ANIMAL POISONS AND THE NERVOUS SYSTEM: WHAT THE NEUROLOGIST NEEDS TO KNOW

J B Harris, A Goonetilleke


The vast majority of us experience trivial and sometimes inconvenient bites and stings, but we never imagine that the next bite or sting might precipitate a medical emergency. Similarly, we consume seafood with little real caution, confident that at worst we might suffer a brief gastrointestinal upset. There are, however, numerous animals capable of inflicting a fatal bite or sting, and it can be estimated that around 100,000 persons per year worldwide die following an envenomation. Similar numbers of people are made seriously ill following the consumption of poisonous seafood. Most of these events occur within rural or coastal communities in South East Asia, Africa, South America, and the Indo-Paciﬁc. It is commonly thought, therefore, that such problems are too esoteric to warrant serious consideration in the west. The growing interest in travel and the increasing use of exotic foods means that more and more of us may ﬁnd ourselves in a situation where a better understanding of bites stings and poisonous foodstuffs might be both interesting and useful.1,2

BITES AND STINGS BY VENOMOUS ANIMALS

Snakes, spiders, scorpions, ﬁshes, bees, wasps, sea anemones, and jellyﬁsh are just a few of the animals that use venoms. The venom may be used primarily to capture and initiate the digestion of prey or to deter a potential predator, and a bite or sting inﬁlicted on a human subject is most likely to occur because the animal concerned has been molested or disturbed. It is impossible to avoid making generalisations about envenoming bites or stings but it is wise not to jump to conclusions because things are rarely what they seem. For example, most snakes are non-venomous and harmless but some non-venomous snakes bite without hesitation. Some venomous snakes rarely bite (for example, sea snakes) and many venomous snakes will make a dry bite (that is, when no venom is inoculated). Even where snakes are abundant, local people cannot differentiate between venomous and non-venomous snakes. So clinicians invited to help a victim cannot rely on anecdotal information that the bite was by a venomous snake and, even if it was, the victim may experience no ill effects. With the exception of one small family all spiders are venomous as are all scorpions, but although it is easy to be more frightened of large spiders and scorpions than small ones, their venoms are no more powerful than those of their small relatives.

Whether life threatening or of no clinical signiﬁcance, bites and stings are invariably painful and are usually accompanied by local swelling and inﬂammation. Clinical signs of envenoming may develop slowly. Only one safe generalisation can be made: a victim should be observed for several hours before it is decided that the event is benign.3 One speciﬁc example emphasises the need for caution. A young child seen by one of us in a hospital in India claimed she had been bitten by a frog. There was no need for alarm. In fact she had received a very severe envenoming bite by a cobra. She had been in the school playground. She had bent down to pick up her school bag, disturbed the animal and been bitten on the ﬁnger. She had seen only the tip of the head of the snake and decided it was a black frog. Fortunately she was kept under observation and could be transferred to hospital as the classic signs of neurotoxic poisoning developed.

Envenoming bites by snakes may be inﬁlicted by members of ﬁve families: Elapidae (a family that includes the cobras, kraits, coral snakes, and taipans); Hydrophiidae (sea snakes); Viperidae (vipers and adders); Crotalidae (pit-vipers); Atractaspidae (a small family of African burrowing adders). One other family, Colubridae, composed primarily of rear-fanged snakes, contains a few dangerous members such as the boomslang of South Africa. Elapids and sea snakes possess short fangs. The fangs do not penetrate deeply and the bite site might only exhibit a few scratch marks.

Envenoming bites by snakes of these families always present with signs of neurotoxicity: paresis, dysphonia, inability to smile, open the mouth properly or protrude the tongue, neuromuscular weakness (ﬁg 1). Death usually occurs as a result of respiratory failure. Clotting time is usually increased but haemorrhage is rare. Local signs are relatively uncommon but envenoming bites by the monocelate cobra (widespread in SE Asia) cause severe localised soft tissue necrosis, and bites by a number of Australasian snakes (particularly the tiger snakes, the common brown, the
red-bellied black, and the taipan) can cause severe necrosis of skeletal muscle. Envenoming bites by viperids and crotalids typically result in coagulopathies and haemorrhage. Bleeding occurs from the bite site, old wounds, gum margins, etc, and bruising and blood filled blisters can cover extensive areas of the bitten limb. Muscle necrosis accompanies severe bites by a number of species including the South American rattle-snake, some North American rattlesnakes, and Russell’s viper—particularly those of South India and Sri Lanka. The combination of coagulopathy and haemorrhage is important as it may give rise to the rare but serious neurological complication of central nervous system haemorrhages. The haemorrhages are usually generalised, with the exception of pituitary haemorrhage that is a feature of envenoming bites by Russell’s viper in Myanmar and can result in a delayed irreversible pituitary failure.4

The peripheral neurotoxic signs that accompany envenoming bites by so many snakes result from the action of three major groups of toxins. The post-synaptically active neurotoxins present in the venoms of all elapid and sea snakes bind with high affinity to the \( \alpha \) subunits of the acetylcholine receptors at the neuromuscular junction, preventing the binding of acetylcholine (Ach) and thus blocking neuromuscular transmission. The neuromuscular paralysis can be fatal, but if ventilatory support is provided most victims will resume natural breathing within 12–24 hours. If appropriate antivenom is available recovery will be more rapid because there is some evidence that the rate of dissociation of toxin from receptor is accelerated by the presence of anti-toxin IgG.

Envenoming bites by kraits and taipans are particularly difficult to treat because the patient does not respond to antivenom. The venoms of these snakes and a number of other Australasian elapids contain neurotoxic phospholipases A\(_2\) toxins. These presynaptically active neurotoxins bind to motor nerve terminals causing an early depletion of synaptic vesicles and the delayed degeneration of the motor nerve terminal. Recovery occurs when the nerve terminal has regenerated and this can mean subjects being ventilated for many days before spontaneous ventilation returns. The degeneration of skeletal muscle also gives rise to profound weakness and to the typical sign of pain during both active and passive movement and myoglobinuria (fig 1).

Fatalities have occurred as a result of acute renal failure in a number of cases of myotoxic snake bite.6 The most potent of the myotoxic agents are the myotoxic phospholipases A\(_2\). The phospholipases often possess both neurotoxic and myotoxic activity and so a subject bitten by an Australian elapid or a krait might be weakened as the result of circulating...
postsynaptically active, presynaptically active, and myotoxic components. Signs of damage to the autonomic nervous system are rare in snake bite; however, one case report concerned an incident in which mydriasis, tachycardia, constipation, and defective micturition lasted for two years following an envenoming bite by a Malayan krait.

Relatively few spiders and scorpions are truly dangerous. Of the six major families of scorpions, for example, only one family (Buthidae) constitutes a significant risk to humans. What is more significant is that members of this family are found across the world in North Africa, Asia, North and Central America, and South America. Scorpions in particular constitute a significant risk in North Africa and South/ Central America. Children playing in the dirt digging up stones and rocks and digging under the bark of trees and logs are particularly vulnerable and estimates suggest that up to 1000 deaths per year in Mexico and in North Africa are attributable to scorpion stings. Of the spiders the feared “tarantulas” are generally unable to harm a human subject, although the Funnel Web spiders of Australasia (genus *Atrax*) and the armed spider of Brazil (genus *Phoneutria*) are large, and able to inflict a very nasty envenoming bite. The most important spiders are probably the very small button, red back or widow spiders (genus *Latrodectus*) because these are found all over the world except for cold and cool temperate regions. These spiders attract a certain ribald appreciation as it is claimed in some regions (for example, Australia) that some species inhabit the underside of the seats in outside privies.

Spiders and scorpions are entirely carnivorous, feeding primarily on invertebrates although larger spiders may also feed on small vertebrates. They are not generally aggressive but larger male spiders such as the Sydney funnel web spiders and the Brazilian armed spider are reputed to be aggressive if encountered while they are seeking a female mate. Bites and stings by spiders and scorpions are almost always very painful. The onset of pain is immediate but further clinical signs of envenomation may develop over several hours. The toxins elaborated by these animals are polypeptides of varying size and structure. Most selectively target Na\(^+\), K\(^+\), Ca\(^{2+}\) and Cl\(^-\) ion channels and, by changing the gating properties in the channels, induce a state of hyperexcitability in the peripheral nervous system. The toxins affect both somatic and autonomic nervous systems, and the excessive excitability leads to repetitive firing in axons and axonal terminals, repetitive firing at motor end plates, and an excessive discharge of neurotransmitters in all components of the peripheral nervous system. Other toxins cause a major influx of Ca\(^{2+}\) into nerve terminals and this enhances transmitter release. Not surprisingly, the clinical syndrome of severe envenoming by spiders and scorpions comprises pain at the site of the bite or sting, fasciculation, weakness, shivering, sweating, hyperthermia, salivation, cardiac instability, and variable blood pressure, the variability often overlying a progressive and insidious decline. Cardiac insufficiency may lead to pulmonary oedema and convulsions (caused by hypoxia).

**TREATMENT OF ENVENOMING BITES AND STINGS**

The cardinal rules for the management of subjects thought to have sustained an envenoming bite or sting are continual observation and the monitoring of blood pressure, heart rate, and respiration. The subject should be reassured and helped to relax. Apart from swabbing the bite/sting site (the swab should be kept if possible as it may help subsequent investigations) the wound should be left alone. Cutting, biting, sucking or excising tissue at the site is contraindicated (fig 2). None of these measures help to remove venom, they may introduce an infection, and may result in serious bleeding if the envenomation has caused a coagulopathy. Tight tourniquets and ligatures should never be used but supportive pressure bandages may be of major benefit if properly applied (fig 3).

Care should be exercised when removing a pressure bandage as there may be a surge of venom into the circulation. Care is also needed if there is a real risk of severe local necrosis which might be exacerbated if the toxins responsible are retained at the bite site. If the suspect is a widow spider a pressure bandage may intensify the pain. A clear description of the offending animal and the circumstances of the bite should be obtained whenever possible. If the animal is brought in it should be kept for formal identification (fig 2).

Subjects exhibiting signs of systemic envenomation should be transferred to a local hospital or clinic with as many details of the incident as possible. Respiratory difficulties should be treated with assisted ventilation. Pain should be treated with standard mild analgesics. Narcotic analgesics should not be used as their use may confound any developing neurotoxic signs.

Specific antivenoms should be used in accord with local guidelines as soon as signs of systemic poisoning become apparent. Antivenom administration should not begin until facilities are in place to treat any immediate or delayed immunological reactions. Antivenom should never be inoculated into the site of the bite or sting.

Some subjects may be sensitised to spider bites or scorpion stings. Any adverse immune response should be treated symptomatically, as should the clinical signs of autonomic overactivity. Envenomming animals do not regulate the amount of venom inoculated according to the size of the victim. Thus small subjects should receive the same amount of antivenom as large (fig 2).

**TICK PARALYSIS**

Ticks are blood sucking relatives of spiders and scorpions responsible for the transmission of a number of diseases in man and animals. Human tick paralysis is caused by three ticks: *Dermacentor andersoni* and *D variabilis* in the USA and *Ixodes holocyclus* in Australia. During sucking the ticks release toxins that block transmitter release from motor nerve terminals. The result is a progressive descending neuromuscular paralysis that is often mistaken for polymyelitis, myasthenia gravis, or Guillain-Barré syndrome. Weakness typically starts 3–7 days after the tick has become attached. The tick will usually be found on the scalp, within the external meatus, behind the ear, or in some other moist warm, unexposed place. Removal of the tick is the primary treatment. The tick should be paralysed with an approved insecticide and then lifted out with fine forceps, taking care to ensure the removal of the mouth parts. Alternatively the tick can be paralysed by infiltrating a local anaesthetic around the point of attachment before removal. Removal of the tick results in the very rapid reversal of paralysis in the case of the American ticks, but in the case of the Australian ticks paralysis may continue to get worse for 2–3 days before improvement is seen. Severely affected children may require hospitalisation and intensive care. For these patients a canine antivenom is available but its
use should be limited to severe cases because of the number of side effects associated with its use.10

SEA FOOD POISONING

All of the well documented syndromes characteristic of “neurotoxic” sea-food poisoning11–13 result from the consumption of food items contaminated with toxins produced by dinoflagellates or marine bacteria. The most common syndrome is “ciguatera”. This syndrome results from the consumption of coral grazing fishes or fish that enter coral reefs to feed on the grazers. These predatory fishes—snappers, groupers, sea trout, barracuda—are high quality food items, caught by both commercial and private fishermen. Ciguatera is primarily a problem of the Indo-Pacific, and hot spots include the north eastern coast of Australia, the Florida coast, the islands of the tropical Pacific, and the Caribbean; however, increasing global travel and the global trade in high quality fish has resulted in subjects presenting to general practitioners in western Europe. One such traveller shared a snapper, commercially caught in the Caribbean, with friends in a New York restaurant before leaving for the UK. She was ill on the aeroplane, arriving the following day in Sunderland, UK. Her confused GP was called to make a home visit to meet his first case of ciguatera. The signs and symptoms of ciguatera usually occur between 1–6 hours of ingestion, but may be much slower. The presenting symptoms may be either gastrointestinal (abdominal cramps, nausea, vomiting, watery diarrhoea) or neurological (paresthesia, dyesthesia, blurred vision, vertigo, ataxia, tremor). Cardiovascular instability and hypotension are common, and temperature reversal is characteristic.

Serious poisoning requires hospitalisation, and in such cases recovery may take 7–14 days. Chronic fatigue is a common long term problem and has led some to speculate that fatigue following ciguatera is often misdiagnosed as chronic fatigue syndrome. Other long term effects include hypersomnia, peripheral neuropathy, and inflammatory muscle disease. Repeated exposure leads to increasingly severe illness, and recurrence of illness years after the primary event appears to be common. Mortality rates are low (less than 0.1% of the affected subjects).

Numerous lipid soluble toxins appear to be involved in ciguatera. Ciguatoxin, a large polyether, appears to be the major toxin. It is generally thought to be produced by the dinoflagellate Gambierdiscus toxicus, but the cultured microorganism does not produce the toxin. This dinoflagellate also produces maitotoxin and this is also considered to be involved in the syndrome. A third toxin, scaritoxin, has been identified in the viscera of coral grazing fish. All the toxins affect the excitability of nervous tissue, probably by increasing Na⁺ permeability and changing the gating properties of voltage gated Na⁺ channels.

There are no specific treatments available. Most signs and symptoms are treated symptomatically, although infusion of hyperosmotic mannitol may reduce the severity of the illness. Gastric lavage, emesis, and the administration of activated charcoal are measures used in an attempt to reduce toxin absorption.

Shellfish poisoning typically arises after the consumption of filter feeding shellfish (for example, mussels, scallops, clams). The causative agents are dinoflagellates that are ingested by the shellfish during feeding. The toxins responsible are stable and resist most of the forms of rapid cooking typically applied to seafood. Paralytic shellfish poisoning (PSP) is caused by the
ingestion of shellfish contaminated with gonyautoxins, a family of toxins produced by *Gonyaulax* and related dinoflagellates. The best known toxin is saxitoxin. The gonyautoxins block voltage gated Na\(^+\) channels, thus blocking action potential generation in skeletal muscle and sensory and motor axons. The early signs of gastrointestinal disturbance (3–6 hours) may progress to include numbness of mouth and digits, visual disturbance, dysphagia, neuromuscular weakness and, in severe cases, a potentially fatal respiratory paralysis. Treatment is symptomatic, but observation is essential because the development of severe paralysis may be relatively slow (up to 24 hours). Recovery takes three to seven days and is usually uneventful.

Neurotoxic shellfish poisoning (NSP) is much rarer than PSP. It is largely confined to the Florida coast, the Gulf of Mexico, and possibly the east coast of South America. The responsible dinoflagellate is usually *Gymnodinium breve*. This is accumulated by filter feeding shellfish, which in turn become a carrier for a group of toxins collectively known as the brevetoxins. These toxins are lipid soluble and they bind to a poorly defined region of the Na\(^+\) gated channel to cause repetitive firing of action potentials. The toxins may also enhance the release of transmitters from autonomic nerve terminals. It has also been suggested that they initiate the degranulation of mast cells which contributes to respiratory problems (see below). The symptoms of NSP depend on the route of ingestion. If infected shellfish are eaten the symptoms are similar to, but less severe than, those associated with PSP. The brevetoxins are powerful irritants and inhalation of aerosols containing the toxins (for example, sea spray, or sprays created during storms) causes bronchoconstriction and lacrimation rather than “neurological” signs. The possible role of histamine and other peripheral mediators...
from mast cells has been noted. No human fatalities have been reported and recovery is rapid and eventful.

Amnesic shellfish poisoning is also caused by consumption of filter feeding shellfish that have accumulated domoic acid from the causative dinoflagellates of the genera *Pseudonitzschia*. Domoic acid is an excitatory neurotoxin active at Kainate receptors in the central nervous system. A major outbreak occurred in Nova Scotia in 1987 and 1998 and minor outbreaks have occurred in the Pacific coast of USA, Scandinavia, and New Zealand. The syndrome begins with gastrointestinal disease, but in severe poisoning patients become dizzy, ataxic, and experience cognitive difficulties. Treatment is symptomatic, but the loss of short term memory, confusion, and seizures may be permanent.

Diarrhetic shellfish poisoning is widespread and causes gastrointestinal problems without neurological symptoms. The responsible toxin is okadaic acid. Recovery is uneventful after 2–3 days.

Tetrodotoxin poisoning usually results from the consumption of puffer fish, but bites by the blue ringed octopus (an Australian species) can also result in the introduction of tetrodotoxin from the saliva. The toxin is probably produced by a marine *Vibrio* that enjoys a symbiotic relationship with the host. The toxin is concentrated in the skin and viscera of fish. Most cases of poisoning occur in Japan or in Japanese communities elsewhere where puffer fish are eaten as a delicacy. Tetrodotoxin blocks the voltage gated Na⁺ channel at the same site as saxitoxin and causes numbness, tingling, visual disturbances, and a potentially fatal neuromuscular weakness within 10 minutes of ingestion. Treatment is symptomatic and recovery is usually uneventful provided the patient in neuromuscular paralysis is artificially ventilated and the circulation is maintained.

Palytoxic poisoning is encountered in the Indo-Pacific and Caribbean, and results from the consumption of fish, soft crabs or other animals that graze on the tropical soft anthozoan *Palythoa*, or of the larger predatory fish that feed on the primary grazers. The toxins responsible are known as palytoxins. They are large, lipid soluble polyethers, and produce symptoms indistinguishable from those of ciguatera.

The biological basis of the toxicity is still controversial but there is no doubt that it is neurotoxic. It is probable that many cases of “ciguatera” are misdiagnosed cases of palytoxic poisoning. Properly documented cases are very rare but there is no doubt that palytoxic poisoning can be fatal.

**GENERAL MEASURES TO PREVENT SEAFOOD POISONING**

It can be difficult to predict cases of seafood poisoning. The toxic animals exhibit no obvious signs of being poisonous and of two animals caught in the same area at the same time only one might be poisonous. Therefore care should be taken when eating shellfish, and special caution exercised with very large predatory tropical fish—ideally smaller fish should be consumed. The broth in which the seafood has been cooked should be discarded, and the viscera of any fish should not be consumed. A simple precaution for potentially problematic fish includes rubbing a little raw flesh on the lips before cooking and eating the entire fish—if the lips go numb the fish should be discarded. Extensive washing of seafood is not a suitable precaution—for example, boiling mussels for three hours only reduces okadaic acid levels by 50%. It can take days to reduce the toxicity of affected food items by simply soaking in clean water. No seafood should be collected or consumed during or for several days after a bloom (red or green tide) because the blooms often include toxic dinoflagellates. No seafood should ever be eaten uncooked and only freshly caught fish should be purchased.

**DIFFERENTIAL DIAGNOSIS OF SEAFOOD POISONING**

The differential diagnosis of seafood poisoning is by exclusion. The following factors may be helpful:

- Was the food properly cooked? The consumption of uncooked seafood can be the cause of botulism and meningitis (a result of infestation with *Ansiastraurosoma cantonensis*). This form of meningitis has an incubation period of 4–6 weeks.
- Was the food fresh when purchased and prepared? Some fish (especially mackerel, tuna, and bonito) convert histidine to histamine if kept at ambient temperature for several hours, and this causes scromboid poisoning. The symptoms are caused by the histamine (headache, nausea, urticaria, flushing and fever, gastric pain) and can be treated with antihistamines. Other fish kept for long periods may be dusted with organophosphates or other insecticides to allow flies to be brushed off easily.
- Were the food items invertebrate (for example, filter feeding shellfish) or vertebrate? Ciguatera is unlikely to be the diagnosis for invertebrate food poisoning. Of the types of shellfish poisonings paralytic shellfish poisoning, with
its neurological features of neuromuscular weakness, is the most important.

- Was the fish consumed a large pelagic fish? If yes, the problem is almost certainly ciguatera. The likelihood of ciguatera is also stronger if the place where the fish was caught was from a reef area anywhere in the Caribbean or Pacific, or off the coast of Florida or Queensland. Palytoxic poisoning will be indistinguishable from ciguatera even if small reef grazers (file fish, parrot fish, surgeon fish) have been consumed as all of these fishes may accumulate either (or both) ciguatoxins and palytoxin.

- Was the fish a puffer fish? If so a tetrodotoxic poisoning is probable. As a note of caution, it is becoming increasingly clear that in the tropics animals that either graze on coral reefs or feed in the benthos may accumulate a range of potential toxins, all of which enter the food chain. The hapless human victim may, in turn, have accumulated a cocktail of toxins.

Authors’ affiliations
J B Harris, School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne, Newcastle upon Tyne, UK
A Goonetilleke, Department of Neurology, Newcastle General Hospital, Regional Neurosciences Centre, Newcastle upon Tyne, UK

REFERENCES

- A good recent multi-author text covering most of tropical neurology. It places “bites, stings and seafood poisoning” into its broader context.


- This is an excellent guide to the management of snake bite prepared under the guidance of the leading authority in the world.


- A detailed description of acute renal failure in a number of cases of bites by Australian tiger snake.


- A patchy book but comprehensive and of great interest.


- A good discussion written explicitly for the physician.


- Still the most complete text on this very important syndrome.


- An excellent review of all forms of shellfish poisoning.


- The definitive text book of neurotoxicology in which short monographs may be found on every significant natural toxin.