly supported by apparent DNA coding for toxins [234]. This issue of what constitutes "venomousness" in colubrid snakes is an ongoing and unresolved issue that will not be further canvassed here. Among those few colubrid snakes with definite venom-producing glands and distinct enlarged teeth (some considered as fangs) for venom delivery, in all cases situated towards the middle to back of the upper mouth (so-called "back-fanged" or opisthoglyphous), several species are capable of causing severe, even lethal systemic envenoming, usually associated with deranged blood coagulation and a bleeding tendency. Colubrid snakes are global in distribution.

Boomslang (*Dispholidus*) and vine snakes (*Thelotornis*): These southern African arboreal snakes have caused a number of fatalities associated with

coagulopathy. A specific antivenom is available in South Africa for the boomslang.

Keelbacks (*Rhabdophis*): The keelbacks and yamakagashi were originally thought to be harmless, but several severe, even fatal bites confirmed their potential to cause major envenoming and coagulopathy. A specific antivenom is available in Japan.

Other venomous and toxic colubrids: A number of other colubrid snakes have caused bites with varying degrees of envenoming, although generally not lethal. As more cases are accumulated it is probable that further colubrid species will be added to this list and it is no longer valid to assume a colubrid snake, not previously associated with significant bites, will be always harmless. However, those species that are small in size are less likely to inflict significant bites, although some large species of colubrids are not known to cause medically significant bites. No antivenoms are available for these snakes.

*Elapid snakes (Elapidae)*

Elapid snakes are, without exception, venomous, possessing well-developed venom glands and paired anterior placed proteroglyphous fangs. Many elapid snakes are small and may not be capable of significantly envenoming humans, but there are also many large species very capable of inflicting lethal bites. The range of elapid snakes is global, reaching a peak of diversity in Australia.

Cobras (*Naja*, *Hemachatus*, *Walterinnesia*): Cobras represent the single largest, most widely distributed group of elapid snakes of major medical importance, causing mortality and morbidity in thousands to tens of thousands of humans every year. They cover several genera, but most fall within the single genus *Naja*, with recent taxonomic changes moving several related genera into *Naja*. Clinically cobras divide into two broad types of envenoming: (1) predominantly local envenoming with necrosis, mild to moderate neurotoxicity, and (2) predominantly neurotoxic envenoming, without major local effects. The former group contains many species in Africa and Asia capable of spitting venom and causing severe venom ophthalmia. A variety of antivenoms are available for cobra envenoming, i.e., for covering more common species only, specific for particular species, species groups, or regions. Not all important species are covered and it is important to use the most specific antivenom available, particularly noting differences between African, West Asian and East Asian species, each covered by different products.

King cobra (*Ophiophagus*): The king cobra, although certainly cobra-like in origin and appearance, is separated because of its sheer size, at over 4 m, the longest of all venomous snakes. Found in much of eastern Asia, this snake causes both local effects and severe paralysis. Several specific king cobra antivenoms are available.

Kraits (*Bungarus*): As we understand more about snakebite epidemiology it becomes clear just how important kraits are in Asia as a cause of lethal envenoming. The numerous species are widely distributed and are generally nocturnal hunters, common in rural, even urban areas, where they mostly bite at

night, with a painless bite and later development of progressive severe paralysis, often associated with abdominal pain and, at least for some species, myotoxicity as well. Most, but not all, species show some degree of body banding. Antivenom is available for some krait species.

Coral snakes (*Micrurus*, etc.): Coral snakes are of most medical significance in the Americas, especially in South and Central America, where they can cause severe paralysis and/or myolysis, with minimal local effects. There are a few species found in the southern USA, but throughout their range they are an infrequent, although sometimes fatal cause of bites. Several specific coral snake antivenoms are available in South and Central America.

Mambas (*Dendroaspis*): The African mambas (Fig. 7) have a ferocious reputation, but available data indicates they likely cause relatively few bites, although some species have a high lethality potential. The venom causes complex neurotoxicity, leading to both muscle fasciculation and paralysis, but generally few local effects. At least one African polyvalent antivenom covers mambas.

Australian and New Guinea elapids (*Pseudonaja*, *Pseudechis*, *Notechis*, *Tropidechis*, *Austrelaps*, *Hoplocephalus*, *Acanthophis*, *Oxyuranus*, *Micropechis*): Australian and New Guinea elapid snakes have developed rather separately from elapids elsewhere and present a distinct set of clinical problems. Local effects of bites vary, depending on species, from trivial to moderate swelling, but it is systemic effects that dominate, again varying between species, but including pre- and post-synaptic paralysis, severe myotoxicity, coagu-

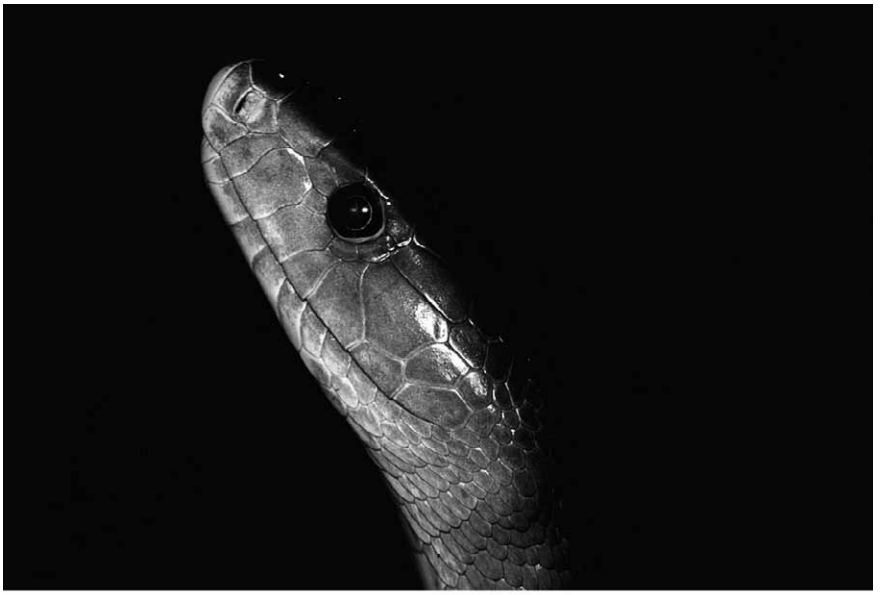

Figure 7. Black mamba, *Dendroaspis polylepis* (original photo/illustration copyright © Julian White).

lopathy and haemorrhage, renal failure and cardiotoxicity. Several "monovalent" and a polyvalent antivenom are available for Australian snakes.

Sea snakes: Long considered a separate family, sea snakes are now included within Elapidae and are thought to have evolved from early Australasian elapids. They are subdivided into two broad groups; the purely marine Hydrophiinae, encompassing the bulk of species, and the Laticaudinae that come onto land during their breeding cycle. Both groups have potent venoms, principally neurotoxins and/or myolysins, this being reflected in clinical envenoming, with both flaccid paralysis (post-synaptic) and systemic myotoxicity possible, either separately, or both together. The myolysis can cause secondary renal failure and cardiac toxicity and be severe enough to cause weakness that can mimic true neurotoxicity. Only one sea snake antivenom is currently available, but while it is made against venom from just one species, it appears to be effective for bites by most other sea snake species.

Other elapids (*Paranaja*, *Pseudohaje*, *Boulengerina*, *Aspidelaps*, *Elapsoidea*, *Homoroselaps*): This mixed group of elapids do not collectively cause significant numbers of bites, but some species can cause moderate to severe envenoming and have lethal potential. The taxonomic status of some genera is in flux; some are proposed to be subsumed within *Naja* (the cobras). There are no antivenoms available for these snakes.

*Atractaspid snakes (Atractaspididae)*

Burrowing or mole "vipers" have been the subject of considerable taxonomic instability, but currently are considered a distinct family of habitually subterranean venomous snakes, limited to Africa and the Middle East, mostly small and generally not involved in envenomings in humans. There are several larger species within genus *Atractaspis* that have potent venoms and do cause human envenoming and are potentially lethal. Within this group the unique sarafatoxins, similar to human endothelins, can cause severe or lethal cardiac effects. However, local tissue injury and sometimes necrosis is a far more common consequence in envenomed humans. They are adapted for a subterranean existence, burrowing in search of prey and have evolved a unique fang structure allowing side-swiping envenoming.

*Viperid snakes (Viperidae)*

Vipers comprise a diverse assemblage of venomous snakes, with a wide global distribution. They have front-placed fangs on rotating modified maxillae, allowing the fang to be folded against the roof of the mouth, then erected when biting, an arrangement that permits development of long fangs, and referred to as solenoglyphous dentition (Fig. 8). In some viperids, fangs can exceed 2.5 cm in length and these large fangs are often combined with large venom glands, able to effectively deliver a substantial venom load. While many viper venoms may not be as toxic as selected elapid venoms, this is frequently counterbalanced by their ability to deliver more venom. Viperid snakes are the single most important cause of snakebite to humans globally,

Figure 8. An eastern diamondback rattlesnake, *Crotalus atrox*, with mouth open and fangs moved to erect position, but with fang sheath not yet retracted (original photo/illustration copyright © Julian White).

ahead of elapids. There are two subfamilies of viperid snakes, Viperinae and Crotalinae.

Viperinae

This subfamily contains classic vipers, found throughout much of the "old world" and responsible for a substantial portion of the human snakebite toll, particularly groups like the carpet vipers (genus *Echis*), Russell's vipers (genus *Daboia*) and African adders (genus *Bitis*).

Classic vipers and adders (*Vipera*, *Macrovipera*, etc.): These small vipers (or "adders") have a wide distribution from Europe right across northern Asia and south into North Africa and the Middle East. While they can cause severe, even fatal envenoming, in most cases envenoming is less severe and mostly local, with swelling, pain, bruising, and uncommonly necrosis. Systemic effects can include shock, coagulopathy and renal damage, with occasional mild neurotoxic features, such as ptosis, although at least one species (*Vipera ammodytes*) can cause more severe paralysis. Several antivenoms are available.

Puff adders (*Bitis*): These African vipers range from small species to large snakes such as the Gaboon viper, *Bitis gabonica* and the notorious puff adder, *Bitis arietans*, an important cause of sub-Saharan snakebite. These snakes cause severe local envenoming, including swelling, pain, bruising, blistering and necrosis, plus systemic effects including shock, coagulopathy and haemorrhage. Several antivenoms covering the puff adder are available, but not specifically for other species, although cross-reactivity is likely among some of these.

Russell's vipers (*Daboia*): Russell's vipers, *Daboia russelii* and *D. siamensis*, are the most important members of this genus and are found from Sri Lanka, through the Indian subcontinent, to Southeast Asia, Indonesia and Taiwan. Throughout their range they cause a significant number of often severe or fatal bites, characterised by both severe local effect, including blistering and necrosis, and severe systemic effects, including coagulopathy, haemorrhage, shock and renal failure. Some populations, particularly in Myanmar and parts of India, can also cause anterior pituitary infarction, resulting in Sheehan's syndrome. Other populations, notably those in Sri Lanka, can cause myolysis and paralysis. This diversity of venom actions and clinical effects, even intra-species, means that antivenom choice is crucial; the antivenom, to be effective, must be against the particular population of snakes causing the bite. Using specific anti-*Daboia* antivenom from one region, to treat bites by the same species from a different region, can result in treatment failure and death.

Carpet vipers (*Echis*): Carpet or saw-scaled vipers, genus *Echis*, are common, relatively small vipers, with a range extending from west Africa to India, covering a number of species that collectively likely cause more snakebite fatalities than any other genus of snakes. Their bites cause severe local effects, including blistering, haemorrhage and necrosis, plus severe systemic coagulopathy and haemorrhage. Venom variability between species means that antivenom must be sourced from the correct region and species; Indian anti-*Echis* antivenom will not be effective in Africa and *vice versa*.

Other vipers (*Eristocophis*, *Cerastes*, *Causus*, *Pseudocerastes*, *Atheris*, *Montatheris*, *Proatheris*, *Adenorhinos*, *Azemiops*): A variety of lesser viperids exist, some of which are not known to cause significant envenoming in humans, while others, such as the horned vipers, *Cerastes* spp., can cause severe, even life-threatening envenoming characterised by coagulopathy and haemorrhage. Antivenoms covering these species are mostly unavailable, although a few antivenoms cover some taxa.

### Crotalinae

The other viper subfamily, Crotalinae, contains all the "pit vipers", those vipers with two heat sensing pits on the anterior head, allowing detection of prey by infra-red. Pit vipers occur in both the Old World and New World, although they predominate in the latter, throughout the Americas, where they are the dominant cause of snakebites to humans.

Rattlesnakes (*Crotalus*, *Sistrurus*): The rattlesnakes, genus *Crotalus* (Fig. 9), and the related genus of "pigmy" rattlesnakes, genus *Sistrurus*, are the leading cause of North American snakebite, but are also important in Central and South America. The North American species cause often severe local envenoming, with swelling, bruising, pain, sometimes blistering/bleb formation and occasionally necrosis, particularly for bites to digits. There may be associated shock, and with some species, major coagulopathy. A few species can cause at least minor neurotoxic paralytic features, such as ptosis, but some populations of the Mojave rattlesnake, *Crotalus scutulatus*, can cause severe paralysis, as their venom contains a potent presynaptic neurotoxin. Some rattlesnakes, such as canebrakes, *Crotalus horridus atricaudatus*, can cause major myolysis and secondary renal failure and cardiotoxicity. A single antivenom covering all North American pit vipers is available. In Central and South America, rattlesnake bites have a quite different clinical pattern; major local effects are not common, but severe systemic envenoming is common, including neurotoxic paralysis, myolysis, coagulopathy and renal failure. A variety of South and Central American antivenoms cover one or more of these rattlesnake species.

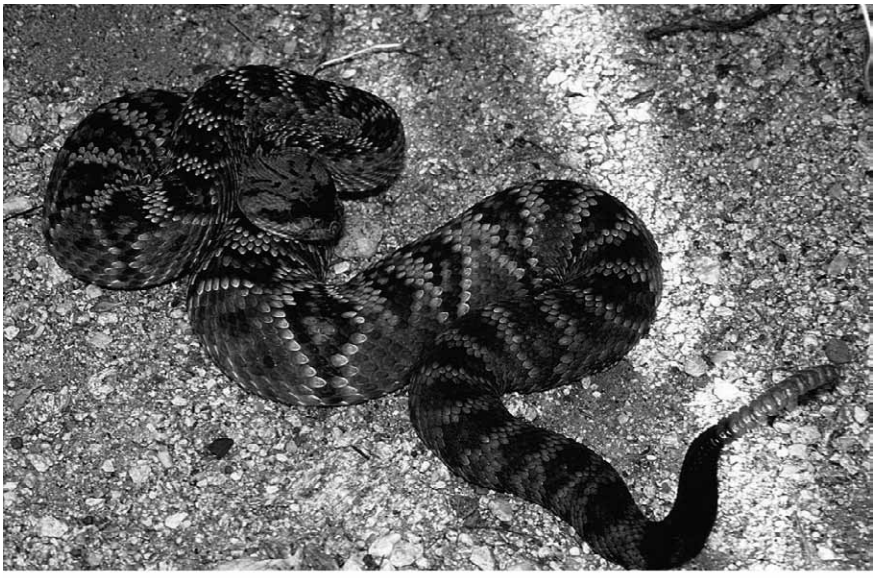

Figure 9. Blacktail rattlesnake, *Crotalus molossus* (original photo/illustration copyright © Julian White).

Lance head pit vipers (*Bothrops*, *Bothriechis*): Snakes of the genus *Bothrops* are the single most important cause of snakebite in South and Central America. Most of the major species cause severe local and systemic effects,

including local tissue injury/necrosis in the bitten limb and systemic coagulopathy and shock. Some species commonly cause local infection with abscess formation. Renal failure, including permanent injury (bilateral renal cortical necrosis) is described. Two species in the Caribbean, *Bothrops lanceolatus* and *B. caribbeus*, cause thrombotic problems, as discussed earlier in this chapter. A variety of antivenoms are available in South and Central America to cover some of the major species of *Bothrops*, but it is important to select an antivenom with coverage for the species involved in a bite. Many of the lesser *Bothrops* species, although capable of causing envenoming, seem rarely to do so and are not specifically covered by any antivenom. The same applies to the variety of smaller pit vipers, such as the eyelash viper, *Bothriechis schlegeli*. Some polyvalent antivenoms, particularly from Central America, may provide some cross neutralisation for some of these species.

Bushmasters (*Lachesis*): The bushmasters are formidable snakes, of large size, but throughout most of their range, bites are infrequent. Moderate to severe local effects occur, including bruising, but necrosis is uncommon, while systemic effects include shock, coagulopathy and haemorrhage. Several antivenoms covering these snakes are available.

Copperheads, mokasins and cantils (*Agkistrodon*): In parts of North America, bites by some *Agkistrodon* spp. are common and, while not generally as severe as rattlesnake envenoming, can still cause potentially lethal effects, particularly in children. Moderate to severe local effects are common, including tissue injury, but major systemic effects are less common. They are covered by the North American polyvalent antivenom.

Mamushi, etc. (*Gloydius*, *Deinagkistrodon*): The snakes currently assigned to genus *Gloydius*, restricted to Asia, were formerly in genus *Agkistrodon*, and some species are important as a cause of snakebite, particularly the mamushis of Japan (*Gloydius blomhoffii blomhoffii*) and China (*G.b. brevicaudus*). The Japanese subspecies can cause both severe local effects, including blistering, and systemic effects, including shock, coagulopathy, haemorrhage, renal damage and mild neurotoxicity. The Chinese subspecies causes similarly severe systemic effects and possibly myolysis as well, but less severe local effects. Bites by other members of this genus are less well understood. Antivenoms against the mamushis are available in China and Japan. The hundred pace snake, *Deinagkistrodon acutus*, also found in parts of Asia, can cause severe or lethal envenoming, characterised by severe local effects, including blistering and necrosis, and systemic effects such as shock, coagulopathy and haemorrhage. Specific antivenom is available in China and Taiwan.

Malayan pit viper (*Calloselasma*): In Southeast Asia the Malayan pit viper is a most important cause of severe and lethal bites. It causes major local effects, including blistering and necrosis, and systemic effects including shock, coagulopathy and haemorrhage. Several antivenoms covering this species are available.

Green pit viper (*Trimeresurus*, *Protobothrops*, *Crypteletrops*, *Viridovipera*, *Popeia*, *Garthius*, *Parias*, *Peltopelor*): These Asian pit vipers, mostly previ-

ously contained within the single genus *Trimeresurus*, have recently been split into eight distinct genera [235–237]. They encompass a diverse range of mostly arboreal snakes, some of which are important causes of snakebite within their specific distribution. Clinical effects vary between species, from trivial local and no systemic effects, to extensive local swelling and bruising, with systemic coagulopathy and haemorrhage, to severe local effects including necrosis, plus shock, with or without coagulopathy. This latter group includes the habu, *Protobothrops flavoviridis* and *Protobothrops mucrosquamatus*. Antivenoms are available for some of the more medically significant species.

Hump nose vipers (*Hypnale*): Hump nosed vipers from India and Sri Lanka are now recognised as a cause of significant bites, causing both local effects, including blistering, but not necrosis, and systemic effects including shock, coagulopathy, haemorrhage, renal damage and MAHA, although most bites may be less severe. No antivenom is available at present.

Other crotalines (*Atropoides*, *Cerrophidion*, *Ermia*, *Ophryacus*, *Ovophis*, *Porthidium*, *Tropidolaemus*): A number of other New World and Asian pit vipers in several genera can cause bites but are mostly considered of comparatively minor medical importance. None are covered by specific antivenoms.

### *Venomous lizards*

Until recently, only two species of lizards, *Heloderma suspectum* and *H. horridum*, family Helodermatidae, were considered venomous. These large lizards, from arid areas of Mexico and southwestern USA, have venom glands in the lower jaw, which connect to the base of sharp grooved teeth. The venom is likely used in prey acquisition, but bites to humans can result in excruciating local pain and mechanical injury, and in some cases, major systemic effects, including hypotension and shock, but not paralysis, myolysis, or coagulopathy. Treatment is symptomatic and supportive, as no antivenom is available.

Recent controversial research has indicated that several other groups of lizards, notably the varanids/goannas (family Varanidae) and the dragons (family Agamidae) have genes for venom production and may produce oral secretions containing toxins [234]. Some researchers consider that for at least large varanids, such as the massive Komodo dragon (*Varanus komodoensis*), these toxic oral secretions are effectively venom and are used in prey acquisition. Further research is needed to confirm the validity of this work.

### *Scorpions*

Most of the nearly 2000 described species of scorpions are of no medical significance, their stings causing either no effects in humans, or minor or short-

lived local pain, rarely with any systemic effects, and the latter are of a minor and self-limiting nature. However, several hundred species, nearly all within family Buthidae, can cause envenoming, varying from mild to severe, even lethal, depending on species and the size of the victim.

*Buthid scorpions of medical importance*

Buthid scorpions (Fig. 10) capable of causing medically important envenoming occur in the Americas, Africa, the Middle East and Asia. All cause a form of neuroexcitatory envenoming, in many cases characterised as a catecholamine storm effect. A wide variety of scorpion toxins have now been fully elucidated and these include potent potassium and sodium channel neurotoxins. In some regions, such as North Africa, scorpion sting is both more common, and of greater medical importance, than snakebite. In Mexico around 280 000 scorpion sting cases are admitted to hospital every year. With adequate antivenom therapy, mortality is now low, even in those at most risk, younger children, in regions where it is widely used. In contrast, some regions not using antivenom still have significant mortality from scorpion stings. Antivenoms are available for only some major scorpion species, sourced in their native regions. However, the management of scorpion envenoming is controversial, with several different approaches extant. Some clinicians consider antivenom ineffective, instead emphasising both supportive intensive care and use of cardiovascular drugs such as prazosin. Confusing studies suggesting antivenom is ineffective have created more uncertainty about treatment. Nevertheless, evidence from countries including Mexico and Brazil,

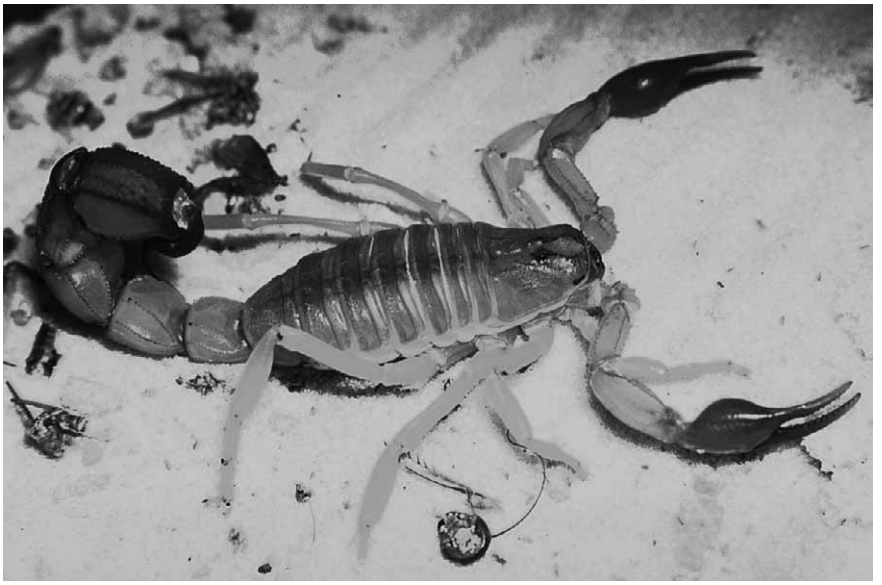

Figure 10. *Androctonus australis* (original photo/illustration copyright © Julian White).

where severe scorpion stings are very common, indicates that the widespread use of antivenom has been associated with a dramatic fall in mortality.

*Non-Buthid scorpions of medical importance*

The most important non-Buthid scorpion is undoubtedly *Hemiscorpius lepturus*, found in Southwest Iran [238–240]. This scorpion, uniquely within all scorpions, causes local sting-site necrosis and often a systemic syndrome of haemolysis, coagulopathy, renal failure and shock, which can be lethal. It does not cause neuroexcitatory envenoming, unlike other medically important scorpions. A polyvalent scorpion antivenom, which is claimed effective against *Hemiscorpius*, is available in Iran.

## *Spiders*

Spiders undoubtedly cause large numbers of bites to humans, most of which are trivial, requiring no medical treatment, but a few species can cause major effects, and one group is potentially lethal. Spiders are generally grouped into two suborders, Mygalomorphae and Araneomorphae. These two groups can be distinguished by anatomical features and both contain species of medical importance.

*Mygalomorphs*

These spiders, often described as "primitive", are generally large spiders of robust build, with comparatively long fangs. Most cause minor local effects only on biting humans, but one group, the Australian funnel-web spiders and related mouse spiders are lethal to humans. Some others cause dermal and ophthalmic irritation through shedding abdominal hairs.

Australian funnel-web spiders: These spiders, of genera *Atrax* (Fig. 11) and *Hadronyche*, found only in Australia, are the World's most dangerous spiders. While "dry" or trivial bites are common, they can cause rapidly lethal envenoming, even in healthy adults, with death in less than 30 minutes in some cases in the pre-antivenom era. Envenoming is a rapid, fulminant neuroexcitatory type, with catecholamine storm effects, similar to major scorpion envenoming. It responds rapidly to antivenom, even given late, and since antivenom was introduced, fatalities are now essentially unknown. This specific antivenom actually is effective for all funnel-web species. The related mouse spiders, genus *Missulena*, have a similar venom, also responsive to funnel-web spider antivenom, but clinically significant envenoming is very rare, so antivenom is generally not required for bites by these spiders.

Other mygalomorphs: A number of other large mygalomorph spiders can cause at least local effects such as intense pain, sometimes with non-specific systemic effects, usually mild and of limited duration, but for the majority of species there is no evidence, despite their large size and long fangs, that they are of any medical significance.

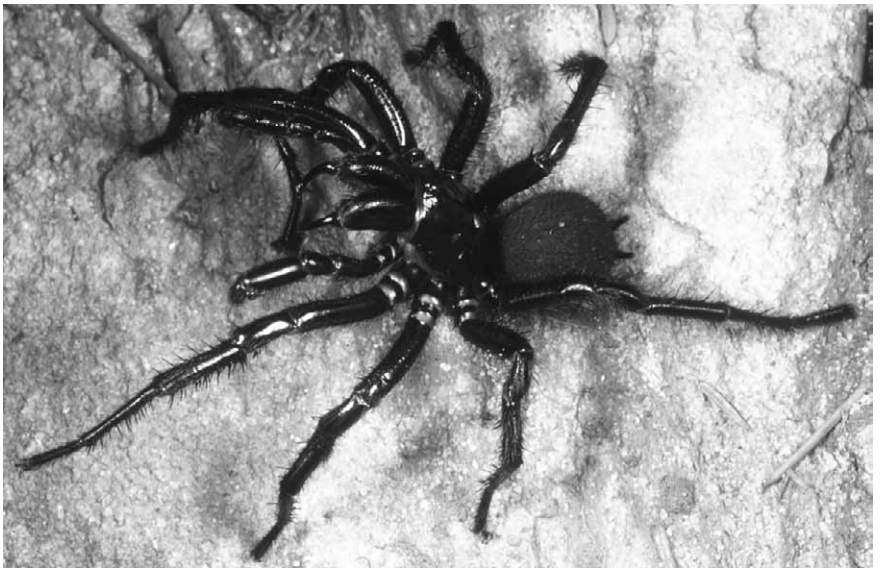

Figure 11. The Sydney funnel-web spider, *Atrax robustus* (original photo/illustration copyright © Julian White).

*Aranaeomorphs*

The bulk of all described spider species are araneomorphs. These diverse spiders span a wide array of families, body size and shape and prey capture methods, the latter ranging from classic web capture, to hunting and stalking. Most are of no medical significance, but a few groups can cause problem bites.

Widow spiders (*Latrodectus*): Widow spider bite is probably the most common medically important form of spider bite globally. Widow spiders, mostly of the genus *Latrodectus*, are distributed across most continents, are often common and adapt well to human habitation, so opportunities for bites can be many. In Australia more patients are treated with antivenom for widow spider (red back spider) bite than all other types of envenoming combined (including snakebite). Although widow spiders are reported to have caused fatalities, available evidence suggests this is most likely a result of secondary problems, not direct primary venom toxicity, but there is no doubt that significant widow spider envenoming, latrodectism, is an unpleasant problem for affected patients. The venom causes neuroexcitatory envenoming, but usually without the severe and life threatening systemic effects seen with scorpion and funnel-web spider envenoming. Instead, envenoming is characterised by local, then regional or generalised pain, often with associated sweating, sometimes nausea and hypertension, lasting up to several days. A number of antivenoms are available and evidence suggests any anti-latrodectus antivenom will be effective against bites by all widow spider species. Recent research has questioned the effectiveness of antivenom for latrodectism, but further research will be

required to resolve this issue, as there is a large body of published case experience (but not randomised control trials) suggesting antivenom is the only effective treatment.

Banana spiders (*Phoneutria*): Banana spiders are restricted to South and Central America, but cause most problems in Brazil, where they are, by far, the most common cause of major spider bite. Effects are similar to widow spiders and most distressing for patients, but with low lethality potential. An antivenom is available in Brazil, but most patients are managed conservatively, including analgesia, without antivenom.

Recluse spiders (*Loxosceles*): Recluse spiders (Fig. 12) are global in distribution, but a more restricted group cause medical problems, which are quite distinctive. An effective bite, although rarely felt at the time, will cause either just local effects, principally necrosis of skin (cutaneous loxoscelism), plus some self limiting systemic effects, or these local effects plus a potentially lethal systemic illness (viscerocutaneous loxoscelism), characterised by haemolysis, coagulopathy, renal failure and shock. An antivenom is available in Brazil, although its effectiveness, given the usual very late presentation, is doubtful. Most cases elsewhere, such as in the USA, are managed conservatively. Early debridement of necrotic areas is generally inadvisable as it can extend the necrotic area. Loxoscelism is sometimes characterised as "necrotic

Figure 12. North American recluse spider, *Loxosceles reclusa* (original photo/illustration copyright © Julian White).

arachnidism" (spider bite causing skin necrosis), but is an over-diagnosed condition in some countries, notably the USA, and also in Australia (where *Loxosceles* is not a native species and is likely present, if at all, in very restricted areas and numbers).

Other aranaeomorphs: A number of other larger araneomorph spiders can cause mild local envenoming, usually just local pain and/or swelling, occasionally with mild self-limiting general symptoms. None require antivenom.

### *Ticks and mites*

There are many tick and mite species, all parasites of various hosts, sometimes mammals, but also birds, reptiles, even spiders and insects. Very few produce saliva with toxin (venom) effects in humans. Indeed, medically, ticks are far more important as vectors of disease transmission.

#### *Australian paralysis ticks*

Hard bodied ticks of the genus *Ixodes*, limited to eastern Australia, produce a potent paralysing neurotoxin in their saliva, so that when an adult female tick attaches to a human, enough toxic saliva may be inoculated, over several days, to cause a slowly progressive, but potentially lethal, flaccid paralysis. More people have died from tick paralysis in Australia than from funnel-web or red back spider bite. Once the tick is removed, paralysis can still progress for up to 48 hours, before slowly resolving. Severe paralysis can cause respiratory failure, requiring mechanical ventilation. This is the current treatment, as the previously available antivenom was of doubtful effectiveness and has been discontinued.

#### *North American paralysis ticks*

North American paralysis ticks are hard bodied species, principally *Dermacentor andersoni* (western North America) and *D. variabilis* (eastern and central North America), causing progressive flaccid paralysis, which regresses immediately on tick removal. No antivenom is available and respiratory support is the mainstay treatment in those rare cases with full respiratory paralysis, often required for only a brief period.

#### *Other paralysis ticks*

Tick paralysis is less well described outside North America and Australia, although it is reported to occur, probably rarely, in Africa, possibly elsewhere.

### *Centipedes*

Centipedes have paired fangs and venom glands adjacent to the head, in the maxillipedes; the apparent "venomous" spines at the tail region are not ven-

omous. Bites from large species can cause local mechanical trauma and intense pain from the venom, but systemic effects are not generally seen and local effects usually settle quickly. However, secondary infection is a risk. No antivenom is available or required.

### *Insects*

Insects comprise a large proportion of animal species diversity, so it is hardly surprising some utilise venom for defence or offence. However, comparatively few cause medically significant effects from venom and in most of these, it is allergy, not primary venom toxicity, that is the risk.

#### *Hymenopterans (bees, wasps, ants)*

With a few notable exceptions, all the important venomous insects are hymenopterans, either bees, wasps, or stinging ants. In all of these, a single sting in the tail, with an intra-abdominal venom gland, can deliver a small quantity of venom, containing potent and often highly allergenic peptides. Most stinging hymenopterans can sting multiple times, but the honey bee, *Apis mellifera*, is only able to sting once, resulting in the death of the bee, with the sting and pumping venom gland left behind in the skin of the victim. While mass attacks, involving many hundreds, more usually thousands of stings, can result in primary, even lethal venom toxicity, often with fulminant haemolysis, shock and renal failure, these events are generally rare. In a few areas, such as Vietnam and Brazil, such mass attacks by hymenopterans are more common and cause occasional deaths. For most people and regions, it is allergy from a single sting that causes most concern, and most fatalities. In many western countries, bee sting anaphylaxis is considered to kill more people than any form of envenoming. Not all bees sting, nor do all wasps, but some wasps, particularly the large communal species, such as European wasps and North American and Asian hornets, regularly sting humans, either singly, or multiply. Most ants lack effective stinging capacity, although bites can cause local pain and some species can spray venom under pressure from abdominal venom glands. Some species do sting and can cause intense local pain, irritation, redness, and allergic responses in some humans. The pain can last many hours, with "sores" developing around each sting site, which can take days to resolve. A few of these stinging ants, such as the jumping and inch ants (*Myrmecia* spp.) of Australia, can cause major anaphylaxis, more potent than even honey bees. Similarly, the fire ants (*Solenopsis* spp.), originally from South America, but now well established in North America, Australia and elsewhere, can cause intense local pain, sore formation, and major allergic reactions.

#### *Lepidopterans (caterpillars)*

Most caterpillars, moths and butterflies are of no medical significance, but the caterpillars of some species have locally irritant hairs and in some cases, notably

*Lonomia* spp. in Brazil, can cause major, even lethal envenoming, on skin contact with these hairs. *Lonomia* caterpillars cause potentially fatal coagulopathy, with potent procoagulants in their venom; there is a specific antivenom in Brazil. Contact with the hairs of some other caterpillars, across several continents and many species, either through touching the caterpillar, or through shed hairs in the air, can cause not just local skin irritation, but in the eyes, corneal irritation, and if inhaled, bronchial irritation, and potentially severe allergic reactions are also possible. The term lepidopterism is used to cover these diverse clinical effects. In some species, the hairs may be present on the outside of pupae and adverse effects from contact with these is known as erucism.

*Coleopterans (beetles)*

A variety of beetles can produce toxic secretions, which can cause injury to humans, most commonly skin irritation, staining, blistering or necrosis. Of particular note are beetles of the family Meloidae, the "blister beetles", sometimes known as "Spanish fly". These beetles produce the potent toxin cantharadin, exuded from limb joints (they have no specific venom gland), and direct contact with human skin can cause classic blistering and skin necrosis. Similarly Staphylinidae beetles can cause local effects by squirting toxins, notably pederin, under high pressure from anal glands. These are defensive actions by the beetles, not primary prey acquisition. Management of such local lesions is symptomatic and supportive. No antivenom is available.

*Other insects*

While a variety of other insect species, across diverse families, possess sucking mouthparts and can attack humans, often as a food source, they are not primarily venomous, though their saliva may contain substances that might be considered toxic. They will not be further discussed here.

## *Venomous mammals*

Several species of mammals, across two suborders, produce toxic secretions. In the case of monotremes, the Australian platypus, *Ornithorhynchus anatinus*, a hind leg spur attached to a venom gland is used in male:male combat and in defence, with accidental stings to humans causing intense local pain lasting many hours. Treatment is symptomatic and no antivenom is available. Toxic oral secretions from shrews can cause local effects in bitten humans, but these are generally minor and managed symptomatically.

## *Venomous birds*

Until 1990, birds were not considered as toxin producers, but the discovery of toxin-producing birds in Papua New Guinea, the pitohuis and infritas, which

principally contain batrachotoxins in their feathers and skin, has changed this view. However, in these birds, the toxin is used only in defence, when in contact with the bird. There is also uncertainty about the origin of the toxin (is it made by the bird or concentrated after uptake from the environment). For the present, then, these birds should be considered poisonous rather than venomous.

### *Venomous amphibians*

As with the birds, mentioned above, those frogs possessing toxic secretions are generally considered poisonous, not venomous. Interestingly, some venomous frogs, such as larger *Bufo* toads, can squirt toxic secretions from posterior parotid glands in the head-neck region, as a defensive measure. This can almost be considered venomous, not just poisonous. Toxic secretions in amphibians, including species of frogs (and toads) and newts, can be highly potent, such as the batrachotoxins, pumiliotoxins, samandarines and bufotoxins, many being low molecular weight alkaloids affecting nerve transmission or cardiac function. Many are lethal to humans, even at a low dose, but humans rarely come in contact with these toxins. Most recent reported human deaths from amphibian toxins follow ingestion of herbal medicines or extracts used for recreational drugs containing toad toxins such as bufotoxin and bufogenin. Some of the highly toxic poison arrow frogs from the New World are very colourful and popular in captivity, but generally loose their toxicity after a period of captive care, supporting the environmental origin of the toxins.

### *Venomous fish*

There are numerous fish with venomous spines, in a diverse array of families, in all cases using the venom and spines predominantly for defence, not prey acquisition. Venom glands envelop spines, which are often grooved, and when contact is made with a potential target, as the spine enters the tissue, the gland may be compressed and venom forced subcutaneously into the target. This is particularly effective in fish such as the stonefish (*Synaceia trachynis*), the most venomous of all fish, when a human steps on the dorsal spines. Here, as with other venomous spined fish, the venom causes local pain, which may be excruciating and crippling. Similar, but lesser pain can occur with other species, when stepped on or picked up in the hand. The location of spines varies with species and includes dorsal, ventral, lateral, tail fins and behind the head. Some species, such as lionfish (*Pterois* spp.) can have many spines providing a defensive screen around the fish. Only a few of these fish venoms have been studied, notably the most toxic to humans, the stonefish, which has a potent neurotoxin, although this does not cause paralytic features in envenomed humans.

There are no substantial data on rates of venomous fish stings, but it is likely that minor stings are very common, while severe stings are uncommon to rare. For most of these fish stings, symptomatic care is the only treatment, with hot water immersion widely recommended as both first aid and hospital treatment to abate pain. A specific antivenom is available for stonefish stings and may be useful for severe effects by some closely related species, although this is unproven.

### *Cnidarians: jellyfish*

Jellyfish occur in vast numbers, often in swarms, that can be encountered by swimming humans, often off popular beaches and in bays in summer. The total number of stings to humans is almost certainly measured in the many millions per year, but apart from local pain and wheal formation, generally of short duration and not requiring medical treatment, the vast majority of these stings are of no consequence. However, medically, a few species commonly cause significant effects, even potentially lethal envenoming in the case of the Australian box jellyfish, *Chironex fleckeri*, and Irukandji jellyfish (covers several species, including *Carukia barnesi*).

The box jellyfish (Fig. 13), clearly the most deadly jellyfish globally, can inject large amounts of venom rapidly, some thought to directly enter capillar-

Figure 13. The Australian box jellyfish, *Chironex fleckeri* (original photo courtesy of Jamie Seymour).

ies, because of its large size and great tentacle length. As with other jellyfish, venom is produced in and injected by individual stinging cells, nematocysts (cnidocils), found in vast numbers on the surface of tentacles (Fig. 14). A major box jellyfish sting can inoculate venom from millions of nematocysts instantly. As the tentacle contacts the skin, a trigger on the surface of each nematocyst initiates extrusion at high speed of the everted stinging tube, through the skin, ejecting venom along the extrusion track. A sting is invariably painful, often with distinctive ladder track marks and the pain can be excruciating. Sometimes local necrosis and scarring can occur along tentacle contact tracks. Box jellyfish venom includes toxins that are cardiotoxic and in a major sting, within a few minutes even an adult human can suffer cardiac arrhythmia and arrest, so death can occur within 5 minutes of being stung, probably the most rapid and dramatic lethal envenoming of any venomous animal. This has resulted in great fear of box jellyfish stings, but in reality, such a dire outcome is only likely if the area of tentacle contact is large, usually from a large specimen. Nets around swimming beaches exclude such large specimens and the majority of human box jellyfish stings are comparatively minor. Close relatives of the box jellyfish exist in waters north of Australia and there are reports of fatal jellyfish stings around Southeast Asia, Indonesia and the Philippines. An antivenom is available for Australian box jellyfish stings, but there is recent evidence that while it neutralises the venom effectively, it cannot be given soon enough

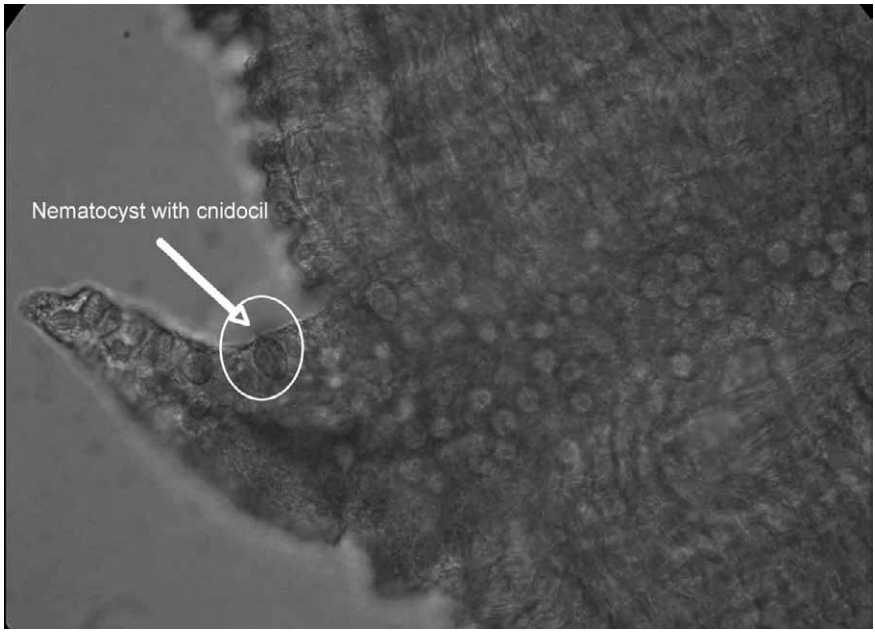


Figure 14. Photomicrograph of a jellyfish tentacle showing embedded unfired nematocysts (original photo courtesy of Jamie Seymour).

to be effective in a clinical setting, although until further research is performed, this is not a reason to cease using it in severe cases.

The Irukandji syndrome, caused by stings from a variety of jellyfish species, not just *Carukia barnesi*, causes a very different pattern of envenoming. The sting itself may be trivial or not even felt, and involve a tiny area of only a few $cm^2$. Many, but not all of these Irukandji jellyfish are tiny, so are not excluded by protective nets around beaches. A variable time after the sting, but usually within an hour, systemic effects develop, notably severe muscle pain in the back, limbs, or elsewhere, often accompanied by severe hypotension, sweating, and in severe cases, pulmonary oedema. The whole syndrome is similar to a catecholamine storm and is potentially, but very rarely, lethal. Treatment is supportive and symptomatic, including strong analgesia. There is no antivenom available.

The Portuguese Man-of-War or bluebottle (*Physalia* spp.), is a very common colony organism "jellyfish" that invades swimming areas in mass swarms in summer months mainly, sometimes causing large numbers of humans to be stung. In most cases, local pain, sometimes intense, but usually short lived, often with wheal formation, is the only effect. In a small number of cases, allergy may be stimulated and rarely, anaphylaxis can occur. Recent research indicates that hot water, most commonly a hot shower, can dramatically reduce symptoms, more so than other first aid or treatments. No antivenom is available.

### *Venomous molluscs*

Snails are slow moving, so it is perhaps surprising that more predatory species are not venomous, at least as far as currently known.

#### *Cone snails (Conus)*

Of the known venomous predatory marine snails, the vast array of species of cone snails, *Conus* spp., is the most important medically, and the best studied. These snails divide into three broad groups, based on major prey type; fish eaters, snail eaters and worm eaters. All use a system of venom-coated fired "harpoon" like radula "teeth" to acquire prey, but some have such potent venom that they can extrude it into the surrounding water to immobilise or disorient prey such as fish, to facilitate capture. In some cases this may involve stunning multiple small fish simultaneously. To achieve capture of fast moving fish, venom must act almost instantly, which may explain why cone snails have evolved such a diverse and rich array of small peptide-based specialist toxins. These conotoxins are proving of interest as models for new pharmaceutical agents, and have an almost bewildering range of activities and targets, mostly within the nervous system, but often very highly specific, hence their immense value as neuropharmacological tools in research.

Most cone snails appear unable to effectively or significantly envenom humans, but a few species can cause severe or lethal envenoming, although

reported cases are few. So from a human epidemiological perspective, their importance is trivial. Most cases occur in the Indo-Pacific, particularly around the Philippines. Envenoming occurs when the snail is interfered with or picked up, with rapid venom inoculation from the fired radula tooth, which may cause either local pain, or minimal local symptoms. Systemic envenoming can develop rapidly, with flaccid paralysis a particular risk. In severe cases, without respiratory support, death may ensue. Treatment is supportive and symptomatic. No antivenom is available.

*Blue ringed octopus (Hapalochlaena)*

The blue ringed octopuses, genus *Hapalochlaena*, are common in waters around Australia and to the north. They are small and derive their name from dramatic blue rings that form in the skin when the octopus is alarmed. Their saliva contains tetrodotoxin, a potent and rapidly acting neurotoxin that targets sodium channels on nerves, causing flaccid paralysis. It is now considered likely the octopus does not produce the toxin itself, but accumulates it, or a precursor, from the environment. Bites are often apparently trivial, with little or no pain, but in a minority of cases, systemic neurotoxic paralytic envenoming occurs within 10–30 minutes. Without respiratory support, death can rapidly follow. Treatment is supportive. Antivenom is not available.

*Other marine venomous animals*

A wide variety of marine animals use toxins in defence, to establish territory (such as sedentary corals to maintain or expand living space against competition), or in prey acquisition. However, they are generally of minor or no medical importance and are not discussed further here.

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