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REVIEW ARTICLE

Animal toxins

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Throughout history, envenoming by animal toxins has fascinated humans. Rarely has a medical phenomenon had so much religious association, symbolism, anecdotal communication, and provoked so much violent professional disagreement. Animal toxins have made a significant contribution to enhancing knowledge in human physiology and pharmacology. Information on the nature and mechanism of action of these toxins has enabled a more scientific approach to the treatment of their intoxications. Early and specific therapy is frequently required after envenoming and often includes life support and maintenance of vital functions by mechanical ventilation, i.v. fluid and drug therapy.

The total number of snake bites throughout the world has been estimated at 500000 per year, with approximately 40000 deaths [5, 60, 81]. The majority of these incidents occur in Asia, South America and Africa. Snake bite is the fifth most common cause of all deaths in Burma [6], and in Sri Lanka, two people die each day of snake bite [21]. In the USA, 45000 snake bites occur each year of which 7000–8000 are venomous and there are between 10 and 15 deaths [13]. In the UK several incidents of bites inflicted by foreign venomous snakes have been recorded [67] and although there have been 11 deaths caused by adder bites from 1876 to 1941, in recent years there have been no deaths from snake bites. The British Military Hospital, Dharan, Nepal, managed 58 cases of snake bite in 1989 [35]. Eighteen deaths attributed to snake bite were reported in Australia from 1981 to 1991 [79]. In Sweden, 44 deaths were reported from snake bite from 1911 to 1978, while in Finland and Sweden there are 200 bites annually. Bee and wasp stings caused 61 deaths in the UK during a 13-yr period ending in 1972, while in the USA, hymenoptera stings cause 40–50 deaths annually [74]. At present, an average of five deaths occur from bee and wasp stings in the UK annually [61]. Scorpion stings are responsible for 1000–2000 deaths each year in Mexico, and high mortalities are also encountered in Brazil, Israel, Trinidad, Algeria, India [85] and Jordan [37]. A total of 38068 cases of envenoming by scorpion stings during 1981–1986 were treated in the city of Leon, Mexico [20]. Spider bites are associated with a mortality of 1–17% in Chile, Brazil [50], the Mediterranean region [85], Israel, North Africa and in some regions in the former Soviet Union [45]. Black widow spiders caused 63 deaths in the USA from 1950 to 1959 while the funnel-web spider is responsible for some morbidity in Australia. Tick bites cause poisoning and sometimes death in Australia and western North America. Puffer fish poisoning is responsible for 250 cases of poisoning a year in Japan with a 50–60% mortality rate.

Ciguatera is the most commonly reported food-borne intoxication of marine origin in the United States, accounting for 7.4% of all food-borne outbreaks from 1978 to 1982 [73]. It is a public health hazard in the Pacific and Caribbean islands. In 1968 an outbreak of paralytic shell fish poisoning occurred in the north east coast of England affecting 78 people [55]. Scuba diving and similar recreational activity has been associated with poisoning caused by marine animals, particularly in the Indian and Pacific oceans.

Figure 1 shows the principal sites of action of the animal toxins discussed.

Snake venoms

Of the nearly 2000 different species of snakes, only approximately 300 are venomous. Venomous snakes are found in the families Colubridae (boomslang, vine snake), Elapidae (cobra, krait, mamba, taipan, tiger snake, coral snake), Hydrophidae (sea snakes), Viperidae (old world vipers found in Europe, Africa, Asia but not in America or Australia, saw scaled viper, Russell's viper, puff adder, Gaboon viper), and Crotalidae (pit vipers, found in America, Asia and Europe, copperhead, cotton mouth, rattlesnakes).

Snake venoms are used primarily for attack and contain components designed to immobilize prey and facilitate their digestion. Over 95% of the dry weight of most venoms is polypeptide which includes enzymes, toxins and small peptides, each class being capable of modulating the physiological response of envenomed animals. More than 20 enzymes have been detected in snake venom and 12 are found in the majority of venoms. Hyaluronidase is present in all snake venoms facilitating the distribution of other

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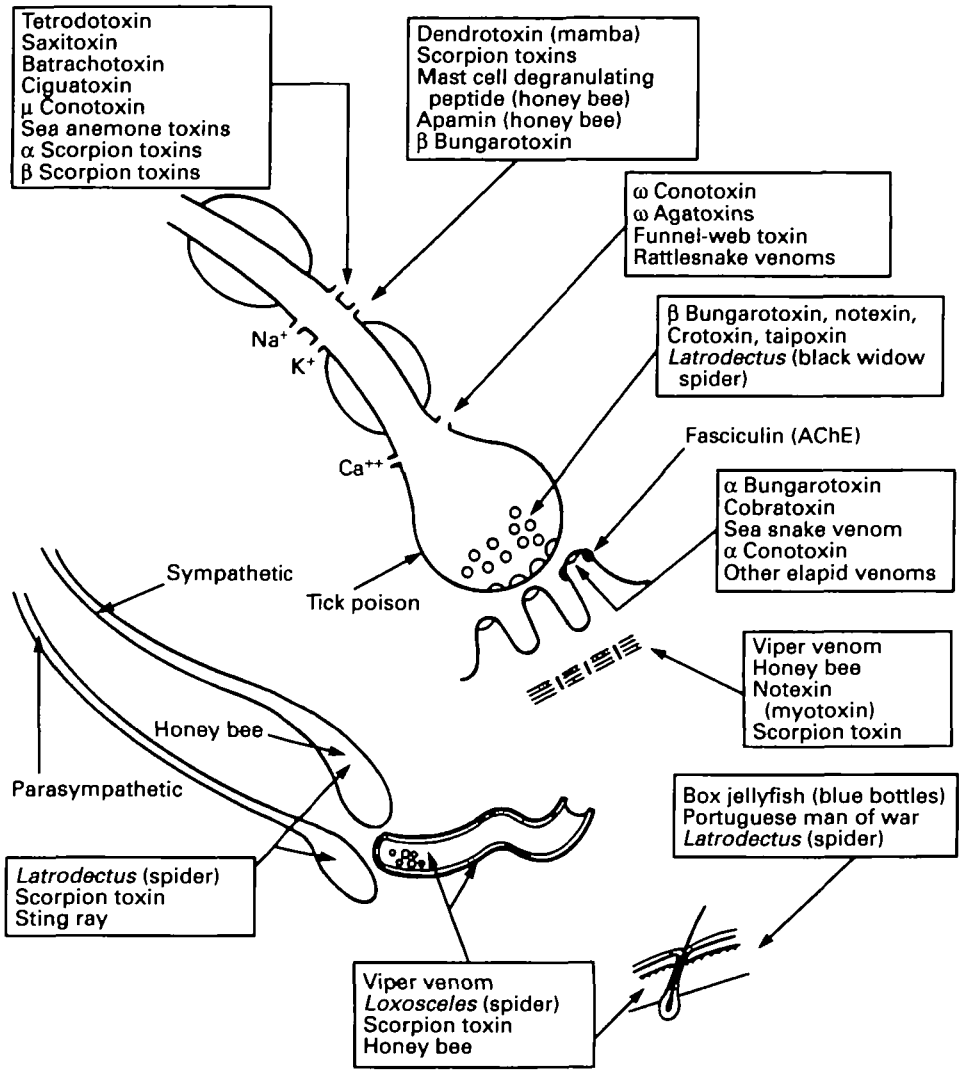

Figure 1 Principal sites of action of animal toxins.

venom components throughout the tissues of the prey.

Elapids account for the vast majority of deaths worldwide, particularly as a result of toxins that act at the neuromuscular junction. The action may be at presynaptic, postsynaptic or at both sites. Elapid envenoming progresses along a neurotoxic course with occasional early numbness or weakness of the bitten extremity. Systemic manifestations occur after about 30 min to 1 h and include ptosis, external ophthalmoplegia, dysphagia, salivation followed by general paresis and respiratory failure. There are many different snake venom neurotoxins that act presynaptically to inhibit the evoked release of acetylcholine. These presynaptically acting toxins exhibit phospholipase A_2 activity [11]. All agents that inactivate phospholipase A_2 activity also inactivate their neurotoxicity. Beta bungarotoxin (krait), notexin (Australian tiger snake), crotoxin (*Crotalus durrissus terrificus*) and taipoxin (taipan) inhibit the release of acetylcholine from the terminals of neurones and some cholinergic neurones of the autonomic nervous system. It takes approximately 1.5–3 h for beta bungarotoxin to cause complete neuromuscular block when incubated with an isolated neuromuscular preparation. Block occurs more rapidly if the nerve is repetitively stimulated during incubation. Among the most toxic components in elapid and Hydrophidae venoms is a neurotoxin which binds to the nicotinic acetylcholine receptor in the postsynaptic membranes of skeletal muscles, thus preventing binding of acetylcholine. As this pharmacological action is similar to that of curare, these neurotoxins are also termed curaremimetic neurotoxins. However, in view of the presynaptic binding shown by curare and similar non-depolarizing neuromuscular blocking agents, this description is not wholly accurate as these unique neurotoxins act only postsynaptically. The amino acid sequences of most of these neurotoxins are available [25] and accordingly they are classified into two subgroups: short neurotoxins with 60–62 amino acid residues; and long neurotoxins with 70–74 residues. One species of snake may have more than one neurotoxin and often has both short and long chain neurotoxins. Binding studies using radiolabelled alpha neurotoxins revealed that the toxin binding sites overlapped acetylcholine binding sites [93]: thus the toxins are competitive inhibitors. Binding of a neurotoxin to the acetylcholine receptor does not

induce ion channel opening; the result of binding is flaccid paralysis [43].

Of the elapid and sea snake neurotoxins, alpha bungarotoxin from the krait has been the most extensively studied. Alpha bungarotoxin has been used widely for tagging, solubilization, extracting and purifying acetylcholine receptors from muscle and the electric organ of the Torpedo eel [54]. When purified this polypeptide, with a molecular weight of approximately 8000, has no detectable prejunctional effects, anticholinesterase activity or ganglion blocking properties. The most characteristic feature of the neuromuscular block produced by alpha bungarotoxin in contrast with the neuromuscular block produced by curare is the absence of tetanic fade and the presence of marked post-tetanic facilitation. The train-of-four fades only minimally or not at all [48]. Thus postjunctional non-depolarizing neuromuscular block is not necessarily characterized by fade. The neuromuscular blocking action of some cobratoxins (type 1 cobra NT) is reversible more easily than that of alpha bungarotoxin.

Sea snakes are the most abundant venomous reptiles found throughout the Indian and Pacific oceans. All sea snakes are poisonous. Although sea snake venom is extremely toxic, the amount of venom injected per bite is small. Venom components include presynaptic and postsynaptic neurotoxins and some venoms appear to inhibit the actions of acetylcholine at autonomic ganglia. A typical manifestation of sea snake poisoning is muscle pain. In severe poisoning myoglobinuria is detected several hours after the bite [83].

Notexin and a myotoxin from *Enhydrina schistosa* (sea snake) induce oedema and necrosis of muscle fibres, the fibres most affected being those rich in mitochondria [11]. The venom of the Eastern green mamba (Kenya, Tanzania) enhances neuromuscular transmission *in vitro* and the compound dendrotoxin has been found to be 500 times more potent than 3,4-diamino pyridine at augmenting responses to indirect stimulation [25]. Release of acetylcholine is increased by the toxin-blocking, voltage-dependent neuronal potassium channel, thus delaying repolarization and increasing quantal release. Fasciculin from the same venom inhibits acetylcholinesterase by binding to a peripheral anionic site on the enzyme. Fasciculin and dendrotoxin act synergistically increasing acetylcholine content at the neuromuscular junction [25]. Mambas also possess toxins that bind to muscarinic cholinoceptors. In addition, and in common with other elapids they have postsynaptic alpha neurotoxins.

Venom of the burrowing asps of the genus *Atractaspis* have no pre- or postsynaptic neurotoxins and the most prominent action of the toxins, sarafotoxins, was on the heart, causing signs of coronary insufficiency from vasospasm [7].

Cardiotoxins which cause augmentation of myocardial contraction at low concentrations and systolic arrest at high concentrations have been identified from cobra venoms [49]. Crotamines from rattlesnake venoms have a specific and unique effect on the sodium channel of excitable membranes [49]. Phospholipase A_2 neurotoxins (e.g. beta bungarotoxin) have been shown to block potassium channels while a component from the venom of the rattlesnake (*Crotalus atrox*) affects calcium channels [33].

Haemorrhagic symptoms are a frequent accompaniment of bites by vipers and of some venomous colubrids [12, 34]. Venom procoagulants activate prothrombin, and factors V and X. Some venom components have a direct thrombin-like effect. Rattlesnake venoms can cause defibrinogenation by activating the endogenous fibrinolytic system. Thrombocytopenia may occur and platelet function may be affected. Spontaneous systemic bleeding is caused by haemorrhagins which damage the vascular endothelium. Massive intravascular haemolysis leading to renal failure follows envenomation by Russell's viper (India [4, 53], Sri Lanka [40]), which inhabits 10 South Asian countries. In Pakistan, India, Sri Lanka, Bangladesh, Burma and Thailand it ranks among the most important causes of snake bite mortality. The venom procoagulants activate the clotting system with such speed and efficiency that McFarlane was "left feeling it was too clever to be true" [86]. Renal failure is the most devastating effect of Russell's viper bite in Burma and Sri Lanka. Deposition of microthrombi in the kidney contributes to the acute tubular necrosis which is the commonest cause of death [6, 36]. When the patient's blood has become defibrinated and incoagulable, the activity of the haemorrhagins, which damage the vascular endothelium, and platelet abnormalities [30] may lead to spontaneous systemic haemorrhage.

The saw scaled or carpet viper (*Echis* species) probably causes more bites and deaths than any other venomous snake worldwide [16]. Demonstration of non-coagulating blood is the single most important diagnostic test. The simple whole blood clotting test developed in Nigeria by Warrell and colleagues [personal communication, 1993] should be repeated every 6 h after the first dose of antivenom until clotting is re-established. The test should then be repeated daily for 3 days to ensure coagulability. This simple all or nothing whole blood clotting test proved a reliable way of identifying patients with systemic envenomation (those that required antivenom) [71]. The clot quality test [66,69] is of little use in clinical management at present. After a bite from Russell's viper it was found to be insensitive to detect evolving systemic envenoming. The Malayan pit viper produces minimal or no haemorrhagic symptoms in spite of the fact that the patient's blood may be incoagulable for days. This "defibrinogenation syndrome" (hypofibrinogenaemia) without thrombocytopenia or fibrinolysis was studied extensively by Reid, Chan and Thean [70] and the use of this purified venom fraction has been under clinical investigation as an anticoagulant [8, 84].

The small scaled snake (inland taipan, *Oxyuranus microlepidotus*) found in remote areas of Western Queensland lays good claim to being the most venomous snake in the world, in view of its lethal potency. The venom contains a presynaptic neurotoxin and a prothrombin activator [56].

TREATMENT

The clinical management of poisonous snake bites continues to provoke controversy. First-aid measures should be determined primarily by the time and distance from medical facilities, the species of snake involved and the background of the health care individuals. In all instances the victim should be reassured, the bitten limb immobilized and rapid transport arranged to an institution. Identifying the snake is important and the snake should be killed if it can be done so quickly and without danger. Snake bite victims in remote areas may find additional first-aid measures helpful. Short skin incisions, 5–6 mm in length, through the fang punctures running parallel to the extremity should be made. Cruciate incisions are not recommended as the corners of the flaps tend to become necrotic. Suction should be applied and continued for 30–60 min. In laboratory animals, if incision and suction are started within 2 min of envenomation, 50–90 % of the venom can be removed [41]. However, many authorities such as Warrell [personal communication, 1993] strongly oppose incision and suction as these procedures could induce the risk of persistent bleeding and damage to vital structures.

Application of tourniquets is an area of great controversy. A light lymphatic constriction band proximal to the site of the bite is agreed by many. If the offending snake has been identified as an elapid, in particular a black mamba, taipan, cobra or krait, a tourniquet should delay the onset of respiratory failure until the victim reaches hospital. Tourniquets should not be used if the venom is known to cause tissue necrosis [78]. Tourniquets applied in 94 % in a series of 36 patients after bites by the Philippine cobra produced a delay in the onset of respiratory paralysis; four were asymptomatic before release of the tourniquets and in 11 symptoms worsened precipitously after release. Most importantly, four patients developed complete respiratory paralysis, requiring artificial ventilation on removal of the tourniquet [90].

Tourniquets should be released only when ventilatory support is at hand. In hospital, a quick assessment of vital function should be carried out and monitoring of these functions initiated. Level of consciousness, respiratory function (tidal volume, ventilatory frequency, blood-gas measurements), heart rate, arterial pressure, blood coagulability, urine output and renal function should be monitored closely. The extent of local swelling and limb girth should be assessed at regular intervals. Hypovolaemia must be corrected and when necessary ventilatory care started. Antivenom is the only specific remedy and practical experience in Malaya and Australia [80] suggests that the antivenom is best given by slow i.v. infusion over 15–30 min after diluting with isotonic fluid. Adrenaline should be available for management of an anaphylactic reaction to the antivenom.

There has been a shift in opinion since the BNF stated that "the bite is less dangerous than the antiserum" [10]. Although administration of antivenom is a rare clinical situation in Europe, in the rural tropics, correct administration of antivenom is a daily matter of life or death [23]. Administration of antivenom has potential complications. In several studies the incidence of hypersensitivity reactions was 5–33 %. The incidence of serum sickness was 36–75 % occurring from 2 to 23 days after administration of antivenom [17]. It is necessary to be aware that antivenom is potentially dangerous and should not be administered without a definite indication (certainty of systemic envenomation), and should not be routine for every instance of snake bite. Sensitivity tests are unreliable and not worthwhile, and anaphylactic reactions respond well to adrenaline given promptly.

It is recommended that a test dose of edrophonium be given to patients with neurological signs who have been bitten by any species of snake, especially cobras. Atropine sulphate 0.6 mg for adults and 50 $\mu g\ kg^{-1}$ for children i.v. is followed by edrophonium chloride (Tensilon) 10 mg for adults and 0.25 $mg\ kg^{-1}$ for children. If improvement occurs, patients may be given a maintenance dose of neostigmine 0.5 $mg\ h^{-1}$ with atropine 0.15 $mg\ h^{-1}$ [88, 92].

Advocates of antivenom record the potentially harmful result of aggressive surgical treatment. Many eschew antivenom and recommend excisional therapy or excision and fasciotomy [31, 38]. Therapeutic efforts directed at the site of injury are advocated in the belief that a localized process with destruction of platelets and coagulation factors occurs as fluid passes through vessels or extravascularly in areas of injured or necrotic tissue and this may be a major factor in many bleeding states [77]. In 1991 a report suggested that US pit viper bites tend to cause more tissue necrosis and may more often require surgical therapy [94]. Early limited bite excision when anatomically convenient was recommended as 75 % of the injected venom had been demonstrated to be removed for up to 2 h after the bite. Surgical releasing incisions were recommended for any signs of circulatory compromise in peripheral tissues or to release envenomated muscular compartments.

Coagulation studies should always be carried out before surgical intervention, and coagulability should be restored. Antivenom is the first-line treatment to restore blood coagulability [58]. Antivenom is effective even 2–3 days after a bite and there is report of success 7 days after envenomation [82]. Blood products and heparin have been proved to be of little or no value [12, 58].

Prophylactic penicillin or erythromycin should be given with a tetanus toxoid booster. Necrotic tissue should be debrided surgically at an early stage and denuded areas should be covered by skin grafts. Fasciotomy should not be attempted before blood coagulability has been restored and is indicated only if there is objective evidence of intracompartmental hypertension (intracompartmental pressure exceeding 45 mm Hg) [87].

Local reaction is minimal with krait [43, 47], coral snake and sea snake envenoming, but with cobra bites (except the Philippine and Egyptian cobras [91]) local necrosis is a feature. Russell's viper and

the tropical rattlesnake (*Crotalus durissus terrificus*) produce negligible local envenoming and are important exceptions to the generally useful rule that absence of local swelling after a viper bite excludes significant envenoming [68].

Spider venoms

Neuroactive spider toxins found so far can be classified into three main groups. *Latrodectus* spider venom, as from the black widow spider (alpha latrotoxin), has polypeptide toxins which act on presynaptic nerve terminals opening cationic channels and causing massive release of transmitter [14] followed by depletion of synaptic vesicles at the neuromuscular junction [29]. Alpha latrotoxin has been used in studies of the mechanisms of transmitter release [39].

Petrenko and colleagues reported that the alpha latrotoxin receptor is a membrane protein and is the only presynaptic marker for which a function has been identified [65]. A toxin acting postsynaptically on glutamate receptors blocking synaptic transmission in the squid giant synapse was identified in 1980 from the "Joro" spider (Japan, East Asia) [44].

Recently, a third group of spider neurotoxins (agatoxins) was found in the venom from the family Agelenidae (funnel-web spider, Australia) which contains several substances affecting synaptic transmission acting primarily on calcium channels, blocking entry of calcium into presynaptic terminals and preventing release of transmitters [3].

Spider bites cause two main clinical syndromes: necrotic and neurotoxic. Necrotic araneism follows *Loxosceles* bites (Central and South America and USA) where burning pain at the site of the bite is followed by tissue necrosis and formation of a black eschar. In about 12% there are systemic effects including macular erythema, fever, haemoglobinuria, jaundice and renal failure.

Bites from black widow, red back and hour glass spiders (*Latrodectus*, found in the Americas, Mediterranean, Australia, New Zealand, South and Eastern Africa) cause muscle spasms and respiratory embarrassment which may require ventilatory care. Other features include vomiting, tachycardia, irritability and hypertension.

Funnel-web spiders (*Atrax*, found in South Eastern Australia and Tasmania) cause a painful bite followed by numbness, nausea, vomiting, abdominal colic, sweating, salivation, dyspnoea, localized or generalized muscle fasciculations and spasms. Bites by *Phoneutria* (South American "banana" spider) are the main cause of neurotoxic araneism in Brazil and neighbouring countries.

Splinting of the bitten limb or a tight tourniquet may delay the spread of venom until the patient reaches hospital. Antivenoms are available for *Latrodectus*, *Atrax* and *Loxosceles* bites in many countries. Calcium gluconate, corticosteroids and β blockers have been used in the management of spider bites. Although calcium gluconate has usually been considered first-line treatment for severe envenoming by black widow spiders, Clark and colleagues found it ineffective for pain relief compared with a combination of i.v. opioids and benzodiazepines [15].

Scorpion venoms

Scorpion venom are known to enhance the excitability of nerve and muscle cells [2]. Some venoms appear to act preferentially on muscle cells [72] while others have effects on neurones and neurotransmitter release. Scorpion venoms have been shown to release acetylcholine, noradrenaline and serotonin.

The alpha scorpion toxins delay inactivation of sodium channels and thus prolong the action potential. The beta scorpion toxins affect activation in addition to slowing inactivation of sodium channels. The sodium channel opens at a membrane potential level at which the channel would be normally closed [42].

A component of scorpion venom was also found to facilitate and then block neuromuscular transmission in chick biventer cervicis preparations. It was shown to induce spontaneous contractions, partly by releasing acetylcholine from nerve endings and partly by increasing the sodium permeability of muscle membranes [76]. The first toxin that was shown to block voltage-dependent potassium channels was from the venom of a Mexican scorpion. Chloride channels are important components of receptors for inhibitory transmitters such as GABA and glycine and a component of scorpion venom was found to affect chloride channel activity.

The effect of the venom in producing a contracture, an initial increase in amplitude of electrically induced muscle contractions and spontaneous twitching, has been attributed to interference with the stabilizing function of calcium at the muscle membrane [2]. Increased concentrations of calcium lessened the effects of the venom and lower concentrations enhanced them. The venom has also been shown to interact with receptors of the muscle sarcoplasmic reticulum. Scorpion bites cause intense local pain followed by sign of autonomic nervous system excitation such as dilatation of pupils, hypersalivation, vomiting and diarrhoea. Generally, cholinergic features are followed by adrenergic features. Release of catecholamines produces hypertension, toxic myocarditis, arrhythmias, heart failure and pulmonary oedema. The latter is seen following bites in India, North Africa and the Middle East. Scorpions found in California and New Mexico cause muscle fasciculations, spasms and respiratory paralysis.

Pain requires local infiltration or ring blocks with local anaesthetic. Antivenom is available. Aggressive symptomatic treatment for cardiac and neurological symptoms is a necessity. In patients who develop severe adrenergic cardiovascular features, vasodilators (α blockers, calcium channel blockers or ACE inhibitors) are useful. The role of cardiac glycosides, β blockers and atropine is controversial. Warrell [personal communication, 1993] advocates antivenom when available but this is also a subject of vigorous debate. Serial echocardiography has been recommended in the management of children after scorpion envenomation as myocardial toxicity is a

common and serious complication [46]. Symptomatic patients should be treated in an intensive care unit and be monitored invasively [32].

Hymenoptera venoms (honeybees, wasps, hornets)

It has long been known that histamine is a major factor in the response to bee stings. Bee venom itself contains too little histamine for this to be a major contributor but both phospholipase A_2 and mellitin separately or in combination cause histamine release from skin mast cells as a result of cytolytic effects [52]. In addition to the cytolysis of mast cells, another component (mast cell degranulating (MCD) peptide) causes release of histamine from mast cells [28]. Most deaths from Hymenoptera stings are caused by dysfunction of the body's immune system whereby the venom allergens react principally with cell-bound specific IgE to induce massive release of histamine, leukotrienes, prostaglandins, chemotactic factors and a myriad of other factors [89].

The dermal, respiratory, circulatory and gastrointestinal responses that accompany this type I hypersensitivity reaction occur in response to a sting after one or a few initial sensitizing stings. The striking feature is the rapidity of death: 58% die in less than 1 h and over 75% die within 6 h [26].

This is in marked contrast with the times of death for fatal envenoming from snakes, spiders and scorpions. Autopsy reports of 150 sting-induced deaths showed that 70% were caused by airway obstruction. Anaphylactic shock was the next most important causative factor. Major offending species are the honeybee, yellow jacket wasp, white faced hornet and yellow hornet.

Phospholipase A_2 is the most important allergen in the honeybee. Mellitin, the major component of venom, causes lysis of red cells and consequently a pigment nephropathy which is a manifestation of massive direct poisoning. MCD peptide causes release of histamine from mast cell granules by fusion of the granule membranes with the mast cell membrane and exocytosis of the granule contents without lysis of mast cells. Apamin was the first neurotoxin found to block potassium channels that are activated by increased levels of internal calcium ions. Apamin affects such channels in nerves, muscle, erythrocytes and glandular cells. It can gain access to the central nervous system to produce hyperactivity and convulsions before death [33]. MCD peptide acts on potassium channels [33] and, together with the neurotoxic apamin and mellitin, contributes to intravascular haemolysis, rhabdomyolysis, epidermal necrolysis, airway obstruction and signs of severe histamine overdose which occur with massive honeybee envenomation.

The incidence of hypersensitivity to stings is considerably greater than the incidence of death from such stings. Within the general population, true systemic hypersensitivity rates are reported to vary from 0.1 to 4.0% [95]. In the UK, sensitization to bee venom appears to require more stings (average 81) than sensitization to wasp venom (average four stings) [27].

Of over 1000 deaths recorded mainly from the United States, only 2% occurred in children less than 10 years of age, while 50% occurred in individuals older than 50 years [74]. Hay fever or asthma does not increase predisposition to venom hypersensitivity [74]. Skin testing with pure Hymenoptera venoms and the RAST test for detecting specific IgE in serum are reliable methods for detecting type I hypersensitivity which together with a history of systemic reaction to a sting are useful indicators for prevention and prophylactic desensitization. Adrenaline is the only known effective control of immediate hypersensitivity reactions. Chlorpheniramine orally or i.v., i.v. fluids and close monitoring of respiratory, cardiac and renal function are important constituents of immediate care. The first local treatment is the removal of the stings left in the skin by scraping them out with a knife blade, fingernail or forceps. Patients with a history of severe reactions should carry "sting kits" which contain adrenaline and antihistamine tablets and should wear an identifying tag.

The pain caused by a sting of a vespid wasp is caused mainly by large amounts of serotonin, wasp kinin and protease. Mastoparan, vespid chemotactic peptides and mandarotoxin are structurally different from apamin, mellitin and MCD peptide. However, their sites and modes of actions are similar [59].

Sea snail: cone shells

The genus *Conus* includes several marine snails with beautifully cone-shaped shells. These snails found in the Pacific and Indian oceans produce an extraordinary variety of neurotoxins (alpha, mu and omega conotoxins) that are deadly to their prey and can cause fatal respiratory paralysis in humans [1]. Alpha conotoxins are potent antagonists at the postsynaptic nicotinic receptor while the other components act on sodium and calcium channels [62, 63]. mu Conotoxins differ from tetrodotoxin and saxitoxin as they primarily block sodium channels in skeletal muscle with less effect on action potential conduction in motor nerves [33]. There is no specific remedy. Cardiorespiratory resuscitation and maintenance of vital function can be life saving.

Coral and other coelenterates

The gorgonian coral *Lophogorgia rigida* is a beautiful purple fan-shaped animal that anchors itself to the sea bottom and produces a deadly venom, lophotoxin, which acts on the postsynaptic nicotinic receptor [18].

Box jelly fish (blue bottles found in Australia and South East Asia), man of war (USA) and sea anemones (China)

These animals discharge stinging capsules, nematocytes, which penetrate the skin and inject a venom which may cause cardiorespiratory failure. Sea anemone toxin prolongs nerve action potential and causes spontaneous and repetitive activity in axons [33]. Antivenom for one species of box jelly fish is

produced in Australia. These venoms produce severe local reactions [87].

Puffer fish (Japan), ciguatera (tropical and subtropical regions) and paralytic shellfish poisoning (PSP) (Pacific and Atlantic coasts of North America, Japan and the western coast of Europe and South Africa)

These unrelated groups of animals are a source of one of the commonest forms of intoxification. One of the most potent of the non-protein toxins, tetrodotoxin, which blocks conduction of action potentials in nerves without altering the resting membrane potential is the best known of the toxins involved. The toxin specifically prevents the increase in sodium conductance that follows partial depolarization of the membrane by a stimulating electric current. It does not affect the secondary increase in potassium conduction, demonstrating that this change in conductance is an independent event and not a secondary consequence of the primary increase in sodium conduction. There is evidence that tetrodotoxin displaces thiamine phosphate and occupies its site in the membrane, thus blocking exchange of potassium for calcium that precedes the increase in sodium conductance. Block of sodium channels leads to failure of action potentials to propagate along axons. Sensory neurones are affected first but at higher doses motor nerves are also blocked leading to skeletal muscle weakness and ultimately muscle paralysis and respiratory collapse [33]. Tetrodotoxin does not block conduction in smooth muscles in which the depolarizing current is carried mainly by ions other than sodium.

Tetrodotoxin is about 100000 times more potent than cocaine, although it is not used in medicine as a local anaesthetic. Puffer fish, ciguatera and paralytic shellfish poisoning cannot be distinguished clinically and these have been grouped together as pelagic paralysis [55]. The clinical picture of each is that of a gastrointestinal illness with associated acute neurotoxic features such as paraesthesia, ataxia and muscular weakness. Paradoxical sensations occur also [55].

A variety of clams and mussels ingest a unicellular dinoflagellate, *Gonyaulux catenella*, which produces saxitoxin which has an action similar to that of tetrodotoxin. Saxitoxin is responsible for paralytic shellfish poisoning [9]. Ciguatoxin activates sodium channels from normal resting potential and produces an irreversible depolarization [33]. Tetrodotoxin and saxitoxin can paralyse skeletal muscle directly [33].

There is no specific remedy for poisoning. However, supportive measures can be life saving.

Blue-ringed octopus (found in Australia)

Envenoming produces toxicity from tetrodotoxin.

Colombian frog

Skin secretions of the brightly coloured Colombian frog used by natives as arrow and dart poisons contain batrachotoxin which prevents inactivation of sodium channels resulting in a massive influx of sodium ions and persistent membrane depolarization. More than 100 biologically active alkaloids have been characterized in skin extracts from these dendrobatid frogs. Pumiliotoxins which block nicotinic receptor-mediated neuromuscular transmission, and histrionicotoxins, which block conductance of acetylcholine receptor-channel complex and shortens the time the channel remains open, are a few [19].

Tick envenoming

Tick paralysis occurs when the tick embeds itself in the victim's skin and introduces the toxin while it engorges with blood. The toxin was considered to cause presynaptic failure to liberate acetylcholine [24], but subsequent studies showed reduction in both amplitude and conduction velocities of mixed motor and sensory nerves [57]. The view held currently is that the toxin causes changes in the terminal part of the motor nerve fibre and failure of mobilization or release of acetylcholine may be secondary to a defect in conduction in the motor axon [22, 51].

The weakness sets in about 5 days after attachment of the tick. The toxin appears to be excreted rapidly or metabolized when the tick is removed as recovery is complete, usually 12–24 h after its removal. However, there has been one report of death after removal of a tick.

Tick paralysis has been reported mostly from Western North America, Eastern United States, Eastern Australia and British Colombia [64]. The tick must be detached without being squeezed. Ventilatory care may be required and an antivenom is available in Australia.

Conclusion

Animal toxins produce a wide range of physiological and pharmacological disturbances. Disorders of function at the neuromuscular junction are of particular interest [75] and most intoxications require close monitoring and some form of intensive care. The role of toxins in the advancement of knowledge of human function is undeniable and further studies may prove invaluable in developing new drugs and techniques.

> "It is unjust that when you have done
> all that a serpent should
> you gather our poisons one by one
> and break them down to your good"
> —Kipling.

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References

1. Abogadie FC, Mena EE, Woodward SR, Hillyard DR, Cruz W. Diversity of conus neuropeptides. *Science* 1990; **249**: 251–264.
2. Adam KR, Weiss CR. Actions of scorpion venom on skeletal muscle. *British Journal of Pharmacology* 1958; **14**: 334–339.

3. Adams KE, Bindokas VP, Hasegawa L, Venema VJ. ω Agatoxin: novel calcium channel antagonists of two subtypes from funnel web spider (Agelenopsis aperta) venom. *Journal of Biological Chemistry* 1990; **265**: 861–867.
4. Ahuja ML, Singh G. Snake bite in India. *Indian Journal of Medical Research* 1954; **42**: 661–686.
5. Arena J, Drew R, eds. *Poisoning*, 5th Edn. Springfield IL: Charles C. Thomas, 1986; 735–747.
6. Aung Khin M. The problem of snake bites in Burma. *Snake* 1980; **12**: 125–127.
7. Bdolah A, Wollberg Z, Kochva E. Safratoxins: a new group of cardiotoxic peptides from the venom of Atractaspis. In: Harvey AL, ed. *Snake Toxins*. New York: Pergamon Press, 1991; 415–424.
8. Bell WR, Bolton G, Pitney WR. The effect of arvin on blood coagulation factors. *British Journal of Haematology* 1968; **15**: 589–602.
9. Biddard JN, Vijverberg HPM, Frelin C, Chunghe E, Legrand AM, Bagnis R, Lazdunski M. Ciguatoxin is a novel type of Na^+ channel toxin. *Journal of Biological Chemistry* 1984; **259**: 8353–8357.
10. *British National Formulary*. London: British Medical Association/Pharmaceutical Society 1974–76; 34.
11. Chang CC. Neurotoxins with phospholipase A_2 activity in snake venoms. Proceedings of the National Science Council Republic of China—Part B. *Life Sciences* 1985; **9**: 126–142.
12. Charak BS, Charak KS, Ram Pal V, Parikh PM, Gupta VK. Coagulopathies in viper bites. *Journal of Postgraduate Medicine* 1988; **34**: 80–83.
13. Christopher DG, Rodning CB. Crotalidae envenomation. *Southern Medical Journal* 1986; **79**: 159–162.
14. Clark AW, Hurlbut WP, Mauro A. Changes in the finite structure of the neuro-muscular junction of the frog caused by black widow spider venom. *Journal of Cell Biology* 1972; **52**: 1–14.
15. Clark RF, Wethern-Kestner S, Vance MV, Gerkin R. Clinical presentation and treatment of black widow spider envenomation—a review of 163 cases. *Annals of Emergency Medicine* 1992; **21**: 782–787.
16. Coppola M, Hogan DE. Venomous snakes of South West Asia. *American Journal of Emergency Medicine* 1992; **10**: 230–236.
17. Corrigan P, Russell FE, Wainschel J. Clinical reactions to antivenin. In: Rosenburg P, ed. *Toxins: Animal, Plant and Microbial*. Oxford: Pergamon, 1978; 457–465.
18. Culver P, Burch M, Polenza C, Wasserman L, Fenical W, Taylor P. Structure activity relationships for the irreversible blockade of nicotinic receptor agonist sites by lophotoxin and congeneric diterpene lactones. *Molecular Pharmacology* 1985; **28**: 436–444.
19. Daly JW. Biologically active alkaloids from poison frogs (Dendrobatidae). *Journal of Toxicology Toxin Reviews* 1982; **1**: 33–86.
20. Dehesa-Davila M. Epidemiological characteristics of scorpion sting in Leon, Guanajuato, Mexico. *Toxicon* 1989; **27**: 281–286.
21. De Silva A, Ranasinghe L. Epidemiology of snake bite in Sri Lanka: a review. *Ceylon Medical Journal* 1983; **28**: 144–154.
22. Donat JR, Donat JF. Tick paralysis with persistent weakness and electomyographic abnormalities. *Archives of Neurology* 1987; **38**: 59–61.
23. Editorial. *Lancet* 1980; **1**: 1009–1010.
24. Emmons P, McLennan H. Failure of acetylcholine release in tick paralysis. *Nature (London)* 1959; **183**: 474–475.
25. Endo T, Tamiya N. Structure–function relationships of postsynaptic neurotoxins from snake venoms. In: Harvey AL, ed. *Snake Toxins*. New York: Pergamon Press, 1991; 165–222.
26. Ennik F. Deaths from bites and stings of venomous animals. *Western Journal of Medicine* 1980; **133**: 463–468.
27. Ewan PW. Allergy to insect stings: a review. *Journal of the Royal Society of Medicine* 1985; **78**: 234–239.
28. Fredholm B. Studies on a mast cell degranulating factor in bee venom. *Biochemical Pharmacology* 1966; **15**: 2037–2042.
29. Frontali N, Ceccarelli B, Gorio A, Mauro A, Siekevitz P, Tzeng MC, Hurlbut P. Purification from black widow spider venom of a protein factor causing the depletion of synaptic vesicles at neuro-muscular junctions. *Journal of Cell Biology* 1976; **68**: 462–479.
30. Gan ZR, Gould RJ, Jacobs JW, Friedman PA, Polokoff MA. Echistatin. A potent platelet aggregation inhibitor from the venom of the viper Echis carrinatus. *Journal of Biological Chemistry* 1988; **263**: 19827–19832.
31. Glass TG jr. Early debridement in pit viper bites. *Journal of the American Medical Association* 1976; **235**: 2513–2516.
32. Gueron M, Ilia R, Sofer S. The cardiovascular system after scorpion envenomation. A review. *Clinical Toxicology* 1992; **30**: 245–258.
33. Harvey AL, Anderson AJ, Rowan EG. Toxins affecting ion channels. In: Harvey AL, ed. *Natural and Synthetic Neurotoxins*. London: Academic Press, 1993; 129–163.
34. Hasiba U, Rosenbach LM, Rockwell D, Lewis JH. DIC like syndrome after envenomation by the snake Crotalus horridus horridus. *New England Journal of Medicine* 1975; **292**: 505–507.
35. Heap BJ, Cowan GO. The epidemiology of snake bite presenting to British Military Hospital, Dharan during 1989. *Journal of the Royal Army Medical Corps* 1991; **137**: 123–125.
36. Hla-Mon. Patterns of acute renal failure in Burma. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*, 2nd Edn. Oxford: Oxford University Press, 1987; 18, 179.
37. Hmr ZS, Hyland KE, Kinzelbach R, Amr SS, Defosse D. Scorpions et piqures de scorpions en Jordanie. *Bulletin de al Societe de Pathologie Exotique Filiales* 1988; **1**: 369–379.
38. Huang TT, Lynch JB, Larson DL, Lewis SR. The use of excisional therapy in management of snake bite. *Annals of Surgery* 1974; **179**: 598–606.
39. Hurlbut WP, Ceccarelli B. Use of black widow spider venom to study the release of neurotransmitter. In: Ceccarelli B, Clementi F, eds. *Neurotoxins: Tools in Neurobiology*. New York: Raven Press, 1979; 87–115.
40. Jeyarajah R. Russels viper bite in Sri Lanka—A study of 22 cases. *American Journal of Tropical Medicine and Hygiene* 1984; **33**: 506–510.
41. Johnson CA. Management of snake bite. *American Family Physician* 1991; **44**: 175–180.
42. Jover E, Courand F, Rochet H. Two types of scorpion neurotoxins characterised by their binding to two separate receptor sites on rat brain synaptosomes. *Biochemical and Biophysical Research Communications* 1980; **95**: 1607–1614.
43. Karalliedde LD, Sanmuganathan PS. Respiratory failure following envenomation. *Anaesthesia* 1988; **43**: 753–754.
44. Kawai N, Yamagishi S, Saito M, Furuya K. Blockade of synaptic transmission in the squid giant synapse by a spider toxin (JSTX). *Brain Research* 1983; **278**: 346–349.
45. Krasnonos LN, Kovalenko AF, Ukolov NE. Sluchai massovykh ukusov karakurta v Uzbekistane. *Meditsinskia Parazitologia, Parazitarnye Bolemi (Moskva)* 1989; **4**: 39–42.
46. Kumar EB, Soomvo RS, Hamdani AA, Shimy NE. Scorpion venom cardiomyopathy. *American Heart Journal* 1992; **123**: 725–729.
47. Kuo Tp, Wu CS. Clinicopathological studies on snake bites in Taiwan. *Snake* 1972; **4**: 1–22.
48. Lee C, Chen D, Katz RL. Characteristics of nondepolarising neuro-muscular block. 1. Post junctional block by alpha bungarotoxin. *Canadian Journal of Anaesthesia* 1977; **24**: 213–219.
49. Lee CY, Chang CC, Chin TH. Pharmacological properties of cardiotoxin isolated from formosan cobra venom. *Naunyn-Schmiedebergs Archives of Pharmacology* 1968; **259**: 360–374.
50. Lucas S. Spiders in Brazil. *Toxicon* 1988; **26**: 759–772.
51. McLennan H, Oikawa I. Changes in function of the neuromuscular junction occuring in tick paralysis. *Canadian Journal of Physiology and Pharmacology* 1972; **50**: 53–58.
52. Markovic O, Rexova L. The components of various types of honeybee venoms. *Chemicke Listy* 1963; **17**: 767–784.
53. Merchant MR, Khanna LB, Almeida AF, Acharya VN, Mittal BV. Clinico-pathological study of acute renal failure following viperine snake bite. *Journal of the Association of Physicians of India* 1989; **37**: 430–433.
54. Miledi R, Potter LT. Acetylcholine receptors in muscle fibers. *Nature (London)* 1971; **233**: 599.
55. Mills AR, Passmore R. Pelagic paralysis. *Lancet* 1988; **1**: 161–164.
56. Morrison J, Pearn J, Covacevich J, Tanner C, Coulter A. Studies on the venom of Oxyuranus microlepidotus. *Journal of Chemical Toxicology* 1983–1984; **21**: 373–385.

57. Murnaghan MF, McConaill M. Peroneal nerve conduction in tick paralysis. *Irish Journal of Medical Sciences* 1967; **6**: 473–477.
58. Myint-Lwin, Warrell DA, Phillips RE, Tin-Nu-Swe, Tun-Pe, Maung-Maung-Lay. Bites by Russell's viper (vipera Russelli Siamensis) in Burma. Haemostatic, vascular and renal disturbances and response to treatment. *Lancet* 1985; **1**: 1259–1264.
59. Nakajima T. Pharmacological biochemistry of vespid venoms. In: Piek T, ed. *Venoms of the Hymenoptera*. London: Academic Press, 1986; 309–327.
60. Nelson BK. Snake envenomation. Incidence, clinical presentation and management. *Medical Toxicology and Adverse Drug Experience* 1989; **4**: 17–31.
61. Office of Population Census and Surveys (OPCS), London: OPCS, 1993.
62. Olivera BM, Gray WR, Zeikus R, McIntosh JM, Varga J, Rivier J, de Santos V, Cruz LJ. Peptide neurotoxins from fish hunting cone snails. *Science* 1985; **230**: 1339–1343.
63. Olivera BM, Rivier J, Clark C, Ramilo CA, Corpuz GP, Olivera BM, Gray WR, Zeikus R, McIntosh JM, Varga J, de Sentos V, Cruz LJ. Diversity of Conus neuropeptides. *Science* 1990; **249**: 251–264.
64. Pearn J. Neuro-muscular paralysis caused by tick envenomation. *Journal of Neurological Sciences* 1977; **34**: 37–42.
65. Petrenko AG, Kovalenko VA, Shamotienko IN, Surkova IN, Tarasyuk TA, Ushkaryov, Yu A, Grishin EV. Isolation and properties of the alpha latrotoxin receptor. *EMBO Journal* 1990; **9**: 2023–2027.
66. Pugh RNH, Theakstone RDG. A clinical study of viper bite poisoning. *Annals of Tropical Medicine and Parasitology* 1987; **81**: 135–149.
67. Reid HA. Bites by foreign venomous snakes in Britain. *British Medical Journal* 1978; **1**: 1598–1600.
68. Reid HA. Snake bite. Part 1. Clinical features, Part 2 Treatment. *Tropical Doctor* 1972; **2**: 155–163.
69. Reid HA. Snake bite and other venomous bites and stings. In: Maegraith B, ed. *Clinical Tropical Diseases*, 7th Edn. Oxford: Blackwell Scientific Publications, 1980; 411.
70. Reid HA, Chan KE, Thean PC. Prolonged coagulation defect (defibrination syndrome) in Malayan pit viper bite. *Lancet* 1963; **1**: 621–626.
71. Reid HA, Theakston RDG. The management of snake bite. *Bulletin of the World Health Organization* 1983; **61**: 885–895.
72. Romey G, Abita JP, Chicheportiche R, Rochat H, Lazdunski M. Scorpion neurotoxin: mode of action on neuro-muscular junctions and synaptosomes. *Biochimica et Biophysica Acta* 1976; **448**: 607–619.
73. Sanders WE. Intoxications from the seas: Ciguatera, scombroid and paralytic shell fish poisoning. *Infectious Disease Clinics of North America* 1987; **1**: 665–676.
74. Schmidt JO. Allergy to Hymenoptera venoms. In: Piek T, ed. *Venoms of the Hymenoptera*. London: Academic Press, 1986; 509–546.
75. Senanayaka N, Roman GC. Disorders of neuro-muscular transmission due to natural environmental toxins. *Journal of Neurological Sciences* 1992; **107**: 1–13.
76. Shiau Lin SY, Tseng WC, Lee CY. Pharmacology of scorpion toxin II in the skeletal muscle. *Naunyn-Schmeidebergs Archives of Pharmacology* 1975; **289**: 359–368.
77. Simon TL, Grace TG. Envenomation coagulopathy in wounds from pit vipers. *New England Journal of Medicine* 1983; **305**: 443–447.
78. Snyder CC. Animal bite wounds. *Hand Clinics* 1989; **5**: 571–590.
79. Sutherland SK. Deaths from snake bite in Australia 1981–1991. *Medical Journal of Australia* 1992; **157**: 741–746.
80. Sutherland SK, Lovering KE. Antivenoms: use and adverse reactions over a 12 month period in Australia and Papua New Guinea. *Medical Journal of Australia* 1979; **ii**: 671–674.
81. Swaroop S, Grab B. Snake bite mortality in the world. *Bulletin of the World Health Organization* 1965; **10**: 35–37.
82. Tiwari I, Johnston WJ. Blood coagulability and viper envenomation. *Lancet* 1986; **1**: 613–614.
83. Tu AT. Biotoxicology of sea snake venoms. *Annals of Emergency Medicine* 1987; **16**: 1023–1028.
84. Viger JR, Glynn MFX. Ancrod (Arvin) as an alternative to heparin anticoagulation for cardiopulmonary bypass. *Anesthesiology* 1989; **71**: 870–877.
85. Warrell DA. Animal poisons. In: Manson-Bahr PEC, Bell DR, eds. *Manson's Tropical Diseases*. London: Bailliere Tindall, 1987; 855–898.
86. Warrell DA. Snake venoms in science and clinical medicine; Russell's viper: biology, venom and treatment of bites. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989; **83**: 732–740.
87. Warrell DA. Venomous bites and stings. *Medicine International* 1992; **107**: 4529–4533.
88. Warrell DA, Looareesuwan S, White NJ, Theakston RDG, Warrell MJ, Kosakarn W, Reid HA. Severe neurotoxic envenoming by Malayan krait Bungurus candidus (Linnaeus): response to antivenom and anticholinesterase. *British Medical Journal* 1983; **286**: 678–680.
89. Wasserman SI. Mediators of immediate hypersensitivity. *Journal of Allergy and Clinical Immunology* 1983; **72**: 101–118.
90. Watt G, Padre L, Tuazon L, Theakstone RDG, Laughlin LW. Tourniquet application after cobra bite. Delay in the onset of neurotoxicity and dangers of sudden release. *American Journal of Tropical Medicine and Hygiene* 1988; **38**: 618–622.
91. Watt G, Padre L, Tuazon L, Theakston RDG, Laughlin L. Bites by the Philippine cobra (Naja Naja Philippinensis): Prominent neurotoxicity with minimal local signs. *American Journal of Tropical Medicine and Hygiene* 1988; **39**: 306–311.
92. Watt G, Theakston RDG, Hayes CG, Yambao ML, Sangalang R, Ranoa CP, Alquizalas E, Warrell DA. Positive response to edrophonium in patients with neurotoxic envenoming by cobras (Naja Naja Philippinensis). A placebo controlled study. *New England Journal of Medicine* 1986; **315**: 1444–1448.
93. Weber M, Changeux JP. Binding of Naja nigricollis (3H) alpha toxin to membrane fragments from Electrophorus and Torpedo electric organs. 1. Binding of the tritiated alpha neurotoxin in the absence of effector. *Molecular Pharmacology* 1974; **10**: 1–14.
94. White RR, Weber RA. Poisonous snake bite in Central Texas. Possible indicators for antivenin treatment. *Annals of Surgery* 1991; **213**: 466–472.
95. Zova JA, Swanson MC, Yunginger JW. How common is unrecognised Hymenoptera venom allergy in the general population? *Journal of Allergy and Clinical Immunology* 1984; **73**: 139.