1 Introduction

Our knowledge of animal and human physiological processes owes much to over a century of study of natural toxins. The neurotoxins of kraits (bungarotoxins from *Bungarus* spp.) and cobras (*Naja* spp.) have helped define the acetylcholine receptor and neuromuscular transmission. Axonal trafficking and sodium channels have been studied using tetrodotoxin from the blue-ringed octopus (*Hapalochlaena* spp.) and puffer fish (fugu). Unravelling the complexities of the human coagulation pathways (intrinsic and extrinsic) has involved studies using haemotoxins from various snakes, including Russell’s vipers (*Daboia russellii*), the saw-scaled vipers (*Echis* spp.) and the Australian taipans (*Oxyuranus* spp.). Ancrod is a snake venom enzyme from the Malayan pit viper (*Calloselasma rhodostoma*) which has been successfully used to treat thrombotic stroke.

The kallikrein – kinin (bradykinin) system was discovered and elucidated by the Brazilian scientists Mauricio Rocha e Silva and Sergio Ferreira, who were looking at the properties of the South American pit vipers, including *Bothrops jararaca*. In 1949, Rocha e Silva discovered that bradykinin, a hypotensive peptide, is produced when *B. jararaca* venom is injected into the blood circulation of mammals (Rocha e Silva et al. 1949). Ferreira subsequently worked on this venom with the Nobel Laureate John Vane, resulting in the discovery and subsequent manufacture of the multi-billion dollar angiotensin converting enzyme class of drugs – “That would not have happened without the “blue-sky” research on the snake venom which started in Brazil and then went on in my laboratories in London. There were so many extraordinary coincidences that were needed in order for that process to fructify, including Ferreira’s choice to visit my laboratory rather than Oxford.” [http://www.medschool.lsuhsc.edu/neuroscience/bluesky_research.asp](http://www.medschool.lsuhsc.edu/neuroscience/bluesky_research.asp) (accessed October 2006).

Snake venom peptides continue to be used in contemporary research. For instance while the small polypeptide neurotoxic bungarotoxins have been used for decades to study the nicotinic acetylcholine receptor, more recently these peptides and their receptors have been used to study trafficking and function of other receptors, such as AMPA and GABA receptors (Sekine-Aizawa and Huganir 2004;
In addition, there remains enormous potential for novel therapeutics in yet to be discovered natural toxins from other animals such as cone snails, scorpions and poisonous frogs.

2 Toxins and Clinical Relevance

While laboratory scientists discover and evaluate individual toxins from venomous creatures, clinicians are primarily interested in the clinical syndromes resulting from envenoming by an individual species. These clinical syndromes are the result of combined actions of the multiple toxins present in the envenoming animal’s venom. Sometimes venoms contain toxins which are potent in vitro, but which rarely or never cause clinical problems. An example is the Australian “brown snake paradox.” The Australian brown snakes (*Pseudonaja* spp.) contain complex presynaptic neurotoxins such as textilotoxin, yet neurotoxicity is extremely rare after bites from brown snakes. It is thought likely that slow or inefficient toxin-receptor binding may account for this, coupled with early antivenom use in the majority of envenomed cases where rapid onset coagulopathy dominates the clinical picture (Currie 2004). Furthermore, the specific toxins responsible for some envenoming syndromes remain to be characterised. Such is the case with the early collapse and loss of consciousness seen after bites from some species of snakes.

3 Snakebite

The epidemiology of snakebite is poorly documented, but the most recent estimate is that there are 5 million snakebites globally each year, with 2.5 million envenomed and up to 125,000 deaths (Chippaux 1998). Around a quarter of deaths are in children, suggesting possibly up to 30,000 deaths annually (D. Warrell, personal communication). As with most envenoming scenarios, children have a higher mortality because of their smaller body mass being exposed to a (relatively) fixed venom dose. The vast majority of severe envenomings are from snake species from the family Elapidae (cobras, kraits, mambas, Australasian elapids and sea snakes) or the family Viperidae (true vipers, lance-headed pit vipers and rattlesnake pit vipers) (Gutierrez et al. 2006). The species most responsible for snakebite fatalities are saw-scaled (true) vipers (*Echis* spp.) in northern Africa, cobras (*Naja* spp.) and kraits (*Bungarus* spp.) in Asia and lance-headed pit vipers (*Bothrops asper* and *B. atrox*) in South and Central America (Gutierrez et al. 2006). Paradoxically, two of the most feared snakes, with reputations for great speed, agility, biting prowess and venom potency, have been associated with far fewer well documented fatalities; the black mamba (*Dendroaspis polylepis*) of eastern and southern Africa and the Australian taipan (*Oxyuranus scutellatus*). In Europe the diminutive but widely distributed European adder (*Vipera berus*) still causes occasional deaths, although