Snake bite

David A Warrell

Snake bite is a common and frequently devastating environmental and occupational disease, especially in rural areas of tropical developing countries. Its public health importance has been largely ignored by medical science. Snake venoms are rich in protein and peptide toxins that have specificity for a wide range of tissue receptors, making them clinically challenging and scientifically fascinating, especially for drug design. Although the full burden of human suffering attributable to snake bite remains obscure, hundreds of thousands of people are known to be envenomed and tens of thousands are killed or maimed by snakes every year. Preventive efforts should be aimed towards education of affected communities to use proper footwear and to reduce the risk of contact with snakes to a minimum through understanding of snakes' behaviour. To treat envenoming, the production and clinical use of antivenom must be improved. Increased collaboration between clinicians, epidemiologists, and laboratory toxinologists should enhance the understanding and treatment of envenoming.

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Introduction

> "At tibi, Laeve miser, fixus praecordia pressit Niliaca serpente cruor, nulloque dolore Testatus morsus subita caligine mortem Accipis et socias somno descendis ad umbras."
>
> "But as for you, unlucky Laevus, your blood, congealed by a serpent of the Nile, choked your heart; you evinced no sign that the bite was painful, but in sudden darkness embraced death and went down to join the ghosts of your comrades."[1]

Fear of snakes is a powerful, primordial, and, possibly, innate human emotion that has fascinated experimental psychologists[2] and evolutionists.[3] But snakes are not yet taken sufficiently seriously as agents of human disease,[4] and the scientific insights provided by the clinical phenotype of human envenoming have been ignored for a long time. More than a century of research has shown that snake venoms are rich sources of pharmacologically active peptides and proteins (table). Therefore, every patient envenomed by snake bite becomes a natural experiment, providing new insights into the pathophysiological actions of venom toxins, while presenting a humanitarian and therapeutic challenge. This experiment is, however, biologically inappropriate since venoms have been evolutionarily selected to subdue prey animals that are much smaller than human beings. The scientific study of snake bite is part of clinical toxinology, that subspecialty of toxicology that deals with the effects of natural toxins of microbial, animal, and plant origin on human beings and domestic animals, particularly their prevention, diagnosis, treatment, epidemiology, and pathophysiology. For a long time, the specialty has had an inadequate evidence base, uncritical attitudes to results that scarcely deserved consideration as data, rigid adherence to outworn traditional ideas, poor understanding of pathophysiological mechanisms, and inadequate discussion and collaboration with laboratory scientists. Some features of snake bite that are of scientific interest and importance for improved understanding of a neglected specialty of medicine are discussed here.

Snake evolution, taxonomy, and behaviour

The proper study of snake bite toxinology requires an understanding of snake zoology. Venomous snakes are widely distributed in almost every country between latitudes 50°N and 50°S in the western hemisphere and 65°N (Scandinavia) and 50°S in the eastern hemisphere. Sea snakes are found in the Indian Ocean and Pacific Ocean between latitudes 30°N and 30°S. On land, venomous snakes have been found from sea level up to altitudes higher than 4000 m in the Americas[5] and Himalayas,[6] and sea snakes dive to depths greater than 100 m in the oceans.[7]

Fossils of snakes with venomous fangs from at least the Lower Miocene have been discovered.[8] Most of the roughly 2650 advanced species of snakes (*Caenophidia*)—families *Viperidae* (vipers, adders, pit vipers, and mocassins), *Elapidae* (cobras, mambas, kraits, coral snakes, Australasian venomous snakes, and sea snakes), *Atractaspididae* (burrowing asps), and *Colubridae sensu lato*—have the ability to inject or inoculate, using modified teeth (fangs), venom secreted by oral glands (figure 1).

Search strategy and selection criteria

The Cochrane library, Google, and PubMed were searched from their inceptions with search terms "snake bite", "envenomation", "envenoming", "snake venom", "snake venom toxin", "antivenom", "antivenin", and scientific (Latin) names of individual snake species. There were no language restrictions. Although the focus was on papers published in the past 5 years, frequently referenced and highly respected older publications are also included. Reviews and book chapters are cited to give readers more details and references than are provided in this Seminar. The reference list was modified in response to comments from peer reviewers. Other sources included are the author's personal archive of books and papers, many pre-dating PubMed and published in local journals that are not listed by PubMed, in other European languages and Thai; and discussions and correspondence with colleagues during the past 40 years.

	Example of toxin	Snake	Function
Three-finger-fold polypeptide toxins	α bungarotoxins	*Bungarus* spp (other *Elapidae*, *Colubridae*)	Paralysis by blocking nicotinic acetylcholine receptors
Angiotensin-converting enzyme inhibitors and bradykinin-potentiating peptides	..	*Viperidae*	Hypotension
Acetylcholinesterase	..	*Elapidae*	Paralysis by destroying acetylcholine
Anticholinesterase	Fasciculins	*Dendroaspis* spp	Paralysis (with dendrotoxins) by depolarising neuromuscular block
Disintegrin and metalloproteinase (ADAM)	Haemorrhagins (atrolysins, jararhagin); procoagulants (fibrolase, ecarin, Russell's viper venom factor-X activator)	*Viperidae, Elapidae*	Endothelial damage, bleeding, necrosis
AVIT sequence cysteine-rich proteins	Mamba intestinal toxin (prokineticin)	*Dendroaspis polylepis*	Painful gut spasm, hyperalgesia, CNS effects
Cobra venom factor, complement C3	Cobra venom factor	*Elapidae*, *Viperidae*	Tissue damage
Small basic myotoxic peptides	Crotamine and crotasin	*Crotalus durissus* subspecies (some circumscribed geographical populations)	Muscle necrosis and spasm
Calcium dependent-type galactose-binding lectins	Rhodocytin	*Calloselasma rhodostoma* (and other *Viperidae*, *Elapidae*)	Platelet effects
Cysteine-rich secretory proteins	..	*Elapidae*, *Viperidae*, *Colubridae*	Smooth muscle inhibition
Cysteine proteinase inhibitors	Cystatin	*Viperidae*, *Elapidae*	Inhibit metalloproteinases
Endothelins	Sarafotoxins	*Atractaspis* spp	Hypertension, myocardial effects
Factor-V, factor-X activators	..	*Viperidae*, Australasian *Elapidae*	Coagulopathy
Kallikrein (kininogenase) serine proteases	..	*Viperidae*	Hypotension
Kunitz-type proteinase inhibitors	Dendrotoxins	*Dendroaspis* spp (and other *Elapidae*)	Depolarising neuromuscular block (inhibition of circulating serine proteases)
L-amino oxidase	..	All	Apoptosis
Natriuretic peptides	..	*Elapidae*: atrial-type and brain-type; *Viperidae*: C-type	Hypotension
Nerve growth factor	..	Many	Not known
Phospholipases A_2	β bungarotoxins	*Bungarus* spp (many phospholipases A_2 in venoms of most snakes)	Paralysis by presynaptic block and destruction of nerve terminals, myotoxicity, haemolysis, inflammation, necrosis, platelet effects
Vascular endothelial growth factor (VEGF)	VEGF-homologous potent hypotensive factor	*Viperidae*	Endothelial damage, permeability, oedema, hypotension

Table: **Some groups of snake venom proteins and peptides of scientific and clinical importance**

A few venom toxins are modified salivary gland secretions, whereas most venom genes originated from other organs through repeated episodes of gene duplication and recruitment.[9,10] Recruited toxins retain the bioactivity of the ancestral proteins in at least some of their isoforms. Cysteine crosslinked ancestral proteins are the most likely to expand into functionally diverse, new toxin multigene families (table).

Taxonomic and evolutionary associations of many existing snake taxa have been established, increasingly through DNA-derived phylogeny.[11,12] Of special importance for clinicians and antivenom producers has been the clarification of the nomenclature and identification of several groups of snakes of recognised medical importance, such as African spitting cobras,[13] African–Asian saw-scaled vipers,[14] Asian cobras (*Naja* spp),[15] Russell's vipers (*Daboia russelii* and *D siamensis*),[16] and arboreal pit vipers.[17] Much of the world's medically important venomous herpetofauna has been identified,[18] and the geographical distribution of important species is known. However, new species of clinical and toxinological interest continue to be discovered.[19–22] Information about snakes' habits and cycles of diurnal and seasonal activity that determine the risk of interactions with people is almost uniformly lacking for most species, except for some species of rattlesnakes and other New World pit vipers.[5,23] This knowledge is essential to plan community education to reduce the risk of accidental encounters between people and dangerous snakes.

Venom biochemistry and pharmacology

Snake venoms are the most complex of all natural venoms and poisons.[24,25] The venom of any species might contain more than 100 different toxic and non-toxic proteins and peptides, and also non-protein toxins, carbohydrates, lipids, amines, and other small molecules. Venomous animals and their venoms have evolved to take full advantage of many ecological niches and prey species that include a range of animals and their eggs—ie, annelids, onychophorans, molluscs, arthropods, amphibians, reptiles, fish, birds, and mammals.[26,27] Evolutionary pressures have selected venom toxins that are specific for many targets in animal tissues (table).[9,10] The toxins of most importance in human envenoming include those that affect the nervous, cardiovascular, and haemostatic systems, and cause tissue necrosis.

Snake venom neurotoxins block or excite peripheral neuromuscular junctions by acting at various sites

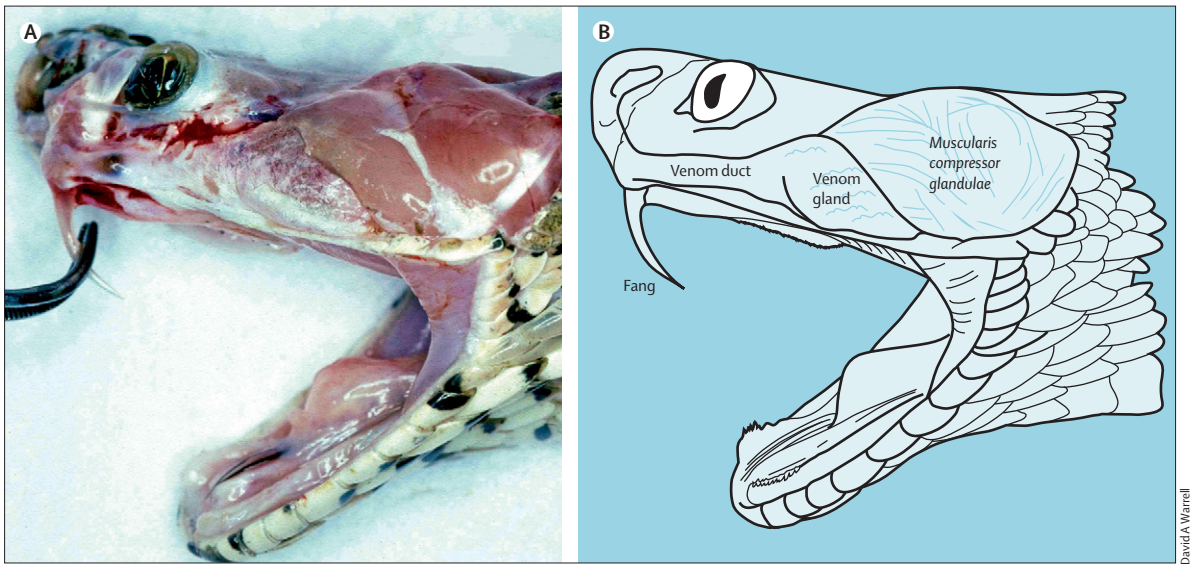

Figure 1: **Venom apparatus of Russell's viper (*Daboia siamensis*)**
(A) Dissected specimen. (B) Annotated diagram of dissected specimen.

(figure 2). Snake venom neurotoxins are thought to be virtually excluded from the CNS[29]—eg, two low-molecular-weight phospholipases A_2 from the venom of Russell's viper were innocuous when given intravenously to rodents but were lethal or sedative when given intraventricularly.[30] However, a common symptom of snake bite is drowsiness, suggesting the possibility of a central sedative action such as that associated with a small non-protein toxin that is found in king cobra (*Ophiophagus hannah*) venom.[31]

Most venom neurotoxins bind to their receptors with high affinity, making reversal of paralysis by antivenom implausible. However, rapid improvement in neurotoxicity has been noted when postsynaptic toxins were implicated—eg, after envenoming by Asian cobras and Australasian death adders (*Acanthophis* spp).[32] Binding of toxin α, a three-finger-fold polypeptide from the venom of the black-necked spitting cobra (*Naja nigricollis*), to the acetylcholine receptor was reversible by antibodies in vitro and in rodents,[33,34] although this venom is not neurotoxic in man.[35] By prolonging the effect of acetylcholine, anticholinesterases sometimes reverse postsynaptic neurotoxicity in envenomed patients.[36,37] Paralysis in envenomed people starts with ptosis, external ophthalmoplegia, and mydriasis, descending to involve muscles innervated by the other cranial and spinal nerves and leading to bulbar and respiratory paralysis and, if ventilation is supported, eventually to total flaccid paralysis (figure 3). The initial involvement of levator palpebrae superioris, as in botulism, myasthenia gravis, and Graves' disease, might be attributable to the small size, unusual anatomy and physiology, and the low safety factor of the neuromuscular junctions of this muscle, features shared by all the extraocular muscles.[38–40] The subsequent pattern of descending paralysis is difficult to explain neurophysiologically.

Hypotension after snake bite is attributable to various venom activities, including permeability factors that cause hypovolaemia from extravasation of plasma (figure 4), and toxins acting directly or indirectly on cardiac muscle, vascular smooth muscle, and on other tissues. An oligopeptide from the venom of the Brazilian jararaca (*Bothrops jararaca*) activated bradykinin[41] and, through a bradykinin-potentiating peptide, prolonged bradykinin's hypotensive effect by inactivating the peptidyl dipeptidase that destroys bradykinin and converts angiotensin I to angiotensin II. This discovery led to the synthesis of captopril and other angiotensin-converting enzyme (ACE) inhibitors. Bradykinin-potentiating and ACE-inhibiting peptides have been found in several other crotaline and viperine venoms. Venom of the Israeli burrowing asp (*Atractaspis engaddensis*: *Atractaspididae*) contains sarafotoxins that have 60% sequence homology with endo genous mammalian endothelins. Sarafotoxins and endothelins are 21-aminoacid polypeptides that potently vasoconstrict coronary and other arteries, and delay atrioventricular conduction.[42] Natriuretic peptides in mammalian tissues and in many snake venoms reduce blood pressure by several mechanisms. The B-type natriuretic peptide in the venom of the green mamba (*Dendroaspis angusticeps*) has therapeutic potential.[43]

Some snake venoms contain serine proteases, metalloproteinases, C-type lectins, disintegrins, and phospholipases that disturb haemostasis by activating or inhibiting coagulant factors or platelets, and disrupting vascular endothelium.[44] Viperid and Australasian elapid venoms contain procoagulant enzymes—eg, thrombin-like fibrinogenases and activators of prothrombin, factors V, X, and XIII, and endogenous plasminogen. Toxins bind to a range of platelet receptors, inducing or inhibiting aggregation. Anticoagulant venom

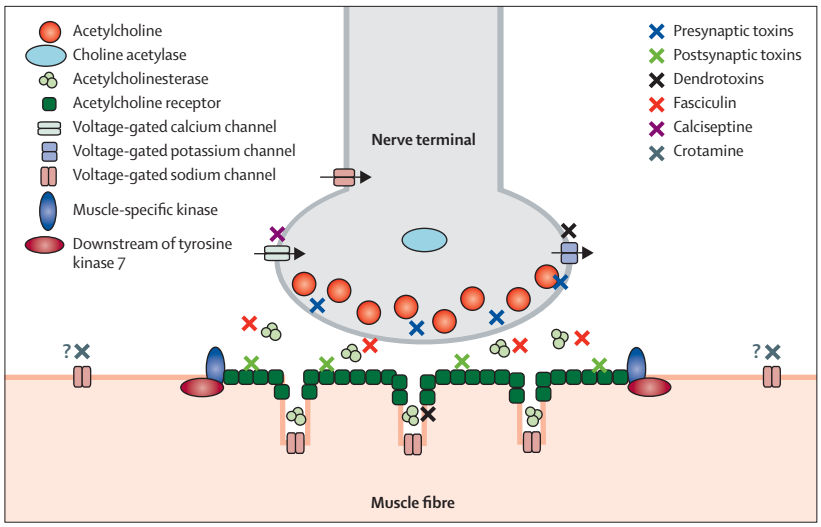

Figure 2: **Neuromuscular junction showing ion channels and sites of action of presynaptic and postsynaptic snake venom neurotoxins, and three neurotoxins specific to mamba (*Dendroaspis*) venoms—ie, dendrotoxins, fasciculins, and calciseptine**

Binding of crotamine to voltage-gated sodium channel is tentative. Adapted with permission of Oxford University Press.[28]

phospholipases A_2 hydrolyse or bind to procoagulant phospholipids and inhibit the prothrombinase complex. Spontaneous systemic bleeding (figure 5) is caused by haemorrhagins (metalloproteinases, some with disintegrin-like and other domains), which damage vascular endothelium. The combination of consumption coagulopathy, anticoagulant activity, impaired and few platelets, and vessel wall damage can result in severe bleeding, a common cause of death after bites by *Viperidae*, Australian *Elapidae*, and some *Colubridae*.

A range of venom myotoxic and cytolytic factors might contribute to local tissue necrosis at the site of the bite (figure 6). Studies of terciopelo (*B asper*) venom-induced necrosis implicate zinc-dependent metalloproteinases and myotoxic phospholipases A_2.[45] Other digestive hydrolases, hyaluronidase, polypeptide cytotoxins (*Elapidae*), and perhaps secondary effects of inflammation are implicated in envenomings by different snake species. In some cases, ischaemia, resulting from thrombosis, intracompartmental syndrome, or application of a tight tourniquet, contributes to tissue loss. Myotoxic phospholipases A_2 in venoms of some species of *Viperidae* and *Elapidae*, especially sea snakes, cause generalised rhabdomyolysis that is often complicated by acute renal failure (figure 7).

For **estimates of snake bite mortality in India** see pp 107–108 of http://cbhidghs.nic.in/writereaddata/mainlinkFile/Health%20Status%20Indicators.pdf

Epidemiology: burden of human suffering

In 2009, snake bite was recognised for the first time by WHO as a neglected tropical disease.[46] In tropical countries, it is largely an occupational disease for agricultural workers, and, as a result, can affect food production. Snake bite causes substantial human mortality and disability—physical and psychological—but its recognition as an important international public health issue has been hindered by insufficient epidemiological data.

South and southeast Asia were identified as having the highest snake bite incidence and associated mortality.[47–49] Few reliable absolute data are available because snake bite occurs predominantly in rural areas of tropical developing countries and is, therefore, likely to be under-reported. Swaroop and Grabb[47] recognised that their global total of 30 000–40 000 deaths from snake bite per year underestimated the true mortality rate because they relied on hospital and dispensary admissions and excluded central Europe and north Asia. Chippaux[48] extrapolated point incidences obtained in particular locations within countries to estimate global totals per year of 5 400 000 bites, more than 2 500 000 envenomings, and about 125 000 deaths. Kasturiratne and colleagues[49] did not include the essential heterogeneity of the incidence of snake bite within and between countries, and generalised the incidences between adjacent territories, with some unexpected results (eg, in Caribbean and west Pacific islands). Their estimated ranges per year were very wide—ie, 421 000–1 841 000 envenomings and 20 000–94 000 deaths worldwide.[49] These reviews[47–49] were incomplete or flawed, or the methods of data acquisition were not disclosed, and data extrapolations were unjustified. However, results of well designed national surveys in Bangladesh (6000 deaths estimated per year)[50] and India[51] begin to show the true scale of the predicament.

In 1924, 19 867 deaths from snake bite were reported in (then) British India (including modern Pakistan, Bangladesh, and Burma).[52] Ever since, India has been credited with a higher mortality rate from snake bite than has any other country, but reported estimates of its yearly snake bite mortality range from 1331 (revised) in 2007 and 1364 (provisional) in 2008 (Government of India) to about 50 000.[53] The Million Deaths Study, which was done in India during 2001–03, was based on representative, resampled, routine household interviews about death with medical assessment.[51] Its results might finally convince those who doubt the importance of snake bite in this populous country.

The only reliable way to assess the true rates of morbidity and mortality caused by snake bite in a particular area is with properly designed community-based epidemiological studies that are independent of all the vagaries of hospital reporting. In the west African savanna, per 100 000 population per year, there were up to 500 snake bites and between four and 40 deaths,[54–56] In Malumfashi, Nigeria, 19% of survivors had persistent sequelae.[55] In Kilifi, Kenya, per 100 000 population per year, there were 151 bites and seven deaths (about 1% of all deaths) and 36% of survivors had permanent sequelae.[57] In Burdwan, west Bengal, per 100 000 population per year, there were 160 bites and 16 deaths,[58] and in eastern Terai, Nepal, per 100 000 population per year, there were 162 deaths.[59]

To improve precision, clinicians and pathologists should be encouraged to use the specific International

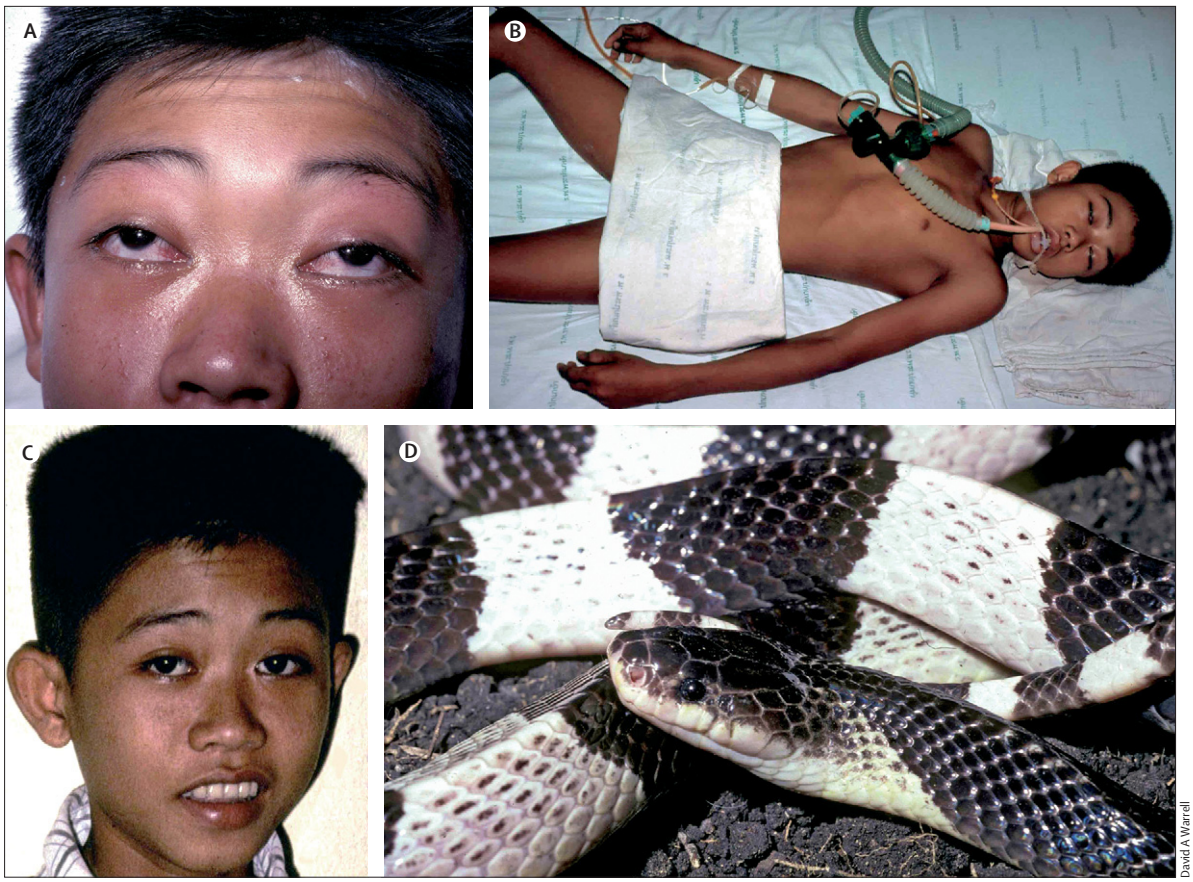

Figure 3: **Descending paralysis of muscles innervated by cranial and spinal nerves in a boy envenomed by a Malayan krait (*Bungarus candidus*) in eastern Thailand**[37]
(A) Early ptosis, 3 h after the snake bite; (B) complete flaccid paralysis on manual ventilation for 49 h; (C) recovery after discharge from hospital 5 days after the snake bite; (D) Malayan krait (*Bungarus candidus*), the species responsible for the bite, in Chantaburi, Thailand. Patient's parents provided verbal permission for publication of images.

Classification of Diseases code T63.0 (toxic effect of contact with snake venom) in certification of death.[60] Forensic diagnosis of snake bite can be improved by use of immunodiagnosis.[61,62] Designation of snake bite as a notifiable disease would greatly improve its chances of being reported.

In survivors of snake bite, the main cause of permanent disability is local necrosis.[45] Large areas of skin necrosis necessitate debridement and grafting (figure 6), whereas destruction of deep tissues might necessitate amputation. Arthrodesis, chronic ulceration, osteomyelitis, and malignant transformation are long-term consequences. Cerebral hypoxia from delayed resuscitation after respiratory paralysis and strokes cause permanent neurological deficits. Chronic dialysis-dependent renal failure is unsustainable in some developing countries, such as Sri Lanka. Acute haemorrhagic infarction of the pituitary and adrenal glands leads to panhypopituitarism in victims of Russell's viper envenoming in Burma and south India.[63]

Prevention of snake bites

In the USA,[5] India and Pakistan,[54,64] and Burma,[65] attempts to eradicate venomous snakes by offering bounties in parts of the countries were often initially successful. Such efforts, however, are unwise for ecological reasons and because control of rodent populations by snakes is important for agriculture and human health. In Tharrawaddy (Burma), Chainat (Thailand), and Kerala (India), declining numbers of venomous snakes are seen as the underlying cause of depredation of crops by rats and leptospirosis epizootics. Community education to reduce the risk of bites is a better approach than is the eradication of venomous snakes. It should be based on knowledge of the circumstances in which most bites occur, the preferred habitats of dangerous species, and their peak periods of activity—ie, time of day, season, and climate. For example, people are bitten by kraits (genus *Bungarus*) in south Asia almost exclusively at night while lying asleep on the ground in their homes.[59,66] Such distinctive epidemiology predicates a means of prevention. In a high-risk area of eastern Terai, Nepal, sleeping under a mosquito net afforded protection.[67]

In tropical countries, most snake bites are on the lower legs and feet, but local attitudes to wearing protective footwear are highly ambivalent. In Burma,

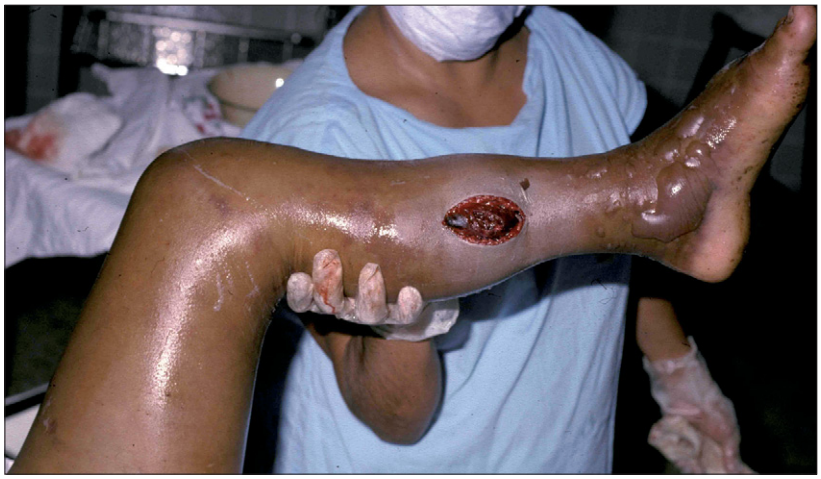

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Figure 4: **Massive swelling of a bitten limb with bruised muscle bulging out of a fasciotomy wound in a Waorani boy bitten by a common lance-head (*Bothrops atrox*) in eastern Ecuador**
Patient's parents provided verbal permission for publication of image.

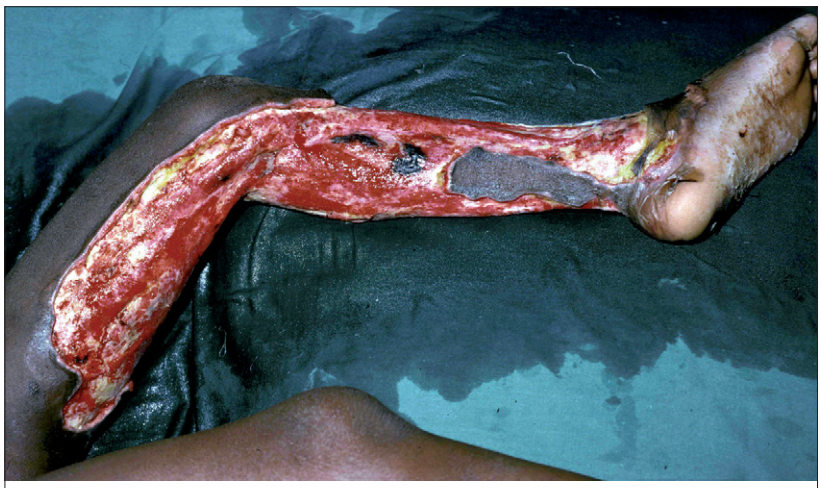

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Figure 5: **Spontaneous bleeding from the gingival sulci of a boy bitten by a Papuan taipan (*Oxyuranus scutellatus canni*) near Port Moresby, Papua New Guinea**
Patient's parents provided verbal permission for publication of image.

Russell's vipers are so common in the paddy fields that some farmers wear boots made of leather, plaited palm leaves, or woven grass for protection whereas others avoid this sensible practice for fear of provoking the snakes.[65] Light-weight boots, impervious to snake fangs, were developed in Burma and proved to be acceptable and affordable.[68]

First aid

The priorities for treatment of people bitten by snakes are transport to medical care as quickly as possible and the delay of life-threatening shock and respiratory paralysis until professional care is available. In most tropical developing countries, traditional healers undertake the immediate treatment of snake bite, using topical and ingested herbs, incisions, snake stones, ligatures, and other injurious techniques.[69–71] Traditional treatment delays presentation, distorts the clinical picture, and can cause bleeding, infection, gangrene, and other complications. Modern methods of health promotion should be applied to educate affected communities. Swift transport to hospital or dispensary should be encouraged, and ineffective and harmful traditional treatments should be discouraged.

Unless a bite by a neurotoxic elapid can be excluded, the bitten limb should be bandaged at a pressure of about 50–70 mm Hg and immobilised with a splint (pressure immobilisation),[72] or a pressure pad should be applied at the site of the bite.[73,74] Obstruction of lymphatic and venous drainage delays systemic absorption of large-molecular-weight neurotoxins without the use of tight tourniquets, which are dangerous. However, the clinical efficacy of these methods has not been adequately investigated.[74] Both techniques require the use of equipment, diminishing their practicability in developing countries, and pressure immobilisation has been difficult to teach and apply effectively.[75] Investigations of other methods—such as the early use of antivenom, rapid transport of patients to hospitals in rural areas by volunteer motorcyclists, and education of paramedics and ambulance crews about how to resuscitate patients in transit to hospital—are in progress.

Identification of envenoming species

The enormous interspecies diversity of venom actions is ignored in reports of unidentified snake bites. Such descriptions are as futile as those of cases of undiagnosed fever. Attempts to capture or kill the snake that has bitten someone are dangerous and ecologically destructive, and should be discouraged. However, even if the snake is available for examination, it might be misidentified, leading to inappropriate treatment.[76] Expert herpetologists have made fatal errors of species recognition.[77] Identification of the species on the basis of descriptions provided by the victims or their companions or recognition from pictures is often unreliable. A useful method is to distinguish clinical syndromes of envenoming by analysis of a series of reliably identified bites.[53,76] When the identification of the snake species cannot be confirmed by examination by an expert, indirect confirmation is possible by immunological detection of toxin antigens in the victim's blood or tissue fluids. Immunodiagnosis of snake bite has been refined from initial simple immunoprecipitation,[61] immunodiffusion and counter-current immunoelectrophoresis,[78] to a sensitive RIA,[79] EIA (now available commercially in Australia),[80,81] and avidin-biotin EIA.[82] mRNA from the venom gland has been detected in stored samples with RT-PCR.[83] Repeated measurement of

venom antigenaemia in patients is a useful method to assess the severity of envenoming, venom pharmacokinetics, response to antivenom treatment, and recurrence of envenoming.[81,84,85] A limitation of the use of immunoassays is that venom antigens differ in their immunogenicity. Small molecules with little immunogenicity, such as oligopeptides, might not be detected with immunoassays or neutralised by antivenoms. Disappearance of detectable venom antigenaemia is often equated imprecisely with elimination of all venom toxins, with misleading conclusions.[81,86–88]

Antivenom

Role of antivenom

The only specific antidote to the toxins in snake venom is hyperimmune globulin from an animal that has been immunised with the appropriate venom.[18] Albert Calmette's introduction of sérum antivenimeuse for the treatment of envenoming in 1895 was quickly accepted without formal clinical trials.[89] More than a century later, immunoglobulin antivenoms are accepted as essential drugs but reappraisal is needed. The limitations of antivenom treatment should be recognised. Patients with respiratory, circulatory, and renal failure need urgent resuscitation as well as antivenom.

Restoration of blood coagulability

Blood incoagulability, usually resulting from consumption coagulopathy caused by venom procoagulants, but rarely by venom anticoagulants, is a common outcome of envenoming by many species of *Viperidae*, Australasian *Elapidae*, and a few species of *Colubridae*. Incoagulability is easily assessed with the bedside 20 min whole-blood-clotting test,[90] and is associated with plasma fibrinogen concentrations of less than 0·5 g/L.[91]

Most authorities have considered placebo-controlled trials of antivenoms to be unethical, but results of observational and randomised controlled clinical studies have provided persuasive evidence that these agents can correct venom-induced haemostatic abnormalities. For example, in 43 patients with abnormal blood clotting after envenoming by Malayan pit vipers (*Calloselasma rhodostoma*) who could not be treated with antivenom, the duration of coagulopathy was 2–26 days.[92] However, in seven patients given small doses of specific antivenom intravenously 9–64 h after they were bitten, normal clot quality was restored within 2–28 h.[93] One patient envenomed by *C rhodostoma* developed local and intrapulmonary bleeding, incoagulable blood, and venom antigenaemia that persisted for 88 h after the bite.[94] However, within 6 h of administration of specific antivenom, blood coagulability was restored and venom antigenaemia became undetectable.[94] These results were confirmed in a randomised controlled trial in which blood coagulability was restored within 6 h after administration of the first dose of three different antivenoms in 40 of 46 patients bitten 2–72 h before treatment.[95]

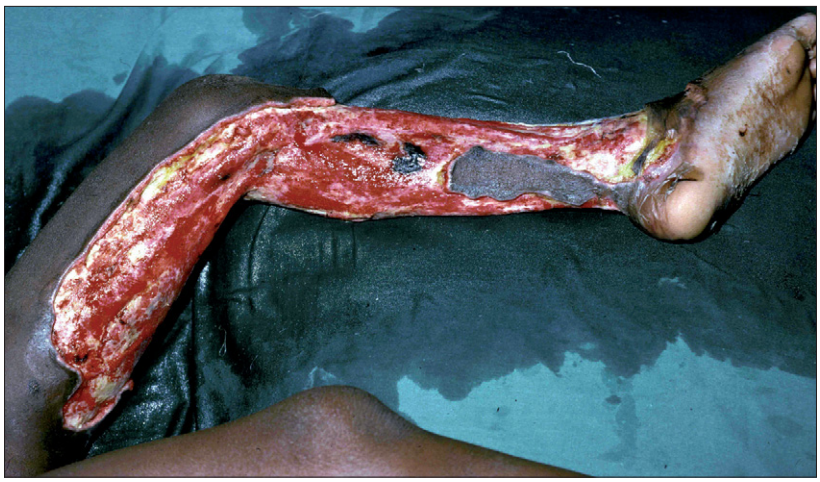

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Figure 6: **Extensive dermonecrosis in a girl 3 weeks after being bitten by Ashe's spitting cobra (*Naja ashei*) near Kilifi in coastal Kenya**
Patient's parents provided verbal permission for publication of image.

In patients admitted with incoagulable blood, indicative of consumption coagulopathy, at various times (hours to days) after being envenomed, the median time for restoration of blood coagulability after a loading dose of specific antivenom several times higher than would normally be considered sufficient, was 6 h or less for bites by Nigerian saw-scaled viper (*Echis ocellatus*),[90,96–98] *D siamensis*,[99] *C rhodostoma*,[95,100] *Cryptelytrops albolabris* and *macrops*,[101] *B jararaca*,[102] *B atrox*,[103] and *B atrox* and *B bilineatus*.[104] When venom antigenaemia was measured it rapidly became undetectable. These results indicate that, if venom antihaemostatic toxins are neutralised by a sufficient dose of specific antivenom, the liver can restore coagulable levels of clotting factors within a median of about 6 h, as was first reported by Rosenfeld and colleagues[105] in envenoming by *B jararaca*. For example, in Burma, 18 patients with incoagulable blood after envenoming by Russell's viper were given 2·5 times the normal recommended dose of antivenom. In seven who were tested every hour, coagulability was restored after 3–6 h. In the other 11 patients, blood was coagulable when first tested 6 h after treatment.[99] Therefore, the 20 min whole-blood-clotting test should be repeated about 6 h after every dose of antivenom as an indication of whether antihaemostatic toxins have been neutralised; as a basis to decide whether another dose of antivenom is needed; and to ensure that the patient does not remain susceptible to fatal or debilitating haemorrhage for any longer than is necessary after administration of an inadequate first dose of antivenom.

The results of two studies, however, have contradicted the efficacy of antivenoms produced by Commonwealth Serum Laboratories for Australasian snake venom-induced consumption coagulopathy.[86,87] Data for blood coagulation from patients envenomed by taipans (*Oxyuranus scutellatus canni*) in Papua New Guinea,[86,106]

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Figure 7: **Neurotoxicity (bilateral ptosis and facial paralysis), myoglobinuria resulting from generalised rhabdomyolysis, and acute renal failure in a girl bitten by Russell's viper (*Daboia russelii*) near Anuradhapura, Sri Lanka**
Patient's parents provided verbal permission for publication of image.

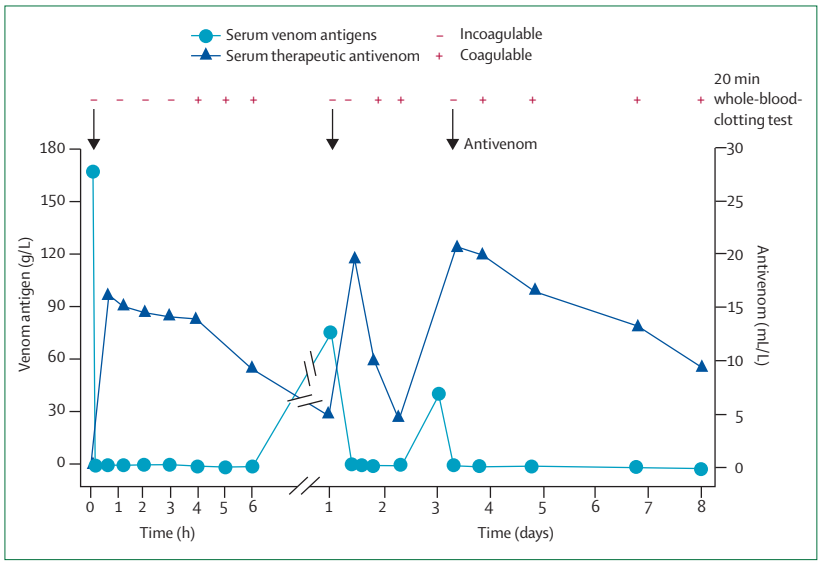

Figure 8: **Recurrent coagulopathy and venom antigenaemia in a patient envenomed by Malayan pit viper (*Calloselasma rhodostoma*) who needed three doses of antivenom to restore blood coagulability**

and venom antigenaemia and clotting factors measured in blood samples from clinical cases of bites by different snake species throughout Australia[87] were modelled mathematically. The authors concluded that antivenoms had no effect on the transient coagulopathy in these patients and they also questioned the usefulness of antivenoms generally. Their conclusions are incompatible with the data for coagulopathy and clinical experience with antivenoms, and some of their assumptions about the mechanism of coagulopathy have been questioned.[107]

Recurrent envenoming

Clinical and laboratory evidence of recurrent systemic envenoming after the initial reversal by antivenom was first described in patients bitten by Malayan pit vipers who had been treated with conventional $F(ab')_2$ antivenoms.[95,100] This recurrence was common when rapidly cleared Fab antivenoms were introduced—EchiTab (Micropharm, London, UK) for envenoming by Nigerian saw-scaled viper,[108] PolongaTab (Micropharm) for envenoming by Sri Lankan Russell's viper (*D russelii*),[109] and CroFab (BTG, London, UK) for envenoming by North American rattlesnakes.[110] Possible mechanisms for recurrent envenoming are continued absorption of venom from the venom depot at the bite-site after antivenom has been cleared or has complexed with venom (figure 8),[100] and redistribution of venom from extravascular to intravascular spaces after dissociation of the venom–antivenom complexes.[111] Since recurrent envenoming can be associated with fatal haemorrhagic complications, further doses of antivenom should be given to the patient.[108,112]

Antivenom safety

Antivenom, especially when given intravenously, not infrequently results in early reactions, ranging from pruritus and urticaria to potentially fatal anaphylaxis. Pyrogenic reactions indicate contamination with endotoxin during manufacture. Late serum-sickness-type reactions, attributable to damage by immune complexes, can also cause distressing symptoms. Incorrect assessment of risk versus benefit can lead to the unnecessary use of antivenom in patients with mild or even no envenoming, and in those bitten by snakes whose venoms are not neutralised by available antivenoms.[76] Conversely, antivenom might be withheld from a patient with severe envenoming, in whom the benefits of antivenom outweigh the risks of this treatment, because of an exaggerated fear of antivenom reactions. Dependent on the dose, route, and speed of administration, and the quality of refinement, the risk of any early reaction varies from about 3% to more than 80%, but only about 5–10% of reactions are associated with severe symptoms such as bronchospasm, angio-oedema, or hypotension.[102,113,114] Most reactions can be controlled with intramuscular epinephrine if they are detected early.[115] The incidence of fatal reactions is not known because of confusion with the direct effects of envenoming, especially if the victim's terminal symptoms pass unnoticed.[69] Conventional phase 1 safety and dose-finding studies for the clinical assessment of antivenoms are unethical because of the risk of reactions and the possibility that a healthy volunteer might become sensitised to the animal proteins of which the antivenom is composed.[18] Attempts to improve safety by pepsin

digestion of whole IgG to obtain $F(ab')_2$ fragments without complement-binding Fc receptors, or prolonged papain digestion to produce Fab incapable of crosslinking, seem to have gone full circle with the reintroduction of the manufacture of whole IgG antivenoms extracted with caprylic acid.[116] As with improvement of human autologous immunoglobulin production, the emphasis should be on elimination of aggregation that activates complement.[18]

Prediction of antivenom reactions

A widely held but erroneous notion, perpetuated by the misleading use of terms such as allergic reactions or immediate-type hypersensitivity reactions,[115] is that most antivenom reactions are caused by IgE-mediated type 1 hypersensitivity to equine or ovine proteins. For this reason many manufacturers recommend hypersensitivity testing before antivenom is given. Although there have been quibbles about the technique of skin testing,[117] these tests, which can only detect antivenom-specific IgE, are non-predictive and therefore clinically misleading. They also waste time and are capable of inducing sensitisation.[113,118]

Prevention of antivenom reactions

Although attempts to prevent early reactions have included pretreatment with epinephrine, antihistamines H_1 and H_2, and corticosteroids, and reduction of the speed and concentration of intravenous antivenom administration, they have not been effective in adequately designed clinical trials. Epinephrine, the most promising treatment, carries significant risks in older patients with pre-existing vascular disease.[114] In the absence of any proven effective method of prevention of antivenom reactions, patients should be observed carefully for at least 2 h after they are given antivenom, and epinephrine should be given at the first sign of anaphylaxis.

Antivenom manufacturing issues

Improvement of the treatment of snake bite requires solutions to many economic, logistical, marketing, distribution, and storage difficulties associated with production and supply of antivenom, and provision of improved training for medical personnel so that the best possible use of antivenom and other treatments is achieved.[119] The development of safe, effective, and affordable antivenoms is a priority addressed by WHO.[18] A fundamental difficulty associated with antivenom use, and recognised since the early 20th century, is the absolute requirement for specificity. Therefore, appropriate venoms need to be used in the production of antivenoms, which means that the market for a particular antivenom is restricted to a geographical area for which its specificity is relevant, usually in impoverished developing countries. Attempts to overcome this difficulty by discovery of universal venom antigens or immunogens have so far been unsuccessful. Design of an antivenom for use in a particular part of the world involves decisions about whether monospecific or polyspecific cover is needed, and selection of venoms of the snake species of greatest medical importance in that geographical area. Traditionally, antivenoms were produced in horses, but sheep, dogs, rabbits, camelids,[120] and chickens[121] have also been used. Whole IgG, $F(ab')_2$, or Fab fragments will be produced, depending on the method of refinement (traditional digestion with pepsin or papain, or extraction with caprylic acid). The size and other properties of these proteins will determine how well antivenom pharmacokinetics and pharmacodynamics will match those of the most important venom components. The preparation of freeze-dried antivenom is expensive and technically demanding, but is important when the cold chain is vulnerable.[18,122]

Conclusions

Snake bite is a neglected disease that afflicts the most impoverished inhabitants of rural areas in tropical developing countries. It is an unusually challenging medical problem that deserves further investigation after the prolonged neglect by medical science.

Contributors

I am sole author and contributor.

Conflicts of interest

I declare that I have no conflicts of interest.

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