Venomous snakes, facts no fiction

J.J. Wijnker
Wijnker, Joris Jan
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Joris Jan Wijnker
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CHAPTER 1

Introduction & incidence
Introduction
When man started thinking of himself as being the greatest creation on earth and everything around him as a tool for a better life, nature became a threat in many shapes and forms, especially animals whose lives differ greatly from ours. From that day on snakes became more of a symbol than a life form. Its shape and size, its obscure expression, the capability to move without the use of limbs, and the threat to hurt or kill in mysterious ways, gave man a symbol for fear, worship and an excuse to hunt and destroy the snake without thinking twice. Only in parts of the world where man stayed more in touch with nature, did he allow the snake to remain itself. A secretive animal with its own way of living, highly adaptive and as we've found out, a useful source of information about ourselves. Now, man has begun to understand nature, to learn from it and treat it with the respect it deserves. In this new situation the snake itself became an object of interest and many people have dedicated their time and their lives to unravel the mysteries surrounding this intriguing animal. During the past three decades much has been found out about snake venom and its effects. The thought of imminent death, after being bitten by a snake, has luckily been abandoned when we learned more about the composition of the venom and the symptoms it created. Many therapies and preventive methods have been developed and adjusted over a long period of time. Ranging from folklore remedies to scientifically based research.

This paper is written to integrate the present knowledge of venomous snakes with a new view on the classification of venomous snakes, their venom characteristics, its symptoms and current treatment.

Incidence
In a recent report on epidemics published by the World Health Organization WHO (1995), it is estimated that up to 5 million snakebites, scorpion stings and anaphylactic reactions to hymenoptera stings (bees, wasps and ants) occur worldwide, each year. These bites and stings probably cause more than 100.000 human deaths in the world each year. Most snakebites occur on the feet and ankles of agricultural workers and hunters in rural areas of tropical countries of Asia, Africa and Latin America. For these people, envenomation is an occupational hazard.

The highest incidence of snakebites occurs in Asian countries, with an estimated 30.000 annual deaths. For Africa and Latin America about 1.000 deaths may occur in each area annually. Some data recently presented, give an idea of the magnitude of the problem in some developing countries:

- Mexico reported more than 63.000 snakebites and scorpion stings per year with more than 300 deaths. In Brazil about 20.000 snakebites and 7 to 8.000 scorpion stings occur annually with a case fatality rate of 1.5% for the former and between 0.28 and 1% for the latter;
- A study conducted in Ouagadougou, Burkina Faso, revealed a rate of snakebite occurrence of 7.5 per 100.000 inhabitants in peri-urban areas. This rate was even exceeded and reached 69 per 100.000 inhabitants in more remote areas with a case-fatality rate of 3%;
- As reported in Brazil, environmental changes, especially deforestation, has lead to the disappearance of many snake species. This was however, not followed by a decrease of the number of reported cases of snakebites in many
areas as other, and sometimes more dangerous species proliferated in these open area;
- Similar observations were made in West Africa (Togo, Ivory Coast), where decreased rain falls and reduction of the vegetal cover favoured the development of Echis carinatus ocellatus (saw-scaled viper);
- Snakebites are also a problem in developed parts of the world. The USA report 45,000 snake bites each year. Although in view of the available health care the number of deaths remains small, with between 9 to 15 deaths annually;
- Australia has some of the most venomous snakes in the world. But due to the concentration of people in cities and settlements and the sparsely populated remainder of the country, the incidence of snakebite ranges from 300 to 500 with an average of 2 deaths each year.

In view of these findings, the need for further research about the understanding of snakes and the development of new treatments for snakebite is highly justified.
CHAPTER 2

Classification according to Linnaeus and Rosenfeld
Classification of venomous snakes (Linnaeus)

- class: reptilian
- order: squamata
- sub-order: serpents
- infra-order: caenophidea

- family: viperidae elapidae colubridae
- sub-fam: azemiopinae elapinae colubrinae
- sub-fam: viperinae hydrophiinae aparalactinae
- sub-fam: crotalinae laticaudinae homalopsinae

Classification based upon positioning and shape of the teeth (Rosenberg)

Aglyphs
Maxillary teeth are solid; they have no groove or canal. The size may be equal or evenly graded with the largest teeth posterior, or may have the posterior ones abruptly enlarged and fanglike. Aglyphs may also have anterior fangs.

- all nonvenomous snakes belong to this group.

Opistoglyphs
Posterior maxillary teeth are grooved longitudinally for the transport of venom. They are nearly always enlarged, sometimes greatly. Most often there are two grooved teeth, but sometimes three or four in series. All rear-fanged snakes are presumably venomous.

- Sub-family:
  - colubrinae
  - aparalactinae
  - homalopsinae
Proteroglyphs
Anterior maxillary teeth are deeply grooved, usually with the edges fused to enclose a canal. They are enlarged and there are usually smaller teeth behind the fangs, up to about eight in number. Sometimes they too are grooved.

- Sub-family:
  - elapinae
  - hydrophiinae
  - laticaudinae

Solenoglyphs
The fangs are tubular, usually with complete fusion of the groove; there are no solid teeth on the maxilla. The fangs are hinged in the maxilla, so they can be erected when biting.

- Sub-family:
  - azemiopinae
  - viperinae
  - crotalinae
CHAPTER 3

Venomous snakes of major medical importance
United States and Canada

Diamondback rattlesnakes (Crotalus adamanteus, C. atrox)
Timber rattlesnake (C. horridus)
Prairie rattlesnake (C. viridis viridis)
Pacific rattlesnake (C. v. helleri, C. v. oreganus)
Mojave rattlesnake (C. scutulatus)
Sidewinder (C. cerastes)
Pigmy rattlesnake (Sistrurus miliarius)
Massasauga rattlesnake (S. catenatus)
Copperhead (Agkistrodon contortrix)
Cottonmouth (A. piscivorus)
Eastern coral snake (Micrurus fulvius)

Mexico, Central America, and West Indies

Western diamondback rattlesnake (Crotalus atrox)
Mexican west-coast rattlesnake (C. basiliscus)
Tropical rattlesnake (C. durissus) several subspecies
Aruba Island rattlesnake (C. unicolor)
Barba amarilla or terciopelo (Bothrops atrox)
Eyelash viper (B. schlegelii)
Jumping viper (B. nummifer)
Arizona coral snake (Micruroides euryxanthus)
Black-banded coral snake (Micrurus nigrocinctus)
Bushmaster (Lachesis mutus)
Fer-de-lance (B. lanceolatus, B. caribbaeus)*

*Islands of Martinique and St. Lucia only. The name "fer-de-lance" is often applied to mainland populations of Bothrops atrox

Northern South America (to about 15' S)

Tropical rattlesnake or Cascabel (Crotalus durissus) several subspecies
Barba amarilla or terciopelo (Bothrops atrox)
Amazonian tree viper (B. bilineatus)
Bushmaster (Lachesis mutus)
Amazonian coral snake (Micrurus spixii)

Southern South America

Brazilian rattlesnake, also Cascabel (Crotalus durissus terrificus)
Jararaca (Bothrops jararaca)
Jararacussu (B. jararacussu)
Jararaca pintada (B. neuwiedi)
Urutu (B. alternatus)
Brazilian giant coral snake (Micrurus frontalis)
Europe

European viper (Vipera berus)
Asp viper (V. aspis)
Long-nosed viper (V. ammodytes)

Near and Middle East

Palestine or Turkish viper (Vipera xanthina)
Levantine viper (V. lebetina)
Saw-scaled vipers (Echis coloratus, E. carinatus)
Persian horned viper (Pseudocerastes persicus fieldii)

Indian Subcontinent and Sri Lanka

Russell's viper (Vipera russelli)
Saw-scaled vipers (Echis carinatus)
Indian green tree viper (Trimeresurus gramineus)
Indian krait (Bungarus caeruleus)
Indian cobra (Naja n. naja, N. n. kaouthia)

Sea snakes, especially the beaked or common sea snake (Enhydrina schistosa), are important in some coastal areas.

Southeast Asia including Philippines and most of Indonesia

Russell's viper (Vipera russellii)
Malayan pit viper (Agkistrodon rhodostoma)
White-lipped tree viper (Trimeresurus albolabris)
Mangrove viper (T. purpureromaculatus)
Wagler's pit viper (T. wagleri)
Malayan krait (Bungarus candidus)
Many-banded krait (B. multicinctus)
Asian cobras (various races of Naja naja, chiefly N. n. kaouthia, N. n. atra, N. n. sputatrix, and N. n. philippiensis)
King cobra (Ophiophagus hannah)
Beaked or common sea snake (Enhydrina schistosa)
Annulated sea snake (Hydrophis cyanocinctus)
Hardwicke's sea snake (Lapemis hardwickii)

Far East (most of eastern China, Korea, Taiwan, Japan)

Hundred-pace snake (Agkistrodon acutus)
Mamushi (A. halys blomhoffi, A. h. brevicaudus)
Okinawa habu (Trimeresurus flavoviridis)
Chinese habu (T. murosquamatus)
Chinese green tree viper (T. stejnegeri)
Many-banded krait (Bungarus multicinctus)
Chinese cobra (Naja naja atra)
Annulated sea snake (Hydrophis cyanocinctus)
Yamakagashi (Rhabdophis tigrinus)
New Guinea, Northern Australia and associated islands

Death adder (Acanthophis antarcticus)
Brown snake (Pseudechis australis)
Taipan (Oxyuranus scutellatus)
Inland taipan (O. mucrolepidotus)
Mulga snake (Pseudechis australis)
Papuan blacksnake (P. papuanus)
Red-bellied black snake (P. porphyriacus)
Brown tree snake (Boiga irregularis)
Black whip snake (Demansia olivacea)
Australian brown snake (D. textilis)
Copperhead (D. superba)
Tiger snakes (Notechis scutatus, N. ater)

North Africa (to southern edge of Sahara)

Desert horned viper (Cerastes cerastes)
Saw-scaled viper (Echis carinatus)
Puff adder (Bitis arietans)
Sahara rock viper (Vipera mauritanica)
Northern mole viper (Atractaspis microlepidota)
Egyptian cobra (Naja haje)
Desert black snake (Walterinnesia egyptia)

Central and southern Africa

Saw-scaled viper (Echis carinatus)
Puff adder (Bitis arietans)
Horned puff adder (B. caudalis)
Gaboon viper (B. gabonica)
River Jack (B. nasicornis)
Night adder (Causus rhombeatus)
Cape or yellow cobra (Naja nivea)
Egyptian cobra (N. haje)
Spitting cobra (N. nigrigollis)
Mozambique spitting cobra (N. mossambica)
Ringhals (Hemachatus hemachatus)
Green mambas (Dendroaspis viridis, D. angusticeps)
Black mamba (D. polylepis)
Jameson's mamba (D. jamesoni)
Boomslang (Dispholidus typus)
Twig or bird snake (Thelotornis kirtlandi)
CHAPTER IV

Classification based on venom
The composition of snake venom
Snake venom has a very complex heterogeneous composition, containing enzymes, lethal peptides, non-enzymatic proteins, metals, carbohydrates, lipids, biogenic amines, free amino acids and direct hemolytic factors. This composition makes it possible to see many different symptoms after envenomation. 90% of the dried venom consists of proteins and polypeptides. One can distinguish enzymes and toxins without enzyme activity. Many enzymes themselves are hardly or non-toxic at all. Only when they interact will they show the effects, which are seen after envenomation.

Enzyme-free toxins are e.g. the postsynaptic neurotoxins of the elapids, which have a curare-like ganglion blocker action. Another example is the beta-bungaru toxin (krait), which blocks the release of acetylcholine neurotransmitter. Toxic enzymes are e.g. the presynaptic neurotoxins, composed of several subunits, one of which is a phospholipase A2. Furthermore, the hemotoxins are important, especially proteinases, peptidases and phospholipases. There are also enzymes in snake venom that are not toxic but support the digestion. They probably also facilitate the entering of the venom and the transport to the target tissue. One can also find proteins which structure is homologous with that of neurotoxins, but have no toxic action.

Enzymes
Snake venoms contain at least 26 different enzymes although no single venom has all of these. However, at least 10 enzymes are found in almost all venoms. A few of the more important ones are as follows:

- Proteolytic enzymes
  It's important to remember that snake venoms probably evolved as digestive enzymes and juices. It is not unusual, therefore, to find a great many enzymes present in these substances. Snake venoms contain a variety of trypsin-like substances, which break down or digest tissue proteins. These are referred to as the proteolytic enzymes or as peptide hydrolases, proteases, endopeptidases, peptidases and proteinases. Pit viper venoms tend to be rich in such enzymes. True viperid venoms have fewer. Elapid and sea snake venoms have small numbers and amounts of proteolytic enzymes and a few species have none at all. Most of the necrotic or tissue "killing" powers of venoms, especially at the local level, are due to these enzymes. Such enzymes, once they reach other tissues and internal organs, cause destruction of those structures as well;

- Arginine Ester Hydrolase
  This is a noncholinesterase enzyme found in many pit viper and true viper venoms. It's lacking in most elapid venoms but is found in the venom of the King Cobra. It is believed that the bradykinin releasing and clotting activities of many types of venom are related to ester hydrolase activity;

- Thrombin-like enzymes
  The pit vipers and true vipers contain thrombin-like enzymes, which act as defibrinogenating anticoagulants in vivo and as procoagulants or clotting agents in vitro. The thrombin-like enzymes are glycoproteins;
- Collagenase
  This is a unique type of proteinase that digests the intracellular matrix, collagen;

- Hyaluronidase
  This enzyme breaks down the hyaluronic barrier and decreases the viscosity of connective tissue. It allows venom to penetrate adjacent tissues and probably is the agent most responsible for the extensive swelling or oedema of the limb where the venomous bite has occurred. It is also known as the spreading factor;

- Phospholipase A
  This substance is widely distributed among the elapids, sea snakes, true vipers and pit vipers. It is also found in some colubrid venoms. Phospholipase B works in alliance with phospholipase A;

- Phosphomonoesterase
  This enzyme is widely distributed in all snake venoms (mainly elapids) except the colubrids, but its exact function is unknown. It breaks down cell nuclei phosphorids;

- Acetylcholinesterase
  These enzymes are found in almost all elapid venoms. There is none or very little present in some viper venoms. This enzyme inactivates acetylcholine, by hydrolyzing it to acetic acid and choline;

- Ribonuclease (RNase)
  This is found in many types of venom in very small amounts. As its name implies, it breaks down RNA, which is responsible for directing protein synthesis in cells;

- Deoxyribonuclease (DNase)
  This occurs in elapids and vipers and breaks down DNA;

- 5'Nucleotidase
  This enzyme is a common component of many types of venom. It breaks down phosphate monoesterase and is one of the most active phosphates in venom. It is found more frequently in crotalid and viperid venoms, compared to elapid venoms. By itself it is not very lethal;

- L-amino Oxidase
  This enzyme gives venom its yellowish-to-amber coloration. It is absent in sea snakes, some elapids, newborn snakes, and a few species of true viper. It is found in most other venoms, however. Purified L-amino oxidase is about four times as lethal as an equivalent weight of whole crude venom. It is an important digestive enzyme that catalyses many substances. On a weight-for-weight basis, however, it is estimated to contribute 1% of the total lethality of the venoms in which it is found. It is said it may serve to activate other venom components. It has no neuromuscular effects;
- Adenosine Triphosphatase
  This enzyme is probably present in all snake venoms. It destroys ATP, which is the main source of cellular energy for all cells to carry out various chemical reactions. It may play an important role in the rapid production of hypotension and shock seen in many venomous snakebite victims.

Antigenic allergens
In viperid venom certain components are found, which are much less active in elapid venom. Many of these can be classified as proteins. As such they should provoke hypersensitive reactions in their victims. But amazingly, the occurrence of allergic reactions to snakebite envenomation is rare, even in potentially presensitized individuals, who have been envenomated by the same snake species on previous occasions. The incidence of anaphylactic reactions to the bites of bees, wasps and other insects is much more frequent compared to that of snakebite. Immediate hypersensitive reactions and delayed reactions (serum sickness) are much more likely to occur as a result of antivenom administration, than as a result of the bite itself.

Citrate
Citrate has been identified as a major component of snake venoms. The venom of pit vipers, (Crotalus atrox, C. viridis viridis, C. adamanteus, C. horridus horridus, Sistrurus miliarius barbouri, Agkistrodon contortrix mokasen, A.c. contortrix and A. piscivorus piscivorus) contains citrate at concentration levels, which can serve as effective buffers. Calcium, magnesium, zinc, iron, sodium and potassium salts of citrate would thus be components of these venoms.
Citrate is said to be an endogenous inhibitor of snake venom by metal-ion chelation. By forming complexes with divalent metal ions, citrate markedly reduces the activities of selected enzymes in snake venoms. They are found in pit vipers, true vipers and elapids.

Conclusion
Snake venom is, as we know, a mixture of biologically high active proteins and polypeptides. Their function is mainly supporting the digestion of food. The influence on the blood coagulation seems to be more or less a side effect, because the killing or paralysing of the prey is accomplished by the neurotoxins or the cardiotoxins.

Hemotoxins
The hemotoxic enzymes are classified based on their specific effects on the blood coagulation proteins:
- Most enzymes have in vitro a procoagulant effect, while in vivo there is an anticoagulant effect;
- Most venoms contain more than one enzyme, which effect on the blood coagulation is synergistic or antagonistic;
- A purified enzyme can influence several coagulation factors simultaneously;
- The level of influence on the blood coagulation depends on the concentration of the purified enzyme;
- Several enzymes are able to influence all stages of the blood coagulation;
- The activity of non-purified venom depends on the enzyme concentration;
- It is proven that there are individual differences in venom composition and activity between snakes of the same species.
Many differences are based on age and geographic location.
**Fibrinogenic effect**
These three types of enzymes are found in crotalid venom:
- Thrombin-like enzymes. Catalyzing the release of fibrinopeptid A or B, having a defibrinating effect;
- Fibrinolytic enzymes. Stopping coagulation by blocking the effect of thrombin on fibrinogen;
- Plasminogen activating enzymes. These enzymes act as indirect fibrinolytica.

**Prothrombin effect**
The possibility to change prothrombin into thrombin is only known in a few snake species, most of them Australian elapids, two African colubridae, Dispholidus typus and Thelotornis kirtlandi, and two Afro-Asian viperidae, Echis carinatus and Echis coloratus.

**Factor X effect**
Factor X activating enzyme is isolated from the venom the Russell's viper. This group of enzymes is called "Russell's viper venom coagulant" (Rvvc). Rvvc is present in all viperids and crotalids.

**The effect on thrombocytes**
Four different groups of Platelet Activating Factors (PAF) can be found:
- Nonenzymatic substances, which operate through the activation of the prostaglandin metabolism: Convulxin (Crotalus durissus cascavella) and Aggregoserpentin (Trimeresurus gramineus, T. murosquamatus, T. okinavensis);
- Thrombocytin and Crotalocytin are Serinproteases found in several Bothrops species and Crotalus horridus horridus. Thrombocytin induces platelet aggregation and is inhibited by heparin;
- Bothrocetin, found in Bothrops jararaca. This substance aggregates platelets in normal plasma but not in plasma from patients with von Willebrand's defect, making it useful as a diagnostic agent for this syndrome;
- Phospholipases A2 (Ph), which effects can be divided into three groups:
  1. Ph, which are Ca-depended, activate the thrombocytes aggregation, normally in a dosage-depended biphasic reaction;
  2. Ph, which block the thrombocytes aggregation;
  3. Ph, which have no effect on the thrombocytes.

The PAF are present in venom of Naja naja atra, Trimeresurus murosquamatus and Vipera russelli.

The Platelet Inhibiting Factor (PIF) is present in venom of T. gramineus and Agkistrodon halys.

**Hemorrhagic effect**
Hemorrhagic venom components are usually proteases, which induce local or general hemorrhaging. These symptoms are closely associated with envenomation by crotalids and can be expected after a rattlesnake bite.
Classification based on specific venom toxins
Man's high susceptibility to many reptile venoms actually seems to be something of a biological accident. Almost certainly all the genera and practically all the species of poisonous snakes had evolved before man appeared. No poisonous snake today feeds upon primates, nor is there real reason to think any species has done so in the past.

The Gaboon viper, which has been known to dine on small antelopes, would have no trouble swallowing a 5-or 6-pound monkey. Neither would the Bushmaster or some of the other very large venomous snakes of Africa and tropical America, but only rarely would these ground-dwelling nocturnal snakes have the chance.

Gaboon viper and rat

**Neurotoxins**

 Postsynaptic neurotoxins: These toxins bind to nicotinic acetylcholine receptors and thereby prevent the depolarizing action of acetylcholine. They are referred to as curaremimetic, curariform or simply neurotoxins.

 Presynaptic neurotoxins: These toxins inhibit the release of acetylcholine and their lethality is much higher than that of the postsynaptic toxins.

 Snakes belonging to the families Elapidae and Hydrophidae have typical neurotoxic venoms with a high neurotoxin contents. Curaremimetic toxins have not yet been isolated from venoms of other families, which does not necessarily mean that such toxins are not present.

 Presynaptic neurotoxins are extremely lethal and structurally related to phospholipase A. Whether the inhibition of the transmitter release is due to the phospholipase activity is not yet known, but indirect evidence indicates that this might be the case. Some of the presynaptic toxins can also act as myonecrotic toxins producing necrosis of muscle fibres.

 Despite the great variety of activities, all postsynaptic and presynaptic neurotoxins are clearly homologous with regard to their structure. The two structural classes are defined as follows:

 - Class 1, molecules with a postsynaptic neurotoxin membrane toxin structure. Curaremimetic toxins, membrane toxins and some proteins with an unknown function belong to this group;
 - Class 2, molecules with a phospholipase structure. Presynaptic neurotoxins, myonecrotic toxins, basic phospholipases with high lethality or pathologic activity and other proteins having phospholipase structure are referred to this group.

 These venom toxins are very resistant molecules: most of them survive boiling in neutral or weakly acid solution and are only reversibly denatured by urea or guanidine hydrochloride. They are, however, rapidly inactivated by strong alkali as a result of desulphurization and/or disulfide interchange. It has also been
known for a long time that the toxicity of cobra venom withstands boiling. This reflects the heat stability of neurotoxins, membrane toxins and phospholipases.

The stable protein structures of the two classes of toxins probably have evolved first for some unknown reason. The different activities have then arisen through mutations, while the features responsible for the stability of the structure didn’t change. However, all of these toxins, except crotoxin, referred to in the two groups, are from Elapidae or Hydrophiidae.

- Class 1a), curaremimetic toxins. As the name implies, these toxins mimic the action of curare, but there are also differences between them. The onset of the action is slower but the duration is longer with the venom toxins. They appear to be specific for the nicotinic cholinergic receptor, whereas curare also binds mucopolysaccharides and other proteins such as acetylcholinesterase. The venom toxins are bound much more strongly to the receptors than curare and they are 15 to 40 times more potent.
- Class 1b), membrane toxins. Membrane toxins form another large group of toxins. They change the permeability of the membranes in a great variety of cells and tissues. As a result they are often referred to as cardiotoxins, lytic factors, cytotoxins, etc. Names that indicate the great variety of the cells affected.

Membrane toxins have been isolated only from elapid venoms. Death is due to the cardiotoxic effects. It is of rapid onset and can occur within 10 minutes following an intravenous injection of a 100% lethal dose. The lethality is greatly increased in the presence of phospholipase A, which also has a potentiating effect on other activities displayed by these toxins, such as massive hemolysis. Death by "shock" follows quickly, hastened by K⁺ ions, released from the lysed red blood cells, causing a cardiac arrest.

Phospholipase A alone doesn’t have the same effects. The toxin-induced permeability change has many biochemical, pharmacological and pathological consequences:
1. hemolysis, species dependent, great differences in susceptibility;
2. cytotoxicity, causing lysis of a number of cells, such as human leukocytes;
3. depolarization of excitable membranes, with such effects as block of axonal conduction in peripheral nerves, contracture and paralysis of skeletal muscles and ventricular fibrillation and systolic arrest of the heart muscle;
4. transport effects, such as the inhibition of accumulation of anions, amino acids, glucose etc. in tissues (thyroid, kidney) and cells;
5. an activity increasing effect on membrane enzymes;
6. inactivation of Mg^{2+} dependent Na⁺, K⁺ activated ATPase, which requires an intact membrane in order to function properly.

Toxin gamma liberates calcium from muscle fibres. Since all membrane toxins qualitatively appear to have the same effect on different membranes, it is likely that they also liberate calcium from all membranes susceptible to their action. Consequently, calcium antagonizes the effects of membrane toxins.

- Class 2), toxins with a phospholipase (ph) structure. Several of the most potent venom toxins are either a basic ph-A or contain a subunit, which is a basic ph-A. To this group belong presynaptic toxins, myonecrotic toxins and
toxic phospholipases. The presynaptic toxins inhibit the release of acetylcholine, especially in the respiratory muscles, so intoxicated animals die from respiratory paralysis. Myonecrotic toxins damage muscle fibres and can cause myoglobinuria. Basic Ph can cause bleeding from the nose and bloody sputum.
Many of the toxins display both neurotoxicity and myotoxicity and the classification of such molecules as neurotoxins or myonecrotic toxins indicates only their most conspicuous characteristic.

**Notexin and its homologous**
The Australian tiger snake has both curaremimetic and presynaptic toxins. Three homologous proteins have been isolated from the tiger snake venom. Two of them, notexin (notechis toxin) and notechis II 5, have a presynaptic effect, whereas the third one, notechis II 1, shows neither toxicity nor enzymatic activity. There seems to be only quantitative differences between the first two. Notechis II 5 is less toxic than notexin but has higher phospholipase A activity.

**Taipoxin**
The Australian taipan has extremely potent venom, even more potent than notexin. The toxin taipoxin (taipan toxin), which is mainly responsible for this extreme lethality, accounts for about 16% of the dry weight of the venom. The contents of curaremimetic toxins are low, less than 5%.

**Crotoxin**
Crotoxin is the main neurotoxin of the South American rattlesnake. The high toxicity is due to a complex between a basic phospholipase A, also called crotoxin B (basic), and an acidic protein, crotoxin A (acidic) or crotapotin. The components alone are slightly toxic, but are lethal when brought together. However, this synergistic effect doesn't depend on the physical complex formation.

**Beta bungarutoxin**
The venom of Bungarus multicinctus (krait) was initially fractionated into three neurotoxic fractions, called alpha-, beta- and gamma-bungarutoxin. A postsynaptic type of muscular blocking activity was found in the alpha fraction, whereas the action of the beta- and the gamma fractions appeared to be exclusively presynaptic.

**Enhydrina schistosa myonecrotic toxins**
The postsynaptic neurotoxins account for about 60% of the protein fraction of Enhydrina schistosa (common sea snake) venom. Nevertheless the clinical picture of envenomation is myotoxic rather than neurotoxic. Muscle movement pains and myoglobinuria are the most characteristic symptoms in human snakebite victims. The toxicity involves two symptoms, which are due to different pharmacologic and pathogenic mechanisms. One is a fast ensuing paralytic death, the other a wasting death. Myoglobinuria appears at 30 µg/kg, which indicates the extreme toxicity this toxin has for skeletal muscles.

**Other toxic phospholipases A**
Basic Phospholipases A in general, appear to be toxic, having lethal doses of about 500 µg/kg mouse, or even considerably less as exemplified by the presynaptic and myonecrotic toxins. Many of the acidic phospholipases A,
however, are much less toxic and not even lethal, even at a dose level of 2000 μg/kg, although there are exceptions. E.g. from Naja nigricollis, which has a lethality of 800 μg/kg mouse.

**Summary**

Taipoxin, beta bungarotoxin (the most lethal) and crotoxin inhibit the release of acetylcholine in a similar way. Notexin and taipoxin produce the same type of neuromuscular block. All of these toxins eventually lead to a depletion of storing acetylcholine, since application of high doses of K⁺ to completely blocked nerves does not cause any further release of the transmitter. All presynaptic snake venom toxins, or at least one of their subunits, are phospholipases A. However, all organisms contain phospholipases A and it is plausible to assume that the enzymes arose first and evolved later to toxins. The catalytic activity associated with the toxins might, therefore, only be an evolutionary vestige.

**Other toxins**

**Crotamine**

Crotamine is a basic polypeptide from the venom of Crotalus durissus terrificus (Cascabel) and has hemolytic and neurotoxic activity by way of a presynaptic block of the neuromuscular nerve endings. This may cause the victim to die of a broken neck, caused by uncontrolled contraction of the neck muscles.

**Convulxin and Gyrotoxin**

Both are acidic, non-dialyzable proteins, also from the venom of Crotalus durissus terrificus. Convulxin produces convulsions and gyrotoxin fast rolling movement of the body along its longitudinal axis after injection into mice. Convulxin is said to be twice as lethal as crotamine. Gyroxin is not lethal, but disrupts the central nervous system.

**Mojave toxin**

The Mojave rattlesnake, Crotalus scutulatus scutulatus, has one of the most potent of all rattlesnake venoms. The mojave toxin is claimed to be cardiotoxic rather than neurotoxic, but its lethality is in the range observed with presynaptic toxins other than taipoxin.

**Viperotoxin**

Viperotoxin from Vipera palestinae is a neurotoxin, with its primary effect in the medullary vasopressor centre. This will lead to a peripheral vasodilatation followed by heart- and circulatory failure.

**Toxins from Bungarus caeruleus venom**

Cerulotoxin. This toxin has a postsynaptic type of action. It blocks the postsynaptic response to acetylcholine but doesn't compete with the binding of curaremimetic toxin, because it doesn't bind on the cholinergic receptor. Death occurs after a long delay of up to 48 hours, which has also been observed with notexin. It has also been shown that notexin has a postsynaptic effect decreasing the sensitivity of the motor end plate for acetylcholine. Cerulotoxin might, therefore, be another member of the phospholipase toxin group.
Toxins with myonecrotic effects
Myonecrotic toxins are polypeptides, which effects are contraction of the skeletal muscles and local myonecrosis. Until now they have only been found in crotalid venom.

Angusticeps type toxin
Although there is a resemblance with postsynaptic neurotoxins and cardiotoxins, they are clearly distinguishable. Their lethal capacity is very small and their pharmacological effect is yet unknown. Angusticeps type toxin can be found in several Dendroaspis species.

Synergistic type protein
This protein, which is also found in the venom of Dendroaspis species, increases the activity of angusticeps type toxin.

Proteinase blocker and homologous
This concerns polypeptides with proteinase blocking activity. Structurally homologous peptides without this activity also exist, although their effect is different on the neuromuscular plate. These polypeptides are found in elapid and viperid venoms.

Cobra venom factors (cvf)
Cvf are components of cobra venom, which interfere with the complement system. These anticomplement proteins split the complement molecule proteolytically. Four anti-complement proteins are found in Crotalus atrox venom.

Active peptides
Several small peptides, which potentiate the effect of bradykinin or lower the blood pressure, are found in some snake venoms. Bpp (bradykinin potentiating peptides) are found in the venom of Agkistrodon halys blomhoffi, A. halys pallas, Bothrops jararaca and Vipera ammodytes ammodytes. Bpp potentiates the effect of bradykinin on the smooth muscles. From the venom of Crotalus atrox a peptide is isolated, which induces a rapid fall in blood pressure. It is called "hypotensin".

Cryptotoxin
C.C Pollitt of the University of Queensland (1980) found a myotoxic factor in the venom of the Australian Small-eyed snake (Cryptophis negrescens). This elapid possessed an extremely toxic myolytic factor rather than the expected neurotoxins. Being named "cryptotoxin" is to indicate its hidden or cryptic nature: destruction of muscle continues for many days after envenomation until the victim becomes moribund, succumbing from the combined effects of aspiration pneumonia, renal failure secondary to myoglobinuria, dehydration due to cachexia and paralysis.
CHAPTER 6

Pharmacokinetics of snake venom
Absorption
Due to the polypeptide nature of their toxic principle, snake venoms introduced by the oral route are usually nontoxic. The differences in molecular weight of the venoms make it possible to delay spreading of the venom by blocking the lymphatic drainage of tissues for high molecular weight venoms, while lighter venoms can be absorbed through the capillaries.

Distribution
The highest concentration of cobrotoxin is found in the cortex of the kidney, while cardiotoxin is more concentrated in the liver, spleen, lung and intestine than cobrotoxin. In contrast to elapid venoms, the greatest accumulation of crotalid venom is in the lung, followed closely by the kidney and than the heart, thymus, lymph node, liver and thyroid gland. Viperid venom is found to be highly concentrated in the liver, kidney and spleen. Phospholipase A is greatly concentrated in the liver. However it is found that the distribution of an active component of the venom could be influenced by other components of the same venom. The distribution of venom into the central nervous system is slowed down because of the blood-brain-barrier and the venom polypeptides pass it with difficulties, but it is not true to say that none of them can penetrate the blood-brain-barrier. The interaction of hyaluronidase, proteolytic enzymes and phospholipase A of the venom components must be considered for the distribution of venom, since these enzymes have been shown to increase the permeability of the blood-brain-barrier.

Excretion
The venom is excreted in the urine, either as an intact toxin or as degraded fractions of the venom. The time it takes to be excreted differs with each venom, based on the target site and way of binding to this target site.
CHAPTER 7

Symptomatology
Facts
Panic is the most common reaction to snakebite. As a result, the victim may become emotionally unstable with thoughts of imminent death, or conversely, the victim may enter a state of extreme lethargy and withdrawal. Fear may cause such symptoms as nausea, vomiting, diarrhoea, dizziness, fainting, tachycardia and cold, clammy skin. It is important that these autonomic reactions are not mistaken for systemic symptoms and signs resulting from the bite, despite their great similarity.

Different factors
The symptoms, signs and the gravity of snake venom poisoning are depending on a variety of factors, one can divide into three groups:
- Group 1 concerns the age, size and condition of the victim, the victim's sensitivity to the venom, the nature, location and number of bites, and the length of time the snake holds on;
- Group 2 concerns the extent of anger or fear that motivates the snake to strike, the amount of venom injected, the species and size of the snake involved, the condition of its fangs and venom glands, the differences between snakes held in captivity or free in the wild, and the pathogens present in the snake's mouth;
- Group 3 concerns the degree and kind of first aid and subsequent medical care given.

Venom regulation
Venomous snakes are capable of regulating the amount of venom excreted from their fangs. To snakes, the use of venom is a sophisticated way of capturing prey with little risk for its own well-being. The amount of venom injected in the process of acquiring food is believed to be related to the size of the prey. This also means that the amount of venom present varies in different stages of the snake's feeding cycle. If a snake has just fed it is likely less venom is ready to be used, then when a snake is out hunting. Most snakebites are "startled" bites or "defensive" bites, an accidental encounter between man and snake, where the victim does not receive a "full fanged bite", a bite with a full load of venom injected. This means that the snakebite is not always followed by evidence of envenomation and will not lead to a certain death, although several human lethal doses of venom may be present in the venom glands at the time of the bite. It is also stated that snakes held in captivity and "milked" at a regular base for their venom, have a more potent venom than snakes in an other situation.

Sea snakes in particular
Sea snakes, being a very specific group of snakes, are the most abundant and widely dispersed of the world’s venomous reptiles. Around the coastal seas of the Indian and Western Pacific oceans, fishermen encounter sea snakes every day. Sea snake venoms are highly toxic. One "drop" (about 0.03 ml) contains enough venom to kill three adult men. Some sea snake species can eject seven to eight such "drops" in a single bite. Fortunately for fishermen, sea snakes are not aggressive, and even when they do bite man, rarely inject much of their highly toxic venom.
Snake identification

If a person gets bitten, one must try to identify the offending snake. In captivity it’s usually clear what kind of snake is involved, and its specific conditions are usually known. This information is vital to make a clear assessment of a possible envenomation and must be taken into account in further treatment of the victim. In an outdoor situation this is not so easy.

Proper identification of the snake can be possible if the snake is clearly sighted or killed after the attack and at least the head and tail are brought along for identification. The search and killing of the snake must be done with great care, for the snake is capable of striking again. This time it is alerted and therefore more dangerous and able to endanger another person. If a snake is killed one must remain careful. Recently decapitated or dying snakes are still capable of inflicting bites, probably as a result of the bite reflex. Some cobras (Hemachatus hemachatus, Naja naje and Naja nigrigollis) can also play dead when they are surprised or when there is no way out. They will strike with lightening speed when they are picked up. Therefore carefully approach the snake with a stick and place the head, tail or dead snake (make sure the snake is really dead) in a bag and keep it with the victim for further use.

Usually the snake is not available for identification and accurate diagnosis and treatment then depend on objective signs and symptoms of snakebite envenomation. Remember, every snakebite is toxic until proven otherwise.

Inspection of the wound

Close inspection of the bite site may give useful information about the kind of bite delivered. The presence of teeth marks, their number and pattern and possibly the presence of venom on the skin may make an early assessment possible. However, it must be stressed that, regarding the circumstances when the victim was bitten, no conclusions must be made solely on the information found.

Because there is a great difference in teeth and fang-size, shape and positioning, many different markings can be found. A clear semicircular pattern indicates a non-venomous bite. Sometimes the traditional double puncture mark is visible and when the snake was able to grip the body part firmly in its jaws, some of the lower teeth impressions are visible. Usually one sees only one puncture or a number of scratches in various sizes and depths to mark the bite. It is safe to say some insight to the identity of the offending snake can be obtained from the puncture wounds, but, again, they should never be relied upon for positive identification. Positive diagnosis of snake venom poisoning is dependent upon identification of the snake and evidence of envenomation.

Diagnosis of crotalid envenomation is dependent upon the presence of one or more fang marks, and immediate and usually progressive swelling oedema and pain. In most cases swelling and oedema are constant findings and are usually seen within 10 minutes after the bite. In the
absence of treatment, the swelling progresses rapidly and may involve the entire injured extremity within one hour. Generally, however, swelling and oedema spread more slowly and usually over a period of 8 to 36 hours. Swelling and oedema are most marked following bites by the North American rattlesnakes (excluding the Mojave, massasaugas and pigmy rattlesnakes) and the American lance-headed vipers (Bothrops). Swelling is slightly less marked following bites by the Malayan pit viper (Agkistrodon rhodostoma) and related species, the Asian lance-headed vipers (Trimeresurus), and the American moccasins (Agkistrodon). It is least acute following bites by the Cascabel (Crotalus durissus terrificus).

In many cases, discoloration of the skin and ecchymosis appear in the area of the bite within several hours. The skin appears tense and shiny. Vesicles may form within 3 hours and are generally present by the end of 24 hours. Hemorrhagic vesiculations and petechiae are common. Pain, immediately following the bite, is a common complaint in most cases of crotalid envenomation. It is most severe following bites by the South American pit vipers (except for the Cascabel, which is less severe), the Eastern diamondback, Western diamondback, and timber rattlesnakes of North America, and the Asian lance-headed vipers. Weakness, sweating, faintness and nausea are commonly reported. Regional lymph nodes may be enlarged, painful and tender. A very common complaint following bites by some rattlesnakes and one sometimes reported following other pit viper bites is tingling or numbness over the tongue and mouth or scalp. Paresthesia about the wound is sometimes reported. Viperid venom poisoning is characterized by burning pain of rapid onset, swelling and oedema and patchy skin discoloration and ecchymosis in the area of the bite. Extravasation of blood from the wound site is common in Russell's and saw-scaled viper envenomation. The failure of the blood to clot is a valuable diagnostic finding. Bleeding from the gums and the intestinal and urinary tracts is common in severe Russell’s and saw-scaled viper bites.

Cobra envenomation is characterized by pain usually within 10 minutes of the bite and this is followed by localized swelling of slow onset, drowsiness, weakness, excessive salivation and paresis of the facial muscles, lips, tongue and larynx. The pulse is often weak, blood pressure is reduced, respirations are laboured and there may be generalized muscular weakness or paralysis. Ptosis, blurring of vision and headache may be present. Necrosis is not an uncommon consequence of cobra venom poisoning. In bites by the kraits a similar clinical picture is seen, except that there is very little or no local swelling, nor severe pain. The systemic manifestations may often be more severe and shock, marked respiratory depression and coma may rapidly develop. Abdominal pain is often intense following poisoning by the kraits, mambas
and taipans. Envenomation by coral snakes may resemble krait venom poisoning. The bite is usually less painful and there is occasionally a sensation of numbness about the wound.

Chest pain, particularly on inspiration, is sometimes reported. The use of elective endotracheal intubation to guard against aspiration and in anticipation of respiratory failure is justified when the swallowing-reflex has stopped. Intubation is only possible if the patient is sedated. This may hinder the proper observation of the patient. One should, therefore, make all the necessary preparations to intubate the patient and observe its situation closely.

Early local signs and symptoms of coral snakebites are mild and therefore misleading. The most serious neurologic signs and symptoms can occur 12 hours post-bite, and then may occur precipitously. Patients with possible coral snake envenomation should be observed for at least 24 hours. Localized oedema is minimal and necrosis is rare. Weakness, nausea and vomiting, blurred vision, slurred speech, excessive salivation, headache and abdominal pain characterize mamba venom poisoning. These findings are often followed by hypotension, respiratory distress and shock.

Envenomation by most of the Australian-Papuan elapids produces drowsiness, visual disturbances, ptosis, nausea and vomiting, headache, abdominal pain, slurring of speech, respiratory distress and generalized muscular weakness or paralysis. Hemoglobinuria may be found early in the course of the poisoning. Sea snake poisoning is usually characterized by multiple pinhead-sized puncture wounds, little or no localized pain, often tenderness and some pain in the skeletal muscles and, in particular, the larger muscle masses and the neck. This pain is increased with motion. The tongue feels thick and its motion may be restricted. There may be paresthesia about the mouth. Sweating and thirst are common complaints, and the patient may complain of pain on swallowing. Trismus, extra ocular weakness or paralysis, dilatation of the pupils, ptosis and generalized weakness may be present. Respiratory distress is common in severe cases. Myoglobinuria, preceded by proteinuria, is diagnostic in serious sea snake envenomation.

Compared to the study of viper, pit viper, elapid and sea snake venoms and envenomation, very little progress has been made in the characterization of venoms and envenomation of colubrid species. Most colubrid envenomations are mild. The most dangerous and life threatening colubrids are the Boomslang (Dispholidus typus), Twig (Bird) snake (Thelotornis kirtlandi) from Africa and the Yamakagashi (Rhabdophis tigrinus) from Asia. Another rear-fanged snake, the Brown Tree Snake (Boiga irregularis), is the subject of recent intense interest because it has overrun the Island of Guam in the South Pacific, thus creating ecological havoc as well as posing a threat to people living there. In fact, this species is probably the only snake in recent history to be the subject of a federal
law calling for its eradication and control (The Brown Tree Snake Control Act). According to Weinstein et al. (1991), the liquid secretion of Boiga irregularis contains 15% protein and has relatively low proteolytic activity. Although the venom has a low order of lethality, the researchers conclude that this species with its myotoxic fraction and large snakes, which are capable of delivering high yields of venom, are especially dangerous to infants and children. Envenomation by both Twig Snakes and Boomslangs result in severe bleeding diatheses, but especially so in the Boomslang.

Other species of colubrids, some with enlarged grooved fangs and some with solid teeth, are known to bite and may be venomous. The manifestations of poisoning by known venomous colubrids, such as the mangrove snake (Boiga dendrophila) of Southeast Asia, the West Indian racers (Alsophis), the "culebra de cola corta" (Tachymensis peruviana) of western South America, the parrot snakes (Leptophis) of tropical America and several other species, are local pain and swelling, sometimes accompanied by localized skin discoloration and ecchymosis. In cases of more severe envenomations, signs are increased swelling and oedema, which may involve the entire injured extremity, general malaise and fever. The acute period of the poisoning may persist for 4 to 7 days. It is important to differentiate envenomation by colubrids from that by the more dangerous elapids and vipers.

In summary, any snakebite associated with immediate (and sometimes intense) pain and followed within several minutes by the appearance of swelling and subsequently oedema is usually diagnostic of snake venom poisoning by a viper. Elapid envenomation, on the other hand, is not so easily diagnosed during the first 10 minutes following the bite. Pain, usually of minor intensity, may appear within the first 10 minutes, although in some cases it is not reported for 30 minutes or even longer. Swelling usually appears 2 or 3 hours following the bite and tends to be limited to the area of the wound. The first systemic sign of elapid venom poisoning is usually drowsiness. This is often apparent within 2 hours of the bite. Ptosis, blurring of vision and difficulties in speech and swallowing may also appear within several hours of the bite. Clearly it is very important in cobra, mamba, krait, taipan, tiger and coral snake bites to determine the identity of the offending reptile as quickly as possible.

Time is limited when dealing with an elapid envenomation, but this does not mean rash decisions should be made, which may endanger the victim's life even further.

**Clinical classification of pit viper and coral snake bites**
These classifications were intended to assist physicians in determining the severity of the envenomation and to serve only as a guide in the treatment. For
example, the preponderance of oedema seen in many cases may be the result of a tightly applied tourniquet rather than the severity of the envenomation. On the other hand, victims of large rattlesnake bites, seen immediately after the bite, may exhibit intense pain but will show few other symptoms until later. Elapidae envenomations (coral snake) differ markedly from pit vipers. There may be little or no pain or swelling immediately after the bite. Occasionally there is a delay of 1 to 5 hours before the onset of these systemic symptoms from elapidae envenomation.

<table>
<thead>
<tr>
<th>Degree of Viperid Envenomation</th>
<th>Degree of Crotalid Envenomation</th>
<th>Degree of Elapid Envenomation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0 None</strong></td>
<td>Fang marks and minimal pain</td>
<td>Fang scratches or punctures.</td>
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<tr>
<td></td>
<td>No envenomation..</td>
<td>No envenomation.</td>
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<tr>
<td></td>
<td>Edema and erythema, 2.5 cm in 12 hours.</td>
<td>Minimal local swelling.</td>
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<tr>
<td></td>
<td>No systemic manifestations,</td>
<td>No systemic symptoms within 24 hours after the bite</td>
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<tr>
<td></td>
<td>normal laboratory findings.</td>
<td></td>
</tr>
<tr>
<td><strong>I Minimal</strong></td>
<td>Fang marks, and severe pain.</td>
<td>Fang punctures and minimal local swelling. Envenomation has occurred.</td>
</tr>
<tr>
<td></td>
<td>Envenomation has occurred.</td>
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<tr>
<td></td>
<td>Edema and erythema, 2.5–12 cm in first 12 hours.</td>
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<tr>
<td></td>
<td>No systemic manifestations,</td>
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<td></td>
<td>normal laboratory findings.</td>
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<tr>
<td><strong>II Moderate</strong></td>
<td>Fang marks and severe pain.</td>
<td>Fang punctures and minimal local swelling. Envenomation has occurred.</td>
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<td></td>
<td>Envenomation has occurred.</td>
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<td></td>
<td>Edema and erythema,15-30 cm in first 12 hours.</td>
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<td></td>
<td>Mild systemic manifestations,</td>
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<td></td>
<td>mildly abnormal laboratory</td>
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<td></td>
<td>findings.</td>
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<tr>
<td><strong>III Severe</strong></td>
<td>Fang marks, and severe pain.</td>
<td>Fang punctures and minimal local swelling. Envenomation has occurred.</td>
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<td></td>
<td>Envenomation has occurred.</td>
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</tr>
<tr>
<td></td>
<td>Edema and erythema, &gt;30 cm in first 12 hours.</td>
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<tr>
<td></td>
<td>Severe systemic manifestations,</td>
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<td></td>
<td>highly abnormal laboratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>findings, including coagulation defects.</td>
<td></td>
</tr>
<tr>
<td><strong>IV Very severe</strong></td>
<td>Fang marks, and very severe</td>
<td>As in grade II, but complete paralysis occurs within first 36 hours after the bite.</td>
</tr>
<tr>
<td></td>
<td>pain.</td>
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<td></td>
<td>Multiple envenomations.</td>
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<td></td>
<td>Rapid edema and erythema</td>
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<td>beyond involved extremity,</td>
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<td>ipsilateral ecchymoses, and</td>
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<td>blebs.</td>
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<td></td>
<td>Very severe systemic</td>
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<td></td>
<td>manifestations, profoundly</td>
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<td></td>
<td>abnormal laboratory findings,</td>
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<td></td>
<td>including coagulation defects.</td>
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Envenomation grading scale
Grading should take place immediately and every 15 to 30 minutes thereafter for up to 12 hours. There are no fixed rules regarding the course of treatment, once it has been established that envenomation has occurred. Any patient within Grade 1 or above with two or more symptoms in the moderate-to-severe range is a candidate for antivenom therapy. Remember that on arrival in a hospital, the severity or nature of the bite may not appear serious, but, as time passes, the degree of severity may change when the appearance of new signs and symptoms start to occur. Therefore the measurement of vital signs and physical and laboratory evaluations, should be done serially and frequently over the first 6 to 12 hours.

**Unusual symptoms**

Snakebite in women can lead to specific problems. A review by Dunnihoo et al. (1992) indicates that envenomation by crotalids during pregnancy, carries a fetal wastage of 43% and a maternal mortality rate of 10%. Pit viper bites result in a bleeding diathesis, and its procoagulant (resulting in a consumption coagulopathy) activity results in defibrination and widespread hemorrhage. In a case history, Estrada et al. (1989) report on the occurrence of severe pulmonary embolism in a young woman bitten by a Fer-de-lance (Bothrops lanceolatus). These thromboembolic phenomena do not usually occur after Fer-de-lance envenomation as patients are usually hypocoagulable due to a consumption coagulopathy, secondary to disseminated intravascular coagulation (DIC). It was postulated that pulmonary thromboembolism probably resulted from the procoagulant effect of thrombin-like enzymes in the venom, which interacted with oral contraceptive medication the patient was taking. If a woman is envenomated during menses by a snake, with venom that has procoagulant characteristics which results in DIC, the consumption coagulopathy that occurs can markedly increase menstrual blood flow.

Another group of specific problems are those caused by venom-squirting snakes. These snakes rear up and squirt their venom, often in the general direction of their target's eyes. These species include the Ringhals Cobra (Hemachatus hemachatus), the Mozambique Cobra (Naja mossambica), the Black-necked Cobra (Naja nigricollis), the Indochinese Cobra (Naja naja), the Indonesian Cobra (Naja sputatrix), the Equatorial Cobra (Naja sumatrana), and the Red Squirting Cobra (Naja mossambica pallida).

Ismail et al. (1993) recently studied the effects of Ringhals Cobra ocular envenomation. The venom of this species caused extensive chemosis, prolonged corneal oedema, and marked miosis when applied to the eyes of both pigmented and albino rabbits. In pigmented rabbits, corneal oedema progressed to complete corneal opacification with corneal and conjunctival neovascularization, which persisted until the end of the experiment, 70 days post-envenomation. In albino test-subjects corneal cloudiness and conjunctivitis resolved 21 days post-envenomation. Treatment with heparin and tetracycline markedly improved the opacification.
syndrome, while specific antivenom treatment resulted in only partial improvement. It is hypothesized that the venom owes its ocular effects to its cardiotoxin, the only venom fraction capable of inducing the corneal opacification syndrome. The protective effect of heparin is probably the result of its electrostatic binding to the cardiotoxin in the venom. Tetracycline is also capable of forming an ionic bond at several sites in the strongly basic cardiotoxin. The ability to induce the corneal opacification syndrome was associated exclusively with snakes that squirt their venom, as this characteristic is absent from the venom of cobras, which do not engage in this behaviour.

**Compartment syndrome**

Stripping of skin and flesh from the bones of the hand, arms, legs, and feet are most commonly seen as the result of traumatic crushing injuries to these areas. Such injuries damage both large vessel and capillary circulation, resulting in ischemia and tissue anoxia. The resulting oedema often raises the intracompartmental pressure. Oedema can also occur as a result of injury and necrosis in areas where snakebites only penetrate the subcutaneous lymphatic beds. Oedema increases the distance oxygen must diffuse from functioning arterioles to reach tissues and this often causes frank sloughing of damaged tissue and acute compartment syndrome. Compartment syndrome is usually treated by surgical fasciotomy. However, most experts do not recommend such intervention until the intra-compartmental pressure reaches 30 mm Hg or more. The use of hyperbaric oxygen (HBO) as an alternative to fasciotomy has also been recommended for acute compartment syndrome but few cases involving snakebite have recently been reported in the literature. HBO therapy reduces the blood flow to muscle-tissue, thereby reducing oedema while increasing the amount of oxygen dissolved in the tissues. Tissues receive oxygen even though capillary circulation may be significantly reduced. It is believed that such treatment greatly reduces the amount of anoxic necrosis, which would otherwise occur in severely damaged compartments. Dr. Thomas G. Glass, Jr. (1992) recommends that all serious rattlesnake bites be surgically explored and debrided immediately. He states that surgical intervention at the outset not only releases both subcutaneous and compartment pressure at the site, but also serves to evaluate the envenomation and remove venom physically (by irrigation) from the area. He has assembled an impressive set of more than 600 cases treated wholly or partially (antivenom was used in some cases) by this treatment. This HBO therapy is not yet accepted as a treatment in all cases where tissue is lacking oxygen. However, it is especially promoted by the owners of the expensive high-pressure tanks, needed for this kind of therapy. Maybe in this case money talks louder than the noble art of medicine (H. Pijning).

Arthur et al. (1991) report an interesting change in erythrocyte morphology as a result of envenomation by the Coastal Taipan (Oxyuranus Scutellatus). The red blood cells in this victim underwent sphero-echinocytic transformation at ng/ml concentrations. This led to a significant increase in whole blood viscosity. The authors state that this case demonstrates this phenomenon for the first time and highlights the value of blood film examination in cases of snakebite envenomation.

**Lymphopenia**

A group of Australian researchers, J. White, V. Williams and B. Duncan, reviewed the incidence of lymphopenia as a result of envenomation by a number of
Australian elapids. Six out of eleven patients envenomated by Brown snakes (Pseudonaja sp.) had absolute lymphopenia and two had lymphocyte counts at the low end of the normal range. All five cases envenomated by the Tiger snakes had an absolute lymphopenia. In three cases of Mulga Snake (Pseudechis australis) bite, two patients with envenomation had lymphopenia whereas the third case, with only mild envenomation, had no evidence of depressed lymphocyte count. All patients envenomated by the Coastal Taipan (Oxyuranus scutellatus) had definite lymphopenia. In two cases of Death Adder (Acanthophis antarcticus) bite, both had lymphocyte counts at the lower end of the normal range. In all elapid bites with confirmed envenomation, there was an increase in the total white blood cell count. So the lymphopenia observed could not be explained on the basis of a decline in total circulating white blood cells. Some cases with definite lymphopenia, had tender lymph nodes draining the bitten limb. Such tenderness is often associated with Australian elapid envenomation. This does not, however, satisfactorily explain the presence of lymphopenia. The writers suggest that it may be the result of a stress response with acute relapse of cortisol, causing a rise in total white blood cells with a simultaneous fall in lymphocytes. Another possibility is that the venoms themselves contain an unidentified lymphotoxin. Neither of these theories explains the prolonged lymphopenia seen in some cases. Another theory is, that since the inoculated venom often is injected into the lymphatic bed, it reaches the draining lymph node where its presence stimulates sequestration of circulating lymphocytes to the node. According to S.A. Minton, Jr., swelling and tenderness of the regional lymph nodes is also seen in pit viper envenomation. He says it is an important diagnostic indicator in that it helps to distinguish "blank" or "dry" bites from those where envenomation has occurred.

The overlapping nature and appearance of more than 40 signs, symptoms and sequelae among victims of different types of snakebite, present a dilemma in designing a specific plan which best presents that information. These signs and symptoms are more important than the species or type of snakebite. There is a tendency to compartmentalize signs and symptoms by species. But as more and more case histories are reported with diverse pathology not subject to such compartmentalization, then the pathology assumes more importance. Obviously some species will always show signs and symptoms that are more prevalent than others. Identification of the offending species is critical when deciding on which antivenom to use and may alert physicians to the types of effects likely to be encountered, based on the great variety of factors present in various snake venoms.
CHAPTER 8

Treatment of venomous snakebite
Myths and make-believe
Being a mysterious animal, much time and effort has been spent to try to understand the snake and unravel its secrets. Having said this, even more time and effort is spent to find "The Cure" for snakebite. Using snake charms, shaman' spells, magic stones and other ritual methods, man has tried to safeguard himself from snakebite in early days. Later a more pragmatic approach was taken. To name a few:

- The whiskey therapy. A popular method because it also involved the imbibing of large amounts of whiskey as a safety measure against the dangers of a possible encounter with a venomous snake;
- Chopping off fingers or toes or, more drastically, blasting the envenomated digit to shreds with a gun might indeed be lifesaving, but chances are the effects caused by the inflicted trauma are as serious as or even more lethal than the bite itself. And now, as man has developed a more scientific approach to solve the problems surrounding him, real solutions and feasible methods are being found to treat the victims of venomous snakebite.

As we know now, many aspects of the treatment are based on the understanding of the complexity involving the composition of snake venom. The circumstances of the actual envenomation, being the snake itself, the victim and other related factors, play a major part in choosing the right path, which will lead to the full recovery of the patient. This chapter reviews the current concepts of first-aid treatment and their background. An attempt is also made to show how other methods are outdated, useless and even dangerous. At the end of the chapter an emergency protocol is given and a list of preventive actions to avoid or minimize the risk of envenomation.

Venom injection
Another important factor we must understand before we are able to give proper treatment is how the venom gets into the blood circulation. The great variety in fang size and position make it difficult to give a clear picture of how the venom enters the body. Most snakes have relatively short fangs, and venom is therefore injected into the subcutaneous tissues. Large adders, with fangs over 1 cm. long, may inject venom deeper into the muscles. Very rarely, the fangs may hit a major blood vessel, and in such circumstances little can be done. The venom is injected straight into the systemic circulation, and the medical emergency is immediate and first-aid is useless. In these exceptional cases, death, even from a Puff adder bite, can occur in 20 minutes. However, in most circumstances venom is injected superficially, and must diffuse into the blood before serious symptoms develop. Analysis of bite sites reveals that over 98% occur on the limbs, mainly on the lower limbs (85%). This lends itself to first-aid treatment. Bites to the head or trunk are much more difficult to treat, but are fortunately rare. Exceptions to this situation are the bites from the Black Mamba. Due to the size and behaviour of these dangerous elapids, a relatively large proportion of bites occur on the head and body.
The pressure/immobilisation (P/I) treatment

Dr. S. Sutherland and his colleagues at the Commonwealth Serum Laboratories, Australia, developed this first-aid treatment. Its efficacy stems from a reappraisal of the importance of lymphatic drainage of the bite site. The lymphatic circulation acts as an auxiliary plumbing system, collecting interstitial fluid forced by body movements from the blood vessels into the surrounding tissues. Lymph vessels are thin-walled, and fluid circulates within them by pressure exerted on the vessels by neighbouring body muscles. Small valves in the lymph vessels prevent back flow, and body movements tend to force lymph along the vessels. It eventually drains into the blood system through a connection in the neck. This is one of the main functions of the lymphatic circulation, and now, with the genius of hindsight, it's not really obvious why the topic was overlooked for so long. The important aspects of these observations are that:

- 98% of snakebites occur on limbs;
- venom is usually injected into tissues, not into the blood circulation;
- the lymphatic system collect interstitial fluid draining from the tissues;
- body movements generate and circulate lymph;
- lymph vessels are thin-walled and can be occluded by simple pressure from a broad, elastic bandage, whilst full blood circulation to the limb is maintained.

Many herpetologists and medical authorities believe that while compression bandages are of value for Australian elapid and sea snake bites, they question their use on viper, pit viper, and elapid bites, which produce local tissue damage. Their argument is that trapping the venom at the site increases the potential for local tissue destruction, whereas allowing the venom to spread; its effectiveness is diluted by the total of body water. This theory may work when the amount of venom injected is small. If it is large, then even dilution in the total body water may not prevent it from attacking platelets, altering coagulation factors, causing disseminated intravascular coagulation and haemorrhage. It may induce irreversible damage to muscle tissue and major vital organs such as the pituitary, kidneys, liver and heart. At recent seminars and meetings, authorities have said they recommend the use of compression bandages. They also advice victims to risk localized tissue damage in favour of delaying the spread of the venom to the circulatory systems. The following consequences that would result if a believed-to-be seriously envenomated victim were far from medical assistance and immediate availability of appropriate antivenom in sufficient quantities, are better to be faced.

One of the best things about compression bandages, besides their effectiveness, is that if it turns out that the victim was not seriously envenomated, or not envenomated at all, these appliances will do no harm to the patient.

By contrast, there are numerous cases of snakebite victims who were bitten by a nonvenomous snake who endured serious, often permanent, tissue injury as a result of other first-aid techniques. Two of these methods are the use of a tourniquet and the Incision/Suction method.

Tourniquets have long been promoted to prevent the proximal spread of venom but now are no longer recommended. Venom uptake occurs through the lymphatics, yet tourniquets occlude venous and arterial blood flow, leading to lymph oedema, ischemia, necrosis, gangrene, arterio-venous fistula formation,
and peripheral neuritis. Further, the release of a tourniquet can lead to rapid dispersal of venom and tissue debris, causing hypotension and shock. In the past, incision and suction (oral or mechanical) have been advocated for the removal of the venom pool from the site of the deposit. Proponents have based this advice on experimental and anecdotal information. Opponents, however, note several problems:

- no controlled experiments have been done on humans;
- survival of experimental animals has not been affected;
- the venom pool can occur anywhere within the area of a circle, the radius of which is determined by the length of the fangs, thereby making accuracy of location, direction, and depth of the incision difficult;
- in inexperienced hands great damage can be done to underlying arteries, veins, tendons and nerves;
- the use of unsterile technique and suction by mouth can result in secondary infection;
- under field conditions, a 5 to 6% retrieval is probably realistic.

Cryotherapy, including ice, ice water immersion, and cold sprays is no longer recommended. Animal studies have shown ice to be effective at retaining venom at the inoculation site, but rapid venom dispersal following removal of the ice, produces shock. Exposure to cold produces vasoconstriction in already compromised tissues. Prolonged exposure can result in gangrene, and the victim could require amputation. The American Red Cross and the committee on Trauma of the American College of Surgeons recommend against its use. Electric shock treatment for snakebite dates back to 1899, but was most recently popularized after its successful use as treatment of snakebite among the Waoroni or Waorani Indians of Ecuador by Guderian et al. in 1986. 78% of the tribe, however, were positive for snake venom antibodies as determined by an ELISA test, indicating at least partial immunity. An argument could be made that Guderian et al. were treating a highly selective group of "immune" patients. In addition, Guderian failed to take into account that approximately 25% of all crotalid (Pit viper) bites are "dry" and do not result in envenomation. In controlled animal studies, electric shock therapy has shown no effect. The use of this method may in fact be dangerous. Besides the danger for heart-rhythm disorder another problem can occur. Low voltage electricity is being seriously explored as a means of enhancing the infusion of medication through tissue, hardly a desirable goal in snakebite envenomation.

**Localised pressure**

S. Grenard (author of Medical Herpetology. 1994:108) also believes that the application of a small (4"x4") wad of folded (to 1"x1" area) gauze dressing strapped tightly in place directly over the fang punctures will serve not only to delay the spread of the venom, but may also hold it in place closer to the immediate point of entry. It may, therefore, limit the spread of "local" tissue damage to a much smaller space than the more widely applied compression bandage. This technique should help to subdue concern over the consequences
of local tissue damage by the detractors of compression bandages. Apply the small, direct compression dressing immediately after the snake has been disengaged. It can be held in place by two or three lengths of adhesive tape. It may be possible to trap some of the venom within a fibrin clot (if one forms) at the bite site, at least for a short period of time. Applying hard, direct pressure using a thumb and a gauze pad directly over the bite site can cause the formation of a fibrin clot in three to five minutes. This should be done immediately after the bite to entrap venom within the bite site. This hypothesis is based on Grenard’s experience using such dressings and/or direct pressure after performing more than 20,000 diagnostic arterial punctures over the last 28 years, even in heavily anticoagulated patients. The elastic compression bandage can then be wrapped over the smaller dressing to limit the spread of any venom that may escape the site into the surrounding lymphatic tissues. Immobilization of the bitten limb by splinting will also help to minimize both pain and spread of venom, but application of splints are secondary to wrapping the affected area with a compression bandage. In the field splints can be constructed of small tree branches broken to a suitable length and held in place by an elastic bandage (extra rolls of such bandages should be part of the "snakebite kit"), torn up shirt, sheet, or other articles of cloth or clothing. Cord, rope, or a belt may also be used to hold the splints in place. Be aware not to fasten these items too tight. The victim must be transported on a litter or stretcher from the place of the incident to the nearest facility for further treatment. The afflicted limb should not be kept at a level lower than the heart, because this will make transportation of the victim more difficult, it will increase the risk of compartment syndrome and it will not stem the lymphatic flow any further. Do not let the victim walk!

Pharmacists can recommend that the following variables be monitored to help determine the severity of the snakebite and the potential efficacy of antivenom therapy. Circumference of the envenomated area, complete blood count, electrolytes, serum creatinine concentration, urinalysis, platelet count, prothrombin time, partial thromboplastin time, blood pressure, a DIC screen, and wound microbiologic cultures. Blood typing and cross-matching, arterial blood gas measurements, erythrocyte sedimentation rate, bleeding time, serum protein levels, clotting time, and an electrocardiogram may also be ordered. The decision to use antivenom treatment is based on the severity of these findings, as well as the severity of symptoms.

The use of antivenom
Authorities on snakebite, with few exceptions, generally agree that antivenom must be administered to all snakebite victims suffering mild, moderate, or severe envenomation based on the grading of symptoms. Grade Zero, under which no symptoms occur, is the only situation in which antivenom need not be administered. The use of antivenom in situations other than Grade Zero is, according to the Oxford School of Tropical Medicine, still too soon. They recommend the use of antivenom when signs of neurotoxicity are apparent, or when the swelling of the limb exceeds the knee or elbow. Those in the US who are opposed to antivenom in principle, are so disposed because of the high incidence of allergic reactions which occur with horse derived sera (the only kind currently available), the alleged impurities in current freeze-dried antivenoms, and the difficulty with which some batches of antivenom reconstitute. North American antivenom comes as a lyophilized powder, which must be gently but thoroughly dissolved in 10 ml of sterile water. A small sample of horse sera
preparation is included with the antivenom, which the manufacturer provides, so that the victim can be subcutaneously tested for the horse serum allergy. Physicians in Australia generally feel that testing the patient for horse serum allergy is a needless protocol for several reasons. False negatives and positives have been known to occur and it wastes time if the antivenom is definitely needed. It can cause anaphylaxis itself, further complicating an already complex situation and, regardless of the result, it may be necessary to administer the antivenom and deal with the effects of any anaphylaxis, which may occur with adrenaline, antihistamines and corticosteroids anyway. Other problems in using antivenom are those concerning storage. It should be kept at low temperatures, thus meaning the use of a refrigerator. Failure in keeping the proper temperature, can seriously affect the antivenom's activity.

**First-aid protocol in case of possible envenomation**

To make a proper protocol a few aspects should be considered. In captivity the identification of the offending snake is fairly easy and there is usually a one-or two-person situation. It must be stressed that handling venomous snakes alone creates a high-risk situation and must be avoided at all times. In the field, solo excursions should be kept to a minimum, and when they do occur, one should remain alert in this unknown environment to minimize the risks.

The First-aid protocol is available in the Snakebite Kit. The protocol also includes a detailed instruction on how to apply the compression bandages.

If a person gets bitten the following actions should be taken:
- Do not panic, take control of the situation, reassure the victim, assume the bite is serious until proven otherwise;
- Alert other group members of the incident;
- Move the victim out of the snake’s territory;
- Instruct group members to try and identify the snake involved without placing themselves at risk. If alone, focus on the patient and assume the snake is venomous until proven otherwise;
- Let the victim lay down, locate the bite and try to inspect the wound;
- Cover the wound with gauze pads, strapped in place with adhesive tape and apply firm pressure to confine the venom in the gauze pads. Do not waste time cleansing or disinfecting the wound, this can be dealt with later;
- Wrap a broad short stretch, high compression bandage over the bitten area, start at the bite-site and proceed towards the body as far as possible. At least include the first joint, usually knee or elbow. The bandage should only be as tight as for a sprained ankle. Do not waste time taking off clothes. The movement will help spread the venom;
- Bind a splint to the whole limb to keep it immobile;
- Again reassure the victim to reduce stress and fear;
- If possible when alone, now is the time to try and identify the snake. Remember: the victim depends on you, so no unnecessary risks can be taken;
- Let the victim remain lying down, making it as comfortable as possible. Keep the victim warm and make transport arrangements;
- If help can not be reached or takes too much time to reach you, the victim must be transported, using a litter or stretcher. The victim must walk as little as possible;
To help proper assessment of the situation at the nearest medical facility, all available information regarding the snake’s identity must remain with the victim;
- If the snake has been killed, place it in a bag using a stick for even a dead snake is still able to inflict a serious bite;
- Has the incident occurred in a zoo or other facility where specific antivenom is kept in storage, this must be brought to the hospital with the victim;
- When trained medical emergency personnel are involved, they should (in addition to assuring the placing of compression dressings, bandages and splints) immediately establish one to three intravenous sites that can be used when indicated. These IV-sites may be difficult to establish later due to shock or vasoconstriction. When the bite is on an arm or hand, the opposite limb should be used for the IV-sites;
- If possible, the medical emergency personnel should inform the receiving hospital on the type of snake involved in the snakebite incident in order to have the specific antivenom available and ready in the event that subsequent symptoms warrant administration.

Actions you MUST NOT take!
- Do not waste time or cause additional harm by the use of constricting bands (tourniquets) or application of ice or cold packs;
- Do not incise, cut, apply suction, or use a mechanical extractor or electric shock device;
- Do not offer medication or alcoholic beverages;
- Do not provide anything to eat or drink;
- Do not remove the pressure bandages or compression dressings until antivenom is available, reconstituted and ready to administer, and a treatment protocol has been established. There may be some wisdom in leaving the bandages in place until the antivenom has started, except for the fact that it suppresses symptomatology;
- Do not start antivenom therapy as a first-aid measure. This can lead to an uncontrollable situation endangering the victim’s life even further. Remain with the protocol or follow instructions given by the proper medical authorities.

Preventive actions to reduce the risk of snakebite
When handling venomous snakes, approach with care and keep the animal in sight. Do not handle them alone. Remain calm and make sure enough time has been reserved to finish the job at hand without the need to rush. Venom and alcohol don't mix, never did, never will.

Make sure all materials and equipment are in good order and the people assisting you are aware of the situation present. In the field other actions can be taken to reduce the risk of a possible dangerous encounter with a snake.
Before entering snake territory get as much information about the local species and their habits. Familiarize yourself with the current first-aid treatment for snakebite and upgrade your first-aid kit with a Snakebite Kit. Do not venture out in to the bush alone. Wear protective clothing i.e. ankle length boots, trousers instead of shorts. All clothing should be loosely fitting. Use a stick when walking trough areas with dense undergrowth to warn the snake of your presence. Do not turn over rocks or logs with your hands, a snake may be resting underneath it. Don’t put your hands in holes or crevices without being able to see in to them. If a snake is encountered, remain calm and retreat if possible. If not, don't move
and give the snake a chance to escape. Hardly any snake will attack right away unless it is stepped upon.

Make sure a Snakebite Kit or medical kit with up-to-date equipment is brought along each time people go out into the bush. And most important: a human being has the capability to think, act or react. A snake has its instincts to deal with the situation at hand. If we can respect the snake for what it is, it doesn't have to be a threat to our own well-being and we can learn more about the snake and ourselves.

Conclusions

A number of statements and conclusions can be made regarding the findings of this paper.

Yes, venomous snakes are potentially dangerous animals and because of a freak mishap of Mother Nature, man has a high susceptibility to their venom. However, all the efforts made in understanding this animal, have given man a lot of information and insight in the specifics of the snake's life and, even more important, of what snake venom is all about. This however, doesn't mean we now fully understand the intricacies of the venom. Many symptoms can be ascribed to specific venom components. But due to the fact that no component works alone and every envenomation is unique because of the snake and the victim involved, no standard therapy can be applied.

Over the years many scientists have tried to come up with "The Cure", but as it has turned out it is not that simple. The consensus reached at this time is, that because of the widespread incidence of snakebite around the world and its many symptoms, continuing attention to this subject is needed.

The great variety of snakebite therapies is reduced to a well-described First-Aid treatment and a very thorough observation and grading of the patient when hospitalization has been established. The use of antivenom is advocated, but only when it is needed, not as a fail-safe method. Close monitoring of the symptoms and laboratory findings, expecting the unexpected, and listening to the information given (even by non-medical personnel) presents the best scenario to a full recovery of the patient.

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