THE SYNDROMIC AND SPECIFIC MANAGEMENT OF

SNAKEBITE IN SOUTHERN AFRICA

BY

R. S. M. BLAYLOCK

Submitted to the Department of Surgery, Medical School, University of Natal, in fulfilment of the requirements for the degree of Doctor of Medicine (MD) 2002.

DECLARATION   This is my own unaided work and has not been submitted previously or to any other university.

DEDICATION   To my family.

PUBLICATIONS EMANATING FROM THIS THESIS

1. Blaylock, R.S.M., (2000). Antibacterial properties of KwaZulu-Natal snake venoms. *Toxicon* **38**: 1529 - 1534.
2. Blaylock, R.S.M., (2001). Normal oral bacterial flora from some southern African snakes. *Onderstepoort J Vet Res* **68**, 175 – 182.
3. Blaylock, R. (2001). Snakebites and hands. In: *The Finger Print*, April – June, pp. 19 – 21.
4. Blaylock, R. (2002). Snake Bites. *Surgery* **20** (2), 25 - 29.
5. Blaylock, R.S.M., Tilbury, C.R., Branch, W.R., (2002). Anaphylaxis following exposure to snake venoms in South Africa. *Current Allergy & Clinical Immunology* **15** (2), 65 - 68.
6. Blaylock, R.S.M. Immediate active movement following *Bitis arietans* or *Naja mossambica* venom injection diminishes or prevents necrosis in mice. Accepted by *Toxicon,* June 2002.
7. Blaylock, R.S.M. Acute adverse reactions to South African manufactured snakebite antivenom. *Current Allergy & Clinical Immunology* **15** (3) 107 - 113.
8. Publication No 3 above, slightly modified, has been accepted for inclusion in a textbook on Tropical Surgery partly edited by Professor J. Lumley.
9. Blaylock, R.S.M. Snakebite and pregnancy with reference to Southern Africa. Submitted to *Tropical Doctor,* January 2002. Rejected.
10. Blaylock, R.S.M., The effect of atropine, obidoxime and neostigmine on black mamba induced respiratory failure in mice. Submitted to *Toxicon.* Rejected.
11. Otto, J., Blaylock, R. A vine snake bite in a dog. Submitted to *J S Afr Vet Assoc,* October 2002.
12. Femoral vessel and compartment syndromes following snakebite: a case report. Submitted to *S Afr J Surg,* August 2002.
13. Suggested management of poisonous snakebite in South Africa. Requested by *S Afr Dermatology Review,* November 2002.

SCIENTIFIC PRESENTATIONS

1. "Snakebites". Association of Primary and Occupational Health Practitioners. Fochville, 15 August 2000.
2. "Snakebite". Edendale Hospital. Pietermaritzburg, 16 March 2001.
3. "Envenomation". Primary, perioperative and critical care medicine refresher course, Addington Hospital, 17/18 March 2001.

4. "Snakebite". Leslie Williams Memorial Hospital, Carletonville, 23 March 2001.
5. "Snakebite". Joint Congress of the College of Primary Care Physicians and Pharmaceutical Society of Zimbabwe, Victoria Falls, Zimbabwe, 18 – 21 May 2001.
6. "Geographical footprints of venoms". National Health Laboratory Service - Nature Conservation Mini-workshop, Antivenom Unit, Edenvale, Johannesburg, 12 April 2002.
7. "Snakebite". Invited lecturer to Tropical Medicine and Hygiene diploma course, University of Witwatersrand, 22 August 2002 and August 2003.
8. "Snakebite". Continued Medical Education symposium. Manguzi Hospital, 23 November 2002.
9. "Recognition and Management of Snakebite". Invited speaker: *Matters Medical,* television programme, 21 January 2003.

ACKNOWLEDGEMENTS

LIST OF TABLES

Chapter 9

Chapter 10

Chapter 11

LIST OF PHOTOGRAPHS

Page

GLOSSARY: ABBREVIATIONS AND DEFINITIONS

%	-	Per cent
°C	-	Degrees celcius
ACH	-	Acetylcholine
ADH	-	Antidiuretic hormone
B	-	Bleeding
BE	-	Base excess
BP	-	Blood pressure
BSCs	-	Bite site complications (bite site blister, deep haematoma, abscess or necrosis)
CCF	-	Congestive cardiac failure
CKMB	-	Creatinine kinase – 2
cm	-	Centimetre
cm^2	-	Square centimetre
CPK	-	Creatinine phosphokinase
CVP	-	Central venous pressure
df	-	Degrees of freedom
D-dimers	-	Presence confirms fibrin formation and breakdown
DIC	-	Disseminated intravascular coagulation
ECG	-	Electrocardiogram
ELISA	-	Enzyme-linked ImmunoSorbent Assay
FDPs	-	Fibrin degradation products
GCS	-	Glasgow coma scale
g	-	Gram
g/dl	-	Grams per decilitre
Hb	-	Haemoglobin
HBD	-	Alpha-hydroxybutyrate dehydrogenase
h	-	Hour
IMI	-	Intramuscular injection
IVI	-	Intravenous injection
Illegitimate bite	-	Snakebite sustained when handling or provoking a snake
INR	-	International normalised ratio
LD_{50}	-	Lethal dose for 50% of experimental animals
LDH	-	Lactate dehydrogenase
Legitimate bite	-	Snakebite sustained during an accidental human-snake encounter
meq	-	Milli equivalents
mg	-	Milligram
mg%	-	Milligrams per 100 millilitres
min	-	Minute
ml	-	Millilitre
mm	-	Millimetre
mmHg	-	Millimetres of mercury
mmole	-	Millimole
N	-	Normal
NIV	-	National Institute of Virology
NHLS	-	National Health Laboratory Service
Nil	-	No clinical envenomation
n	-	Total number

nm	-	Nanometres
NMRI	-	National Medical Research Institute
PCO_2	-	Partial pressure of carbon dioxide
PEFR	-	Peak expiratory flow rate
pg/ml	-	Picograms per millilitre
pH	-	Negative logarithm of the hydrogen ion concentrations of a solution
PI	-	Prothrombin index
PO_2	-	Partial pressure of oxygen
PPS	-	Painful progressive swelling
PTT	-	Partial thromboplastin time
PW	-	Progressive weakness
q waves	-	Relates to ECG
SAIMR	-	South African Institute for Medical Research
SAVP	-	South African Vaccine Producers (Pty) Ltd
s	-	Second
SCI	-	Subcutaneous injection
SG	-	Specific gravity
SGOT	-	Serum glutamic-oxaloacetic transaminase
SGPT	-	Serum glutamic–pyruvate transaminase
SIADH	-	Syndrome of inappropriate antidiuretic hormone secretion
sp	-	A single species
spp	-	Two or more species
ST elevation	-	Relates to ECG

SWELLING CLASSIFICATION: Assumes the bite site to be distal extremity. Swelling category can be estimated for other bite sites.

Minimal swelling	-	Minor swelling around the bite site.
Mild swelling		Swelling of a whole foot or hand up to the ankle or wrist.
Moderate swelling	-	Swelling of a limb to the proximal thigh or shoulder.
Severe swelling	-	Swelling of the whole leg to the inguinal ligament or the whole arm to the chest wall.
Gross swelling	-	Swelling of the trunk from a foot bite or to the opposite side of the chest, neck or abdomen from a hand bite.
TEG	-	Thromboelastogram
TPA	-	Tissue plasminogen activator
U and E	-	Urea and electrolytes
WBC	-	White blood cell count
Wt	-	Weight
x	-	Multiply
XDPs	-	Type of fibrin degradation product

PREFACE

The author wrote a dissertation for the Mmed Sc degree entitled *The Clinical Natural History of Snakebite in Southern Africa*, which dealt with the epidemiology of snakebite and the clinico-pathological events in snakebite victims. This thesis is a sequel on the management of snakebite victims.

Publications on the overall management of snakebite in the Southern African region that include original scientific research are those of F.W. Fitzsimons (1912), F.W. Fitzsimons (1929) (assisted by V.F.M. Fitzsimons), P.A. Christensen (1955, 1966, 1969) and Christensen & Anderson (1967). Subsequent books, pamphlets and journal articles have rehashed this knowledge or advocated methods of treatment developed in other countries. An example of the latter is the pressure immobilisation pre-hospital measure advocated for snakebites in Australia (Sutherland *et al.,* 1979, 1981, 1995), which I regard as benefiting less than 1% of snakebite victims here and being deleterious in most cases.

In view of the paucity of research done in Southern African in recent years, many questions remain unanswered, and some strongly held views are without logical or scientific foundation. Most of these questions arose prior to the writing of this thesis, and others arose when the data were analysed. The following are some questions on the management of snakebite that have still have to be addressed.

Is vaccination against snakebite possible and practical? Are folk and traditional remedies advantageous or deleterious? How commonly are they used? Immobilisation of the bitten part and the patient is an internationally recognised first-

aid measure, but is this relevant to the Southern African situation? Tourniquet use in the case of necrotising venoms is considered to aggravate or precipitate necrosis. Does immediate active movement following a bite ameliorate or prevent necrosis without increasing mortality? The majority of clinicians recommend antibiotic prophylaxis, but is this necessary for all snakebites, against which bacteria should antibiotics be administered, and what is the source of these bacteria? Should antivenom be administered to all snakebite victims: for species-specific bites, only if envenomation is present, for severe envenomation, or not at all? Acute adverse reactions to South African manufactured snakebite antivenom has been variously recorded as less than 1% (Visser & Chapman 1978) up to 76% (Moran *et al.*, 1998). What is the truth? Is syndromic management of snakebite efficacious or is it essential to identify the particular snake species? Is the present liberal use of fasciotomy necessary? Is there an optimum time to debride necrotic areas and is surgery necessary at all? Is paresis or paralysis due to neurotoxic envenomation always the result of a post-synaptic block? Would such a block respond to neostigmine or prostigmine in a similar way to post-synaptic anaesthetic muscle relaxants? Is heparin of value when procoagulant toxins induce a consumption coagulopathy? Do fibrin-stabilising agents or fibrinolytics have a role? Does the management of pregnant snakebite patients differ from that of non-pregnant patients? Is snake venom teratogenic? Does snake venom ophthalmia frequently lead to blindness? Are steroids, NSAIDs and antihistaminics, which are commonly used in the management of snakebite, of proven value?

This thesis attempts to answer these questions and more, and comprises six sections. The first section deals with pre-hospital management, the second with infection which

may occur at the bite site wound, the third with SAIMR snakebite antivenom, the fourth with the three envenomation syndromes, the fifth with snakebite in pregnancy, venom ophthalmia and other treatment modalities, and the sixth section includes a summary, appendix and references.

Unless otherwise stated, the materials and methods of each chapter are based on 336 snakebite victims admitted to Eshowe Hospital, KwaZulu-Natal, from January 1990 – July 1993 and other victims treated by the author, the data of which have been prospectively maintained. This has been an ongoing process up to the present time.

ESHOWE HOSPITAL, KWAZULU-NATAL
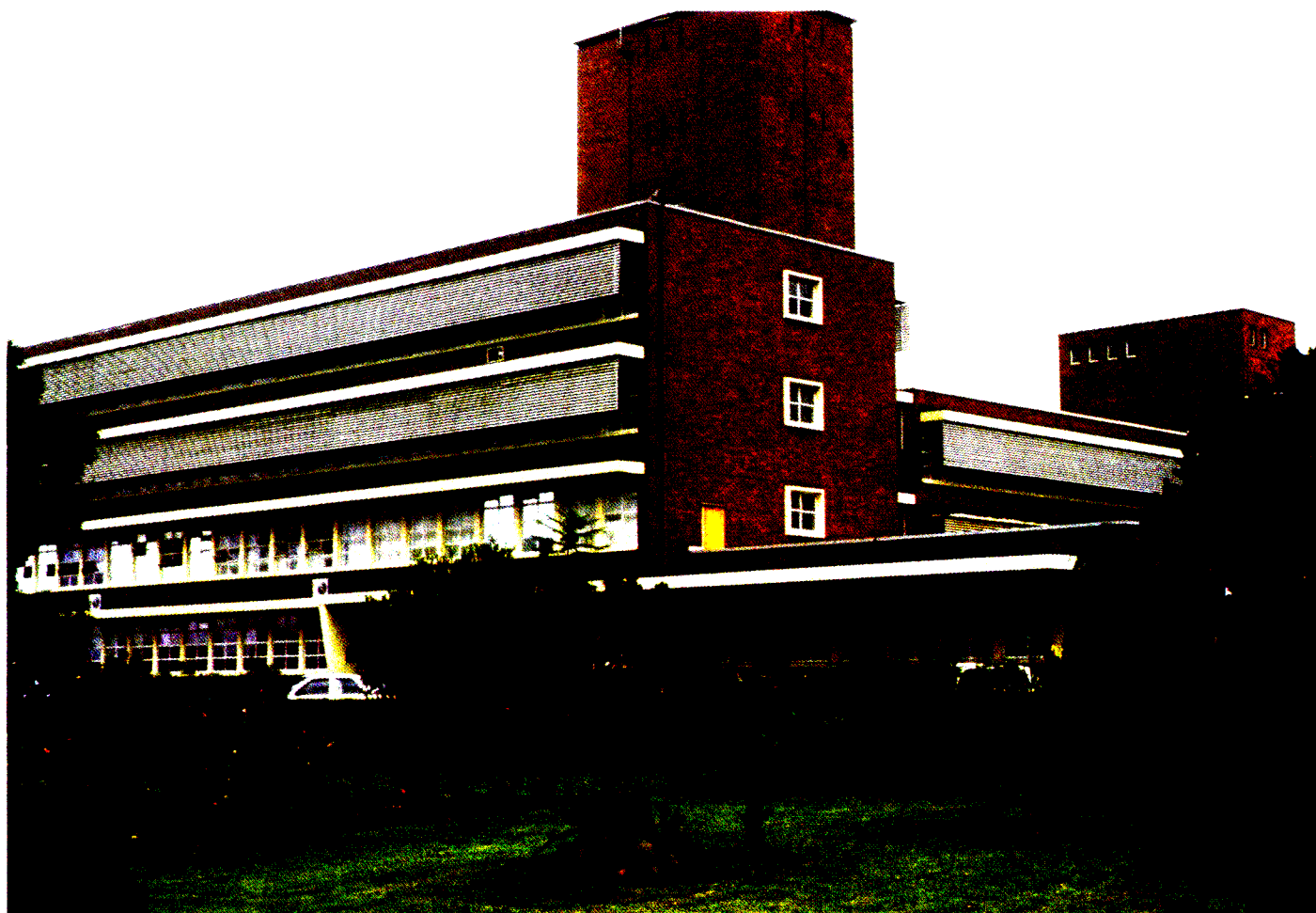
Authorised 460-bed hospital. Snakebite patients from this hospital, other patients managed by the author and published cases form the basis of this thesis.

version of Fisher's exact test, Chi-square test for independence, Chi-square test for trend and analysis of variance (Instat 3 Statistics Package, GraphPad Software, San Diego, California, USA, 1998).

Permission for the animal experimentation was obtained from the NHLS Animal Ethics Committee (project AE01/#074, #075) and the Animal Ethics Sub-committee of the University of Natal (project AE/Blaylock/01/16 – necrotising venom study only).

Results and conclusions

Snake bite prophylaxis and first aid

Prevention of snakebite is a matter of common sense. Clothing is only of protective value if it prevents fang penetration. Bites at night can be prevented by wearing shoes and using a light, measures can be taken to prevent snakes from entering dwellings, and campers can tuck a mosquito net under their mattresses or use a zip-up tent to keep snakes out. Recently killed snakes should be treated with caution as they can bite due to reflex action.

The majority of the Eshowe patients applied a tourniquet and ingested oral "medicine" after being bitten, but there is no effective first-aid measure for all snakebites. Getting the patient to medical help is the most important priority.

Local incisions and suction, cryotherapy or electrotherapy are of no real value. Tourniquets are generally deleterious as they may aggravate or precipitate necrosis, although not commonly they are of some value in specific snakebites. The pressure

immobilisation method is theoretically of value in non-spitting cobra bites where the dominant toxins are lymphatically transported. An arterial tourniquet is of proven value in bites KNOWN to be from mambas and non-spitting cobras, and is recommended for herpetologists and wild life experts away from medical help who have been bitten by snakes which they are able to identify. Pharmaceuticals administered prior to hospitalisation will eventually play a role in first aid.

Immediate active movement (swimming) prevented necrosis ($P = <0,05$) or reduced the area of necrosis ($P = <0,002$) of mice feet injected with puff adder or Mozambique spitting cobra venom. One of 19 ambulant mice died. Consideration should be given to immediate elevation and active finger movement following finger and hand bites in view of frequent necrosis and permanent morbidity. Further epidemiological and experimental studies on this aspect should be carried out.

Bacterial infection due to snakebite

Fifty-two per cent of swabs from healthy snake mouths were positive for bacteria, from which 92 bacteria were cultured. Thirty species were represented, of which 81,5% of the isolates were *Enterobacteriaceae*, 16,3% were Gram-positive aerobic cocci, and 2,2% were anaerobes. Swabs from the mouths of non-venomous snakes were more commonly bacteriologically sterile than those from venomous snakes ($P = < 0,02$). The oral bacterial flora did not differ between captive and newly captured snakes, and were not constant in a single snake with time, in the same snake species, the same serpentarium or the different geographical areas. The bacteria most commonly cultured were *Proteus spp.*, *Pseudomonas spp.*, *Salmonella arizonae* and *Staphylococcus epidermidis.* Colony counts tended to be low. Three or more

bacterial species per venomous snake per occasion were more common in winter than in summer (P = < 0,02). Bacterial flora tended to be scanty in healthy snakes and mainly comprised the *Enterobacteriaceae* which are transient colonisers. Anaerobic bacteria were uncommon.

All snake venoms showed antibacterial activity, with the adder venoms showing the most activity against the aerobes, and the cobra venoms showing lesser antibacterial effects which were equal against aerobes and anaerobes.. Black mamba venom only showed activity against *C. perfringens*. The venoms of snakes in Southern Africa have antibacterial properties which are dependent on the type of venom and bacteria.. This is partly the reason for the low incidence of bacterial infection following snakebite. There is a decrease in the anti-anaerobic bacterial properties of *Naja spp.* venom in winter.

Bacteria isolated from infected snakebites are similar to normal snake mouth flora, suggesting that snake mouths are the primary source of sepsis. Four of 250 (1,6%) patients without bite site complications (BSCs) who were not given antibiotics developed wound infections. Patients with BSCs or gross swelling who received antibiotics were hospitalised for a substantially longer period than similar patients who were not administered antibiotics. Antibiotics are not routinely indicated for snakebite. Empirical antibiotic therapy adequate to control sepsis includes inexpensive preparations such as cotrimoxazole, ampicillin, chloramphenicol and the aminoglycosides, or the more costly antibiotics developed later which have the same spectrum of bacterial cover.

Antivenom

Polyvalent and monovalent boomslang antivenom is manufactured by immunising horses against multiple venoms and a single venom respectively. The indication for the administration of antivenom is severe envenomation, which is life or limb threatening (less than 10% of snakebites). There is no standard antivenom dose, the same volume being administered regardless of the size of the patient. All doses should be administered by slow intravenous injection without prior sensitivity testing. Repeat administration may occasionally be necessary and, if indicated, is of value while the venom is still active.

Acute adverse reactions to polyvalent antivenom administered to patients with progressive weakness, painful progressive swelling (without coagulopathy) and bleeding (active or potential) occurred in 21%, 56% and 60% of cases respectively. Similar reactions to polyvalent antivenom administered to patients within 10 h, 10 – 24 h or >24 h of the bite, occurred in 14%, 75% and 40% of these time periods respectively. Acute adverse reactions to antivenom are partly due to the clinical envenomation syndrome, with the time lapse between bite and administration being a possible contributory factor. The dominant clinical presentations of PW, PPS and bleeding were inversely proportional to the acute adverse reaction rates, demonstrating that the protein load given (98 ml, 51 ml, 25 ml respectively) is not an important factor.

No patient died of an antivenom reaction. Acute adverse reactions to antivenom are common and may be prevented and treated with parenteral adrenaline. Premedication

with adrenaline prior to antivenom administration is suggested if the individual is atopic, if antivenom is administered for boomslang venom-induced coagulopathy, if there is swelling of a whole limb, or if more than ten hours have elapsed after the bite. Late reactions are associated with increasing foreign protein load and may be prevented and treated with a course of glucocorticosteroids. It is suggested that a prophylactic course of glucocorticosteroids be given if administered antivenom exceeds 100 ml (10 ampoules).

The clinical syndromes of envenomation

Categorising patients according to the clinical syndromes of painful progressive swelling (PPS), progressive weakness (PW) and bleeding (B) or combinations of these allows syndromic management of snakebite. Polyvalent antivenom is an essential adjunct to syndromic management. The terms cytotoxic, neurotoxic and haemotoxic refer to the venom.

Painful progressive swelling syndrome

The intravenous fluid requirements are directly related to the rate of swelling progression and the eventual extent of the swelling. . Elevation of a bitten limb may help return third space fluid into the circulation and helps to relieve the pain. Potent analgesics were required most commonly within the first 24 hours of admission for patients with rapidly advancing swelling and for those who developed bite site complications. Antivenom is reserved for severe envenomation, present or anticipated, shown by the swelling of a whole hand or foot within 1 hour of the bite, reaching the elbow or knee within 3 – 4 hours, swelling of a whole limb within 12 hours, threatening the airway, unexplained dyspnoea or an associated coagulopathy.

A dose of 50 ml antivenom is adequate except for Gaboon adder bites, where 200 ml is more appropriate.

Bite site complications (BSCs) occurred 45 times in 42 (15%) of 282 patients with painful progressive swelling. Surgery was more commonly performed on fingers and hands than elsewhere (P = <0,001). Debridement at six days or less usually led to repeat debridement (P = <0,03). Blisters are best left undisturbed, abscesses treated on merit, haematomas drained or aspirated and necrotic areas (including fingers) left for 5 - 7 days prior to debridement. Skin cover follows standard surgical principles. Fasciotomy due to compartment syndromes was indicated in four of 333 (1,2%) of the Eshowe patients and in 282 (1,4%) patients with the syndrome of painful progressive swelling. A bitten limb with PPS and venom-induced hyperalgesia is frequently misdiagnosed as a compartment syndrome. Compartment syndromes of digits, feet and hands, although they do occur, decompress spontaneously without surgery. Those that may require surgery are confined more proximally in a limb and may be successfully treated with intravenous fluids, elevation, antivenom and mannitol. Failure of medical management requires open full-length fasciotomy once a coagulopathy has been treated. Temporary carpal tunnel syndrome may complicate hand and finger bites. Femoral vessel entrapment syndrome was noted in a single patient, and this may require division of the inguinal ligament.

Progressive weakness syndrome

Ventilation without the use of antivenom prevents the death of patients with respiratory failure due to paresis or paralysis. The mental awareness of ventilated

patients necessitates the administration of concomitant sedatives. Muscle relaxants are mostly contra-indicated.

Appropriate volumes of polyvalent antivenom can prevent or reverse respiratory failure or reduce the period of ventilation in the majority of cases. The exception to this is patients bitten by Cape cobras. Suggested indications for antivenom are dyspnoea in the absence of PPS (mambas), generalised paresis in the presence of PPS (non-spitting cobras), generalised paresis and widespread myalgia (sea snakes), and an inability to swallow saliva. The minimum effective dose of polyvalent antivenom is 40 ml, although a starting dose of 80 ml is recommended.

The use of atropine or obidoxime (or combinations) in black mamba-envenomed mice accelerated the time to apnoea. The response to neostigmine suggests that the cause of death is not due to a non-depolarising neuromuscular block.

Bleeding syndrome

A coagulopathy or active bleeding may occur in bites by the puff adder (thrombocytopenia), the boomslang *(Dispholidus typus)* and the vine snake *(Thelotornis spp)*, (DIC by activation of factors II and X), and the Gaboon viper (inhibition of platelet aggregation and conversion of fibrinogen to fibrin). Fenestration of capillaries by haemorrhagins facilitates bleeding. Treatment is with blood component therapy and antivenom, the latter being inappropriate for vine snake bites. Indications for antivenom include active systemic bleeding, non-clotting blood or laboratory evidence of a significant coagulopathy. Suggested volumes of polyvalent antivenom are 50 ml for an unknown snake, puff adder or spitting cobra bite, and 200 ml for a Gaboon adder bite. Twenty millilitres of monospecific

antivenom is usually adequate for boomslang-induced coagulopathy. Concomitant blood component therapy is usually required. Heparin, fibrinolytics and fibrin-stabilising drugs are of no value. Significant venom-induced coagulopathy is not common in Southern Africa.

Aspects of clinical significance

In pregnancy the bleeding syndrome is responsible for the majority of maternal deaths and fetal wastage. Unless the life of the envenomed mother is threatened or a coagulopathy exists, pregnancy is unlikely to be affected. Adequate supportive measures are essential. Minor coagulopathies warrant the use of antivenom. The extent of envenomation-induced foetal abnormalities is unknown.

Venom squirted into the eye by spitting cobras and the rinkhals causes venom ophthalmia, which is an immediate acute conjunctivitis with possible corneal erosions. A single instillation of local anaesthetic eye drops allows bland fluid eye irrigation. The application of antibiotic eye ointment and a pad returns the eye to normal in 24 – 48 h even in the presence of corneal ulceration.

There is no evidence that glucocorticosteroids, NSAIDs or antihistaminics are of value in treating snakebite. In view of delayed wound healing and increased infection rates with the first two of these drugs, they should not be used for snakebite treatment.

SECTION 1

SNAKEBITE

PROPHYLAXIS AND FIRST AID

PREAMBLE

Prophylaxis against snakebite in this instance refers to prevention of bites and is mostly a matter of common sense. Although it is possible to vaccinate people against snake venom, it is unlikely to be efficacious and would in any case be impractical in South Africa due to the many different kinds of venomous snakes that occur here. First-aid measures are designed to reduce the action of venom in patients before they can reach medical help, but only a few such measures are practical and of any use.

A new procedure for limiting necrosis is explored in Chapter 2.

CHAPTER 1

SNAKEBITE PREVENTION AND FIRST AID

CONTENTS

1.2   Prevention

Populous areas where snakes abound have a surprisingly low incidence of snakebite, amounting to 23 - 81 per 100 000 population in eastern South Africa (Chapman, 1968; Coetzer & Tilbury, 1982; McNally & Reitz, 1987; Wilkinson, 1994; Blaylock, 2000), and as high as 602 per 100 000 in the Bambur region of the Benue Valley in Nigeria (Pugh & Theakston, 1980). Taking a few simple precautions can lower this incidence.

1.2.1   Common sense. Do not put your hand in a hole with unknown occupants. Step on a log and not over it. Do not catch or kill snakes unless competent to do so.

1.2.2   Protective clothing and footwear are of benefit only if they prevent fang penetration (Blaylock 2000).

1.2.3   Bites at night

In the rural snakebite series, 34% of bites occurred between 18:00 and 06:00, with 23% between 20:00 and 05:00 (Wilkinson, 1994; McNally & Reitz, 1987; Blaylock, 1982a; Blaylock, 2000). Thirteen of 333 patients in Eshowe (Blaylock, 2000), and 13 of 17 patients with Mozambique spitting cobra bites (Tilbury, 1982) were bitten whilst asleep. Footwear, improved visibility with good light and sleeping in a dwelling that keeps snakes out would prevent many of these bites. A zip-up tent or mosquito net tucked under the mattress is recommended on camping trips.

1.2.4   Dead snakes

Be careful of "dead snakes". Some snakes sham death, notably the rinkhals and some other elapids (Broadley, 1983). Reflex action can still cause a dead snake to bite, especially those with heat-sensitive pits (Suchard & Lovecchio, 1999).

1.2.5   Vaccination

Vaccination of people against snakebite is possible in a similar way to animals hyperimmunised for antivenom production. However, vaccination would have to be repeated every 3 – 5 years with the risk of complications (local necrosis and hypersensitivity), and multiple vaccinations would have to be used for all the major venomous snakes. This is feasible in geographical regions harbouring only one or two poisonous snakes where snakebite is a common cause of morbidity and mortality (not in Southern Africa), or for some snake handlers, but the enhanced secondary immunological response would be too late to be of value.

1.3   First-aid measures

1.3.1   Introduction

The purpose of first-aid measures is to limit venom action before medical help can be reached, which "buys time" These measures are designed to extract the venom (incision, excision and suction at the bite site), denature it (electrotherapy) or slow its systemic absorption (cryotherapy and the various types of tourniquet). A further necrosis-limiting measure is investigated in Chapter 2.

1.3.2 Traditional first-aid measures

A prospective study was undertaken of 100 snakebite patients at Eshowe who were asked five questions. These questions covered the use of a tourniquet and its site of application, the ingestion and topical application of 'medicine', incisions at the bite site and the use of an enema.

Results: Table 1 – 1

Table 1 - 1   Traditional first-aid measures

	Eshowe Blaylock n : 100	Chapman 1968	Coetzer & Tilbury 1982 n : 163	Blaylock 1982a n : 50	McNally & Reitz 1987
Study type	Prospective	Retrospective	Prospective	Prospective	Retrospective
Percentages taken to the nearest whole number					
Nil	8		38		76
Tourniquet application	85	11 (90 of 821)		52	7
Local or distant incisions	13	20 (163 of 836)	24	30	15
Topical applications	24		2	10	3
Oral medicine	63		9		2
Enema	2		1		
A combination of these	66		Some		Some
Significant morbidity due to first aid	Nil	6 Tourniquet ischaemia. 1 Bleeding		Nil	
n : number of patients					

1.3.2.1 Discussion

Eighty-two per cent of Eshowe patients applied some form of first-aid, the most common being a tourniquet (85%) comprising string, cloth or a belt, and intake of oral medicine (63%), of which 15% took the Zulu medicine 'isibiba' ('msilinga', which

consists of pulverised roots and snake heads). Christensen (1955) showed that this medicine had no effect on the outcome of snakebite but was harmless to rabbits and mice. Other ingested medicine included other herbs (5%), Jeyes fluid, potassium permanganate, urine, green aloe, venom from the snake, eating part of the snake or an analgesic tablet (1 - 2%). Sixty-six per cent used a combination of these home remedies. The figures for the use of these remedies in Eshowe exceeds those given by Chapman (1968), Blaylock (1982a), McNally & Reitz (1987) and Coetzer & Tilbury (1982), Table 1-1. The discrepancy may be due to the thoroughness of the questioning and social and cultural differences.

These remedies produced no complications in the Eshowe study. Chapman (1968) noted that of 90 applied tourniquets, 46 had caused increased swelling, and in 10 cases the swelling had progressed proximal to the tourniquet with resulting ischaemia in six, of which one was serious. Death from tourniquet use has been reported (Pugh & Theakston, 1987a). In 163 patients (Chapman, 1968) with incisions, minimal damage occurred, with one patient requiring blood transfusion due to bleeding from the incision, and in 18 cases local infection was attributed to incision. Four times as many patients were pyrexial without incisions in comparison to those incised. These measures were recognised as hazardous by Coetzer & Tilbury (1982) and McNally & Reitz (1987). Table 1-2 gives lists of scientifically tested traditional and home remedies thought to be beneficial. Folk remedies are common elsewhere (Russell, 1980; Mebs, 2000).

It would be reasonable to discourage these traditional first-aid remedies, but they should be respected as they are mostly innocuous and provide reassurance.

Table 1 – 2   Scientifically tested traditional and home remedies for South African snakebite

Worthless antidotes	
1* Fitzsimons 1912, pp. 309 – 341, 383 - 390	**2* Christensen 1955, pp. 101 – 102**
Zibida or sebiba (pulverised roots and snake heads) Croft's tincture (ammonia and opium) Alcohol Horniball's Patent Wonderful Extract (extract of male fern) Stockholm tar Blue stone Eau-de-luce Ipecacuana Potash Caustics Strychnine Ammonia Tanjore pills (arsenical preparation) Snake's gall Snake's blood and gall Dried snake venom Snake stones Lizard cure (powder of pulversised body)	Isihlungu Ubuhlungu Isibiba Ammonia Prostigmine British Anti-Lewisite Ergotamine Dihydroergotamine Calcium gluconate Anthisan Coramine Benadryl
	Christensen 1969 Intravenous alcohol

Method 1*   These antidotes were tested on the chacma baboon, vervet monkey, jackal, cat and owl according to the recommendations for use. Application of the remedies was oral, local or regional (with or without incisions) or combinations of these. Snakes used were the puff adder, Cape cobra, night adder and boomslang. Quinine, vinegar and the water cure (immersion in water) were not tested as they had previously been shown to be worthless.

Method 2* Just less than the LD_0 of antidote was injected intravenously or intraperitoneally, followed 5 – 10 minutes later by injection of venom ($>LD_{50}$ but $<LD_{100}$). Puff adder and Cape cobra venom was used for different groups of mice.

Table 1 - 3   Antidotes found to be of value

Permanganate of potash immediately rubbed into the scarified venom injection site with or without a proximal tourniquet (Fitzsimons, 1912).

Common soap (sodium stearate) or carbolic soap injected at the site of venom entry (Christensen, 1955).

1.3.3   Removal of venom from the bite site

1.3.3.1   Incisions and suction

Fitzsimons (1912, 1929) recommended making three to four cuts about a quarter of an inch deep and half to three-quarters of an inch long over each fang puncture. In addition, he suggested the encouragement of bleeding and suction by using the protected mouth or a pump as suggested by Christensen (1955); and the SAIMR antivenom pamphlet (1956).

In elapid bites the venom would have dispersed, and in serious adder bites the venom is too deeply placed to be removed (Chapman, 1968). Incision should be omitted as it is risky, useless, and delays more important forms of treatment; suction was considered ineffectual without incision but harmless and reassuring to the patient (Christenson, 1969, 1983). Incision provides ready access for bacteria (Visser & Chapman, 1978).

A number of suction methods, with or without cutting devices, have been developed. The Venom Ex cutting and suction apparatus was evaluated by Reitz *et al.* (1984),

who found that if used correctly, resulted in complete recovery or prolonged survival of most rabbits after subcutaneous administration of up to four times the lethal dose of Egyptian cobra (snouted, *Naja annulifera*) venom, provided treatment was started early. However, the amount of venom extracted was too low and too variable to account for recovery and some of the protective effect is apparently due to other causes. An interesting finding was that trauma without removal of venom at the site of injection apparently retards absorption of venom and increases survival by more than 50%. The author considers that "some other protective effect" is probably due to the applied venous tourniquet not used in control animals.

Reitz *et al.,* (1986) evaluated the Venom Ex method in rabbits injected with puff adder *(Bitis arietans)* venom. The amount of venom extracted was very low after intra-muscular injection and significantly higher after subcutaneous injection. Extraction did not improve survival or affect local necrosis.

Local incisions are not recommended as a preliminary treatment of snakebite. Suction, however, although ineffective, is harmless and reassuring.

1.3.4   Retarding systemic venom absorption

1.3.4.1   Tourniquets

Tourniquets are of clinical value if they delay the times from the bite to the onset of clinical envenomation or severe (maximal) envenomation. The times to these two clinical parameters can be historically compared in patients with and without tourniquets who were bitten by the same snake species (Blaylock, 1994).   Venom

levels may be estimated by ELISA proximal and distal to a tourniquet, prior to and after removal, in snakebite patients (Tun-Pe *et al.,* 1987). Human volunteer or animal experimentation which measures radiotracer-marked mock or true venom gives an indication of tourniquet efficacy (Sutherland *et al.,* 1979; Anker *et al.,* 1982; Howarth *et al.,* 1994). Theakston (1997) states that there is no convincing general evidence that tourniquets are effective as a first-aid measure in delaying the absorption of venom into the circulation.

At an optimistic estimate, tourniquets would be of value in roughly 10% of bites, where systemic envenomation would lead to early death due to progressive weakness or a disturbance in haemostasis. The syndrome of painful progressive swelling accounts for 92% of cases of clinical envenomation in Southern Africa (Blaylock, 2000b) and the resulting necrosis or ischaemia would be exacerbated by tourniquets (Strover, 1964; Christensen, 1969, 1983; Brossy, 1977; Visser & Chapman, 1978; Blaylock, 1982b, 1994; White, 1984; Rossouw & Bos, 1989; Schrire *et al.,* 1996; Warrell & Fenner, 1993; Warrell, 1999; Black, 2000).

There are different types of tourniquet, namely direct pressure tourniquets placed over the bite site, and venous, arterial and lymphatic tourniquets. They should all be applied within minutes of the bite.

Direct pressure tourniquet

This consists of a pad and retaining bandages applying direct pressure to the bite site with resulting devascularisation of the underlying subcutaneous tissue. This was more

effective in retarding systemic absorption of mock venom than pressure immobilisation in humans (Anker *et al.*, 1982). Radiotracer studies using a direct pressure of 60 mmHg showed delayed absorption of mock venom in one of four human volunteers. It was considered to be ineffective in limiting venom migration from the periphery to the systemic circulation (Howarth *et al.*, 1994). This measure was found to retard the spread of venom in patients bitten by Russell's viper *(Daboia russelli siamensis)* in Myanmar (Tun-Pe *et al.*, 1994, 1995). It is unlikely to be an effective first-aid measure in most snakebites in Southern Africa, as venom is either absorbed too quickly (mambas) or deposited too deeply (adders). It is postulated that it may be of value in non-spitting cobra bites.

Venous tourniquet

The majority of traditional Southern African tourniquets are of this type. Chapman (1968) mentions venous tourniquets only to condemn them, and points out that it is difficult to know how tightly they should be applied, that they cause limbs to swell with consequent disruption of tissue and would worsen viper bites. They are unlikely to be effective where venom is absorbed rapidly or deposited deeply.

There is indirect evidence that venous tourniquets may be of value in non-spitting cobra bites. The traditional tourniquet used in the Philippines (usually cloth applied proximally to the bite with palpable distal pulses) delayed neurotoxicity in 15 of 34 Philippine cobra *(Naja n philippinensis)* bites (Watt, *et al.*, 1988). Reitz *et al.* (1984) evaluated the Venom Ex apparatus (a cutting and suction device) in rabbits injected with snouted cobra venom and found it to have survival value. An integral part of this manoeuvre is the application of a venous tourniquet promoting congestion. The

groups subject to Venom Ex venom extraction and trauma without venom extraction, had a tourniquet applied while controls did not, which probably aided survival.

Arterial tourniquet

Grasset (1933) and Christensen (1969) showed in sheep and mice experimentation respectively that arterial tourniquets following subcutaneous Cape cobra *(Naja nivea)* venom injection was life saving and antivenom sparing, i.e. less antivenom was necessary to save animals after release of the tourniquet than controls.

Saunders (1980) reports on an adult male patient bitten by a 224-cm black mamba *(Dendroaspis polylepis)*. He sustained twelve puncture wounds on his forearm and immediately applied an arterial tourniquet which was released after intravenous administration of antivenom.. Significant local clinical envenomation occurred (fasciculation for five days, erythema and induration for two weeks), with minimal resultant clinical systemic manifestations. A patient who sustained a black mamba bite of the leg with no evidence of paresis was treated by the immediate application of a thigh arterial tourniquet. It was removed after two hours, and fifteen minutes later ventilation was required (Blaylock, 2000).

The immediate application of an arterial tourniquet is advised for a KNOWN mamba or non-spitting cobra bite if medical help is not immediately available. An orthopaedic exsanguinating-type tourniquet is used, with the resulting pain hard to bear. The tourniquet should not be left on for more than an hour, or at most one-and-a-half hours.

Pressure immobilisation

Pressure immobilisation is the application of a firm crêpe or similar bandage to the length of a bitten limb as tightly as for a sprained joint (about 55 mmHg), as described by Sutherland *et al.* (1979, 1981a, 1981b, 1981c), who showed that it retarded the systemic absorption of the venom of the major Australian elapids, the Indian cobra *(Naja naja)* and eastern diamond back rattlesnake *(Crotalus adamanteus)* in monkeys. It retards subcutaneous lymphatic, capillary and venous flow, and is more comfortable and less harmful than venous or arterial tourniquets.

Anker *et a.* (1982), using lymphatically transported mock venom ($Na^{131}1$) and the same technique in human volunteers, found the rate of appearance of the "venom" in peripheral blood to be approximately the same as in untreated controls. Howarth *et al.* (1994), using lymphoscintigraphy and subcutaneous injections of a radio-labelled isotope on human volunteers, showed that bandaging the arms at a pressure of 40 - 70 mmHg, and the legs at a pressure of 55 - 70 mmHg, significantly delayed the systemic absorption of the isotope, provided that there was absolute immobilisation. Pressure above or below this range and any movement negated this effect.

Blaylock (1994) pointed out that in three published mamba bites (two black and one green) where pressure immobilisation was used, the clinical parameters of the time from the bite to the onset of initial symptoms and to maximal clinical envenomation were no different to other mamba bites both published and unpublished. This is commensurate with mamba venom being absorbed directly into the blood stream.

Pressure immobilisation correctly applied and with no patient movement would probably delay systemic absorption of non-spitting cobra venom. In a case of snouted cobra bite, pressure immobilisation may have benefited the patient, as swelling involved the whole arm but there was no neurological deficit (Els, 1988). Reitz (1986) injected vervet monkeys with an LD_{100} dose of snouted cobra venom and applied pressure immobilisation for six hours to the length of the injected limb, which was splinted. Survival was substantially longer compared to the controls. Two herpetologists bitten by a snouted cobra and puff adder respectively, who applied the pressure immobilisation technique, died of venom-induced anaphylaxis (Blaylock, 2000).

In Australia, there is enthusiasm for pressure immobilisation, which is even endorsed by that country's National Health and Medical Research Council. This is at odds with the views expressed in this thesis. The reason is that Australian elapid bites are apparently responsive to this measure as the dominant toxins are lymphatically transported (Sutherland *et al.*, 1979). However, pressure immobilisation in Southern Africa would probably only benefit cases of bites from non-spitting cobras (less than 1% of bites). Pressure immobilisation should not be used in the painful progressive swelling syndrome (nearly 80% of bites and 92% of clinical envenomations (Blaylock, 2000) due to exacerbation of the local effects of the venom. Russell (1982) and Podgorny (1982) had reservations on the use of this technique for North American snakebites.

1.3.5 Popular non-effective measures

1.3.5.1 Electrotherapy for snakebite

Suggested electrotherapy for snakebite involves a high voltage (20 - 25 kV), low amperage (less that 1 mV) direct current applied for 1 – 2 seconds for 4 – 5 shocks. Such a current is generated by a stun gun, or the spark plug of a lawnmower, an auxillary lighting plant or outboard motor. Guderian (1986) presented 34 cases of Ecuadorian snakebite. Within a few minutes of application of the current, local and systemic poisoning ceased without resulting morbidity or mortality. Snakebite victims not treated developed clinical poisoning and two required amputation. It was postulated that venom has a short half-life and electrospasm of local vessels contained the venom long enough for it to be degraded.

Christensen in 1955 demonstrated that both wet and dry South African snake venom had an extremely long half-life in vitro, measured in months and years respectively. Russell (1987) notes that snake venom has about the longest half-life of any known complex protein mixture. The half-life is much shorter in vivo. Venom action continues for one to eight days if swelling is the clinical presentation, and for several days in Cape cobra *(Naja nivea)* and boomslang *(Dispholidus typus)* bites (Blaylock, 2000).

Reitz *et al.* (1989) showed that a similar electric current had no effect on the morbidity and mortality of rats injected with venom pre-treated with electrotherapy or untreated venom of *Naja annulifera* (snouted cobra) or *Naja mossambica* (Mozambique spitting cobra) compared to controls. No change in the composition of the venoms could be detected by electrophoresis after exposure to the current in vitro. Electrotherapy

applied to mice injected with rattlesnake venom (Johnson *et al.*, 1987), or rabbits (Stoud *et al.*, 1989), or a human (Dart *et al.*, 1991) was found to be of no value. Similar results were obtained by Howe & Meisenheimer (1988) who injected *Bothrops atrox* (Ecuadorian pit viper) venom into rats and by Snyder *et al.* (1989), who injected *Crotolus atrox* (western diamond back rattlesnake) or *Agkistrodon piscovorus* (cottonmouth moccasin) venom into dogs. Other authors question the value of electrotherapy for snake bite (Schmutzhard, 1986; Russell, 1987; Bucknall, 1991) and suggest that it should not be used (Ryan, 1987; Warrell, 1996).

1.3.5.2 Local cryotherapy

Local cryotherapy is an imprecise technique used to necrose surface lesions. The rationale for its use in snakebite (ice packs, ethyl chloride spray, immersion of bitten part in cold water) is to induce vasoconstriction, which slows systemic absorption of venom and perhaps denatures it. Southern African authors advocating the use of cryotherapy include the Editorial *Cen Afr J Med* (1956) and Reitz (1978). Those against its use include Chapman (1968), Visser & Chapman (1978) and White & Goodwin (1982). Noted non-South African authors not advocating its use include Russell (1980), Russell *et al.* (1997), Warrell & Fenner (1993) and Warrell (1996, 1999).

Mamba venom is soon absorbed into capillaries (Christensen, 1966; Christensen & Anderson, 1967) with clinical effects occurring within minutes of the bite, while puff adder and Gaboon adder *(Bitis gabonica)* venom is deposited too deeply into the tissues to be affected by surface cooling. There may be diminished absorption of

subcutaneous non-spitting cobra venom where the dominant neurotoxin is lymphatically transported, which comprise less than 1% of South African snake bites.

Cryotherapy is not without complications. A 15-month-old child was bitten on the foot by a juvenile puff adder at 20:00 on 20 January 1998. First aid comprised an ice pack applied intermittently to the foot for 1½ hours. When seen 27 hours after the bite, the foot was cold, swollen, mottled blue and without palpable pulses. Fasciotomy was deferred as it was realised that the foot was frost bitten, and within 24 hours it recovered. Russell (1980) was aware of 30 amputations following the use of cryotherapy in North America.

1.3.6   Future pre-hospital pharmaceuticals that may lessen envenomation

Pre-hospital pharmaceutical measures to prevent or ameliorate envenomation will become available. The safety of such products will be paramount.

Fab antivenom

This is being investigated as a pre-hospital measure (Theakston, 1997).

Inhibitors of metalloproteinases

Snake venom metalloproteinases are responsible for local tissue damage characteristic of crotaline and viperine snake envenomations (Gutiérrez & Rucavado, 2000). Tissue inhibitors of matrix metalloproteinases are found in the sera of animals resistant to snake venom and are being intensely studied (Pérez & Sanchez, 1999). It has been suggested that natural or synthetic metalloproteinase inhibitors could be injected at the

site of venom injection to counteract the cytotoxic effects of crotaline and viperine venoms (Gutiérrez *et al.*, 1999). Calcium sodium ethylene diamine tetracetate showed promise in preventing tissue damage from metalloproteinase Ba Pl found in *Bothrops asper* venom (Gutiérrez *et al.*, 1998) as did batimastat (Escalante *et al.*, 2000).

Inhibitors of PLA_2 enzymes

Phospholipase A_2 enzymes produce cell apoptosis by cleaving membrane phospholipids and by other ill-understood mechanisms. They promote local inflammation at the bite site, may have a systemic action and are found in the venoms of many snakes, especially the *Viperidae*. Para-bromophenacyl bromide (inhibitor of PLA_2) reduced haemorrhage due to *Agkistrodon contortrix laticinctus* venom when applied topically, or reduced myonecrosis when injected intramuscularly in envenomed mice. (Evans & Ownby, 1999).

Trypsin and chymotrypsin

Local trypsin and chymotrypsin injection 10 minutes after Chinese *Elapidae* and *Hydrophidae* snake venom injection in mice and dogs resulted in survival of the animals. This was thought to negate the action of, or decompose, snake venom proteins (Xiong *et al.*, 1998).

In conclusion, there are no good first-aid measures for all snakebites. The best measure is to get the patient to hospital as safely and quickly as possible. Unfortunately, the majority of people in Southern Africa are not within easy reach of a medical facility, which is why many snakebites are fatal.

Algorithm 1 – 1

Snake bite

Prophylaxis and first aid

Use common sense: wear protective clothing and footwear. Be careful handling "dead snakes". At night: use good light, wear shoes, snake-proof sleeping arrangements.

No good first aid for all snakebites.
Get patient to medical help.
Snake handlers: Arterial tourniquet for black mamba or non-spitting cobra bite or the pressure immobilisation technique for the latter.
Future pre-hospital pharmaceuticals.

CHAPTER 2

A MOUSE MODEL DESIGNED TO ASSESS WHETHER IMMEDIATE ACTIVE MOVEMENT INFLUENCES VENOM-INDUCED NECROSIS

CONTENTS

2. Immediate active movement and necrotising snake venoms

2.1 Abstract

Objective: The effect of immediate active movement on the outcome of necrotising

snake venom injection was investigated in mice.

Materials and methods: *Bitis arietans* venom (2,5 µg) was administered

subcutaneously into the dorsum of the right hind feet of 40 mice of which 20 were

previously anaesthetised. The 20 non-anaesthetised mice swam for 10 minutes. All

mice were euthanised on day 4. A further 40 mice were subjected to an identical

experiment using 20 µg *Naja mossambica* venom and were euthanised on day 6. The

areas of macroscopic necrosis were measured in the mice injected with *B. arietans*

venom, and the largest diameter of macroscopic necrosis was determined in the mice

injected with *N. mossambica* venom.

Results: Immediate active movement (swimming) following venom injection

prevented necrosis (P = <0.05) or reduced the area of necrosis (P = <0.002). There

was one death.

Conclusion: Immediate active movement when necrotising snake venom was injected

into mice hind feet prevented or diminished the resulting area of necrosis.

2.2 Introduction

Reid *et al.* (1963b) noted that necrosis was more common in Malayan viper

(Calloselasma rhodostoma) bites of fingers and toes than elsewhere, which they

attributed to a high local concentration of venom. Huang *et al.* (1978) noted that

important hand structures lack an abundant soft tissue cover, making them more

vulnerable to injury by snake toxins. Grace & Omer (1980) found functional losses

due to North American pit viper wounds to be several times more frequent in the upper extremity than the rest of the body. Painful progressive swelling (PPS) in Southern Africa is by far the most common presentation of snakebite, accounting for 77% of 911 patients from four rural snakebite series (Blaylock, 1982a; Coetzer & Tilbury, 1982; McNally & Reitz, 1987; Blaylock 2000). Patients with PPS may develop bite site complications (BSCs) which are defined as local blistering, necrosis, haematoma or abscess, the first two occurring in the hands of Eshowe snakebite patients. Of 333 Eshowe snakebite patients, more hand bites than foot bites developed BSCs (P = <0.0001), and it was more common in finger and thumb bites than toe bites (P = 0.0009). Six of 35 hands and digits that were bitten became permanently disabled, while there was no permanent morbidity in 180 foot and toe bites (P = <0.0001). The Mozambique spitting cobra *(Naja mossambica)*, stiletto snake *(Actractaspis bibronii)* and puff adder *(Bitis arietans)* were the offending snake species (Blaylock, 2000).

Why should the prevalence of necrosis vary anatomically? The same snake species bite hands and feet. Could it be that more venom is injected into hands than feet? Blaylock (2000) noted that significantly more of the Eshowe snakebite patients saw the snake if bitten on the upper extremity than on the lower limb (P = <0.05). An incomplete bite or single fang penetration is more likely on the upper limb due to hand withdrawal on seeing the snake, resulting in a smaller volume of injected venom. This suggests that venom dose is not the cause of differing necrosis rates in hands and feet.

Venom-induced digital angiopathy with resulting ischaemic necrosis is more likely to occur in fingers as they are longer than toes. Similarly, venom has to travel a longer

distance in fingers than in toes before it is dispersed and diluted in the hand and foot respectively. This, however, does not explain why BSCs are more common in hands than in feet, excluding digits. Circulation distal to the proximal interphalangeal joint is poorer than to other areas of the body (Moss *et al.*, 1997), which is equally true of fingers and toes. A possible explanation for increased morbidity in fingers and hands is the venom concentration and the time that it is present at the bite site. All patients bitten on the feet or toes will walk or run after a snakebite, while bitten hands and digits tend to be cradled, especially by adults. Ambulation would disperse and dilute venom due to muscle-activated lymphatic and venous pumps. A tourniquet used by a patient with PPS (more effective than immobilisation) may precipitate a compartment syndrome or aggravate bite site necrosis (1.3.4.2) by containing venom in the bitten region.

The objective in this section is to assess whether swelling and necrosis of envenomed mouse hind feet is different in ambulatory (swimming) and non-ambulatory (anaesthetised) mice after venom injection.

2.3 Objective

2.3.1 Puff adder venom (PAV) and Mozambique spitting cobra venom (MSCV) studies

2.3.1.1 Pilot study

To determine the subcutaneous minimal macroscopic necrotising dose of PAV and MSCV in the dorsum of the hind feet of mice.

2.3.1.2 Full studies

To compare the degree of swelling and areas of necrosis of swimming and anaesthetised (non-ambulatory) groups of mice injected subcutaneously with a minimal macroscopic necrotising dose of PAV or MSCV.

2.4 Materials and methods

2.4.1 Puff adder venom study

2.4.1.1 Pilot study

Ten mice (specified pathogen-free National Medical Research Institute (NMRI) mice) in five pairs, each pair comprising one male and one female, were anaesthetised with 1 mg ketamine (Centaur Labs, Johannesburg, South Africa) and 0,2 mg xylazine hydrochloride (Bayer, Johannesburg, South Africa) by contralateral thigh IMI. This was followed by freeze-dried puff adder venom, (batch PAFD 96), originating from Limpopo Province in South Africa (1966) and supplied by the National Health Laboratory Service Antivenom Unit, Edenvale, South Africa. Concentrations of 0,05 µg, 0,25 µg, 1,25 µg, 6,25 µg and 31,25 µg dissolved in 0,01 ml water were injected into the dorsum of the right hind feet. Each pair of mice received an increasing venom concentration.

2.4.1.2 Full study I

This was the same as for the pilot study. Twenty mice were injected with 1,25 µg of puff adder venom each. Ten were anaesthetised and injected, and ten swam in water at 32^0C for 10 minutes following injection. The water was shallow enough for their

hind feet to reach the bottom if they wished to rest (fig.2-1 to 2-3). After swimming they were dried and allowed to rest, walk or run.

The end results were determined by the measurements of the maximal height of the non-injected and injected feet (between plantar and dorsal aspects of the feet) by an independent observer using electronic digital calliper measurement at 30 minutes and on day 4 (approximately 72 hours) when the mice were euthanised. The end points in millimetres were arbitrarily determined to achieve maximal statistical significance.

2.4.1.3 Full study II

This was similar to the pilot study and full study I. Forty mice were injected with 2,5 µg PAV and all measurements were of the injected feet. The dose of anaesthetic was increased (males: ketamine 2 mg and xylazine 0,4 mg, females: ketamine 1,5mg and xylazine 0,3 mg) and the mice were euthanised on day 5 (95 hours). The areas of necrosis were measured using a manual digital calliper and a dissecting microscope and the feet were photographed. The end points, in millimetres, were determined to achieve maximal statistical significance.

Figs 2 – 1 to 2 – 3   Swimming groups : mice activity
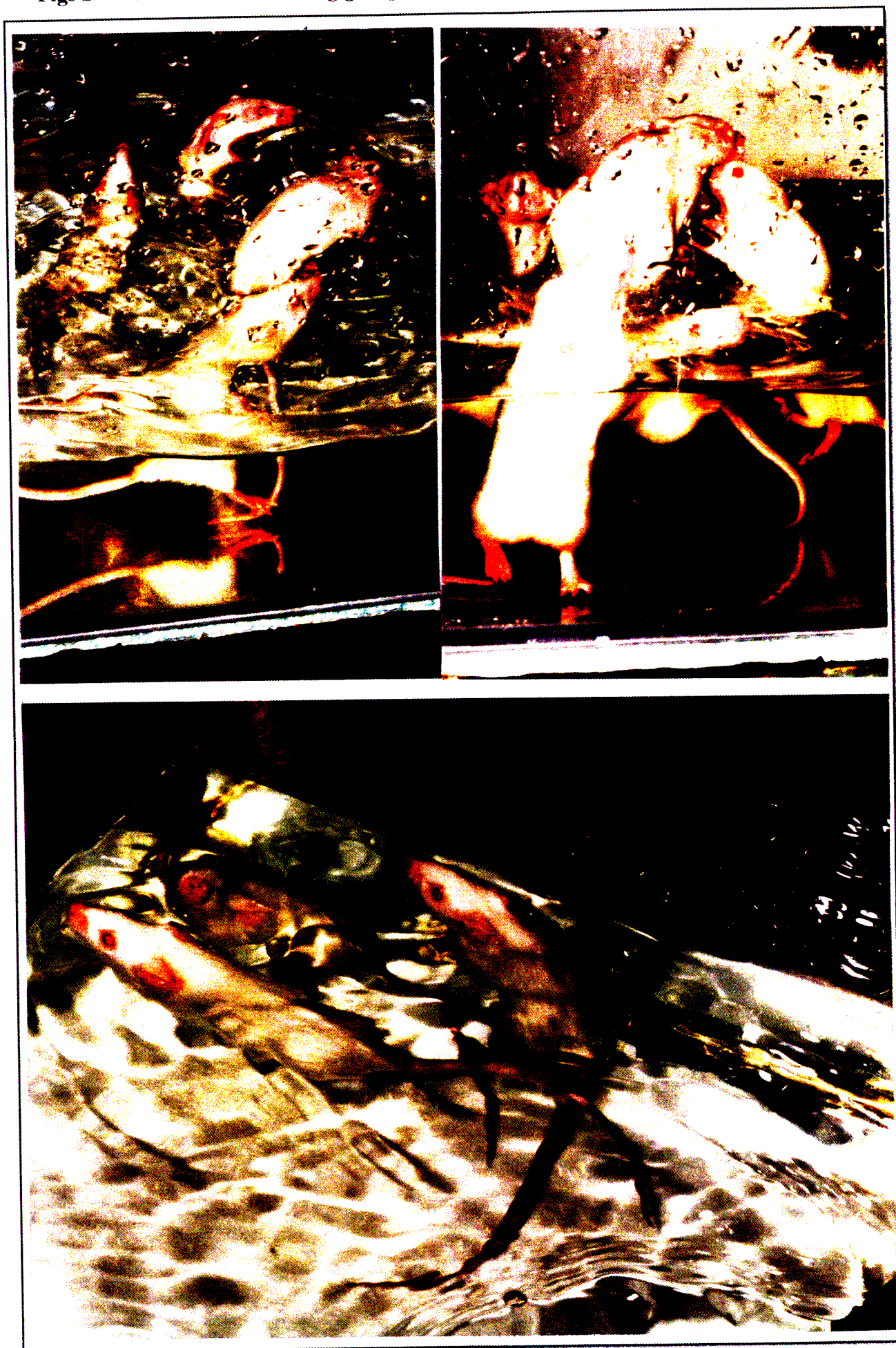
2.4.2 Mozambique spitting cobra venom study

2.4.2.1 Pilot study

This was similar to 2.4.1.1 using venom concentrations of 0,05, 0,5, 5, 10, 20 and 30 µg venom (batch MSC003, 1990) dissolved in 0,01 ml water for injection in six groups of three mice (specified pathogen-free NMRI mice).

2.4.2.2 Full study

This was similar to 2.4.1.3 using 20 µg venom dissolved in 0,01 ml water for injection. The mice were euthanised on day 6 (144 hours).

2.5 Results

PAV

Pilot study and Study I. Tables 2-1 to 2-3.

Study 11. Tables 2-4, 2-5; figures 2-2, 2-7

MSCV

Pilot study. The minimal macroscopic necrotising dose of venom was 20 µg.

Full study. Table 2-6, figures 2-8, 2-11

The non-ambulatory mice remained under the influence of the anaesthetic for about 30 minutes and most were mobile by 40 minutes. Of 128 mice, 124 survived and according to observations by the animal technologists, did not appear to be unduly disturbed by the venom injection.

Table 2 - 1   Pilot study.   Different puff adder venom doses injected into the dorsum of mice hind feet. Changes relate to the dorsum of the foot.

Pair no.	Gender	Weight g	Venom injected µg	First walk after venom injection: minutes	External bleeding	2 hours: appearance of foot and limb	Outcome
1	Male	19,01	31,25	27	Some blood on surrounds and leg	Whole leg blue	Died between 2½ and 18½ hours
	Female	17,22		40	Some blood on surrounds and leg	Whole leg blue	Died between 2½ and 18½ hours
2	Male	19,29	6,25	28	Some blood on surrounds and leg	Whole leg blue	Euthanised at 19 hours
	Female	18,11		30	Some blood on surrounds and leg	Whole leg blue	72 h: 4 x 3mm area necrosis
3	Male	17,2	1,25		Some blood on surrounds and leg	Half leg blue	72 h : Small patchy areas skin necrosis
	Female	17,82			Some blood on surrounds and leg	Half leg blue	72 h: Small patchy areas skin necrosis
4	Male	18,51	0,25	35	Spot of blood at injection site	Foot and ankle blue	72 h: Slightly puffy foot
	Female	18,31		35	Spot of blood at injection site	Foot and ankle blue	72 h: Puffy foot with erythema tibial side
5	Male	18,09	0,05	78	Spot of blood at injection site	Erythematous injection site	72 h: Slightly puffy erythematous foot
	Female	17,06		78	Spot of blood at injection site	Erythematous injection site	72 h: Slightly puffy erythematous foot

The chosen minimal macroscopic necrotising dose of puff adder venom is 1,25 µg.

Table 2 - 2   Subcutaneous puff adder venom injection (1,25 µg) into the dorsum of the right hind feet of mice. Comparison of height of injected and non-injected hind feet between ambulatory and non ambulatory groups at 30 minutes.
Mice weight : 18 - 20 g

Ambulatory group			Non ambulatory group		
Height Injected foot mm	Height Non injected foot mm	Difference mm	Height Injected foot mm	Height Non-injected foot mm	Difference mm
MALES					
2,83	1,59	1,24	3,66	2,56	1,1
2,9	1,93	1,06	3,96	2,09	1,87
3,35	1,84	1,51	3,39	2,68	0,71
3,44	2,71	0,73	3,43	2,24	1,19
2,91	1,78	1,13	3,63	2,31	1,32
FEMALES					
3,04	1,88	1,16	3,70	2,24	1,46
3,23	2,54	0,69	3,85	2,92	0,93
3,17	2,35	0,82	3,82	2,72	1,1
3,26	2,02	1,24	3,75	2,25	1,5
3,33	2,24	1,09	3,38	2,51	0,87
	Difference 51,1%			Difference 49,1%	

Table 2 - 3   Subcutaneous puff adder venom injection (1,25 µg) into the dorsum of the right hind feet of mice. Comparison of height of injected and non-injected hind feet between ambulatory and non ambulatory groups of mice at 70 hours.
Mice weight: 18 - 20 g

Ambulatory group			Non ambulatory group		
Height Injected foot mm	Height Non-injected foot mm	Difference mm	Height Injected foot mm	Height Non-injected foot mm	Difference mm
MALES					
2,1	1,8	0,3	2,6	1,83	0,77
2,14	1,82	0,32	2,33	1,95	0,38
2,3	1,84	0,46	2,33	1,98	0,5
2,17	1,71	0,46	2,37	2,02	0,35
2,35	2,13	0,22	2,33	1,89	0,44
FEMALES					
2,4	2,01	0,39	2,32	1,82	0,5
2,03	1,66	0,37	2,6	1,82	0,78
1,92	1,76	0,16	2,67	2,13	0,54
1,97	1,73	0,24	2,4	1,88	0,52
2,38	1,78	0,6	2,63	2,03	0,6

Fisher's exact test. Ambulatory versus non-ambulatory. Increase of $\geq 0,5$ mm: 1 of 10 and 6 of 10 respectively. P = 0,0573
Increase of less than 0,35 mm : 5 of 10 and 0 of 10. P = 0,0325
Increase in height of 19,3% and 27% respectively

Table 2 - 4 Subcutaneous puff adder venom injection (2,5 µg) into the dorsum of the hind feet of mice. Comparison of swelling pre- and post-venom injection, at 30 minutes in ambulatory and non-ambulatory groups

Ambulatory group				Non ambulatory group			
Mouse No & weight g	Height foot pre-injection mm	Height foot post-injection mm	Difference mm	Mouse no and weight g	Height foot pre-injection mm	Height foot post-injection mm	Difference mm
M A L E S							
1. 29,05	2,24	3,49	1,25	11. 29,00	2,12	3,53	1,41
2. 29,75	2,28	3,71	1,43	12. 29,43	2,13	3,32	1,19
3. 27,70	1,82	4,07	2,25	13. 28,65	2,24	3,65	1,41
4. 27,50	1,96	3,79	1,83	14. 29,12	2,10	3,65	1,55
5. 29,20	2,43	3,91	1,48	15. 28,15	2,29	3,60	1,31
** 6. 28,80	2,12	3,68	1,56	16. 29,25	2,20	3,61	1,41
7. 27,90	2,04	3,76	1,72	17. 29,62	2,12	3,63	1,51
8. 28,60	1,98	3,46	1,48	18. 29,62	2,14	3,36	1,22
9. 29,60	2,26	3,78	1,52	19. 29,48	2,37	3,53	1,16
10. 28,50	2,00	3,94	1,94	20. 30,38	2,21	3,16	0,95
Totals	19,01	33,91	14.9	**Totals**	21,92	35,04	13,12
F E M A L E S							
21. 25,75	1,80	3,68	1,88	31. 25,25	1,95	3,86	1,91
22. 25,50	1,9	4,05	2,15	32. 25,02	2,04	3,21	1,17
23. 24,00	1,85	3,57	1,72	33. 24,96	2,12	3,53	1,41
24. 34,55	1,82	3,04	1,22	34. 25,34	1,93	3,58	1,65
25. 24,95	2,10	3,55	1,45	35. 24,77	2,13	3,40	1,27
26. 24,65	1,84	3,35	1,51	36. 25,72	1,91	3,38	1,47
27. 25,30	2,02	3,92	1,9	37. 5,35	1,89	3,47	1,58
28. 23,60	1,92	3,41	1,49	38. 25,60	2,05	3,58	1,53
29. 23,08	1,92	3,51	1,59	39. 26,06	2,12	3,47	1,35
30. 23,70	1,82	3,37	1,55	40. 4,84	2,33	3,72	1,39
Totals	18,99	35,45	16,46	**Totals**	20,47	35,2	14.73,

Gender	Increase in height injected feet	Ambulatory group	Non-ambulatory group	Fisher's exact test P =
Males	> 1,55 mm	4 of 9	0 of 10	0,0325
	< 1,44 mm	2 of 9	8 of 10	0,0230
Females	> 1,55 mm	5 of 10	3 of 10	0,6499
	< 1,44 mm	1 of 10	5 of 10	0,1409
Combined males and females	> 1,55 mm	9 of 19	3 of 20	0,0407
	< 1.44 mm	3 of 19	13 of 20	0,0031

Percentage increase in height of injected feet.	Ambulatory	Non-ambulatory
Males:	78%	60%
Females:	87%	72%
Combined males and females:	83%	66%

Ambulatory group: Males were more active than females

** Mouse 6 is excluded from all analyses due to incomplete venom injection.

The height of feet is the maximal height between the plantar and dorsal surfaces

Table 2 - 5 Subcutaneous puff adder venom injection (2,5 µg) into the dorsum of the hind feet of mice. Comparison of swelling and macroscopic necrotic areas 95 hours post-venom injection, in ambulatory and non-ambulatory groups. **Figures 2-4 to 2-7.**

Non-ambulatory group				Ambulatory group			
Mouse no. weight g	Increase in height of injected foot mm	Number of areas of necrosis	Total area of necrosis mm²	Mouse n weight g		Increase in height of injected foot mm	Number of areas of necrosis	Total area of necrosis mm²
M A L E S								
1	29,0	0,63	2	10,93	1	29,1	0,53	2	4,73
2	29,4	0,56	1	13,44	2	29,8	0,35	5	2,38
3	28,7	0,91	1	10,51	3	27,7	1,15	1	7,69
4	29,1	1,16	1	11,15	4	27,5	0,62	0	Nil
5	28,2	0,33	1	2,66	5	29,2	0,45	2	3,96
6	29,3	0,51	1	5,53	**6	28,8	0,30	0	Nil
7	29,6	0,73	1	9,98	7	27,9	0,82	1	3,38
8	29,6	1,02	2	10,02	8	28,6	0,78	1	3,06
9	29,5	0,32	1	11,73	9	29,6	0,88	4	6,98
10	30,4	0,55	2	3,34	10	28,5	0,76	3	4,32
Mean 29,3		0,67	1.3	8,93	**Mean 28,7**		0,70	2.1	4,1
F E M A L E S								
11	25,3	0,84	1	17.69	11	25,8	1,22	1	1,36
12	25,0	0,80	2	4.27	12	25,8	1,18	0	Nil
13	25,0	0,54	4	4.58	13	24,0	0,41	1	0,04
14	25,3	0,50	1	10.18	14	24,6	0,61	1	5,99
15	24,8	0,56	2	5.90	15	25,0	0,36	0	Nil
16	25,7	0,57	1	1.49	16	24,7	0,92	1	1,09
17	25,4	0,43	1	17.93	17	25,3	0,48	2	2,67
18	25,5	0,29	1	15.57	18	23,6	0,92	2	1,44
19	26,1	0,38	1	6.90	19	23,1	0,73	1	2,71
20	24,9	0,42	1	8.05	20	23,7	0,50	2	Nil
Mean 25,3		0,53	1.5	9.23	**Mean 24,5**		0,73	0.9	1,53

	Non-ambulatory group	Ambulatory group	Fisher's exact test P =
Necrotic area < 5 mm²	6 of 20	16 of 19	0,0011
Necrotic area > 8 mm²	12 of 20	0 of 19	<0,0001
Macroscopically normal	0 of 20	4 of 19	0,0471
Percentage increase in height of injected feet Males : Females : Combined males and females:	31% 26% 28%	33% 39% 36%	

** Mouse 6 is excluded from all analyses due to incomplete venom injection.
Macroscopic necrosis : erythematous or exuding areas with hair loss.

Subcutaneous puff adder venom injection (2.5μg) into the dorsum of the hind feet of mice. Females 95 hours post injection

2.5 μg PAV.
95 hrs.♀ Amb
16 - 20

Fig 2 – 4   Swimming group 21 – 30

2.5 μg PAV.
95 hrs.♀ non-Amb
11 - 15

2.5 μg PAV.
95 hrs.♀ non-Amb
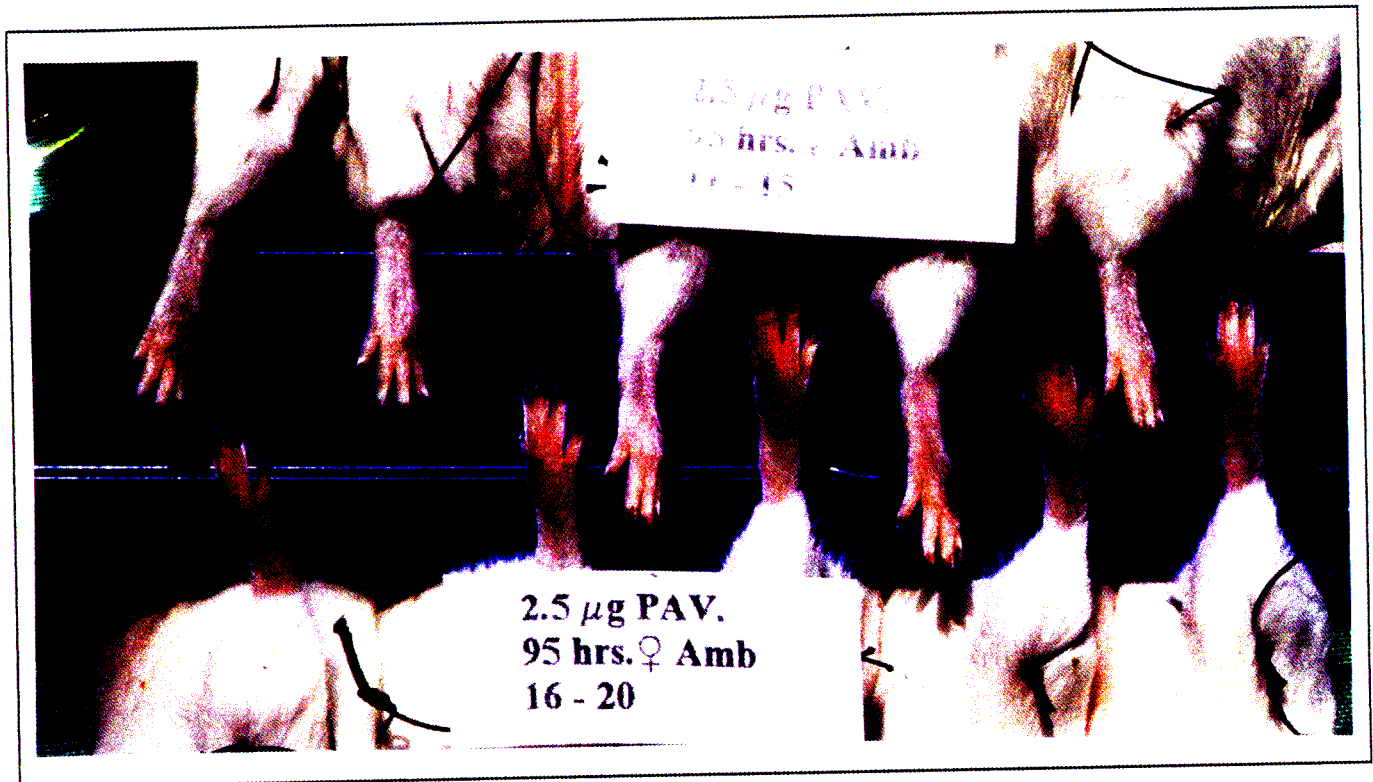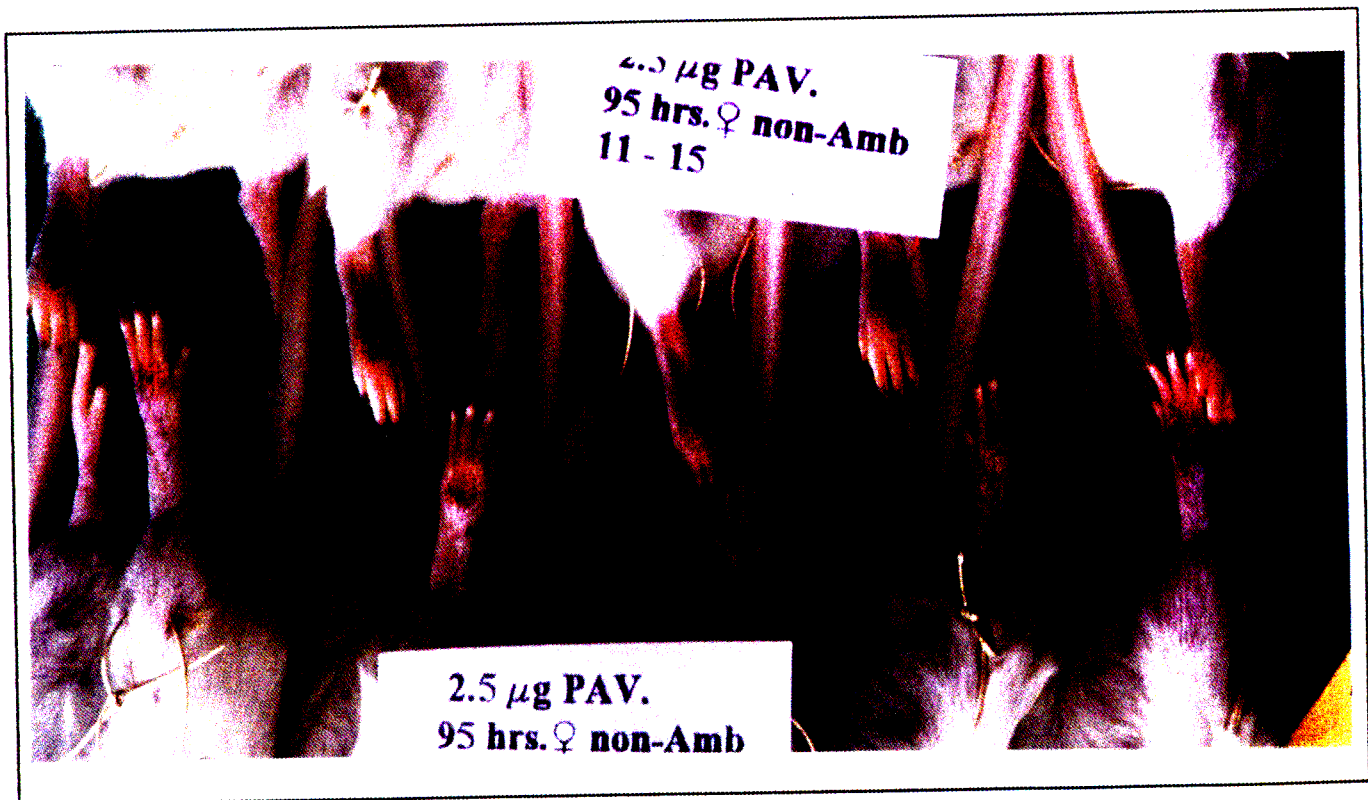
Fig 2 – 5   Anaesthetised group 31 - 40

Subcutaneous puff adder venom injection (2.5μg) into the dorsum of the hind feet of mice. Males 95 hours post injection

Fig 2 – 6   Swimming group 1 – 10

Fig 2 – 7   Anaesthetised group 11 – 20

Table 2-6. Subcutaneous Mozambique spitting cobra venom injection (20 µg) into the dorsum of the hind feet of mice. Comparison of macroscopic necrotic areas 144 hours post-venom injection in ambulatory and non-ambulatory groups. Figures 2-8 to 2-11.

Non-ambulatory group			Ambulatory group		
Mouse no.	Weight g	Greatest diameter of necrotic area mm	Mouse no.	Weight g	Greatest diameter of necrotic area mm
MALES					
1	26,9	5,68	21	26,5	0,75
2	26,9	6,42	22	25,9	1,7
3	27,4	4,7	23	26,5	0
4	26,8	3,86	24	27,7	4,31
5	28,1	2,6	25	26,7	3,08
6	26,2	1,7	26	25,9	4,78
7	27,1	5,04	27	26,1	4,51
8	27,5	4,13	28	27,0	4,59
9	26,8	4,3	29	26,2	1,78
10	27,2	5,25	30	27,3	1,5
Mean	27,1	4,37	Mean	26,6	2,7
FEMALES					
11	27,3	7,13	31	27,2	0
12	27,5	4,36	32	27,3	2,13
13	27,9	6,45	33	26,9	0,5
14	27,8	8,74	34	27,7	3,34
15	27,2	5,33	35	26,9	6,26
16	28,2	4,4	36	26,8	3,34
17	27,9	5,15	37	26,5	0
18	26,8	7,16	38	26,3	Died 3 min after injection
19	27,4	5,43	39	26,0	1,6
20	27,5	4,45+Amp	40	27,0	0
Mean	27,6	5,9+	Mean	26,9	1.7

	Non-ambulatory group	Ambulatory group	Fisher's exact test P =
Greatest diameter < 2 mm	1 of 20	10 of 19	0,0012
Greatest diameter > 5 mm	12 of 20	1 of 19	0,0004
Macroscopically normal	0 of 20	4 of 19	0,0471
Auto-amputation of the second toe occurred in mouse 20. Macroscopic necrosis: erythematous or exuding areas with hair loss. There were single areas of necrosis in each foot.			

Subcutaneous Mozambique spitting cobra venom injection (20µg) into the dorsum of the hind feet of mice. Females 144 hours post venom injection.

Fig 2 – 8   Swimming group 31 – 40

Fig 2 – 9   Anaesthetised group 11 – 20. Auto-amputation of the second toe occurred in mouse 20

Subcutaneous Mozambique spitting cobra venom injection (20µg) into the
dorsum of the hind feet of mice.   Males 144 hours post venom injection.

Fig 2 – 10   Swimming group 21 – 30

Fig 2 – 11   Anaesthetised group 1 - 10

2.6   Discussion

2.6.1   Pilot (PAV) study

The observations were not blinded and the animals were not randomised. In view of the significance of the findings this should be done in a further study.   Human fingers and feet, in common with mice feet, have venous and lymphatic pumps. Consequently the dorsum of mice feet was considered an appropriate injection site. Both mice injected with 31,25 µg venom died. A mouse injected with 6,25 µg was euthanised at 19 hours due to apparent suffering, while the other developed a substantial area of necrosis. Doses of 0,05 µg and 0,25 µg produced localised erythema with the latter dose producing some puffiness. Small areas of macroscopic necrosis resulted from the 1,25 µg dose of venom, and this was the chosen dose. Study I failed to produce significant areas of macroscopic necrosis, resulting in Study II being carried out using 2,5 µg venom.

Calliper measurements of the breadth and height of the feet and the ankle made pre-venom and 30 minutes post-venom injection, showed that the biggest increase post-venom was in height (between the plantar and dorsal surface of foot).   This measurement was used in the full studies

2.6.2   Full study I & II (PAV)

2.6.2.1 Swimming

All the mice swam well but are probably not the ideal animals for this experiment as swimming does not allow compression of their foot pads. Walking, and preferably running, is an alternative but is difficult to achieve for 10 minutes.

2.6.2.2 Swelling

Calliper measurements of the height of the feet 30 minutes post-injection showed an increase of 51,1% and 49,1% using 1,25 µg venom (table 2-2) in the ambulatory and non-ambulatory groups respectively. These figures increased to 83% and 66% when 2,5 µg PAV was used (table 2-4). The increased swelling at 30 minutes in the ambulatory group is hypothesised to be due to movement-induced hyperaemia and venom spread resulting in more widespread inflammation.

The cause of lesser swelling at 70 hours (1,25 µg, table 2-3) in the ambulatory group of mice (19.3% versus 27%) is hypothesised to be due to faster venom dispersion and dilution. The venom did not stay long enough in the same concentration to produce as much tissue damage as in the non-ambulatory group of mice. The situation is reversed in Study II at 95 hours (2,5 µg venom, table 2-5), as the height of the feet in the ambulatory and non-ambulatory groups increased by 36% and 28% respectively. This may have been due to exudation of serum from the latter group where exudative areas were most common.

2.6.2.3 Necrosis (PAV and MSCV)

Tables 2-5 and 2-6 show that immediate movement for 10 minutes after injection of 2,5 µg puff adder venom, or 20 µg Mozambique spitting cobra venom, prevents or significantly diminishes the area of necrosis. One cannot be certain that the anaesthetic may have contributed to necrosis. However, this is unlikely, as ketamine is widely used in humans, including burn patients, where necrosis is undesirable. Furthermore, the package inserts of both ketamine and xylozine hydrochloride and Goodman & Gillmans *The Pharmacological Basis of Therapeutics* (10th edition, 2001) do not mention that these drugs may aggravate necrosis. Experiments on mice using different anaesthetics would answer this question, but is considered unnecessary. The mean areas of necrosis in ambulatory females injected with PAV and MSCV were smaller than the areas in the corresponding males, while it was greater in non-ambulatory females than males. The reason for this difference is not altogether clear. It may be that the lesser necrosis in the ambulatory mice was due to dispersion of the venom by the venous and lymphatic pumps. Venom would not have been present in a particular area in a high enough concentration for a sufficient length of time to produce maximal necrosis, as in the non-ambulatory mice.

The single death in the 19 ambulatory mice at 3 min was probably due to inadvertent IVI, as suggested by widespread petechiae at post mortem. Haemorrhage was confined to the injected leg and associated abdomen in the other mice.

2.7   Consideration

Huang *et al.,* (1978) practiced early excisional therapy on pit viper upper extremity bites to rid the bitten area of venom and reduce the chances of necrosis. Pit viper bites

result in haemorrhagic tissue which is delineated and visible. Haemorrhagic necrosis only occurs in puff adder and Gaboon adder bites, whereas necrosis of Mozambique spitting cobra and stiletto snake bites is non-haemorrhagic. Furthermore, patients in Southern Africa take a long time to reach medical help, by which time local tissue damage is irreversible. Not all Southern African bites lead to necrosis, and many operations would be unecessarily performed (chapter 10).

In view of the frequency of necrosis and permanent morbidity of hands and fingers caused by bites to these areas, consideration should be given to active finger movement and arm elevation for 5 to 10 minutes following such a bite with no subsequent restriction of movement. Further experimentation may justify this approach, which is against current World Health Organisation recommendations. This manoeuvre will not increase mortality except perhaps in non-spitting cobra bites, which comprise less than 1% of bites in Southern Africa (Blaylock 2000). The dominant neurotoxin(s) of *Naja annulifera* (snouted cobra, a non-spitting cobra) is lymphatically transported into the circulation (Reitz *et al.*, 1984). Tourniquets have a first-aid role in bites by the Cape cobra (a non-spitting cobra), especially in the Western Cape in South Africa, where this snake commonly occurs. Active movement may hasten coagulopathy from a boomslang or vine snake bite but, as death only occurs some days after the bite, there is time to reach medical help. Snake handlers are almost exclusively the victims of bites by these snakes, who can readily identify them. Black mamba venom, which is injected subcutaneously, is soon absorbed into the circulation (Christensen, 1966; Christensen & Anderson, 1967), and active movement only plays a small role in systemic absorption. The mortality rate of people who immediately

actively move the hand following a bite to this area will be no different from that of

people bitten on a toe or foot who all walk or run.

Until further studies have been done, it would be premature to assert that immediate

active movement of bitten fingers and hands is an effective first-aid measure

Algorithm 2–1   A POSSIBLE future consideration. Immediate active
movement of bitten hands or fingers following a snakebite

Definitely identified non-
spitting cobra bite

|

Cradle bitten hand

Unidentified snake, or
positively identified
spitting cobra, puff adder
or stiletto snake bite

|

Elevate hand
Actively flex and extend
fingers for 5 – 10 minutes
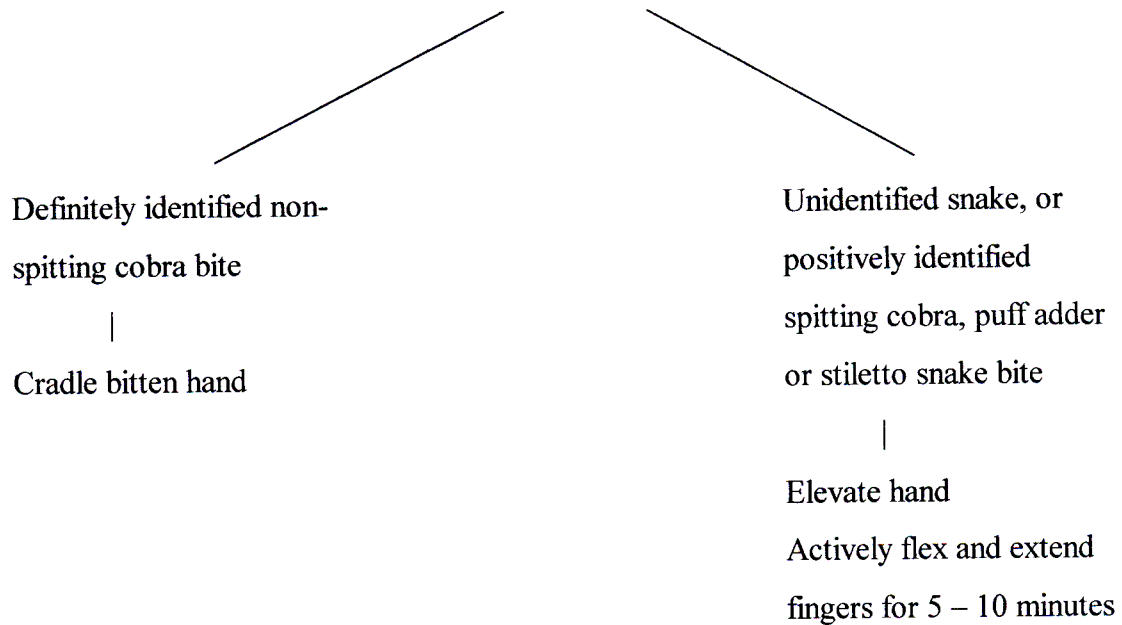
CHAPTER 3

NORMAL ORAL BACTERIAL FLORA OF SOME SOUTHERN AFRICAN SNAKES

CONTENTS

3. NORMAL ORAL BACTERIAL FLORA OF SOME SOUTHERN AFRICAN SNAKES

3.1 Abstract

Objective: To determine the numbers and species of bacteria occurring in the oral cavities of South African snakes, in view of sepsis resulting from some snakebites.

Method: Eighteen snakes representing 11 species were subject to mouth swabs on 50 occasions (103 swabs), which were submitted for microscopy and aerobic and anaerobic culture.

Results: Fifty-two per cent of swabs were positive for bacteria. Ninety-two bacteria were cultured, representing 30 species, of which 81,5% of the isolates were *Enterobacteriaceae*, 16,3% Gram-positive aerobic cocci and 2,2% anaerobes. Swabs from non-venomous snake mouths were more commonly bacteriologically sterile than those of venomous snakes (P = <0,02). The oral bacterial flora did not differ between captive and newly captured snakes, were not constant in a single snake with time, in the same snake species, the same serpentarium or geographically. The bacteria most commonly cultured were *Proteus spp., Pseudomonas spp., Salmonella arizonae* and *Staphylococcus epidermidis.* Colony counts tended to be low. Three or more bacterial species per venomous snake per occasion were more common in winter than in summer (P = <0,02).

Conclusion: This limited study suggests that the mouths of South African snakes have an efficient bacterial cleansing mechanism, bacterial flora tend to be scanty in healthy snakes, mainly comprising the *Enterobacteriaceae,* which are transient colonisers, and anaerobes are uncommon.

3.2 Introduction

This study was undertaken to determine the numbers and species of bacteria occurring in the oral cavities of South African snakes in view of sepsis resulting from some snakebites. Studies on the bacterial flora in snakes' mouths and venom have been undertaken in other countries but not in South Africa (Goldstein *et al.*, 1979; Arroyo *et al.*, 1980; Soveri & Seuna, 1986; Jorge *et al.*, 1990; Theakston *et al.*, 1990).

3.3 Materials and methods

During 1991 and 1992, 11 snakes were captured by the author in KwaZulu-Natal. Their oral cavities were swabbed for bacteriological culture and the swabs submitted to Eshowe Hospital. The mouths of all the snakes were swabbed once, with two being swabbed on a later occasion, giving a total of 13 swabs.

In Gauteng, the study was continued during 1994 and 1995 in a similar way at Gold Fields West Hospital (GFWH) in Westonaria, and at Leslie Williams Memorial Hospital (LWMH) in Carletonville. Each snake was swabbed twice, with one swab being submitted to the bacteriological department of each hospital. Eleven snakes comprising nine species were used in this study, four of which were newly captured. The snake species included puff adders *(Bitis arietans)*, Gaboon adder *(Bitis gabonica)*, rhombic night adder *(Causus rhombeatus)*, rinkhals *(Hemachatus haemachatus)*, Mozambique spitting cobra *(Naja Mossambica)*, python *(Python natalensis)* and three house snakes *(Lamprophis spp.)* from KwaZulu-Natal. All were swabbed on repeat occasions over a six to eight-month period, resulting in 90 swabs

over 45 occasions. This study, designed to last a full year, was aborted due to a puff adder bite to the author's dominant thumb (Figs 10-23, 10-24).

All three hospitals were of second-level status, with consequent limitations of their microbiological capacity. Outside help was occasionally sought for bacterial identification.

3.3.1 Snakes and serpentaria

All the snakes that were swabbed were healthy. In Gauteng, they were housed under three different conditions in the same building. Three puff adders *(Bitis arietans)*, a Gaboon adder *(Bitis gabonica)* and a python *(Python natalensis)* were kept in a room. A rinkhals *(Hemachatus haemachatus)*, a Mozambique spitting cobra *(Naja mossambica)* and a rhombic night adder *(Causus rhombeatus)* were housed in a glass container previously used as an aquarium, and three species of house snakes, *(Lamprophis fuliginosis, L. guttatus, L. inornatus)* were accommodated in a wooden box.

3.3.2 Swabs

These were of the standard type containing a transport medium. For samples collected in Eshowe, Transystem Amies swabs (Copan, Italy) were used and in Gauteng Amies Transport swabs (Clinical Sciences, Johannesburg) were used.

3.3.3 Swabbing procedure

On each occasion, the individual snake was captured by the author who opened the mouth using a sterile instrument, while an assistant rotated the swab on the floor of the mouth between the larynx and mandibular teeth. If a swab was deemed to have become contaminated in any way, it was immediately discarded. Bacteriological examination was commenced within a few minutes, as the swabbing was undertaken in the grounds of or in each hospital.

3.3.4 Aerobic and anaerobic cultures

The swabs were directly inoculated onto culture plates which were incubated both aerobically and anaerobically at 37 ^{0}C.

Aerobic cultures on MacConkey's agar without crystal violet, 5% blood agar and cooked meat broth (South African Institute for Medical Research, Johannesburg) were maintained for 24 h. At GFWH, in the absence of growth at 24 h, all plates were reincubated for a further 24 h, and the cooked meat broth was subcultured onto 5% blood agar and McConkey's agar. If *Haemophilus spp.* was suspected from Gram stain, bacitracin-agar was utilised.

Anaerobic cultures (Gas Generating kit Anaerobic System, Oxoid Ltd, England) on 10% blood agar (not prereduced) were maintained for 48 h. Any growth was subject to an aerotolerance test by subculturing onto two 5% blood agar plates for aerobic and carbon dioxide jar incubation (Gas Generating kit Carbon Dioxide System, Oxoid Ltd, England), and onto 10% blood agar for further anaerobic incubation.

3.3.5 Gram staining and colony counts

Immediately after inoculation, smears were prepared from the same swabs on glass slides for microscopic examination. These were stained with Gram's stain. Colony counts of any bacterial growth on solid media were graded after 24 h as follows: trace: less than 10 colonies, + : 10 to 50 colonies, ++ : 50 to 100 colonies, +++ : more than 100 colonies per plate.

3.3.6 Bacterial identification

The Streptex test (Murex, Biotech Ltd, England) was used for *streptococci.*

The *Staphylococcus* tube coagulase test was used for staphylococci at Eshowe (staphaurex, Murex, Biotech Ltd, England) and the Oxoid staphylase test (Oxoid Ltd, England) was used in Gauteng.

Gram-negative aerobic rods were identified in Eshowe with the aid of Microbact 24A+E (Disposable Products Pty Ltd, Adelaide, Australia), and in Gauteng with the analytical profile index 10 S (Biomérieux sa, France).

Anaerobes were identified with the Rapid ID 32A (Biomérieux sa, France).

3.4 Results

3.4.1 Study in KwaZulu-Natal (Table 3-1)

Fifteen bacterial species were isolated, of which 80% were *Enterobacteriaceae*, 20% Gram-positive aerobic cocci, with a further slightly fusiform Gram-negative organism that was visible but not cultured.

3.4.2 Study in Gauteng (Tables 3-2, 3-3, 3-4)

Twenty-two bacterial species were isolated, of which 81,8% were *Enterobacteriaceae*, 13,6% Gram-positive aerobic cocci and there was one anaerobe (4,5%). There was one further visible but uncultured Gram-negative bacillus. Bacteria identified at the two hospitals in Gauteng were identical in 53,2% of the cases, similar in 22,2 % and totally dissimilar in 6,7 %.

Table 3 - 1 Bacterial species isolated from the snakes in KwaZulu-Natal

SNAKE	DATE	BACTERIA
Psammophis brevirostris (Stub-nosed grass snake)	Dec 1991 Jan 1992	*Acinetobacter lwoffii* *Pseudomonas stutzeri* *Pseudomonas sp*
Telescopus semiannulatus (Tiger snake) Snake 1	Dec 1991	*Aeromonas caviae* *Aeromonas hydrophila* *Staphylococcus aureus*
Snake 2	Dec 1991	*Escherichia coli* *Acinetobacter lwoffii* *Serratia sp*
Naja mossambica (Mozambique spitting cobra) Snake 1		*Klebsiella pneumoniae* *Staphylococcus epidermidis*
Snake 2		*Staphylococcus sp*
Snake 3		*Klebsiella oxytoca* *Enterobacter agglomerans*
Snake 4		*Enterobacter agglomerans* *Staphylococcus sp*
Bitis arietans (Puff adder)	Dec 1991 Apr 1992	*Citrobacter freundii* *Salmonella arizonae* *Staphylococus aureus* No growth
Lamprophis guttatus (Spotted house snake)		No growth
Lamprophis fuliginosis (Brown house snake)		Scanty slightly fusiform Gram-negative bacteria No growth
Lamprophis inornatus (Black house snake)		No growth

All initial swabs were taken from newly captured snakes.

Table 3 - 2   Oral bacterial flora in non-poisonous snakes in Gauteng

	GOLD FIELDS WEST HOSPITAL		LESLIE WILLIAMS MEMORIAL HOSPITAL
DATE	MICROSCOPY	BACTERIA CULTURED	BACTERIA CULTURED
LAMPROPHIS FULINGINOSIS (Brown House Snake) A			
1994.07.11	Scanty Gram-negative bacilli	Nil	Nil
1995.01.23	Nil	Nil	*Staphylococcus aureus*
LAMPROPHIS GUTTATUS (Spotted House Snake) A			
1994.07.11	Nil	Nil	Nil
1995.01.23	Nil	Nil	Nil
LAMPROPHIS INORNATUS (Black House Snake) A			
1994.07.11	Nil	Nil	Nil
1995.01.23	Scanty Gram-negative bacilli	*Proteus sp*	Nil
1995.02.14	Nil	Nil	Nil
PYTHON SEBAE (Python) Swaziland B			
1995.01.23	Nil	Nil	Nil
1995.03.30	Not done	*Pseudomonas sp*	*Stenotrophomonas maltophilia Xanthomonas sp. . Enterobacter aerogenes.*
1995.05.04	Nil	Nil	Nil
1995.06.12	Nil	Nil	Nil
1995.08.10	Nil	Nil	Nil
A : wooden box. B : room.			

Table 3 - 3 - Oral bacterial flora in *Bitis arietans in Gauteng*

	GOLD FIELDS WEST HOSPITAL			LESLIE WILLIAMS MEMORIAL HOSPITAL		
Date	Microscopy	Colony Count	Bacteria Cultured	Microscopy	Colony Count	Bacteria Cultured
SNAKE 1 – GAUTENG						
1995.02.21 A	Nil		Nil	Nil		Nil
1995.03.30	Not done		*Staphylococcus aureus*	Not done		*Staphylococcus*
1995.05.04	Not done		Nil	Not done		Nil
1995.06.12	Nil		Nil	Nil		Nil
1995.08.10	Not done	+	*Salmonella arizonae*	Not done		Nil
SNAKE 2 – ZIMBABWE						
1995.01.23 A	Nil		Nil	Not done		Nil
1995.02.14	Nil		Nil	Not done		Nil
1995.03.30	Not done		*Pseudomonas sp*	Not done		Nil
1995.05.04	Nil		Nil	Not done		Nil
1995.06.12	Nil		Nil	Nil		Nil
1995.08.10	Mixed organisms	++	*Pseudomonas aeruginosa*	Not done		Nil
SNAKE 3 – KWAZULU-NATAL						
1995.01.23	Scanty Gram-negative bacilli	+	*Pseudomonas sp*	Not done		*Proteus mirabilis. Pseudomonas aeruginosa*
1995.02.14	Nil	Trace	*Pseudomonas sp. Proteus sp*	Not done		*Pseudomonas aeruginosa*
1995.03.30	Not done		*Escherichia coli*	Not done		*Escherichia coli. Proteus vulgaris*
1995.05.04	Not done	+	*Pseudomonas aeruginosa*	Not done	Trace	*Salmonella arizonae*
1995.06.12	Not done	++	*Pseudomonas aeruginosa*	Not done	+++	*Pseudomonas aeruginosa Proteus mirabilis*
A : Newly caught.						

Table 3-4 Oral bacterial flora in *Bitis gabonica, Causus rhombeatus, Hemachatus haemachatus* and *Naja mossambica* in Gauteng

Date	GOLD FIELDS WEST HOSPITAL			LESLIE WILLIAMS MEMORIAL HOSPITAL		
	Microscopy	Colony Count	Bacteria Cultured	Microscopy	Colony Count	Bacteria Cultured
BITIS GABONICA (Gaboon adder) B						
1995.01.23	Scanty gram negative bacilli		*Proteus sp*	Not done		*Staphylococcus epidermidis Proteus mirabilis*
1995.02.14	Nil		Nil	Not done		Nil
1995.03.30	Not done		*Pseudomonas sp*	Not done		*Pseudomonas aeruginosa Clostridium sordellii*
1995.05.04	Not done	+ + +	*Morganella morganii Stenotrophomonas maltophilia Pseudomonas vesicularis*	Not done	+ +	*Providentia stuartii Morganella morganii*
1995.06.12	Moderate Gram-negative bacilli	++ ++	*Providencia rettgeri Salmonella arizonae*	Scanty Gram-negative bacilli	+++	*Salmonella arizonae Proteus mirabilis Clostridium sordellii*
1995.08.10	Some mixed organisms		*Tatumella ptyseos*	Not done	+ +++	*Salmonella arizonae Providentia rettgeri*
CAUSUS RHOMBEATUS (Rhombic Night Adder) C						
1995.02.21 A	Nil		Nil	Nil		Nil
1995.03.30	Nil		Nil	Not done		Nil
1995.05.04	Not done	+ +	*Staphylococcus epidermidis Pseudomonas vesicularis*	Not done	Trace Trace	*Staphylococcus epidermidis Salmonella arizonae*
1995.06.12	Not done	+	*Salmonella arizonae*	Nil	Trace	*Salmonella arizonae*
1995.08.10	Nil		*Salmonella arizonae*	Not done	++	*Salmonella arizonae*
HEMACHATUS HAEMACHATUS (Rinkhals) - Gauteng C						
1995.02.14 A	Scanty Gram-negative bacilli	Light growth	*Proteus sp*	Not done		*Proteus vulgaris*
1995.03.30	Mixed organisms		*Proteus sp Staphylococcus epidermidis*	Not done		*Proteus vulgaris*
1995.05.04	Not done	+ +	*Proteus vulgaris Staphylococcus epidermidis*	Not done	Trace + +	*Proteus vulgaris Staphylococcus epidermidis Stenotrophomonas maltophilia*
1995.06.12	Not done	+	*Proteus vulgaris*	Nil		*Proteus vulgaris*
1995.08.10	Mixed organisms	+++ +++	*Citrobacter freundii Providencia rettgeri*	Not done	+ +++ Trace	*Escherichia coli Proteus vulgaris Acinetobacter calcoaceticus*
NAJA MOSSAMBICA (Mozambique spitting cobra) - Mpumalanga C						
1995.06.22	Not done	+	*Salmonella arizonae*	Not done	+ ++ +++	*Salmonella arizonae Moraxella sp Staphylococcus epidermidis*
A - Newly captured. B - room. C - glass container.						

3.5 Discussion

3.5.1 Temperature of culture

Bacterial culture was undertaken at 37 $^{\circ}$C as this is the temperature at which bacterial multiplication occurs in humans. Arroyo *et al.* (1980) and Theakston *et al.* (1990) cultured at 37 $^{\circ}$C, while Goldstein *et al.* (1979) utilised a temperature of 35 $^{\circ}$C. In similar studies by Soveri & Seuna (1986), plates were cultured in parallel at 20 $^{\circ}$C and 37 $^{\circ}$C. It appears that some bacterial flora will grow at 20 $^{\circ}$C while all of them will grow at 37 $^{\circ}$C. It is possible that the capability of growth at the lower temperature may be partly responsible for the bacterial species which cause stomatitis in snakes (Soveri & Seuna, 1986), aided by a possible diminution of winter antibacterial properties of venom (4.5.2), and a proliferation of oral bacteria during this season (3.5.10).

3.5.2 Type of bacteria

In this study, 86,7% of the 30 identified species were *Enterobactereaceae*, 10% were Gram-positive aerobic cocci with one anaerobe *(Clostridium sordellii)*. Of the isolates, 79,8% were *Enterobactereaceae*, 16% Gram-positive cocci, and 2,1% were anaerobes with 2,1% unidentified.

3.5.3 Discrepancies between information from GFWH and LWMH

There was some discrepant information from the two hospitals in the Gauteng study, probably explained by low bacterial numbers in snake mouths. In addition, a swab rotated between the larynx and mandibular teeth only samples a small percentage of the surface area of the buccal cavity. Furthermore, Soveri & Seuna (1986) found no correlation between aerobic bacteria cultured from the mouth and proximal oesophagus of the same snake on the same occasion, although when the flora of both locations were compared in the whole snake population, they were similar.

3.5.4 Geographical variation

Geographical variation is possible (Tables 3-1 to 3-4), as only five of 12 and 17 bacterial species isolated in KwaZulu-Natal and Gauteng respectively were identical. In KwaZulu-Natal (Table 3-1), three bacterial species at two swabbing intervals were cultured from the puff adder. When transferred to Gauteng, after a three-year interval and after five swabbings, one organism was re-cultured *(Salmonella arizonae)*, while four species of Enterobacteriaceae were cultured for the first time (Table 3-3). This phenomenon has been shown previously (Theakston *et al.*, 1990), but is disputed by Arroyo *et al.* (1980).

3.5.5 Newly captured and captive snakes

There is little difference in the quality and quantity of bacteria isolated from newly captured and captive snakes. The initial swabs from five of 15 newly captured snakes were negative for bacteria, while seven of 13 captive snakes which were initially positive for bacteria became temporarily negative. Theakston *et al.* (1990) found a wider range of bacteria (but no *Corynebacterium spp.*) and more positive cultures in newly captured snakes, while Arroyo *et al.* (1980) found a higher bacterial load with no difference in bacterial species in captive snakes. These discrepancies may be due to environmental bacterial load, the season of the year and the mouth-cleansing abilities of the snakes. The latter cause is suggested by this study, which found a variation in the quality and quantity of bacteria in snakes sharing the same serpentarium.

3.5.6 Venomous and non-venomous snakes

Non-venomous snake mouths were sterile on 10 of 15 occasions (66,7%) as opposed to 11 of 43 occasions (25,6%) in venomous snakes, (P = <0,02). These negative results may be due to insensitive culture techniques, although in the present study, where microscopy was performed, little additional information was forthcoming. It may be that a low environmental bacterial load of the wooden box containing the three non-poisonous house snakes affected this result. However, when the python is compared with the four poisonous snakes sharing the same room, then the negative cultures are 60% and 36% respectively. It is possible that the saliva of non-poisonous snakes, which thinly coats the buccal cavity, is antibacterial. Jansen (1983) found that Duvernoy's gland secretions were antibacterial and it is known that the venom of

South African snakes has antibacterial properties (Chapter 4). Venom probably does not always coat the buccal surface as saliva does, which may explain this discrepancy. This antibacterial property of venom probably originated as a conditioner of dental surfaces (Gans, 1978).

3.5.7 Consistency of bacterial flora in the same snake

There is no consistency of bacterial flora in the same snake, since the same bacterium *(Proteus vulgaris)* was grown on all occasions only from the rinkhals (Table 3-4). The same bacterium was grown from two snakes on four out of five and three of five occasions respectively, while three of seven snakes swabbed on five or more occasions failed to grow the same organism more than once. The Gaboon adder, which produced the most bacterial species (11 over six occasions), did not harbour the same bacterium more than twice (Table 3-4).

3.5.8 Consistency of bacterial flora in the same housing

Snakes sharing the same serpentarium for several months did not necessarily harbour the same bacteria. The room serpentarium housed two snakes that frequently produced growth of multiple bacteria, whilst three frequently yielded low bacterial numbers or no growth at all (Tables 3-2, 3-3, 3-4). This suggests that buccal bacterial species and numbers are not totally dependent on the environmental bacterial load.

3.5.9 Consistency of bacterial flora in the same snake species

Snakes of the same species do not necessarily harbour the same bacterial flora and numbers, as shown by three puff adders which shared the same housing (Table 3-3).

3.5.10 Seasonal bacterial flora variation

Oral snake mouth bacterial flora may vary seasonally. It is known that snake venom composition can vary in the same snake over a year, (Williams & White, 1992). Results from the long-term captive venomous snakes (Tables 3-3, 3-4) show that 0,9 bacterial species per occasion were cultured in summer and 1,8 species per occasion in winter, while the largest colony counts (venomous snakes) were also recorded at this time of the year (May, June and August). It was only in winter that three or more bacterial species at a time were cultured from venomous snakes. This occurred on six out of 17 occasions in winter as opposed to none out of 15 occasions in summer (P =<0,02). The activity of fresh cobra venom against anaerobic bacteria diminishes during winter (Table 4-4) and the severity of clinical cytotoxicity in human snakebite patients reduces during this period (Blaylock, 2000b). The decrease in venom potency in winter may explain these differences.

3.5.11 Comparison of bacterial flora in other geographical areas

The bacteria cultured during this study are similar to those described from *Bothrops jararaca* from Brazil (Jorge *et al.*, 1990), where fang sheath and venom were cultured, and bacteria from *Calloselasma rhodostoma* from Thailand (Theakston *et al.*, 1990).

Goldstein *et al.* (1979), however, found 32,6% of the oral bacterial flora to be anaerobic, comprising several *Clostridium spp., Bacteroides fragilis* and *Propionibacterium acnes* in rattle snakes. Arroyo *et al.* (1980) cultured the venom and mouth cavities of Costa Rican snakes. Ninety-six isolates were Gram-negative *Enterobacteriaceae* while 63 were *Clostridia* comprising eight species. The fact that these two studies yielded such a high number of anaerobic bacteria could be explained by the culture of venom and not solely of buccal mucosa, geographic variation of snake oral bacterial flora and the use of better anaerobic culture techniques. However, in Eshowe at the time of surgery on infected patients, crepitus and gas were not encountered, whilst foul-smelling pus was noted in a single patient (Chapter 5).

3.5.12 Buccal cavity and venom bacterial flora

In studies where the buccal cavity and venom have been cultured separately, the buccal cavity produced a higher bacterial load (Goldstein *et al.*, 1979; Arroyo *et al.*, 1980; Theakston *et al.*, 1990).

3.5.13 Origin of bacterial flora

Snakes do not appear to have permanent oral bacterial flora. They are rather transient and probably of environmental origin as suggested by Soveri & Seuna (1986). The same authors found no correlation between snake mouth and oesophageal aerobic bacterial flora in individual snakes sampled on the same occasion, nor between bacterial flora and prey type, time of feeding or time of swabbing. When a snake is awake, and especially when it is on the move, it frequently flicks its tongue in and out

to explore the environment. This, together with feeding and drinking, must inoculate the buccal cavity with bacteria. Occasionally, swallowed prey will defecate before or during swallowing, temporarily giving a high bacterial load that is probably mostly cleared by a self-cleansing mechanism in the buccal cavity in which Duvernoy's gland secretions and venom play a role.

Algorithm 3

Normal snake oral bacterial flora
|
Scanty
Transient colonisers

No consistency of flora
in   - same snake species
     - same snake
     - same serpentarium
     - captive snakes
     - newly captured snakes
     - geographically

More prevalent in winter
Less in non-venomous snakes

Mainly *Enterobacteriaceae*

(*Proteus spp., Pseudomonas spp., Salmonella arizonae* most common)
Few *Staphylococcus epidermidis*
Anaerobes uncommon

CHAPTER 4

ANTIBACTERIAL PROPERTIES OF KWAZULU-NATAL SNAKE VENOMS

CONTENTS

4. ANTIBACTERIAL PROPERTIES OF KWAZULU-NATAL SNAKE VENOMS

4.1 Abstract

Objective: In view of the low incidence of bacterial infection complicating snakebite wounds, the antibacterial properties of some KwaZulu-Natal snake venoms were assessed.

Method: The venoms of the common night adder *(Causus rhombeatus),* Gaboon adder *(Bitis gabonica),* puff adder *(Bitis arietans),* black mamba *(Dendroaspis polylepis),* eastern green mamba *(Dendroaspis angusticeps),* forest cobra *(Naja melanoleuca),* snouted cobra *(Naja annulifera)* and Mozambique spitting cobra *(Naja mossambica)* were collected and, by gel diffusion, tested against the bacteria *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacteroides fragilis, Bacteroides intermedius, Clostridium sordellii* and *Clostridium perfringens.*

Results: All snake venoms showed antibacterial activity, with the adder venom showing most activity against the aerobes, while the cobras showed lesser but equal activity against the aerobes and anaerobes. Black mamba venom only showed activity against *C. perfringens.*

Conclusions: KwaZulu-Natal snake venoms have antibacterial properties which are dependent on venom and bacterial type. This is partly responsible for the low incidence of bacterial infection following snakebite. The antibacterial properties of *Naja* spp. venom for anaerobic bacteria diminish in winter.

4.2 Introduction

Infection following snakebite without necrosis is uncommon in KwaZulu-Natal (Blaylock, 1999), and it is known that some snake venoms have antibacterial properties (Glaser, 1948; Stocker & Traynor, 1986, Theakston *et al.*, 1990, Stiles *et al.*, 1991 and Talan *et al.*, 1991). The purpose of this study was to determine whether KwaZulu-Natal snake venoms are antibacterial.

4.3 Material and methods

The facilities of the Eshowe Provincial Hospital were utilised. Snake venom was milked by the author into sterile containers covered by sterile Opsite®. Within a few minutes, 20 µl of venom was aseptically placed into 4-mm inkwells of culture plates previously lawned with a known bacterium. If enough venom was available, it was diluted with normal saline solution up to 1:28. Plates were cultured either aerobically or anaerobically, and observed at 24 and 48 hours for bacterial growth. Bacterial diameter zones of growth inhibition were measure in mm. The snakes were milked by the same snake handler in the same manner.

4.3.1 Snakes

All the snakes were from KwaZulu-Natal, and included *Causus rhombeatus* (common night adder), *Bitis gabonica* (Gaboon adder), *Bitis arietans* (puff adder), *Dendroaspis polylepis* (black mamba), *Dendroaspis angusticeps* (eastern green mamba), *Naja melanoleuca* (forest cobra), *Naja annulifera* (snouted cobra) and *Naja mossambica*

(Mozambique spitting cobra). All the snakes were healthy and the same snakes were used on all occasions.

4.3.2 Bacteria

The bacteria were obtained from the University of Natal. These included *Staphylococcus aureus* NCTC 1555, *Escherichia coli* NCTC 1077, *Pseudomonas aeruginosa* NCTC 10662, *Bacteroides fragilis*, *Bacteroides intermedius*, *Clostridium sordellii* and *Clostridium perfringens*. Standardisation of inoculum size was achieved by suspending some of the known bacterial colonies in a small volume of sterile water, saline solution or broth, which was further diluted until the turbidity matched that of the 0.5 MacFarland standard.

4.3.3 Culture Plates

Culture plates contained Mueller-Hinton agar, variously modified as brain heart infusion agar, Columbia agar, Oxoid Diagnostic Sensitivity Test (DST) agar with human blood, Dextrose Tryptone (DTA) nutrient agar, or MacConkey agar (Durban, South Africa). Preparation of the bacterial lawn was achieved by streaking squeezed-out sterile non-toxic cotton swabs (Sterilab Gauteng) containing the 0.5 MacFarland standard inoculum. Five to 15 minutes were allowed for the surface of the agar to dry before adding the venom.

4.4 Results

Table 4-1 and Figure 4-1 show the results of neat venom. Dilution of the venom with normal saline resulted in a gradual fall-off of antibacterial activity. Most venoms demonstrated efficiency at dilutions of 1:64.

Table 4 - 1 Antibacterial effects of venom

MONTH	S. aureus	P. aeruginosa	E. coli	B. fragilis	B. intermedius	C. sordellii	C. perfringens	S. aureus	P. aeruginosa	E. coli	B. fragilis	B. intermedius	C. sordellii	C. perfringens	S. aureus	P. aeruginosa	E. coli	B. fragilis	B. intermedius	C. sordellii	C. perfringens
CAUSUS RHOMBEATUS								**BITIS ARIETANS**							**BITIS GABONICA**						
JANUARY								20					10								
FEBRUARY											0	0	16	0							
MARCH												120	0	0	0						
APRIL															18	13	0			0	0
MAY			0	5	13	0									22						
JULY								19	11	7	0	0	0	0							
AUGUST	2	13	12	0	0	0	0														
OCTOBER	25	19	13	6	10	10	9	20	20	12											
NOVEMBER	23	19	11			12															
DECEMBER											0	0	0	22	23 / 25	13	11 / 15	0	0	0	0
NAJA MOSSAMBICA								**NAJA ANNULIFERA**							**NAJA MELANOLEUCA**						
APRIL				0 / 0	13 / 15	24 / 22	34 / 22				0	10	25	23				0	20	25	30
MAY	16		12	0 / 0	0 / 0	0 / 0	18 / 16	17	18	12	0	0	8	8	18	12	13	0	0	8	13
JUNE	12 / 15	11 / 12	0 / 9	0	0	0	0	17	11	10	0	0	0	8	20	12	12	0 / 8	0	0	12
JULY															24	14	14				8
AUGUST								18	12	11											
DENDROASPIS POLYLEPIS								**DENDROASPIS ANGUSTICEPS**													
MARCH	0	0	0																		
APRIL	0	0	0	0 / 0		0	30 / 7														
JULY				0	0	0	6	0	22	0	0	0	11	8							
DECEMBER	0	0	0	0	0	0	8														

Numbers represent zone of growth inhibition in mm. Two figures occurring in the same month represent two milkings of the same snake at different times of that month

Statistical analysis of Table 1

Effect	MS Effect	df error	F	p - level
Snake *(Naja spp)*	29,396	3	2,3207	0.245991
Anaerobic bacteria	162,467	3	12,8263	0,033879
Season: summer or winter	2112,267	3	166,7579	0,001002

Antibacterial properties of snake venom.
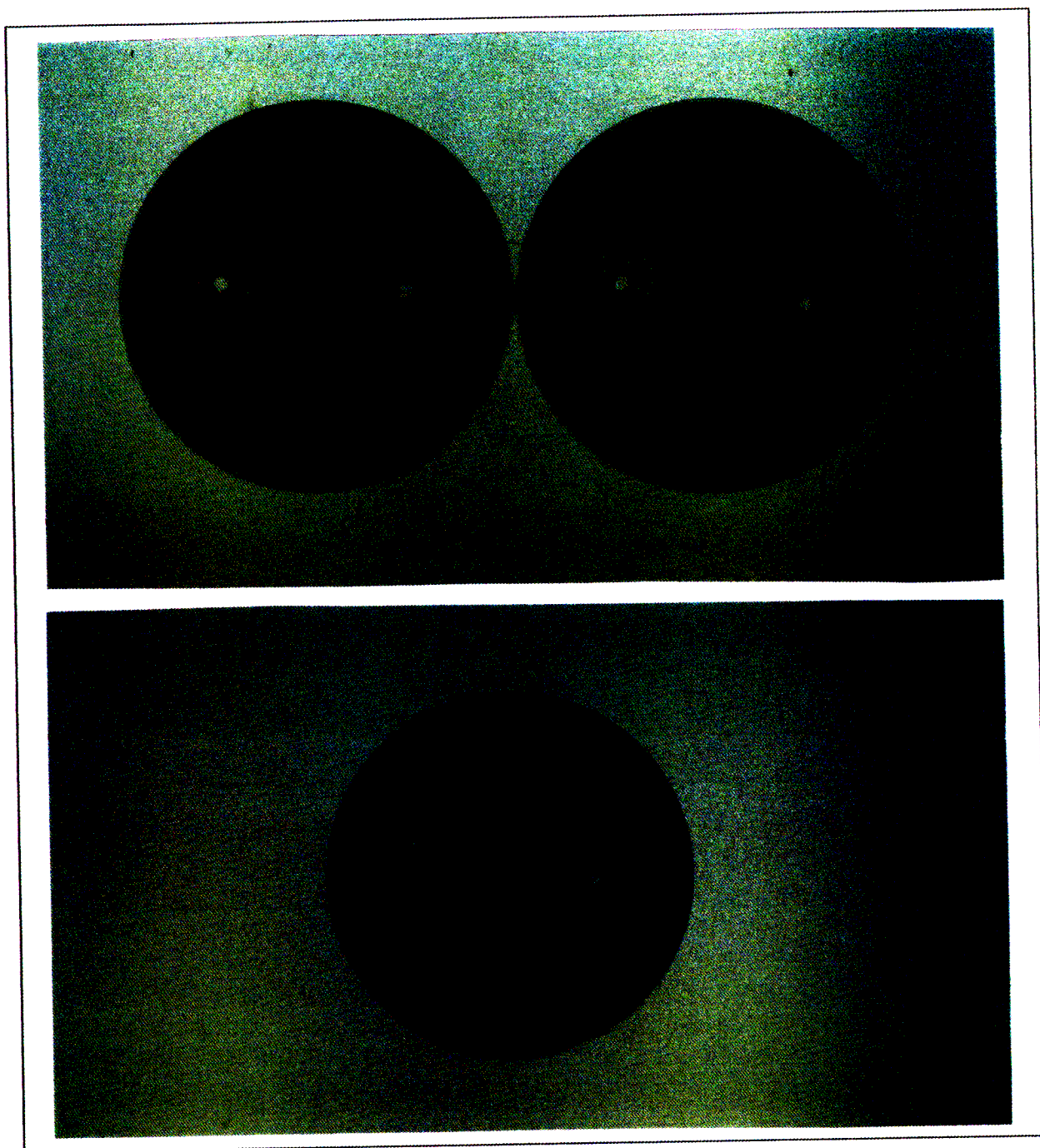
Fig 4 – 1

E. coli : Escherichia coli NCTC 1077.   Staph : Staphylococcus aureus NCTC 1555.
Pseudo : Pseudomonas aeruginosa NCTC 10662.
Venom: F : forest cobra   E : snouted cobra

activity against *S. aureus* (excluding *Naja melanoleuca)*, with no effect of green mamba venom on *P. aeruginosa*. These differences may be due to the following reasons: snake venom of the same snake species is known to vary with individual snakes, season (4.5.2), geographical area and the age of the snake (Reid & Theakston, 1978; Theakston, 1986), different strains of the same bacterium have different sensitivities, fresh venom was used in this study, or dissimilar microbiological techniques were used.

4.5.2 Seasonal antibacterial activity

Analysis of variance of the effect of cobra venom on the zone of growth inhibition of anaerobic bacteria shows that of the factors analysed, the most important contributors were season and bacterial species, with anti-bacterial activity falling off significantly during winter (June) in comparison to summer (April). Blaylock (2000) supports this by showing that the incidence of severe clinical envenomation in the painful progressive swelling syndrome is statistically significantly higher in spring than in winter, and suggests that snake mouth bacterial flora are more prevalent during winter, which reach statistical significance (3.5.10). Furthermore, Williams & White (1992) have shown variation in the composition of venom from a single specimen of *Pseudonaja textillis* (common brown snake) over one year.

4.5.3 Antibacterial components in venom

Aloof-Hirsh *et al.* (1968) showed that a direct lytic factor or cytotoxin of *Hemachatus haemachatus* (rinkhals) had antibacterial properties against *S aureus.* and *E. coli.* Skanes (1970) and Stiles *et al.* (1991) have shown an antibiotic property of snake

venom to be associated with L-amino acid oxidases, of which they isolated two types: LA01 and LA02. They cause apoptosis of human tissue cultures (Du & Clemetson, 2002). The yellow colour of venom is commonly associated with the FAD prosthetic group of L-amino acid oxidase (which produces the oxidant hydrogen peroxide) and this may explain why the antibacterial properties of yellow venom in the study (*viperidae*) were greater than the comparatively colourless venoms of the cobras and mambas.

The anti-bacterial effects of cobra and mamba venom may be due to cytotoxins (direct lytic factors), which sometimes cause tissue necrosis in cobra bites. Phosphatidate 2 - acylhydrolase (Phospholipase A_2 or PLA_2), enzymes contained in all venoms but especially prevalent in viper venoms, cleave cell membranes by acting on phospholipids. These are partly responsible for viper bite necrosis. PLA_2 myotoxin II groups Lys 49 and Asp 49 are both bactericidal (Páramo *et al.*, 1998; Lomonte, 2001) although bacterial cell walls do not contain phospholipids.

This study shows that different venoms affect different bacterial species and, as this property diminishes in winter in *Naja spp.* against anaerobic bacteria, it substantiates the view that there is antibacterial activity of more than one toxic component.

4.5.4 Antibacterial function in snakes

Apart from probably diminishing the infection rate in snakebite patients, the antibacterial property of snake venom may protect the snake against infection by

bacteria coexisting with their prey (Thomas & Pough, 1979), stomatitis (Soveri & Seuna, 1986) and prey putrefaction prior to digestion (Stiles *et al.,* 1991).

Algorithm 4–1

Antibacterial properties of KwaZulu-Natal snake venoms

(requires further research)

Present in all species

Viper / adders   **Cobras**   **Mambas**

Diminishing antibacterial properties →

Activity against aerobes

Gm + ve

& Gm – ve

Equal but less activity

against aerobes and

anaerobes

Diminishes in winter

Due to

L – amino acid oxidases (LA01, LA02)

Cytotoxins

PLA_2 enzymes

Diminishes bite site infection

Protects snake against

- bacteria coexisting with prey

- stomatitis

- prey putrefaction prior to digestion

CHAPTER 5

BACTERIAL SPECIES RESPONSIBLE FOR INFECTED SNAKEBITE

WOUNDS

CONTENTS

5. BACTERIAL SPECIES RESPONSIBLE FOR INFECTED SNAKEBITE WOUNDS

5.1 Abstract

Objective: To determine the bacterial species involved in snakebite sepsis and their antibiotic sensitivities.

Method: The prospectively maintained database is analysed for bacteria cultured from infected snakebite wounds.

Results: The bacteria isolated are similar to normal snake oral flora. The *Enterobacteriaceae* are most commonly isolated, followed by Gram-positive aerobic cocci.

Conclusion: Snake mouths are the primary source of sepsis. Empiric antibiotic therapy adequate to control sepsis includes inexpensive cotrimoxazole, ampicillin, chloramphenicol and the aminoglycosides or the more costly antibiotics developed later which cover the same bacterial spectrum.

5.2 Introduction

Snakebite-induced sepsis has not been much investigated in Southern African. Chapman (1968), in his analysis of 1 067 cases in KwaZulu-Natal, discusses infection but does not name the bacteria involved. Blaylock (1999) has addressed this problem and little additional information has subsequently been gained. There is some information from Thailand (Pongprasit, 1988) and South America (Kerrigan, 1992; Kerrigan *et al.,* 1997; Jorge & Ribeiro, 1997).

The source of bacteria responsible for primary snakebite infection may be the patients' skin or clothing, the venom or mouth cavity of the snake or various first-aid measures

such as incision, bare-mouth suction or the rubbing of various substances into the wounds.

The bacterial species most commonly involved would determine the empiric antibiotic therapy required before the results of culture and sensitivity tests are available.

5.3 Materials and methods

The results of the microscopy and culture of 15 of 45 Eshowe patients with bite site complications (BSCs) and other cases where the author was involved were analysed. A total of 24 bites in 23 patients were investigated.

5.3.1 Swabs, aerobic and anaerobic culture, and bacterial identification

The same methods and materials were used as described in 3.3.

5.4 Results

Tables 5-1 to 5-4

Table 5 - 1   Cultures from Eshowe snakebite patients

Eshowe No.	Snake	Bacteria	Bite site complications
14	Unknown	*Proteus* sp.	Necrosis
24	Unknown	*Proteus* sp.	Necrosis
188	Unknown	*Serratia* sp.	Haematoma
199	*Naja mossambica* Two bites in the same patient Bite 1	*Morganella morganii* Alpha haemolytic *streptococcus*	Necrosis
	Bite 2	*Morganella morganii* Alpha haemolytic *streptococcus*	Necrosis
200	Unknown	*Morganella morganii*	Necrosis
E211	*Causus rhombeatus*	Nil on microscopy No growth	Blister
232	*Naja mossambica*	*Salmonella arizonae*	Necrosis
E255	*Actractaspis bibronii*	*Proteus* sp. *Morganella morganii*	Necrosis
E256	Unknown	Nil on microscopy No growth	Necrosis
281	Unknown	*Morganella morganii* *Enterobacter agglomerans* *Streptococcus* groups B & C	Necrosis
296	Unknown	*Staphylocccus* sp. *Escherichia coli*	Necrosis
300	Unknown	*Serrratia liquifaciens*	Necrosis
318	*Naja mossambica*	*Citrobacter freudii*	Necrosis
319	Unknown	*Citrobacter diversus* *Proteus* sp.	Abscess
320	*Causus rhombeatus*	*Citrobacter diversus* *Escherichia coli*	Blister

Table 5 - 2   **Bacteria cultured from other snakebite victims that involved the author**

Patient no.	Snake	Bacteria	Bite site complications
1	*Naja mossambica* (Pretoria) Bit two patients on the same occasion	**Patient 1** *Proteus vulgaris* *Staphylococcus aureus* **Patient 2** *Streptococcus* group D	Necrosis Necrosis
2	*Naja mossambica* (Swaziland)	*Staphylococcus aureus* *Providentia* sp.	Necrosis
3	*Bitis arietans* (Carletonville)	Nil on microscopy No growth (blister fluid)	Necrosis
4	*Bitis arietans* (Johannesburg)	Nil on microscopy No growth	Necrosis
5	*Naja nivea* (Cape Town)	Normal skin flora	Abscess
6	*Atractaspis bibronii* (Carletonville) Bit two patients on the same occasion	**Patient 1** *Citrobacter diversus* **Patient 2** *Citrobacter diversus*	Necrosis Necrosis

Table 5 - 3   Antibiotic sensitivities of isolated Gram-negative rods

Carletonville patients	Ampicillin	Tetracycline	Cephalothin	Chloramphenicol	Cotrimoxazole	Gentamicin	Day of culture
6.1 Table 5-2	I	S		S	S	S	5
6.2 Table 5-2	I	S		S	S	S	5
Eshowe patients							
14	R	S	R	S	S	S	4
24	S	R	R	S	S	S	12
188	S	S	R	S	S	S	7
199	S	S	S	S	S	S	8
199	S	S	S	S	S	S	8
200	S	S	S	S	S	S	9
232	S	S	S	S	S	S	6
255	R	S	R	I	S	S	4
255	R	S	R	R	S	S	4
281	S	S	R	S	S	S	4
281	S	S	R	I	S	R	4
296	S	S	I	I	S	S	11
300	I	S	I	S	S	S	7
318	S	S	R	R	S	R	7
319	I	S	I	R	R	S	4
319	S	S	I	S	S	S	4
320	S	R	R	R	S	R	7
320	S	S	S	S	R	S	7
Sensitivities. S : sensitive R : resistant I : intermediate							

Table 5 - 4   Antibiotic sensitivities of isolated _Streptococci_

Streptococcal group	Alpha Haemolytic		C	B
Antibiotic	Eshowe number			
	199	199	281	281
Ampicillin	I	R	S	R
Tetracycline	S	S	R	R
Cephalothin	R	R	S	I
Chloramphenicol	S	I	R	R
Cotrimoxazole	S	S	S	S
Gentamicin	S	S	S	S
Day of culture	8	8	4	4
Sensitivities. S : sensitive R : resistant I : intermediate				

5.5   Discussion

5.5.1   Bacterial cultures elsewhere

Cultures of bites by _Ophiophagus hannah_ and _Naja n. siamensis_ in Thailand from 25 infected patients yielded no bacterial growth in three cases (12%), aerobes in 23 cases and anaerobes in 13 cases.   Aerobes cultured included _Proteus vulgaris_ (30,8%), _Escherichia coli_ (19,2%), _Morganella morganii_ (15,4%), _Providentia_ (11,5%), _Pseudomonas spp._ (11,5%), _Staphylococci aureus_ (7,7%) and non-haemolytic _streptococcus_ (3,8%). Anaerobes cultured included _Peptostreptococci_ (23,1%), _Clostridia spp._ (19,2%) and _Propione_ bacterium (5,2%) (Pongprasit _et al.,_ 1988).

Two South American studies in Ecuador at the same hospital and by the same author, without anaerobic culture, yielded the following aerobic bacteria: bacterial isolates from 26 cases of snakebite abscesses in the first study included _Enterobacter_ (5), _Escherichia coli_ (4), _Serratia_ (3), _Proteus_ (1), _Staphylococcus aureus_ (4) and an unidentified Gram-positive rod (1) and Gram-positive coccus (1). Foul-smelling pus was present at the time of surgical drainage in all cases of previously unopened

5 -2). The dissimilarity is evident in the anaerobic cultures in Thailand and Brazil, and the foul-smelling pus and gas in infected tissue of the Ecuadorian patients.

At surgery in the Eshowe patients, including those where pus was not cultured, surgical crepitus and gas were not encountered, nor did the pus have the foul smell of anaerobic sepsis, except for case E199, who was bitten on both hands by the same Mozambique spitting cobra. On the eighth day after the snakebite, the pus of the left hand was odourless, while that of the right hand was foul smelling. Culture of pus from both hands yielded *Morganella morganii* and an alpha haemolytic streptococcus. Except for case 1 in Table 5-2, all patients were operated on by the author. Gas gangrene and tetanus have not been described in Southern African patients following snakebite and it has rarely been reported elsewhere (Reid *et al.,* 1963b).

5.5.2   Snake species

There is no difference in bacterial type isolated from species-specific snakebites resulting in abscess formation. The two puff adder bites (necrosis) and one of two night adder bites (blisters) resulted in no bacterial growth (Tables 5-1, 5-2).

5.5.3   Simultaneous bites

When a snake was responsible for two bites on the same occasion, the bacteria involved were identical in two cases (E199, Table 5-1, and an *Atractaspis* bite, Table 5-2), and dissimilar in one *(Naja mossambica* bite, Table 5-2).

5.5.4   Origin of abscess bacteria

When the bacterial isolates in this study are compared to the normal mouth flora of Southern African snakes, they are found to be similar, comprising mostly enteric Gram-negative rods, namely 80% and 77% respectively. This strongly suggests that the major source of bacteria causing infection is the snake's mouth. Furthermore, as these bacteria occur in small numbers and venom has antibacterial properties, these bacteria do not necessarily cause sepsis. This is illustrated by puff adder bite number 3 in Table 5-2. *Salmonella arizonae* was cultured from a swab taken of the snake's mouth a few seconds before the bite. The patient developed a closed blister over a necrotic area which showed no bacteria on microscopy and culture five days after the bite in spite of the absence of antibiotic therapy.

5.5.5   Antibiotic sensitivities

The Enteric Gram-negative aerobic rods had the following sensitivities: cotrimoxazole 90%, ampicillin 85%, gentamicin 85%, chloramphenicol 80% and cephalothin 55%. All four *Streptococci* were sensitive to cotrimoxazole and gentamicin (Tables 5-3, 5-4). Kerrigan (1992), after excluding *Staphylococcus aureus,* showed that of the remaining isolates, the majority of which were aerobic Gram-negative rods, there was 90% susceptibility to chloramphenicol and 83% to gentamicin.

Algorithm 5–1

Bacteria involved in snakebite sepsis

|

Bite site complications

/ \

Present   **Absent**

Favourable for bacterial multiplication   No sepsis because

| - unfavourable for bacterial

Sepsis   multiplication

| - scanty bacteria

Blisters alone: uncommon   - low pathogenicity of bacteria

| - antibacterial properties of

Deep haematomas: may occur   venom and ? saliva

|

Necrosis: present but benign

|

Mostly *Enterobacteriaceae*

Same Gm + ve aerobic cocci

(consistent with snake oral flora)

CHAPTER 6

ANTIBIOTIC USE IN SNAKEBITE VICTIMS

CONTENTS

6. ANTIBIOTIC USE IN SNAKEBITE VICTIMS

6.1 Abstract

Objective: To assess the rationale for antibiotic use in the management of snakebite.

Method: A prospective observational study was undertaken on 333 Eshowe snakebite patients. It was protocol not to administer antibiotics except in the presence of bite site complications (BSCs) or gross swelling.

Results: Four of 250 patients without BSCs or antibiotics developed wound infections. Patients with BSCs or gross swelling receiving antibiotics had a substantially longer period of hospitalisation than similar patients not administered antibiotics.

Conclusion: Antibiotics are not routinely indicated for snakebite.

6.2 Introduction

Patients with painful progressive swelling, which is the most common presentation of snake envenomation in Southern Africa, exhibit hot, painful, swollen, tender limbs with or without regional lymphadenopathy, pyrexia and leucocytosis. This is a similar presentation to sepsis and is most likely venom toxin or systemic inflammatory response syndrome mediated. An increase in cytokine levels in mice and humans envenomated by *Bothrops asper, B. jararaca, Batrox* and *Crotolus durrisus terrificus* has been shown and includes TNF alpha, ILI, IL6, IL10 and IFN gamma (Lomonte *et al.,* 1993; Barraviera *et al.,* 1995; Barros *et al.,* 1998; Petricevich *et al.,* 2000). Tumour necrosis factor alpha and interleukin-1 are endogenous pyrogens and activate leukocytes, while interleukin-6 is an endogenous pyrogen and causes an acute phase response (Shokuhi & Slavin, 2001).

The use of systemic antibiotics in snakebite in Southern Africa is controversial. Some medical publications advocate their use for all cases (Visser & Chapman, 1978; van der Merwe, 1992), and others reserve their use for bite site tissue damage (White, 1984; Blaylock, 1999).

Opinions differ elsewhere in the world. Antibiotics are not indicated for adder bite poisoning in Britain (Reid, 1976), bacterial infections are uncommon in neurotoxic snake envenomation (Minton, 1990) and, except in the event of local tissue necrosis or interference, antibiotics are not indicated for Malayan viper bites (Reid *et al.,* 1963b); or for snake venom poisoning in the United States (Russell *et al., 1975*). Antibiotic administration has been advocated for all snakebites (Warrell, 1987), for all pit viper bites (Parrish & Hayes, 1971), for all rattlesnake bites (Garfin *et al.,* 1979a) and for Malayan pit viper bites, or if the wound is interfered with (Warrell, 1996, 1999).

In some publications snakebite has been investigated more closely. Of 72 consecutive non-venomous snakebites in Massachusetts, four patients used prophylactic antibiotics while 68 did not. There were no wound infections (Weed, 1993). A prospective observational study of 32 patients with rattlesnake envenomation not receiving antibiotics yielded one wound infection (Clark *et al.,* 1993). A prospective controlled trial of antibiotic treatment (gentamicin and chloramphenicol) and no antibiotic treatment was undertaken on 114 patients with pit viper envenomation. Six abscesses occurred in the treated group and three in the untreated group (Kerrigan *et al.,* 1997). A randomised controlled trial involving 70 children bitten by green pit

vipers in Thailand showed no benefit from a 3-day course of amoxycillin (Lekagul & Nuchprayoon, 2001).

6.3 Materials and methods

Three-hundred-and-thirty-three snakebite patients were admitted to Eshowe Hospital between January 1990 and July 1993. A prospective observational study was undertaken. It was protocol not to give antibiotics to snakebite patients unless bite site complications (BSCs) were present or anticipated; or patients had gross swelling defined as swelling extending from a distal extremity bite (85% of cases), swelling to the abdomen from a lower limb bite, or swelling from an upper limb bite extending to the neck, contralateral chest or abdomen. There was concern that there would be a fatal outcome in the patients with gross swelling. BSCs are defined as blistering, necrosis, haematoma or later abscess formation. An early darkened area around the bite site signified potential necrosis, whilst deep haematoma formation was usually diagnosed some time after admission. The protocol was broken in the case of 29 patients due to unawareness of the protocol, and these patients were used as controls (Table 6-1).

6.4 Results (Annexure A)

Three-hundred-and-ten records are available on antibiotic usage. Seventy-eight per cent of patients were admitted within 24 hours of being bitten. Three patients with coincidental bacterial infection are excluded, as are four patients where the date of the bite and the date of discharge are unknown.

Table 6 - 1   Duration of hospitalisation and period of time from the bite to discharge from hospital, with and without systemic antibiotic use. There were 272 patients without bite site complications

		Envenomation							
		Nil	Painful progressive swelling Severity					Progressive weakness	
			Minimal	Mild	Moderate	Severe	Gross	Not ventilated	Intubated or Ventilated
Antibiotics		**Duration of hospitalisation**							
Nil	Number of patients	34	21	78 (1 abscess)	98 (3 abscesses)	8	1	2	3
	Average stay (days)	2,6	3,2	3,5	5,1	7,4	15	4	3
Administered	Number of patients	3	4	12	9	0	0	1	0
	Average stay (days)	2,3	3,8	4,1	4,6			5	
		Bite to hospital discharge							
Nil	Number of patients	34	22	77	95	8	1	2	3
	Number of days	2,5	3,5	3.8	5,7	7,5	15	4	3
Administered	Number of patients	3	4	12	9	0	0	1	0
	Number of days	2,3	4,3	5,1	5,2			5	

Exclusions : All patients with bite site complications, E38 scabies, E45 coryza, E176 pharyngitis, E208 skin pustules, E250 pneumonia, E237 absconded, non-septic readmitted patients E64, 120, insufficient information E70, 93, 94, 152, 190

Table 6 - 2   Initial chosen antibiotics administered to snakebite victims

	No necrosis	Necrosis
Single antibiotics		
Penicillin V	13	
Ampicillin	9	
Amoxicillin	3	
Benzathine penicillin	2	
Erythromycin		2
Chloramphenicol		2
Cotrimoxazole	1	1
Tetracycline	1	
Cloxacillin		1
Cefradine		1
Antibiotic combinations		
Benzyl penicillin Gentamicin Metronidazole		1
Ampicillin Gentamicin		5
Ampicillin Metronidazole		1
Ampicillin Cloxacillin	1	1
Cotrimoxazole Metronidazole		1
No necrosis: Single antibiotic 29, antibiotic combinations 7. Necrosis: Single antibiotic 1, antibiotic combinations 9. P = < 0,0001. Patients with necrosis were mostly administered antibiotic combinations.		

6.5   Discussion

It is accepted that for antibiotics to prevent infection in surgery, appropriate antibiotic levels are required to be in the tissue prior to incision or contamination. The later these levels are achieved following surgery, the less effective antibiotics are. All the patients who received antibiotics did so post-snakebite, which is theoretically a cure and not prophylaxis.

6.5.1 Patients without bite site complications

Of patients without BSCs who did not receive antibiotics, none without clinical envenomation (34), those with minimal, severe or gross swelling (30), and those with progressive weakness (5), developed an abscess; while one of 78 with mild swelling and three of 98 with moderate swelling did (Table 6-1). This gives an infection rate of four out of 250 patients (1,6%) without BSCs who did not receive antibiotics. Furthermore, it cannot be ruled out that the infected patients had an undiagnosed deep haematoma or minor area of necrosis (BSCs), which would have predisposed them to infection. The duration of hospitalisation or time from the bite to the day of discharge were no different between patients receiving and not receiving antibiotics (Table 6-1). These factors contra-indicate the routine use of antibiotics in patients without bite site complications.

6.5.2 Patients with bite site complications

Of 45 patients with BSCs, 20 received antibiotics (44,4%), and in one patient with a blister the antibiotic status was unknown (E152). Antibiotics were not given to the three patients with haematomas, the four patients with abscesses and the seven of eight patients with blisters but no necrosis. There were 26 patients with necrosis. The average hospital stay of nine patients not receiving antibiotics was 10,7 days as opposed to 44,2 days for the 17 patients receiving antibiotics (Appendix A). This is more a measure of the severity of necrosis in those on antibiotic treatment than the effects of the antibiotics. This suggests that antibiotic administration need not be routine in patients with necrosis.

6.5.3   Patients with gross swelling

There were seven patients with gross swelling (E39 died and is therefore excluded). Three patients with necrosis were not given antibiotics and their average hospital stay was 17,7 days. Four patients (one without necrosis) were given antibiotics and their average hospital stay was 54,8 days (Appendix A), which suggests that this degree of swelling does not warrant routine antibiotic administration.

6.5.4   Spectrum of antibiotic cover used

Where antibiotics were administered to patients with and without necrosis, single antibiotics were administered to 29 of 36 and 1 of 10 respectively (P = <0,0001), which shows that wide-spectrum cover (antibiotic combinations) was used more commonly for patients with necrosis (Appendix A and Table 6-2).

6.5.5   Learning of doctors involved

Ten different single antibiotics were used (Table 6-1) of which penicillin V, benzyl penicillin, erythromycin, cloxacillin and cefradine are considered inappropriate for the organisms that were isolated (Tables 5-3, 5-4).   Ampicillin, amoxicillin, chloramphenicol, cotrimoxazole, tetracycline and the antibiotic combinations are more appropriate. Doctors involved in the study showed learning of the protocol. If the first hundred patients in the study without BSCs are compared to the last hundred, then the number receiving antibiotics is 19 and four respectively (P = 0,002). Appropriate antibiotics were used on 18 of 34 (52,9%) occasions in the first half of the study, and on 12 of 15 (80%) occasions in the last half.

In conclusion, routine systemic antibiotic use is of no benefit to snakebite patients who have no bite site complications regardless of the degree of swelling. Antibiotics need not be routinely administered to patients with an abscess or necrosis.

If empiric antibiotic use is to be considered in snakebite, it should be effective against enteric Gram-negative aerobes and *Staphylococcus* and *Streptococcus* species.

Algorithm 6–1

Antibiotic use in snakebite victims

(trial)

Bite site complications

Absent   **Necrosis or gross**

                                        swelling

4 of 250 patients developed minor sepsis

                    Antibiotics   No antibiotics

                    Duration of hospitalisation
                    decreasing

                    (Serendipity)
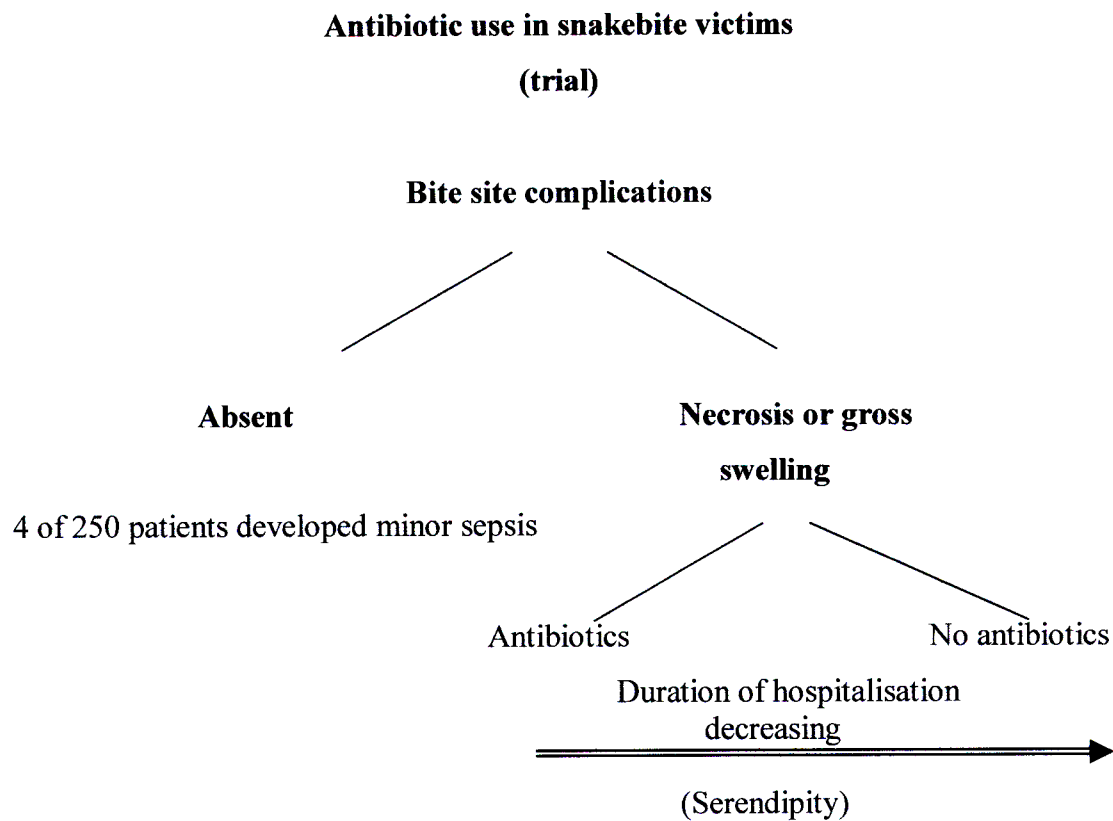
There is no urgency in antibiotic administration. Antibiotics are not routinely indicated.

SECTION III

ANTIVENOM

III Antivenom

Antivenom remains the only specific treatment for snakebite. It comprises IgG or components of IgG derived from vaccinated hyperimmune animals. The manufacturing process is becoming more refined to increase specificity, produce faster systemic absorption, wider tissue distribution and reduce acute and late adverse reactions.

Chapter 7 deals with general aspects of antivenom, Chapter 8 with adverse reactions, while the indications for administration in the three envenomation syndromes are discussed in Chapters 9, 12 and 14.

CHAPTER 7

ANTIVENOM

CONTENTS

7. ANTIVENOM - GENERAL

7.1 Abstract

Objective: The purpose of this chapter is to define antivenom, give a brief description of the manufacturing process at the National Health Laboratory Service Antivenom Unit, note the two types of antivenom available, discuss past and present usage, and note published indications for use, dose, route and rate of administration and sensitivity testing for acute adverse reactions.

Material and methods: Published data are analysed.

Results and conclusions: Hyperimmune plasma is refined to produce $F(ab^1)_2$ antibodies. Polyvalent antivenom and monovalent boomslang antivenom are manufactured by immunising horses against multiple venoms or a single venom respectively. The indication for antivenom is severe envenomation, which is life or limb threatening (occurring in less than 10% of snakebites). There is no standard antivenom dose, the same volume being administered regardless of patient size. All should be slowly administered intravenously without prior sensitivity testing. Repeat administration may be necessary, if indicated, while the venom is still active.

7.2 Introduction

Antivenom remains the only specific treatment for envenomation in Southern Africa. Antivenoms are usually produced from immune horse serum or plasma, and may comprise whole immunoglobulins or the $F(ab^1)_2$ or Fab fragments of IgG produced by pepsin or papain digestion respectively.

Antivenoms produced in South Africa at present comprise $F(ab^1)_2$ fragments derived from hyperimmune horse plasma. Purification methods have remained unchanged since 1970. This antivenom has been shown to be clinically efficacious when compared to antivenom manufactured elsewhere (Warrell *et al.*, 1974). The production of snake antivenom in South Africa began in 1901 in Pietermaritzburg under Dr Watkins-Pitchford, and was tested for therapeutic use in 1903. The South African Institute for Medical Research (SAIMR) began antivenom production in 1928 under Dr E. Grasset and this process has been refined by other workers, namely Drs P.A. Christensen, A. Zoutendyk, P. Price, L. Schrire and J. Southern. The SAIMR Antivenom Department is now called the National Health Laboratory Service Antivenom Unit.

Antivenom production comprises several steps, although different manufacturers may employ different combinations of these to achieve the required quality of their product.

The production process of SAIMR antivenoms in South Africa consists of primary, secondary and routine immunisation schedules in horses, collection of plasma and plasmapheresis. The plasma is preserved with cresol and digestion is with pepsin. After ammonium sulphate fractionation and heat coagulation, followed by dialysis and ultrafiltration concentration, the bulk is sterile filtered and filled as a liquid into sealed glass ampoules. These have a shelf life of three years when stored at $2\ ^0C - 8\ ^0C$, but can be exposed to higher temperatures for limited periods. Deterioration due to heat denaturation is evidenced by the development of turbidity and precipitate in the antivenom (Pantanowitz *et al.*, 1998).

It is recommended that individual countries produce their own antivenom in view of the variability of venom in different parts of the world (Theakston, 1997). Christensen & Anderson (1967) noted that *Dendroaspis* venom varied in lethality from one sample of venom to another. Venom of a specific snake species may vary with the age of the snake (Reid & Theakston, 1978, Tun-Pe *et al.*, 1991), in the same snake (Williams & White, 1992), with season (Marsh & Whaler, 1984; Blaylock, 2000), and geographically (Warrell, 1986; Hyslop & Marsh, 1991; Cavinato *et al.*, 1998; Blaylock, 2000), which suggests that several individual snakes should be milked from different localities in a region for antivenom production. Antivenoms against animal toxins are produced by about 70 laboratories in 37 countries using similar or other techniques (Theakston & Smith, 1997). Other techniques include:

- immunisation of animals using venom with aluminium hydroxide, sodium alginate or venom incorporated into liposomes and an immunostimulant that reduces the need for repeated immunisation

- the use of sheep (or other animals) which are cheaper to keep than horses and have fewer IgG(T) equine antibodies responsible for some sensitivity reactions (Theakston & Smith, 1997)

- the use of caprylic acid instead of ammonium sulphate to remove unwanted proteins (Otero *et al.*, 2001)

- the use of affinity columns containing snake venom to selectively retain specific antibodies (Russell *et al.*, 1985)

- the use of smaller antibody fragments (Fab) with their quicker and more widespread tissue distribution (Meyer *et al.*, 1997; Seifert *et al.*, 1997).

The more expensive lyophilised antivenoms requiring reconstitution are more suitable for the developing world in view of their longer shelf life. Further refinements of antivenom production including monoclonal antibodies are foreseen (Theakston, 1989).

Antivenom is indicated for severe envenomation, which occurs in about 10% of South African snakebites. Lesser envenomation is not associated with mortality provided standard resuscitative procedures are applied, such as fluid replacement should swelling occur. In a sophisticated critical care unit with snakebite expertise, severely envenomed patients may be successfully managed by supportive measures alone except for active bleeding, in which case antivenom is frequently life saving. Antivenom administered to severely envenomed patients is a cost-effective measure as it reduces the period of intensive care needed.

There is no standard recommended antivenom dose. A specific quantity of antivenom will neutralise a fixed dose of snake venom. The venom dose is dependent on the size of the snake, the number of fang punctures and the season of the year. Venom is clinically less potent in winter when snakes feed infrequently or not at all. Small snakebite victims such as children fair worse than adults as far as both local complications and mortality are concerned due to increased venom concentration (Blaylock, 2000). Grasset (1933) and Christensen (1969) both showed that increasing time after venom deposition necessitated increasing the antivenom doses to save envenomed experimental animals. The outcome of severely envenomed patients gives an indication of antivenom efficacy and dose.

Types of SAIMR Snakebite Antivenom

Polyvalent snakebite antivenom comprises horse serum hyperimmunised against the venoms of *Bitis arietans* (puff adder), *B. gabonica* (Gaboon adder), *Hemachatus haemachatus* (rinkhals), *Dendroaspis angusticeps* (eastern green mamba), *D. jamesoni* (Jameson's mamba), *D. polylepis* (black mamba), *Naja nivea* (Cape cobra), *N. melanoleuca* (forest cobra), *N. annulifera* (snouted cobra), and *N mossambica* (Mozambique spitting cobra). Each horse used for producing polyvalent antivenom is immunised with all the above snake venoms rather than mixing the sera from several horses each immunised by a specific venom. Christensen (1966) maintains that the latter process results in dilution of specific venom antibodies, but this has been disputed by Theakston & Smith (1997), who suggest that multiple antigens may lead to competitive antigen-induced suppression, which in turn leads to an alteration or decrease in response to many of the antigens, although this has not been demonstrated in practice. Monospecific *Dispholidus typus* (boomslang) antivenom is obtained by injecting a horse with the single venom.

Antivenom is not produced against the venom of *Bitis atropos* (berg adder) and *Naja nigricollis spp* (other spitting cobras) where, in the latter case, paraspecific antivenom titres are high (Scott, 1995), *Thelotornis spp* (vine snake), *Atractaspis bibronii* (Bibron's stiletto snake) or other minor adders that are potentially lethal to small victims. Antivenom against these venoms is not produced because of the low incidence of bites by these snakes, or rare fatalities and the high cost involved. The paraspecific titre of serum is lower than that of specific serum, and paraspecific antivenom complexes tend to dissociate (Christensen, 1966).

Immunological methods to detect specific snake venoms (venom antigen detection kits) have been used in other parts of the world for immunological surveys and to identify the particular snake species responsible for a bite (Ho *et al.*, 1986). Identification is important if monospecific antivenoms, which are generally more efficacious than polyvalent antivenoms, are to be used therapeutically. Venom detection kits and monospecific antivenoms are successfully used in Australia (Sutherland, 1992), where there are a limited number of lethal snake species. As Southern Africa harbours 15 or more snake species, the bites of which are potentially lethal, it would be prohibitively expensive to manufacture venom detection kits and monospecific antivenoms. Syndromic management of snakebite, together with the administration of polyvalent antivenom, make snake identification less important. A boomslang venom detection kit used in the case of bleeding syndrome in the absence of painful progressive swelling would allow differentiation between a boomslang and vine snake bite, as there is monospecific antivenom for the former but not for the latter.

The efficacy, indications and dose of antivenom for the three envenomation syndromes are analysed in Chapters 9, 12 and 14.

7.3 Material and methods

The prospectively gathered data from the Eshowe series of snakebites is analysed and a literature search was undertaken.

Fig 7 – 1   SAIMR Serum and Vaccine Laboratory Johannesburg 1930
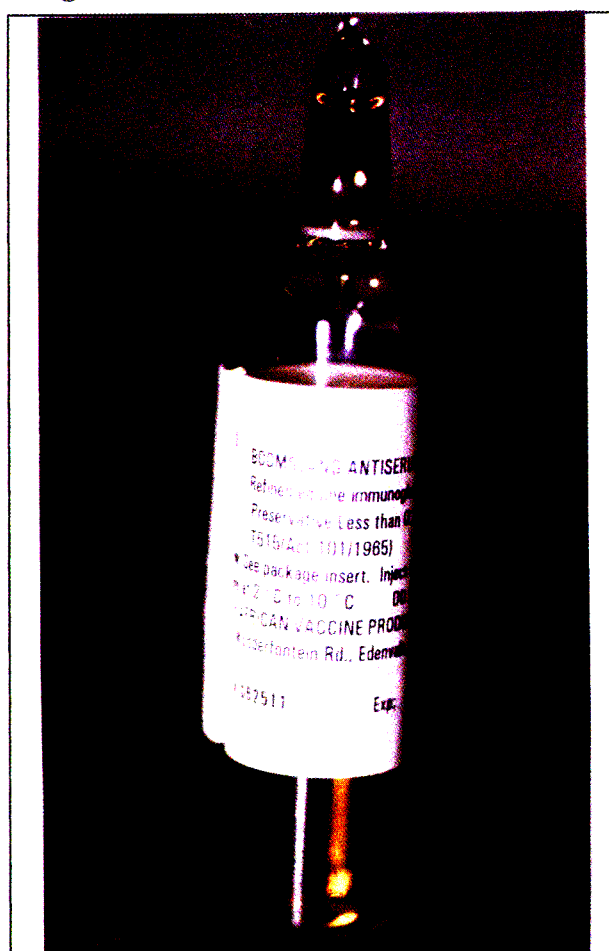
**Fig 7 – 2   Monovalent Boomslang
               Antivenom**

**Fig 7 – 3   Polyvalent Snake
               Antivenom**

Table 7-2   Indications for antivenom administration according to published papers (in chronological order)

	Painful progressive swelling	Progressive weakness	Bleeding
Strover H.M., 1961	Puff adder bites.	Cobra and black mamba bites.	
Mason, 1963	Adder bites.	Cobra and mamba bites.	Boomslang bites.
Strover A.E., 1964	Puff adder bites.	Cobra and mamba bites.	
Schmid, 1966	Puff adder bites. Unknown snake species with symptoms and signs of the above.		
Christensen, 1969	Systemic poisoning. Spreading local damage.	Signs of poisoning.	Boomslang : First signs of poisoning.
Warrell *et al.*, 1975	Puff adder bites. Swelling affecting more than half the limb or systemic poisoning (spontaneous thrombocytopenia, hypotension and bradycardia).		
Brossy, 1977 Any envenomation	Gaboon adder bites.	Black mamba bites.	
Warrell *et al.*, 1976a	Black-necked spitting cobra *(Naja nigricollis)* when swelling involves more than half the limb.		
Fleming, 1977 The author noted it to be inexcusable to administer antivenom without justification	Rapid swelling of affected part extending proximally with blistering and serosanguinous ooze and oligaemia.	Paralysis starting with ophthalmoplegia with glossopharangeal palsy to generalised paresis.	Generalised bleeding tendency.
McNally & Reitz, 1987		Presence of neurotoxic signs.	
Blaylock, 1982b	Puff adder: Whole hand/foot within 1 hour. Gaboon adder bites: Marked systemic toxicity. Other snakes: Swelling to elbow/knee by 6 h.	Marked systemic neurotoxicity.	Boomslang: Incoagulable blood.
Scharf & du Plessis 1993	Puff adder bites: first signs of envenomation.		
Eshowe hospital recommendations. Blaylock, 1993 (unpublished)	Active swelling threatening the airway; reaching the inguinal ligament or chest wall from a foot or hand bite; associated with dyspnoea or coagulopathy. Platelets < 50 x 10^9/L . Incipient compartment syndrome.	Dyspnoea.	Boomslang: bleeding or evidence of disseminated intravascular coagulation.
Wilkinson, 1994	Systemic envenomation. Severe local envenomation.	Systemic envenomation.	
SAIMR antivenom. Package insert (revised 1997)	Swelling severe and spreading.	Severe breathing difficulty or black mamba bite.	Boomslang: Persistent bleeding or prolonged clotting time
Moran *et al.*, 1998	Swelling whole hand and foot 1 hour after the bite. Swelling to knee/elbow 6 hours after the bite. Swelling to shoulder/groin 12 hours after the bite.	Symptoms and signs of neurotoxicity.	Clinical evidence of abnormal bleeding.

Table 7-3   Indications for antivenom suggested in medical booklets

Author	Painful progressive swelling	Progressive weakness	Bleeding
Reitz,. 1978	Swelling affecting more than half the limb. Systemic symptoms. Gaboon adder bite: any symptoms.	Muscle paresis or paralysis. Respiratory difficulty. Black mamba bite: any symptoms.	Haemorrhages.
Potgieter and Linton. Intensive care manual (UCT), 3rd edition.	Systemic toxicity. Whole hand/foot within 1 hour.	Systemic toxicity.	Boomslang: Incoagulable blood.
Van der Merwe, 1992	Severe, rapidly increasing cytotoxic reaction and/or systemic reactions less than 6 hours after the bite.	Paresis eye movements and/or difficulty swallowing and/or paresis skeletal muscles. Peak flow diminishing. Cyanosis, shock, OR worse.	Prolonged clotting time with/or without bleeding.
Schrire, *et al.*, 1996	Painful swelling of the whole hand or foot within an hour of the bite, spreading to the elbow or knee in 3 - 6 hours, or swelling of head, neck or chest wall. Large puff adder or Gaboon adder: as soon as envenomation evident.	Overt neurological signs (dyspnoea and cranial nerve dysfunction).	Boomslang: symptomatic or proven coagulopathy.
	Pregnancy: signs of foetal distress. Child: more than minor signs of toxicity.		
Kloeck, 1999	Painful swelling present.	Dyspnoea.	Coagulopathy.

Table 7-4   Suggested dose of antivenom by various authors

Author	Painful progressive swelling	Progressive weakness	Bleeding	Specific snakes
Strover, 1964		40 - 100 ml		Puff adder 10 - 20 ml
Christensen, 1969. "Impossible to suggest a standard dose"		30 - 40 ml		Puff adder, Gaboon adder: 20 - 40 ml. Boomslang: 10 - 40 ml
Warrell *et al.*, 1975				Puff adder 80 ml
Warrell *et al.*, 1976a				Blacked-necked spitting cobra: 80 ml
Fleming, 1977 (unpublished)	40 - 80 ml	80 - 160 ml		Boomslang: 30 ml
McNally & Reitz, 1987		80 - 120 ml More may be needed		
Reitz, 1978	40 - 100 ml	60 - 100 ml		Boomslang: 20 - 40 ml
Visser & Chapman, 1978	40 - 200 ml	40 - 200 ml		
White & Goodwin, 1982	20 - 40 ml	60 - 80 ml		Boomslang: 10 - 20 ml
Blaylock, 1982b	50 ml	80 ml or more		Boomslang: 20 - 40 ml
Van der Merwe, 1992	80 ml and more if necessary	80 ml and more if necessary (>200ml)		Boomslang: 40 ml
Scharf & du Plessis, 1993				Puff adder: 60 - 80 ml
Eshowe Hospital 1993. Unpublished	50 ml	100 ml and repeat if necessary.	50 ml (associated with PPS)	Boomslang: 20 ml
Schrire *et al.*, 1996	50 ml	100 ml and 20 - 50 ml after 1 - 2 h p.r.n.		Gaboon adder: 100 ml Boomslang: 20 ml
Current SAIMR antivenom pamphlet, 1997	40 - 60 ml	40 - 100 ml		Boomslang: 10 ml
Moran *et al.*, 1998	40 - 60 ml	100 ml. More if symptoms persist		
Kloeck, 1999	50 ml	100 ml. Further 20 - 50 ml if no improvement		Gaboon adder: 100 ml Boomslang: 20 ml May be repeated

7.5 Discussion

7.5.1 Usage (Table 7-1)

Antivenom usage in the various snakebite series is dependent on the availability of antivenom (peripheral hospitals may have none), the venomous snake species in that geographical location, medical expertise and availability of critical care units where measures other than antivenom may be life saving.

Antivenom usage in documented snakebite series ranged from 3% (Eshowe) to 83% (Durban, Chapman, 1968), in contrast to 98,1% of 310 hospitalised patients in Brazil (Caiaffa et al., 1994). The mortality rate in those patients who received antivenom varied from 0 - 30%, and was most common in the progressive weakness group of patients due to inadequate quantities of antivenom administered and a lack of ventilatory support.

7.5.2 Indications and dose

Published indications for antivenom are given in Tables 7-2 and 7-3.

Antivenom should be administered to patients with severe envenomation, present or anticipated, which is life or limb threatening. Lesser envenomation may be managed conservatively in view of the cost and complications of antivenom, and because antivenom cannot prevent necrosis (Christensen, 1969; Theakston, 1997). Initially after a snakebite there may be fang punctures with no venom toxicity, which takes time to develop. This necessitates the time after the bite being an integral part of the assessment of the severity of the envenomation. As children are at greatest risk of mortality (Chapman, 1968; Wilkinson, 1994; Blaylock, 2000), it is expected that more children would receive

antivenom than adults. The indications for antivenom given in Chapters 9, 12 and 14 take account of this, and the time to administration is reached sooner in children. The doses of antivenom can be determined in human trials using enzyme immunoassays for venom and antivenom (Theakston *et al.*, 1992), or retrospectively by the outcome of patients receiving antivenom, the latter method being used in this study.

7.5.3 Route of administration

7.5.3.1 Subcutaneous and intramuscular routes distant to the bite site.

Christensen (1969), using mice, showed that 16% of the injected subcutaneous or intramuscular SAIMR snake antivenom entered the circulation at 30 minutes, with maximal blood concentrations being reached at about 15 hours. Clearly, antivenom administration by this route is too slow to combat a life- or limb-threatening situation.

7.5.3.2 Infiltration at the bite site

The bite site of eight patients bitten by puff adders involved a finger or thumb (Table 9-10). Antivenom was infiltrated at the bite sites of two of these patients (4 and 5)at 1 and 5 minutes respectively, and neither developed necrosis. Patient 3 was injected in a similar manner at 45 minutes and developed minor necrosis. In the other five bites (1, 2, 3, 5 and 7) where antivenom was administered but not at the bite site, all but one (7) developed necrosis. Swift infiltration by serum at the site of venom introduction will either abolish or reduce the effect of viper venom, and will be more effective than elsewhere (Christensen, 1969). Local infiltration at the bite site may be advocated in future as a

first-aid measure against snakebite if Fab or Fv antivenom is manufactured, due to the extremely low acute adverse reaction rate (Theakston & Smith, 1997).

7.5.3.3 Intravenous route

McCollough & Gennaro (1963) showed that 85% of antivenom administered intravenously to dogs reached the envenomed leg within two hours of injection. Recovery when antivenom was injected intramuscularly or subscapularly in similar experiments was less than 2% and 6% respectively. Christensen (1969) injected antivenom intravenously into guinea pigs within 10 - 15 minutes of subcutaneous puff adder venom injection, which reduced the size and severity of lesions at the venom injection site. He also showed that mice injected subcutaneously with Cape cobra venom could be saved by intravenous injection of antivenom, if administered within 30 minutes. The current SAIMR antivenom package insert (revised 1997) recommends the intravenous route. If this is not possible, it is suggested that the contents of one ampoule (10 ml) should be injected subcutaneously or intramuscularly at a single site, with further ampoules being injected at other sites.

7.5.4 Rate of administration

Undiluted antivenom administered intravenously over 10 minutes is as safe as diluted antivenom administered over 30 minutes (Warrell et al., 1985; Malasit et al., 1986). This is a cost-saving measure and also ensures that the doctor is at the bedside when anaphylaxis is most likely to occur. This was the case in the five Eshowe patients experiencing acute antivenom reactions (Table 8-1).

7.5.5   Repeated administration

A single adequate dose of $F(ab^1)_2$ antivenom is usually sufficient to halt further venom activity as shown by Brazilian equine $F(ab^1)_2$ antivenom, which was finally cleared from the circulation after 37 days (Theakston *et al.*, 1992). Uncommonly, recurring venom toxicity in the three clinical envenomation syndromes requires further administration of antivenom. The use of the newer Fab antivenom, due to its shorter half-life, is especially complicated by further venom absorption from the depot bite site, and it is suggested that a further three doses be scheduled 6 hourly (Dart & McNally, 2001).

7.5.6   Sensitivity testing

Skin or subconjunctival sensitivity tests have proved unreliable in predicting reactions to antivenom and other equine antisera (Parrish & Hayes, 1971; Black & Gunn, 1980; WHO, 1981). A test dose of snake antivenom, whether administered intradermally or into the conjuctival sac, did not predict early antivenom reactions to the main dose (Warrell *et al.*, 1985; Malasit *et al.*, 1986). Test results were also negative for five patients who developed late serum sickness type reactions (Malasit *et al.*, 1986). Seven patients with boomslang envenomation who had a coagulopathy were given a test injection (subcutaneous or intravenous) of specific monovalent antivenom. The results were negative, and six of the patients developed an acute reaction to the main dose. Two other patients with boomslang envenomation who were given polyvalent antivenom prior to specific antivenom did not develop an acute adverse reaction to the polyvalent antivenom. One of them was concomitantly given subcutaneous adrenaline. Both developed an acute reaction to the specific antivenom administered after the polyvalent antivenom (Table 8-4). Eshowe patients were not given a test dose.

7.5.7 Time limit to antivenom administration

Antivenom is of value only while the venom is still active and if indicated.

7.5.7.1 Painful progressive swelling syndrome

Patient E148, who sustained a bite on the foot, received 50 ml antivenom at eight hours when swelling had reached the inguinal ligament and there was no further swelling progression. Patients E300 and E318, both bitten on the hand, developed hot, tender and indurated swelling to the proximal arm, and received 40 ml and 50 ml antivenom at 12 and 35 hours respectively. In both cases further cool, soft, non-tender swelling occurred. It is postulated that the hot, tender, indurated swelling was venom induced, whereas the post-antivenom swelling was a reaction to distal venom-damaged tissue. The first patient sustained a clinically diagnosed puff adder bite, while the latter two were clinically diagnosed Mozambique spitting cobra victims. Venom is active in the PPS syndrome while swelling continues to extend, which may be as long a seven days.

7.5.7.2 Progressive weakness syndrome

Patients with progressive weakness who are placed on a ventilator can have respiratory failure for as long as seven days (Blaylock et al., 1985). Ventilation alone will return these patients to normality without the administration of antivenom. Patient E212, bitten by a black mamba, was ventilated at 3 h 25 min and received 60 ml antivenom five hours after the bite with ventilation being required for a further 30 minutes. Patient E259, who was dyspnoeic, received 90 ml antivenom at 5 h 30 min. Following this, intubation without ventilation was required for a further 5 h 30 min. A patient with a rinkhals bite (Table 12-5) was given 60 ml antivenom at 15 h, and showed dramatic improvement of

paresis two hours later. The period of ventilation can be reduced in the case of black mamba bites but not Cape cobra bites (12.5.7.3).

7.5.7.3 Bleeding syndrome

Late antivenom administration is of greatest value in the bleeding syndrome. Antivenom at 41 h in a puff adder bite stopped bleeding (Aitchison, Table 14-2). Monospecific antivenom at 5 and 5½ days reversed boomslang venom-induced coagulopathy (cases 1 and 3, Table 14-3). A snakebite patient in India who was admitted with active bleeding 8 days after the bite had no further bleeding after antivenom administration (Dwivedi *et al.*, 1989). The coagulation defect following Malayan pit viper bites persisted for 6 – 26 days (Reid *et al.*, 1963a), whilst hypofibrinogenaemia, prolonged PT, PTT and thromobocytopenia may be present in patients with pit viper bite up to 2 weeks following envenomation (Boyer *et al.*, 1999).

Algorithm 7–1

<div align="center">

SAIMR antivenom

$F(ab^1)_2$ derived from hyperimmune horses

Best manufactured from venoms from Southern Africa

Neutralises a set venom dose

Same dose regardless of patient size

Indicated for threat to limb or life

May be repeated

Best administered intravenously

Slow intravenous injection

No prior sensitivity testing

Efficacious while venom is active

Types

</div>

Polyvalent   **Monovalent**

Puff adder   Boomslang

Gaboon viper

Rinkhals

Cobra

Mamba
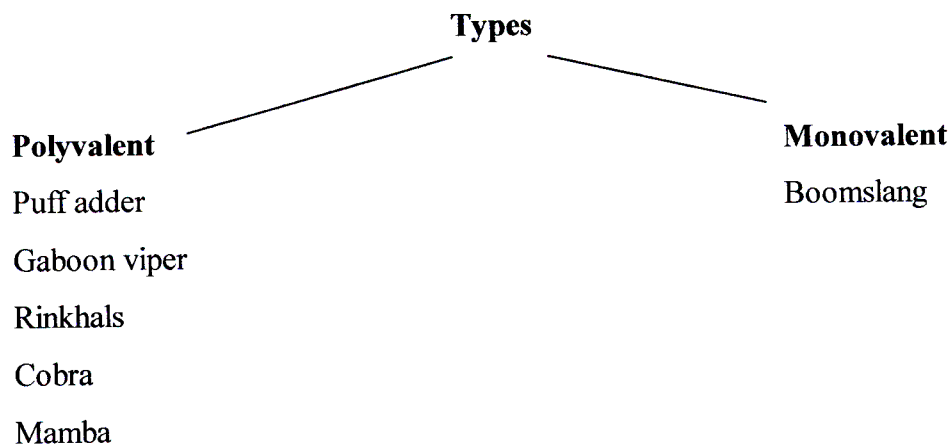
Cross-neutralisation of other venoms is unreliable.

It is not cost effective to manufacture against all snake venoms due to infrequent bites or low morbidity and mortality.

CHAPTER 8

ADVERSE REACTIONS TO SOUTH AFRICAN MANUFACTURED

SNAKEBITE ANTIVENOM

CONTENTS

8. ADVERSE REACTIONS TO SOUTH AFRICAN MANUFACTURED SNAKEBITE ANTIVENOM

8.1 Abstract

Objective: To assess the adverse reaction rate to South African manufactured snakebite antivenom.

Method: Adverse reactions to snakebite antivenom were analysed in 11 prospectively studied patients given antivenom at Eshowe hospital. A literature search for similar reactions to South African manufactured antivenom was undertaken.

Results: Acute adverse reactions to antivenom given for the clinical syndromes of progressive weakness (PW), painful progressive swelling (PPS) (with and without bleeding) and bleeding (boomslang-induced coagulopathy) occurred in 21%, 33% and 80% of patients respectively. The acute adverse reaction rates in patients with PW, pure PPS (without bleeding) and bleeding (active or potential, excluding boomslang-induced coagulopathy), were 21%, 56% and 60% respectively. Similar acute reactions for patients administered polyvalent or monovalent boomslang antivenom during the time periods of 10 h or less, 10 - 24 h, and greater than 24 h after the bite were 18%, 75% and 73%; and for polyvalent antivenom alone 18%, 75% and 40% respectively. The average volumes of antivenom administered for the clinical syndromes of PW, PPS and boomslang venom-induced bleeding were 98, 33 and 26 ml. No patient died of an antivenom reaction.

Conclusion: These reactions may be partly due to the acute phase patient response to envenomation and/or delay in antivenom administration. Acute adverse reactions to antivenom are common, unrelated to protein load, and may be prevented and treated with parenteral adrenaline. Late reactions are associated with increasing foreign protein load and may be prevented and treated with a course of glucocorticosteroids.

8.2   Introduction

Acute adverse reactions to antivenom include febrile, anaphylactic and anaphylactoid reactions, the latter two being clinically indistinguishable. Febrile reactions are caused by contained pyrogens, and are less frequent with modern refining processes. Anaphylactic reactions are IgE-mediated in persons with an allergic predisposition and usually require prior sensitisation. Anaphylactoid reactions are non-IgE-mediated and may be complement activated. C3a and C5a components degranulate mast cells with consequent release of pharmacologically active mediators. Sutherland (1977) reported that most commercial antivenoms are anticomplementary in vitro, but this was not shown in a study of 28 Thai patients (Malasit *et al.,* 1986). Anaphylactic and anaphylactoid reactions are caused by degranulation of mast cells and basophils mainly attached to mucosal surfaces (hyperaemia and secretion), skin (urticaria, tingling and pruritis), and smooth muscle (vasodilatation, bronchospasm and abdominal cramps), and result from production of histamine, prostaglandin D_2, leukotrienes, platelet activating factor, tryptase, chymase, heparin and chondroitin sulphate (Manjra 1994). Pugh & Theakston (1987b) found anaphylactic reactions to antivenom to be uncommon in Africa. An editorial in the Lancet (1976) suggested that allergic disorders should be uncommon in parasitised populations, as IgE can saturate mast cell surfaces. However, Puterman & Nurse (2001), found Ascaris-specific IgE levels to be significantly elevated in atopic children with severe and moderate asthma in comparison to age-matched controls.

Anaphylaxis in Britain is on the increase (Sheikh & Alves, 2000), as is asthma in the developed and developing world (MacIntyre *et al.,* 2001), which suggests that acute adverse reactions to antivenom could increase. Severe reactions are those that are

potentially life threatening and include acute severe dyspnoea, bronchospasm, hypotension and angioedema.

Early antivenom reactions are dependent on prior sensitisation of the individual, individual susceptibility, species protein, molecular protein size, the presence of molecular aggregates or their fragments (Theakston & Smith, 1997) and antivenom type (Cardosa *et al.*, 1993). Early antivenom complications in Brazil were associated with residence in a rural area, the latter thought to be due to more frequent contact with horses (Caiaffa *et al.*, 1994). Protein aggregates formed during fractionation may be responsible for complement activation independently of the presence of Fc fragments, and IgG has higher anticomplementary activity than $F(ab^1)_2$ (León *et al.*, 2001). It may be more important to remove aggregates than Fc fragments to obtain products with low anticomplementary activity (Otero *et al.*, 2001). $F(ab^1)_2$ preparations are frequently contaminated by aggregates and Fc components and even intact IgG molecules (Theakston, 1997). Fab antivenom may have a lower acute adverse reaction as it is a smaller protein (Dart & McNally, 2001).

Late reactions 5 – 24 days after antivenom administration (serum sickness) are manifested by fever, rash, urticaria, arthralgia, haematuria, lymphadenopathy and constitutional symptoms which persist for several days. Late reactions were considered to be due to the formation of circulating antigen-antibody complexes with deposition into tissues. It has been suggested that in situ formation of immune complexes occurs in some tissues, and that complement activation plays a part in the disease (Bielory *et al.*, 1988).

The object of this chapter is to assess the acute adverse reaction rate in Eshowe patients administered South African Institute for Medical Research (SAIMR) antivenom, conduct a literature search for other patients receiving similar antivenom and comment on late reactions.

8.3   Patients and methods

The records of this prospective trial of 333 Eshowe patients were analysed and a literature search conducted for patients receiving SAIMR antivenom. This excludes the herpetological literature, patients known to have received antivenom previously and cases where the clinical presentation is unknown. The time to antivenom administration if given in days, is calculated by subtracting 24 hours from the number of days. For example, day 3 would be assessed as 48 hours.

8.4 Results

8.4.1 Eshowe patients

Table 8 - 1   Eshowe patients administered SAIMR polyvalent antivenom

	Eshowe No.	Age (Years)	Indications for Antivenom	Dose		Time of antivenom administration after the bite	Acute adverse reaction
				Total	Increments		
No envenomation	E266	7	Prior to admission		10 ml	Prior to admission	Nil
Progressive weakness (no patient had significant swelling)	(1) E6	49	Respiratory failure	200	10 ml 90 ml 100 ml	5 h 5 h 30 min 20 h 10 min	Nil Nil Hypotension, puffy eyes
	(1) E87	14	Respiratory failure		100 ml	1 h 5 min	Nil
	(1) E212	3	Respiratory failure		60 ml	4 h 55 min	Rash
	(1) E259	9	Respiratory failure	100	10 ml 90 ml	5 h 5 hr30 min	Nil Nil
	E306	19	Ptosis		90 ml	2 h	Nil
Painful Progressive Swelling	(2) E122	6	Prior to admission		10 ml	Prior to admission	Nil
	(3) E148	12	Severe swelling		50 ml	8 h	Pruritis
	(3) E210	15	Gross swelling Coagulopathy		18 ml	10 h 55 min	Hypotension, bronchospasm
	E286	2	Severe swelling		50 ml	50 h	Nil. Transferred to major centre
	(2) E300	17mths	Severe swelling and dyspnoea		40 ml	12 h	Rash, tachycardia, bronchospasm
	(2) E318	11	Severe swelling and dyspnoea		50 ml	35 h	Nil

10 of 333 in-patients received SAIMR polyvalent antivenom intravenously as a slow intravenous injection without prior sensitivity testing. Nil: no acute adverse reaction.
Suspected snake from clinical presentation: (1) *Dendroaspis polylepis*, (2) *Naja mossambica*, (3) *Bitis arietans.* E212, 122, 318 were accompanied by the dead snake.

Life-threatening acute allergic reactions

1. A 49-year-old female (E6) with chronic obstructive airways disease with reversibility and congestive cardiac failure was bitten by a snake on her right knee, which became swollen and tender. She developed bronchospasm and respiratory failure, requiring intubation and ventilation. An intravenous injection of 100 ml of polyvalent antivenom was given.. Her condition improved and fourteen hours later ventilation was discontinued, with the endotracheal tube left in situ. Following poor respiratory effort, ventilation was recommenced and a further 100 ml of antivenom was given. This was followed by hypotension (systolic BP 60 mmHg) and puffy eyes which responded to 1 ml of adrenaline 1:1 000 intra-muscularly, and hydrocortisone and promethazine hydrochloride intravenously. The puffy eyes and hypotension may have represented an acute hypersensitivity reaction. She was finally extubated 21 hours later.

2. A 15-year-old youth (E210) was admitted 15 hours after sustaining a snake bite to his ankle. His leg was tensely swollen, multiple bullae were present and the swelling extended to his chest wall. He was anaemic (Hb, 3g/dl), and thrombocytopenic (platelets 127 x 10^9/litre), with no detectable fibrinogen. Vigorous intravenous resuscitation was required. Eighteen millilitres of polyvalent antivenom was given at 18 hours. He became hypotensive, tachycardic (170/minute) and desaturated. Reversal was eventually achieved with 3 ml of adrenaline 1:1 000 and 100 mg of hydrocortisone over several minutes. A four-compartment below knee-fasciotomy and thigh fasciotomy, including the inguinal ligament, restored the blood flow to what had been a pulseless leg. The

anterior tibial and peroneal compartments necrosed and he subsequently recovered.

3.   A 17-month-old boy (E300) was bitten twice on a hand whilst asleep. That day he developed a hot, tender indurated swelling involving the whole arm and he became dyspnoeic. Forty millilitres of polyvalent antivenom was administered at 12 hours. After the third ampoule (10 ml) of antivenom, he developed a rash. After the fourth, his pulse was 122/min and there was bronchospasm. He was treated with fenoterol nebulisations, hydrocortisone and promethazine. Necrosis of both bite sites occurred, without permanent morbidity.

Non-life-threatening acute allergic reaction

1.   E142, a 12-year-old girl bitten on a calf, developed swelling of the whole leg 8 h after the bite.   Fifty millilitres of polyvalent antivenom was administered intravenously, soon followed by widespread pruritis which responded to promethazine.

2.   A-three-year-old male (E212) was bitten by a 60-cm black mamba. He was ventilated for respiratory failure and developed a widespread papular rash after 60 ml of polyvalent antivenom was administered intravenously. It rapidly improved with 0,5 ml 1:1 000 adrenaline administered by slow intravenous injection.

8.4.2   Literature search   Tables 8-2 to 8-4

Table 8-2   Acute adverse reactions to South African manufactured antivenom administered to patients with progressive weakness (herpetological literature excluded)

Author	Indication	Dose Total	Dose Increments	Time of administration after the bite	Acute adverse reaction
+ Louw 1967 1.	Dyspnoea		40 ml	4 h	Nil
2.	Nil		10 ml	1 h	Nil
	Dyspnoea	50	40 ml	4 h	Nil
* Strover 1967	?		20 ml		Nil Died 4 h 30 min
* Krengel 1967	Mamba bite		70 ml	< 7 h	Nil
		150	80 ml	± 9 h	Nil
+ Edington, 1973	Dyspnoea		20 ml	< 1 h	Nil
	Respiratory failure		50 ml	1 h	Nil
	Respiratory failure		100 ml	< 3 h 30 min	Nil
	Respiratory failure	270	100 ml	6 h 30 min	Nil
+ Visser & Chapman, 1978 Case 9	Nil		10 ml	25 min	Nil
	Respiratory rate 40/min		10 ml	1 h	Nil
	Laboured breathing		10 ml	2 h 25 min	Nil
	Deterioration	40	10 ml	6 h	Nil
+ Blaylock, 1982a 1.	Dyspnoea		20 ml	2 h	Nil
		60	40 ml	10 h	Nil
2.	Moribund		20 ml	1 h	Nil Died 2 h 20 min
3.	Moribund		10 ml	Same day	Nil
		110	100 ml	Same day	Nil
4.	Collapsed		60 ml	2 h 12 min	Nil
	Collapsed	100	40 ml	2 h 25 min	Nil
5.	Moribund		100 ml	3 h 30 min	Nil
6.	Dyspnoea		60 ml	2 h 15 min	Nil
Blaylock et al., 1985 1.	"Drunk"		10 ml	1 h	Nil
	Flaccid paralysis		90 ml	7 h	Nil
	Flaccid paralysis	190	90 ml	17 h	Nil
2.	?		40 ml	2 h	Nil
	Flaccid paralysis		40 ml	4 h 30 min	Nil
	Flaccid paralysis		60 ml	11 h 30 min	Nil
	Flaccid paralysis	180	40 ml	Day 5	Rigors, tachycardia
* Crisp, 1985	Moribund		40 ml	1 h 55 min	Nil
+ Naidoo et al 1987	Dyspnoea		80 ml	2 h 30 min	Nil
* Hilligan, 1987 1.	Moribund		70 ml	± 1 h	Nil
2.	Dizzy Sweating		70 ml	< 1 h	Pruritis of arm
Oberholzer et al., 1991	Respiratory failure		40 ml	6 h 15 min	Nil
		60	20 ml	9 h 15 min	Nil
* Blaylock & Canter, in Blaylock, 2000	Respiratory failure		90 ml	25 min – 45 min	Nil
Moran, et al., 1998	?		40 ml	?	Hypotension, urticaria, swollen tongue

* *Dendroaspis polylepis* bites.   + Suspected *D. polylepis* bites

Table 8-3   Acute adverse reactions to South African manufactured antivenom administered to patients with painful progressive swelling (herpetological literature excluded)

Antivenom				
Author	**Indication**	**Dose**	**Time of administration after the bite**	**Acute adverse reaction**
Tilbury, 1982 8 cases (Mozambique spitting cobra)	Swelling	55 – 100 ml (735 ml)	?	Generalised urticaria in 2
Warrell, *et al.*, 1976a 4 cases (Black-necked spitting cobra)	Swelling	40 ml	?	Mild hypersensitivity reaction in 3
Warrell *et al.*, 1975 2 cases (Puff adder)	Swelling	Both 40 ml Behringwerke in one	?	Nil
Warrell *et al.*, 1977 48 cases (Carpet viper)	Bleeding but associated with swelling	10 – 50 ml (890ml)	?	Mild reaction in 14 Hypotension in ?3
Moran *et al.*, 1998 16 cases	Swelling or bleeding	1 – 60 ml	?	Urticaria in 11 including hypotension in 1, bronchospasm in 1, periorbital swelling in 2. Hypotension alone 1 Bronchospasm alone 1
Strover, 1973 1.	Swelling	50 ml	?	Nil
2. *Naja mossambica*	Swelling	40 ml	?	Acute reaction
Edwards *et al.*, 1979 (Gaboon adder)	Minor neurotoxicity, falling consciousness level, cardiotoxicity	120 ml	1 h – 1 h 30 min	Rigors, subglottal oedema, urticaria, bronchospasm
McNally *et al.*, 1993 (Gaboon adder)	Dyspnoea Swelling	100 ml 100 ml	< 1 h Day 4	Nil Rigors
Aitchison (unpublished) (puff adder)	Bleeding	40 ml	41 h	Hypotension
Blaylock, 2000 Case 7 (puff adder)	Bleeding	10 ml 10 ml	2 h 3 h 30 min	Nil Nil

Table 8-4   Acute adverse reactions to South African manufactured monospecific antivenom administered for boomslang venom-induced coagulopathy (herpetological literature excluded)

Author	Test dose	Main dose	Time of administration after bite	Acute adverse reaction
Lakier & Fritz, 1969	No reaction	10 ml 30 ml	> 31 h ± 32 – 44 h	Rigors, severe dyspnoea Nil
Mackay *et al.*, 1969	? Performed	30 ml	Day 4	Nil
Nicolson *et al.*, 1974	No reaction	40 ml	Day 5	Rigors, hypotension
Gerber & Adendorff, 1980	10 ml polyvalent No reaction	?	32 h	Dyspnoea, central cyanosis and hypotension
Du Toit, 1980	60ml polyvalent and adrenaline 1ml 1 : 1000 subcutaneously No reaction	20 ml	86 h	Dyspnoeic, highly febrile
Geddes & Thomas, 1985	No reaction	20 ml 10 ml	30 h 45 min 38 h	Rigors, pyrexia (40^{0}C) Nil
Aitchison, 1990 Case 1	No reaction	20 ml	48 – 51 h	Nil
Case 2	No reaction	10 ml	48 h	Urticaria, hypotension and bradycardia
Blaylock, 2000 Case 1	10 ml polyvalent No reaction Monospecific antivenom No reaction	20 ml 10 ml	21 h 26 h	No reaction Rigors, hypotension
Case 2	? performed	10 ml	Day 3	Tachycardia and hypotension

8.4.3 Combined results (Eshowe patients and literature search, Tables 8-1 to 8-4)

Key to Tables 8-5 to 8-8 :

( ) = no. of patients.

Percentages are taken to the nearest whole number.

Excludes two patients who died of progressive weakness and not anaphylaxis.

* Excludes patients reported by Warrell *et al.* (1976a) as it is uncertain how many had acute severe allergic reactions to South African antivenom. Patients who developed diarrhoea, vomiting or abdominal pain after antivenom administration are excluded, as these symptoms are non-specific and could be venom induced. If published papers give the time of antivenom administration in days, 24 h are subtracted, e.g. day 3 is assessed as 48 h.   Acute severe reactions are defined as acute severe dyspnoea, bronchospasm, hypotension or significant angioedema of the head and neck and are included in acute adverse reactions and analysed separately.

Table   8-5 Acute adverse reactions to SAIMR antivenom and envenomation syndromes.

	Syndromes of envenomation		
	Progressive weakness (PW) PVA	Painful progressive swelling (PPS) PVA	Boomslang-induced coagulopathy MVA
Mean volume antivenom	98 ml (24)	33 ml (88)	26 ml (9)
Acute adverse reactions	21% (5 of 24)	33% (29 of 89)	80% (8 of 10)
Acute severe allergic reactions*	8 % (2 of 24)	20 % (8 of 41)	70 % (7 of 10)
Mean time period from the bite to final antivenom administration	<10 h (22)	27 h (9)	54 h (10)
PW and PPS denote the dominant clinical presentation. PVA: polyvalent antivenom. MVA: monovalent boomslang antivenom.			

Table 8–6   Acute adverse reactions to SAIMR polyvalent antivenom and the envenomation outcomes of progressive weakness, pure painful progressive swelling and bleeding (active or potential). Monospecific boomslang antivenom excluded.

	Outcome of envenomation		
	Progressive weakness	Pure painful progressive swelling	Bleeding active or potential from puff adder, Gaboon adder, Nigerian *Naja nigricollis*, or carpet viper bites. Excludes boomslang bites
Mean volume antivenom (ml)	98 (24)	51 (25)	25 (63)
Acute adverse reactions	21% (5 of 24)	56% (14 of 25)	60% (25 of 42)
Acute severe allergic reactions *	8% (2 of 24)	16% (4 of 25)	33% (4 of 12)

Table 8–7   Acute adverse reactions to SAIMR polyvalent and monovalent boomslang antivenom versus time to final antivenom administration after the bite.

	Time to final antivenom administration after the bite		
	0 – 10 h	> 10 – 24 h	> 24 h
Acute adverse reactions	18% (4 of 22)	75% (3 of 4)	73% (11 of 15)
Acute severe allergic reactions*	5% (1 of 22)	75% (3 of 4)	53% (8 of 15)
*Possibly misleading in view of small patient numbers			

Table 8–8 Acute adverse reactions to SAIMR polyvalent antivenom and time to final antivenom administration after the bite (monovalent boomslang antivenom excluded).

	Time to final antivenom administration after the bite		
	0 – 10 h	> 10 – 24 h	< 24 h
Acute adverse reactions	18% (4 of 22)	75% (3 of 4)	40% (2 of 5)
Acute severe allergic reactions*	5% (1 of 22)	75% (3 of 4)	20% (1 of 5)
*Possibly misleading in view of small patient numbers			

8.5 Discussion

8.5.1 Acute adverse reactions

The drawbacks to this survey are that it is mostly retrospective, batches of antivenom vary, boomslang antivenom passes through the freeze-drying process, patients have not been categorised according to race or age, times to final antivenom administration are approximate in some cases, and antivenoms are not tested for the absence of bacterial endotoxins (febrile reactions). These adverse reactions may be caused by other agents given concomitantly with, or prior to, antivenom (e.g. antibiotics). This was not the case in Eshowe, except for patient E6 (asthmatic) where bronchodilators were administered. Despite these criticisms the results are too significant to ignore. That anaphylaxis (excluding febrile reactions) is implicated and not envenomation, is suggested by prompt response to adrenegics, corticosteroids or antihistaminics given singly or in combination.

Acute adverse reaction rates to antivenom in South Africa range from < 1% (Visser & Chapman, 1978) to 76% (Moran *et al.*, 1998). Acute adverse reactions to equine $F(ab^1)_2$ snake antivenom is common in other countries: 57% in Papua New Guinea (Brian & Vince, 1987), 37 – 87% in Brazil (Cardoso *et al.*, 1993), 23 – 56% in North America (Dart & McNally, 2001), 4,6 – 10% in Australia attributed to the use of premedication including parenteral adrenaline (Sutherland, 1992), and less than 1% in Taiwan (Chen *et al.*, 2000). The incidence is critically dependent on the quality of clinical observations in the early hours after antivenom administration.

Red-back spider venom stimulates the release of catecholamines, which may help protect against immediate anaphylaxis (Sutherland, 1992), and children with venom-induced adrenergic manifestations of envenomation after *Tityus serrulatus* scorpion sting are

protected from early anaphylactic antivenom reactions (Amaral, 1994). Clinical adrenergic manifestations due to Southern African snakebite does not obviously occur.

The same polyvalent antivenom is used for patients with progressive weakness (PW) and painful progressive swelling (PPS). Monospecific boomslang antivenom is manufactured in a similar way by the same company.

8.5.1.1 Clinical envenomation syndromes

The acute adverse and acute severe allergic reaction rates to administered antivenom in this limited number of patients increased exponentially for PW, PPS with or without bleeding, and for boomslang-induced coagulopathy (Table 8-5) as well as for SAIMR polyvalent antivenom (Table 8-6). The dominant clinical presentation of PW is induced by the bites of the mambas (most common) and the non-spitting cobras, whilst PPS occurs following bites by the spitting cobras, puff adder, stiletto snake and night adders. Coagulopathy is possible in bites by the puff adder, Gaboon adder, Nigerian black-necked spitting cobra and the carpet viper, whilst it is the dominant presentation of vine snake and boomslang bites. It can be anticipated that hypotension due to anaphylaxis would readily occur in patients with compensated oligaemic shock due to PPS.

The disparity in acute allergic reactions to antivenom in the three clinical syndromes cannot be due to antivenom alone, as the rates of reaction would be the same in the three syndromes. Clearly there must be a contribution by venom, or the venom-induced patient acute phase response.

8.5.1.2 Specific snake bites

Attempts to subset the acute reaction rates to different envenomation syndromes and different snake species have not been made. Barraviera (1994) in Brazil noted that acute reaction rates to antivenom administered for *Crotalus durrisus terrificus* and *Bothrops* spp are 8,3% and 12,5% respectively, with neurotoxicity predominating in the former and PPS and a coagulopathy being common in the latter. Where the identity of the snake is proven or suspected (Tables 8-1 to 8-4), three of 19 (16%) black mamba, four of 12 (33%) Mozambique spitting cobra, three of six (50%) puff adder, both Gaboon adder and eight of 10 (80%) boomslang bite patients developed an acute adverse antivenom reaction.

8.5.1.3 Time to antivenom administration after the bite

Neither have attempts been made to correlate acute adverse reactions with delay in antivenom administration. The state where the life or limb of a patient is threatened, which is an indication for antivenom, would be expected to be reached soonest in bites producing PW, followed by PPS and lastly, by boomslang venom-induced bleeding, which is slower in onset. This is supported by the present analysis (Table 8-5). It is noteworthy that the only two patients with progressive weakness who developed a severe reaction (hypotension) did so on repeat antivenom administration at 20 hours and day 5 respectively (Tables 8-1 and 8-2).

If acute adverse reactions are analysed according to the time of final antivenom (polyvalent with and without monovalent) administration after the bite in the three periods of less than 10 h, 10 to 24 h, and greater than 24 h, then the reactions occur disproportionately less during the first period (Tables 8-7 and 8-8). The fact that there are

fewer adverse reactions if antivenom is administered within 10 h of the bite is perhaps due to the majority of patients with progressive weakness warranting antivenom administration during this time period.

8.5.1.4 Protein load

Tables 8-5 and 8-6 show that the protein load for antivenom is inversely proportional to the acute adverse reaction rates in the three clinical syndromes due to different dose recommendations and the cessation of antivenom administration when an acute reaction occurs.

8.5.1.5 Possible aetiology

Hypogammaglobulinaemic patients appear more susceptible to homologous serum reactions, thought to be due to a less efficient reticulo-endothelial system (RES) removing IgG aggregates (Malasit *et al.*, 1986). In view of this, it may be that the syndromes of PPS and bleeding disrupt the functioning of the RES to a greater extent than that of PW, and/or the greater the interval from envenomation to antivenom administration, the greater the disruption.

8.5.1.6 Prophylaxis

In this survey no patient died as a result of an antivenom reaction, and administration of antivenom should not be discouraged. Slow intravenous injection is as safe as a slow infusion (Malasit *et al.*, 1986), and ensures that the doctor is at the bedside when an acute

reaction would be expected to occur. Promethazine prophylaxis by intramuscular injection 15 - 20 minutes before starting intravenous antivenom infusion did not reduce the acute anaphylactic rate (25%) in Brazilian patients bitten by *Bothrops* snakes (Fan *et al.*, 1999). Premedication with adrenaline is suggested for all Australian snakebite patients receiving antivenom (Sutherland, 1991; 1992; Munro Ford, 1992; Tibballs, 1994). In Sri Lanka, adrenaline premedication significantly reduced the rate of acute adverse reactions to antivenom (from 43% to 11%) at a dose of 0,25 ml 1:1 000 subcutaneously and was shown to be safe (Premawardhena *et al.*, 1999). It is suggested that this regimen be followed prior to antivenom administration in Southern Africa if the patient has a history of allergy, has experienced previous antivenom reactions or has reacted earlier to other horse serum-based products; if antivenom is administered for boomslang venom induced coagulopathy, there is swelling of a whole limb, or more than 10 hours have elapsed after the bite. Adrenaline should at least be kept ready at the bedside.

8.5.2 Delayed reactions

Delayed reactions to antivenom were not prospectively evaluated in Eshowe patients and may have remained undiagnosed. Serum sickness occurred significantly more frequently in patients who received more than 40 ml of Botulinal antitoxin (Black & Gunn, 1980). Corrigan *et al.*, (1978) noted that 75% of patients receiving three of more vials of Wyeth ACP F(ab[1])$_2$ snakebite antivenom developed serum sickness, while Jurkovich *et al.*, (1988) put this figure at 83% if eight or more vials were used.

Late reactions to heterologous protein are associated with an immune response (Warrell, 1995). IgG induces a higher immunoglobulin response in mice in comparison to F(ab[1])$_2$

by virtue of its Fc, which provides a larger antigenic surface for recognition and interaction (Léon *et al.,* 2001). The overall rate of serum sickness after the administration of the smaller molecule Fab AV *(Crotalidae)* was 16% in 42 patients, or 3% when adjusted for purity of product (Dart & McNally, 2001). There is convincing evidence that serum sickness caused by the administration of antivenom is related to complement activation by immune complexes (aggregates) - there is a possibility that the patient's ability to filter out IgG aggregates by the reticulo-endothelial system may determine complement activation (Malasit et *al.,* 1986). A course of glucocorticosteroids (Jurkovich *et al.,* 1988; Sutherland, 1992) may be used to prevent and treat late reactions.

In Southern African consideration should be given to the prevention of delayed reactions if ten vials (100 ml) or more of antivenom are administered.

8.6 Remedial actions to diminish acute and late reactions to antivenom

Remedial actions to diminish acute and late reactions to antivenom include the use of sheep or other animals instead of horses which contain IgG(T) antibodies responsible for some sensitivity reactions (Theakston & Smith, 1997), improved purification of antivenom by fractionation using other salts (caprylic acid) (Rojas *et al.,* 1994; Otero, *et al.,* 2001), the use of affinity columns with absorbed venom to retain specific antibodies only (Russell *et al.,* 1985; Theakston, 1997), the use of smaller molecules such as Fab or FV, (Theakston & Smith, 1997), the use of smaller but effective amounts of antivenom and the use of monoclonal antibodies for venoms containing one or two dominant toxins (Theakston, 1989). Premedication with intramuscular adrenaline to prevent acute reactions is indicated, as is the use of corticosteroids as prophylaxis for late reactions when large amounts of antivenom are used.

Algorithm 8–1

Acute adverse reactions to South African manufactured snakebite antivenom

	Acute (anaphylaxis)	Chronic (serum sickness)
Term:	Acute (anaphylaxis)	Chronic (serum sickness)
Reaction :	Anaphylactic or anaphylactoid	Immune complex disease

Symptoms: Mild:
Pyrexia
Rash
Urticaria

Fever
Urticaria
Polylymphadenopathy
Polyarthritis
Haematuria

Severe: Acute severe dyspnoea
Hypotension
Bronchospasm
Angioedema head
and neck

Protein load (antivenom)

Low

High

Incidence according to indication

Bleeding, PPS, PW
decreasing ⟶

Incidence according to time of administration

Early   Late
? increasing ⟶

Prevention : Adrenaline premedication

Glucocorticosteroid course

Indications for premedication

Atopic individuals
Horse serum previously administered
Previous acute reaction
Swelling of a whole limb
More than 10 hours elapsed since the bite
Boomslang antivenom is administered

Atopic individuals
Large amount of antivenom administered
(100ml or more)

Treatment :
Adrenaline
Beta agonists
Glucocorticosteroids
Antihistamines

Glucocorticosteroids

Decreasing efficacy

SECTION IV

THE CLINICAL SYNDROMES OF ENVENOMATION

IV.   THE CLINICAL SYNDROMES OF ENVENOMATION

Preamble

Snakebite in humans presents as a combination of minor trauma at the bite site, a fearful or hysterical reaction, a venom-induced acute allergic reaction in atopic individuals, or most commonly as an envenomation syndrome.

Hysterical reactions are uncommon but have been reported (Adogu *et al.*, 1992). Severe fang- or teeth-induced trauma may occur from the bites of large pythons (Rossouw & Bos, 1989).

Anaphylaxis to snake venom uncommonly occurs in people previously exposed to venom (Blaylock, 2000). Previous exposure may be due to a bite, skin contact, or inhalation. Of 12 patients, seven developed an early life-threatening reaction, and three of these died. Hypotension, acute dyspnoea, bronchospasm, angioedema, nasal congestion, hyperaemic conjunctiva with epiphora, or an urticarial rash may develop. Similar acute hypersensitivity reactions to snake venom have been reported in the USA (Ellis & Smith, 1965; Hogan & Dire, 1990), Australia (Kirkland, 1990), Europe (Schmutz & Stahel, 1985; Kopp *et al.*, 1993) and the Middle East (Chajek *et al.*, 1974). Treatment is aimed at adequate oxygenation and tissue perfusion. Adrenaline is the drug of choice with its alpha, beta 1 and beta 2 activity. Adrenaline in aqueous solution is administered intramuscularly (0,3 – 0,5 ml of 1:1000 dilution in adults). Additional doses as necessary may be given if shock persists and it is important to individualise treatment for each patient. Histamine 1 receptor antagonists (e.g. diphenhydramine by IVI slowly IMI or orally) at a dose of 1 mg/kg up to 50 mg repeated six hourly for 48 hours is advantageous due to high circulating levels of

histamine. Cimetidine, an H_2 antagonist, was found to be as effective as diphenhydramine but less sedative in the treatment of acute urticaria (Moscati & Moore, 1990). Steroids do not play a major role in the management of acute conditions, but should be started early to prevent relapse and the progression of bronchospasm. The latter may be preferentially treated with inhaled beta 2 agonists.

An analysis of four rural snakebite series from eastern South Africa and Zimbabwe showed that envenomation involved 84% of patients presenting at hospital. Of envenomed patients, 92% presented with painful progressive swelling (PPS), 7% with progressive weakness (PW), less than 1% with bleeding (B) and 1% with unclassifiable conditions. All venomous snakebite patients are encompassed by these syndromes, unless minimal envenomation is present. PPS, PW and bleeding are caused by cytotoxic, neurotoxic and haemotoxic venoms respectively. The syndromes are not nationally or internationally recognised, but are practical as they allow syndromic management of snakebite. Potentially lethal bites were most common above ankle level in standing victims as large adders (vipers) and elapids most commonly strike here.

The time of onset of clinical envenomation, should significant envenomation (limb or life threatening) eventually occur, is within one hour of the bite (Blaylock, 1983). It requires a physician experienced in snakebite to diagnose early envenomation and good communication with the patient. If there is any doubt, it is recommended that patients be observed for several hours, which generally means overnight (Blaylock, 2000).

Snakebite severity classification and scores

Van Mierop (1976) and Russell (1980) in the USA developed envenomation severity classifications, largely clinically based, for pit viper *(Crotaline)* envenomation. These classifications indicated minimal, moderate, severe or very severe envenomation and were devised as a guide to antivenom treatment. Dart *et al.* (1996) developed a scoring system based on abnormalities of the local (bite site) wound, the lungs and the cardiovascular, gastrointestinal, haematological and central nervous systems, which provided an objective instrument for evaluation of the severity and progression of envenomation in patients with *Crotaline* snakebite. This system is of academic value in evaluating different forms of treatment and outcome. The Southern African situation is more complicated as this region has a variety of venomous snakes species that produce the pure clinical syndromes of PPS (spitting cobras, night adders, stiletto snakes), PW (mambas), and bleeding (boomslang and vine snakes). Other bites produce mixed clinical syndromes of PPS and PW (berg adder, rinkhals, non-spitting cobras), PPS and B (puff adder) or all three syndromes (PPS, B and PW), for example the Gaboon adder.

An academic classification of swelling for the painful progressive swelling syndrome (Blaylock 2000, glossary) was of value when it came to statistical analysis but was of little practical value when it came to treatment. Pragmatic treatment requires simple guidelines and not complicated snakebite severity scores. This section includes separate chapters for each clinical syndrome and for surgery of both local (bite site) and regional complications.

CHAPTER 9

PAINFUL PROGRESSIVE SWELLING SYNDROME

CONTENTS

9.   Painful progressive swelling syndrome

9.1   Abstract

Objective: To suggest management strategies for patients with venom-induced painful progressive swelling.

Method: The treatment outcome of prospectively studied Eshowe and other patients was analysed.

Results: The rate of swelling progression and eventual swelling extent are directly related to intravenous fluid requirements. Powerful analgesics are required most commonly within the first 24 hours of admission, for fast advancing swelling, and for patients developing bite site complications. A dose of 50 ml antivenom is adequate except for Gaboon adder bites where 200 ml is more appropriate.

Conclusion: Intravenous fluid in moderate to severe envenomation is life saving. Elevation of a bitten limb helps restore normal circulation and reduce pain. Analgesics are administered as required and antivenom is reserved for severe envenomation present or anticipated.

9.2   Introduction

Painful progressive swelling (PPS) is defined as swelling spreading from the bite site mainly in a proximal direction and is characterised by warmth, pain, tenderness and induration. The degree of PPS is dependent on venom type.. The rate of progression of swelling and its eventual extent (without antivenom administration) gives an indication of the severity of envenomation.

The swelling severity in a snakebite patient determines the period of illness, the development of complications, namely pyrexia (presence, duration and peak), hypovolaemia, anaemia, hypoalbuminaemia, coagulopathy, pulmonary abnormalities (when swelling involves the chest wall or in Gaboon adder bites), bite site complications, and possible death. Bite site complications (BSCs) are defined as bite site blistering, haematoma, abscess or necrosis, whereas compartment and entrapment syndromes are regional complications.

The swelling classification (see glossary) assumes that patients were bitten on an ankle, foot, wrist, hand or fingers and toes, which is true in 80% of cases. Should the bite site be elsewhere, the swelling extent can be estimated and categorised. The classification is important for comparing patient outcome, and comprises minimal, mild, moderate, severe and gross swelling.

Snakes most commonly responsible for PPS include the puff adder *(Bitis arietans)*, spitting cobras *(Naja mossambica, Naja nigricollis)*, stiletto snake *(Atractaspis spp)*, night adders *(Causus spp)*, horned adders *(Bitis caudalis, Bitis schneideri)*, lowland viper *(Proatheris superciliaris)*, Angolan adder (*Bitis heraldica)* and plain mountain adder *(Bitis inornata)*.

Combined painful progressive swelling (PPS) and progressive weakness (PW) occurs from bites by the non-spitting cobras *(Naja annulifera, Naja nivea, Naja melanoleuca)*, the berg adder *(Bitis atropos)*, the shield-nosed snake *(Aspidelaps*

spp.), garter snakes *(Elapsoidea spp)*, the desert mountain adder *(Bitis xeropaga)* and Peringuey's adder *(Bitis peringueyi)*.

Gaboon adder *(Bitis gabonica)* bites are manifest by PPS, PW and bleeding. Bleeding may also occur in puff adder bites (thrombocytopenia) and black-necked spitting cobra bites (platelet defect), the latter noted in Nigeria (Warrell *et al.*, 1976a) but not in Southern Africa.

The above summary is from Blaylock, 2000.

9.3   Material and methods

The prospective Eshowe series of 333 recently bitten patients are analysed for outcome and the administration of intravenous fluids, analgesics and antivenom.

The results are given in each section.

A summary of the Eshowe patients under discussion is given in Table 9-1.

Table 9-1 Summary of painful progressive swelling severity, hospital stay and complications. 282 patients

	SWELLING SEVERITY				
	Minimal	**Mild**	**Moderate**	**Severe**	**Gross**
Number of patients	27	101	131	15	8
Bite site complications no.	0	10	21	7	4
Compartment syndrome	0	0	1	0	3
Systemic illness . no. (Mortality concern)	0	0	2	4	7
Blood transfusion . no.	0	0	3	2	5
Blood given within 48-hours (if required) no.	0	0	0	1	5
Thrombocytopenia no.	0	0	0	1	3
Number given antivenom	0	0	1	3	2
Mortality no.	0	0	0	0	1
Discharge day (mean)	3,9	4,3	9,3	10,9	39
Mean age (years)	21,1	18,4	20	10,6	12,9
Swelling severity versus	**Chi-squared test for trend**		**Degrees of freedom**		**P**
Bite site complications	21,566		1		<0,0001
Systemic illness (combined minimal and mild)	81,078		1		<0,0001
Blood transfusion (combined minimal and mild)	49,208		1		<0,0001

Systemically ill means hypovolaemic shock, significant anaemia and/or thrombocytopenia, unexplained dyspnoea or tachycardia. Bite site complications means necrosis (most common), abscess, deep haematoma or local blisters. Three patients who sustained double bites with necrosis at each bite site are regarded as having a single area of necrosis in this Table.

9.4 Intravenous fluids

9.4.1 Introduction

Swelling due to the painful progressive swelling syndrome has its origin in acute inflammation caused by the toxic components phospholipase A_2 enzymes (Harris, 1991; Lomonte *et al.*, 1994), zinc metalloproteinases (Gutiérrez & Rucavado, 2000), L-amino acid oxidases (Du & Clemetson, 2002) and other cytotoxins. Venom metalloproteinases activate endogenous matrix metalloproteinases and release tumour necrosis factor alpha. Resulting holes in and between endothelial cells allow extravasation of serum, protein and blood cells depending on hole diameter (Gutiérrez & Rucavado, 2000).

It has been pointed out (Blaylock, 2000) that puff adder bites are mainly responsible for gross swelling, early anaemia and thrombocytopenia, with swelling extending up a bitten limb at a rate of 10 - 15 cm per hour or faster. The rate of swelling extension in Mozambique spitting cobra and stiletto snake bites is slower at 1 - 2 cm per hour. In the former case swelling extension is too fast for the body to naturally compensate and acute hypovolaemia results. In the latter case the body compensates more easily.

Fitzsimons (1912) does not mention the use of intravenous infusions in snakebite, while in 1929 he describes the intravenous use of "physiological salt solution", which comprised 80 grains of common salt dissolved in a pint of boiled water. Chapman (1968) considered that eight of nine deaths from unproven puff adder bites were due to "decompensated oligaemic shock caused by the rapid and massive loss of blood". "All except one with severe local swelling had rapidly expanding extravasation of fluid, which extended well proximal to the involved limb in two." More recently,

most authors have advocated intravenous fluids in the management of snakebite but do not emphasise its importance (Visser & Chapman, 1978; Blaylock, 1982b; Coetzer & Tilbury, 1982; White, 1984; Kasilo & Nhachi, 1993; Yerzingatsian, 1997).

9.4.2 Results   Tables 9-2 and 9-3

Table 9-2   Eshowe patients with eventual gross swelling and intravenous fluids administered within 24 hours of admission

Eshowe Number	12	39	58	210	300
Age (years)	6	11	25	15	1.5
Swelling severity on admission	Moderate	Moderate Hb 5,6 g/dl	Moderate	Gross Hb 3,3 g/dl	Moderate
Hypotension on admission	No	Yes	Yes	Yes	No
Crystalloid	5 900 ml	3 900 ml	5 200 ml	9 000 ml	1 250 ml
4% albumin			1 200 ml	1 000 ml	
Freeze-dried plasma		2 500 ml		1 250 ml	
Packed red cells		1 050 ml		2 450 ml	
Dextran 40			200 ml	500 ml	
Mannitol 20%				1 000 ml	
Total volume of intravenous fluids	5 900 ml	7 450 ml	6 600 ml	1 520 ml	1 250 ml
Antivenom	No	No	No	18 ml anaphylaxis	40 ml
Outcome	No morbidity	Fasciotomy Died day 4 Hb 2 gm/dl Platelets 17 x 10^9/L	Local blisters	Fasciotomy Necrosis	Local necrosis

All eight patients required intravenous fluid resuscitation but records for patients E48, E60 and E169 are missing. Patient E39 died.

Table 9-3   Eshowe patients with eventual severe swelling and intravenous fluids administered within 24 hours of admission

Eshowe Number	54	148	205	256	318
Age	19	12	5	19 months	11
Swelling severity on admission	Moderate	Moderate	Moderate	Severe	Mild
Hypotension on admission	No	No	No	No	No
Crystalloid	4 000 ml	3 000 ml	2 000 ml	500 ml	600 ml
4% albumin		400 ml			
Total volume of intravenous fluids	4 000 ml	3 400 ml	2 000 ml	500 ml	600 ml
Antivenom	No	50 ml at 8 hours	No	No	50 ml at 35 hours
Outcome	Local blister	No morbidity	No morbidity	Local blister	Local necrosis

No intravenous fluids were given to six of 13 patients (E147, 174, 182, 247, 264, 272). No patient died. Patients E63 and E286 received an unknown volume of intravenous fluid. The records of patients E97 and D153 are missing.

9.4.3   Discussion

The eight cases with eventual gross swelling required intravenous fluids as did six of 13 cases with eventual severe swelling. A large percentage of 131 patients with moderate swelling did not require intravenous fluids. A further three cases who eventually developed gross swelling were hypotensive on admission, whereas no patient with severe swelling and only one with moderate (E166) swelling was hypotensive. Four patients developed decompensated hypovolaemia after hospitalisation. A 6-year-old (E12), who eventually developed gross swelling,

became hypovolaemic 18 hours after admission despite 3 litres of crystalloid, while another three patients with moderate swelling became hypovolaemic 24 hours after admission having not received intravenous fluids. Patient (E152), with moderate swelling, was dyspnoeic due to fluid overload.

Blood transfusion within 24 hours of admission was given to two patients with eventual gross swelling whose levels of haemoglobin on admission were 5,6 and 3,3 g/dl (E39, E210).

Albumin or freeze-dried plasma was given to three of eight patients, one of 15 and none of 131 patients with eventual gross, severe and moderate swelling respectively.

Platelet concentrates were not available at Eshowe Hospital and patient E39 died on day 4 following a fasciotomy and an infusion of 7,1 litres of crystalloid, 3 litres of packed cells and 6 litres of freeze-dried plasma. At the time of his death, the haemoglobin was 2 g/dl and platelets 17×10^9/l.

Patient E210 (Table 9-2) presented 15 hours after the bite with a blister-covered leg with swelling extending from the foot to the chest wall. He was hypotensive with an Hb of 3,3 gm/dl, Hct 10,2, platelets 127×10^9/l, nearly undetectable fibrinogen, XDPs <200 ηg/dl, albumin 12 g/l, INR 2,45 and PTT 118 seconds (control 34 seconds). There was a femoral vessel entrapment syndrome and compartment syndromes above and below the knee. He survived and his leg was saved, although with loss of the anterior tibial and peroneal compartment musculature. This case illustrates the value

of vigorous intravenous resuscitation aided by central venous pressure measurements, attention to urine output and appropriate surgery.

9.5 Elevation

Elevation is considered second in importance to intravenous fluids. Intravenous fluids replace fluid loss into the swollen area, while elevation may help return third space fluid into the circulation and diminish regional venous hypertension. The latter facilitates arterial input (Cywes & Louw, 1962). Qvarfordt *et al.* (1983) showed that increase of compartment pressures following deep vein thrombosis, and ileofemoral thrombosis may lead to a blue leg from venous congestion, or a white ischaemic leg from impedance of arterial blood flow. This stresses the importance of venous outflow.

That elevation is of clinical benefit is suggested by patients discharged too early, requiring readmission for exacerbated swelling (Blaylock, 1982a), and hand bites become more painful when dependant. Analgesia due to elevation is a secondary benefit. The importance of elevation is supported by the literature on Southern African snakebite (Tilbury & Branch, 1989; Yerzingatsian, 1997).

All patients with PPS in this series were treated by elevation of the bitten limb. Legs may be elevated by raising the foot of the bed or using pillows, or in paediatric patients, using vertical elevation similar to gallows traction or Bryant's traction, without lifting the buttocks off the bed. Correctly applied adhesive strapping does not contribute to compartment syndrome, nor does it prevent finger palpation of

compartments. The arms of patients in bed may be placed on a pillow, across the chest or elevated from a drip stand using a sling. Steep elevation can be achieved by adhesive strapping along the length of the bitten arm and attaching it to a stable overhead support (drip stand, balkan frame). A sling is used in mobile patients.
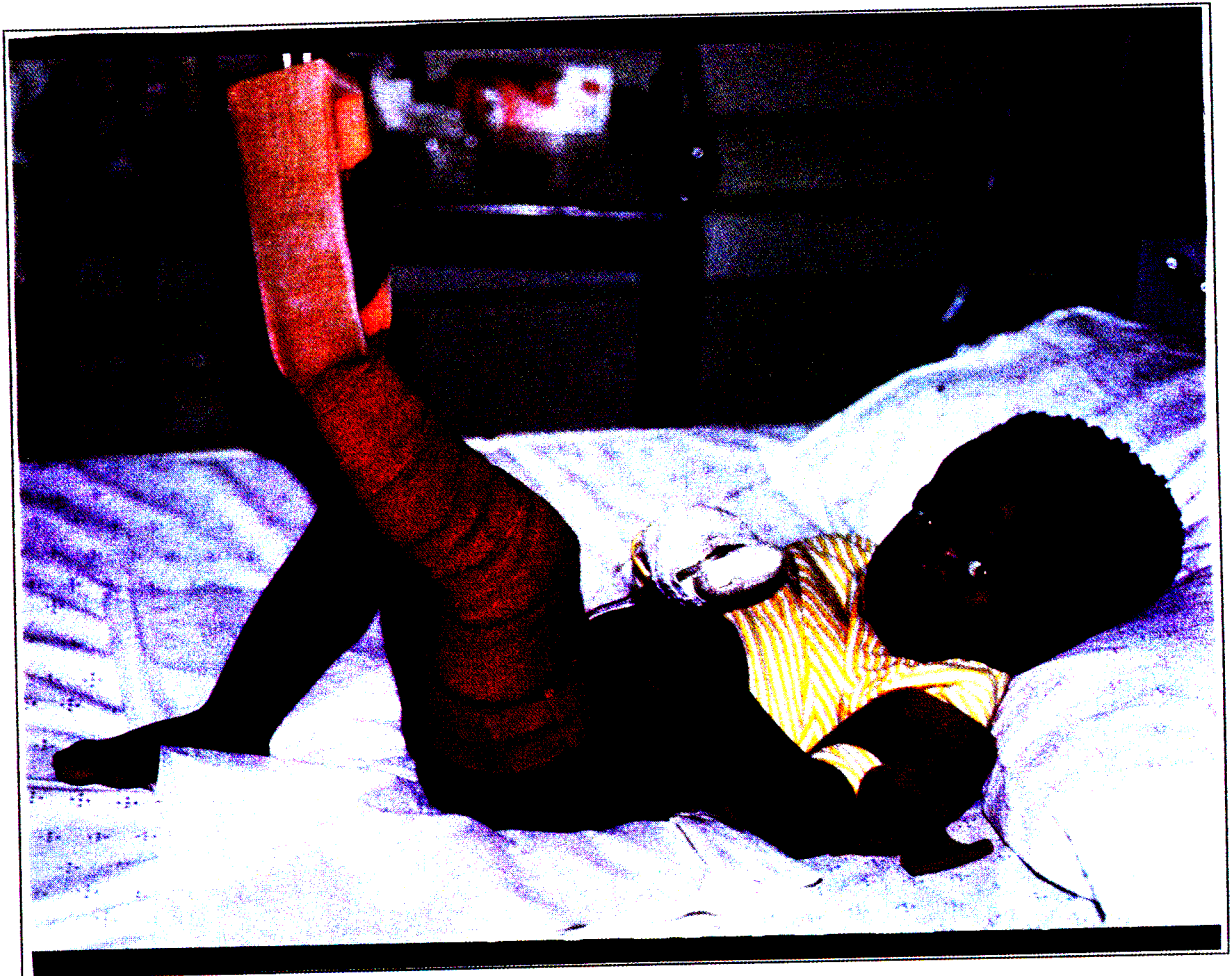
Fig. 9–1   Patient E256.   Vertical leg elevation.   Note blister on dorsum of foot.

9.6   Analgesics

9.6.1   Introduction

Pain is an integral part of the painful progressive swelling syndrome. Hyperalgesia has been shown experimentally to occur in rats injected with South American *Bothrops* venoms (Texeira *et al.*, 1994; Chacur *et al.*, 2001), which is not associated with the development of oedema. Prostaglandins, leukotrienes and platelet activating factor mediate hyperalgesia caused by *B. jararaca* venom (Texeira *et al.*, 1994), while hyperalgesia caused by *B. asper* venom is at least partly mediated by bradykinin, phospholipase A_2 and leukotrienes (Chacur *et al.*, 2001).

Hyperalgesia occurs subjectively in some Southern African human snakebite patients, notably in those cases that can lead to necrosis (Mozambique spitting cobra, puff adder and stiletto snake bites), and may be partly responsible for the excessive diagnoses of compartment syndrome where pain often appears out of proportion to the clinical situation.

Analgesics were prescribed by doctors at Eshowe Hospital on a subjective basis, often determined by availability or financial constraints. Analgesics have been classified into groups of increasing efficacy, namely:

a) aspirin or paracetamol alone

b) codeine, diclofenac and tilidine drops or combinations of aspirin, codeine and paracetamol with or without diclofenac

c) parenteral pethidine with or without supplementary oral analgesics.

Codeine was contained in APCods®, Codis® and Codeine plus®, and aspirin in Codis®. Tilidine drops were used in paediatric patients. Pethidine and diclophenac were administered intramuscularly.

9.6.2 Results: Tables 9– to 9-8, Appendix A

Table 9-4   Analgesics used in Eshowe patients. 321 patients

Medication	Prescriptions	
	Single drug	In combination with other drugs
Oral		
Paracetamol	143	12
Aspirin	3	102
Codeine	1	102
Tilidine drops (paediatric age group)	7	4
Suppository		
Indomethacin	1	0
Parenteral		
Pethidine	8	22
Diclofenac	0	14

Table 9-5   Analgesia and swelling severity. 309 patients

Swelling severity	Analgesia		
	Nil or paracetamol or aspirin	Tilidine, anti-inflammatories, analgesic combinations or pethidine	Chi-square for trend
No envenomation	30	9	$X^2 = 12,647$
Minimal to moderate	142	105	$df = 1$
Severe and gross	7	16	$P = 0,0004$
Potent analgesic administration was proportional to eventual swelling severity.			

Table 9-6   Pethidine analgesia within 48 hours of admission to hospital. 220 patients with painful progressive swelling.

	Admitted to hospital within:	
Pethidine analgesia	First 24 hours	Second 24 hours
Yes	25	1
No	150	44

Fisher's exact test $P = 0,0209$

Pethidine administration was most common during the first 24 hours of admission

Table 9-7   **Pethidine analgesia and bite site complications (BSCs).**
                               268 patients with swelling.

Pethidine analgesia	BSCs present	BSCs absent
Yes	16	12
No	27	213

Fisher's exact test P = < 0,0001
Pethidine analgesia was administered most commonly to patients who developed BSCs.

Table 9-8   **Pethidine analgesia, swelling severity and bite site complications (BSCs). 242 patients**

Swelling severity	BSCs present		BSCs absent		Fisher's exact test
	Pethidine administration		Pethidine administration		
	Yes	No	Yes	No	
Mild	3	7	4	80	P = 0,0247
Moderate	8	11	7	99	P = 0,0002
Severe and gross	5	9	1	8	P = 0,3401

9.6.3 Discussion

Venom-induced pain is part of the acute inflammatory response in a similar way to trauma (Barraviera, 1994). When a person is bitten by a snake, immediate pain is caused by the physical damage caused by fangs and teeth, and after a few minutes the increase in pain is due to inflammation caused by the venom, which peaks within a few hours to three days.

Table 9-5 shows that there is a direct correlation between analgesic potency and eventual swelling severity (P = <0,001). Table 9-6 shows that pethidine is more commonly administered within the first 24 hours than in the second 24 hours of hospital admission (P = < 0,03), which suggests that the bite is most painful during this time. Table 9-7 suggests that patients who eventually develop bite site complications (BSCs), which include bite site blisters, haematoma, abscess or necrosis, require more analgesia than those patients with the same amount of swelling who do not develop BSCs (P = <0.0001). This is born out in the mild and moderate swelling groups, but not in the combined severe and gross swelling group (Table 9-8). This discrepancy is explained by the fact that analgesia was initially withheld from three patients with gross swelling (E39, E210, E300) who were obtunded and severely ill on admission. All three developed necrosis.

9.6.3.1 Bite site

Fingers are tactile organs with a rich supply of sensory nerve endings. It would be expected that potent analgesics would be required more often with PPS originating from this bite site. Pain in a bitten hand or finger may be so severe as to disturb sleep during the night after the bite. This occurred in bites by Bibron's stiletto snake *(Atractaspis bibronii)* as mentioned by Siemers, 1958; Stewart, 1965; and Blaylock, 1982a; and in case E255 in this series. Similar severe pain has been reported in hand or finger bites inflicted by the puff adder as published by Balarin, 1960; Blaylock, 1960; Goddard, 1962; Blaylock, 2000 (case 6.2.2.1). The latter case received morphine intravenous titration up to 5 mg hourly but pain relief was only achieved

after a local anaesthetic axillary block. Similar severe pain in the hand or fingers can

be caused by any snakebite to this site which results in significant PPS.

9.6.3.2 Snake species responsible for differing degrees of pain

Not enough snakebite patients in this series were accompanied by the snakes that bit

them to objectively determine that the venom of a particular snake species produces

more or less pain than that of another species.   It is a subjective impression that

swelling distant to the bite is hotter, more painful and tender in Mozambique spitting

cobra bites than in bites by other snake species.

9.7   Antivenom

9.7.1   Introduction

The object of this section is to determine the efficacy of antivenom in the painful

progressive swelling (PPS) syndrome, and to determine the indications for its use and

the volume that should be administered.

9.7.2   Results

9.7.2.1   Eshowe patients   (Table 9-9)

Table 9-9   SAIMR polyvalent antivenom administered to Eshowe patients with painful progressive swelling

Eshowe number and age of patient	Snake	Site of bite	Clinical condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
122 6 yr	Mozambique spitting cobra	Left calf Right thigh	Swelling ? degree	10 ml prior to admission	Moderate swelling of both legs. Necrosis 100 cm^2 and 200 cm^2
148 12 yr	Unknown	Foot	Severe swelling to inguinal ligament at less than 8 hours	8 h: 50 ml	Swelling did not progress. No necrosis.
210 15 yr	Unknown	Ankle	Swelling to chest wall at 16 hours. Anaemia and thrombocytopenia with compartment syndromes	16 h: 18 ml	Anaphylaxis (hypotension, tachycardia, fall in O$_2$ saturation). Fasciotomy of calf and thigh.
286 2 yr	Unknown	Finger	Swelling involving chest. Tachycardia and tachypnoea.	60 h: 50 ml	Finger amputation.
300 17 months	Unknown	Twice on same hand	Swelling involved proximal arm and dyspnoea	12 h: 40 ml	Anaphylaxis (rash, bronchospasm, tachycardia). Progression of soft, cool and non-tender swelling. Two small areas of necrosis.
318 11 yr	Mozambique spitting cobra	Hand	Swelling to proximal arm and dyspnoea	35 h: 50 ml	Anaphylaxis (shivering, increased tachycardia and increased dyspnoea). Minimal progression of soft, cool and non-tender swelling. Significant local necrosis.
Antivenom was administered intravenously					

9.7.2.2 Patients gleaned from the literature search (Tables 9-10 to 9-12)

Table 9-10   SAIMR polyvalent antivenom administered to puff adder bite patients

Author and age of patients	Bite site	Clinical condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
1. French, 1959 Teenager	Thumb	Unknown	10 min: 10 ml split locally and IMI. 2 h : 20 ml IMI	Minor necrosis
2. Alves, 1960 Adult	Finger	Finger swollen Hand swollen	< 5 min: 7 ml proximal to finger 20 min: 10 ml IMI 35 min: 10 ml	2 h 20 min: Swelling to elbow. 11 h 20 min: Swelling to shoulder. Finger amputated
3. Balarin, 1960 Teenager	Thumb	Hand swollen Blue thumb	45 min: 2 ml into bite site. 8 ml IMI 6 h 40 min: 10 ml IMI	Swelling beyond elbow. Minimal swelling. Minor necrosis
4. Blaylock, 1960 18 yr	Finger	Local pain	1 min: 2 ml into finger. 10 min: 5 ml locally away from swelling. 10 ml	Swelling to shoulder. No necrosis
5. Blaylock, 1960 (unpublished) 19 yr	Finger	Local pain	5 min: 5 ml into finger and hand. 10 ml IMI 15 min: 10 ml	Hand swollen. No necrosis
6. Goddard, 1962 Teenager	Thumb	Pain and some swelling. Whole hand swollen. Blue thumb	Few min: 5 ml IMI 21 min: 10 ml IMI.	3 hr 25 min: Swelling above elbow. 6 h: Swelling to shoulder. Minor necrosis
7. Phillips, et al 1973 22 yr	Index finger	Cyanotic finger swelling to elbow. Axillary lymphadenopathy. Platelets 172 x 10^9/L	2 h: 30ml	Swelling to axilla first day. Day 3: asymptomatic
Blaylock, 2000b 8. Case 7 26 yr	Distal shin	Purpura, bleeding shaving cuts, haematemesis, subconjunctival haemorrhage	2 h: 10 ml 3 h 30 min: 10 ml IMI	4 h: Hb 12.1g/dl. Platelets 86 x 10^9/L. INR 1,73. PTT 57 sec 17 h 20 min: Hb 12,1g/dl. Platelets 172 x 10^9/L INR 1,33. PTT normal. No necrosis
9. Case 8 22 yr	Hand	Swelling to shoulder	24 h: 10ml	Swelling progressed to opposite shoulder and chest. No necrosis
10. Case 12 26 yr	Index finger	Swollen finger. Epitrochlear and axillary lymphadenopathy	4 h 30 min - 5 hr 30 min: 60 ml	Swelling never more than non-tense swelling of finger and hand. Day 40 : Amputation through mid middle phalanx
11. Aitchison (Unpublished) 21 yr	Ankle	Bleeding from gums, haemoptysis, haematemesis, haematuria, periorbital haematoma, subconjunctival haemorrhage, purpura chest wall. 5 h : Hb 19,7g/dl INR 2,7 PTT 133 sec 37 h : Hb 5,1g/dl Platelets 26 x 10^9/L INR 1,79 PTT 52 Fibrinogen normal	41 h: 40 ml	No evidence of further bleeding. 41 h 15 min: Significant improvement in thromboelastogram 44 h: INR 1.2 PTT 35 sec

Antivenom was administered intravenously unless otherwise stated.   IMI : intramuscular injection

Table 9-11 SAIMR polyvalent antivenom administered to Mozambique spitting cobra bite patients (Tilbury 1982)

Case number	Age of patient	Bite site	Evidence of necrosis prior to antivenom administration	Amount and time of antivenom administered	Outcome
3	28 yr	Thigh	Nil Mild swelling	3 h: 100 ml	Marble sized abscess. Swelling did not progress
7	5 yr	Finger	Nil Mild swelling	1 h 30 min: 100ml	Obliteration of distal interphalangeal joint space
15	40 yr	Finger	Nil.	25 min: 90 ml	No necrosis
16	16 yr	Foot	3 cm^2 discoloured area at 3½ hours	3 h 30 min: 100 ml	Necrosis $\pm$ 50 cm^2
17	9 months	Base of thumb	Serosanguinous blister at 5½ hours	5 h 30 min: 55 ml	Necrosis most of palm and dorsum of hand
Probable but unproven Mozambique spitting cobra bites.					
5	10 yr	Foot twice	Heraldic patch 6 cm^2 Severe swelling	9 h: 100 ml	Necrosis 120 cm^2
8	80 yr	Calf	Heraldic patch 6 cm^2 Severe swelling	7 h: 100 ml	Necrosis 200 cm^2
11	28 yr	Foot	Nil. Mild swelling and warmth	2 h: 100 ml	No necrosis
All patients were asleep at the time of the bite, except for case 15 who was handling the snake. Antivenom was administered intravenously.					

Table 9-12 SAIMR polyvalent antivenom administered to Gaboon adder bite patients

Author and age of patient	Bite site	Condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
Visser & Carpenter, 1977 16 yr	Thumb	Dyspnoeic, collapsed	17 min: 10 ml IMI 30 min: 70 ml	20 min: cardiac arrest. Swelling of whole arm. Minor necrosis
Edwards *et al.*, 1979 23 yr	Finger	Inability to accommodate, hearing loss, hyperventilation, mild hypotension, tachycardia, prolonged QT interval, multiple atrial ectopics, falling consciousness level Prothrombin and clotting times normal	1 h: 40 ml 80 - 100 min: 80 ml	B.P. 160/110 mmHg. Atrial arrhythmia, prolonged QT interval, T-wave inversion. Haemostasis difficult at vene-puncture. Semi-conscious. Oedema of arm. Day 3: Slightly ↓ fibrinogen. Days 5 - 8: Raised HBD levels. No necrosis. 30 days: ECG normal
McNally *et al.*, 1993 35 yr	Wrist	30 min: Swelling of wrist to shoulder Dyspnoeic Day 4: thrombin time > 100 s	< 1 h: 100 ml Day 4: 100 ml	Day 2: Swelling progressed to abdomen. Pulmonary oedema. Ecchymosis from cubital fossa to trunk. Day 3: Fibrinogen and factor XIII decreased, increased FDPs. Resolution of haemostatic abnormalities. Minor local necrosis.

Antivenom was administered intravenously unless otherwise stated. HBD - Alpha-hydroxybutyrate dehydrogenase

9.7.3 Discussion

9.7.3.1 Effect on swelling and necrosis

Puff adder envenomation (Table 9-10)

Doses of antivenom of 30 ml or less did not prevent progression of swelling, while a dose of 60 ml commencing at 4½ hours did (case 12). Case E148 (Table 9-9), a clinically diagnosed but unproven puff adder bite, received 50 ml antivenom at 8 hours when swelling was progressing rapidly, after which it ceased. None of the five proven Eshowe puff adder bite patients were given antivenom. Scharf & du Plessis (1993) administered 40 – 60 ml of antivenom to 13 patients with puff adder bites, and thought that this dose helped to stop the advance of the zone of swelling and inflammation. Guinea pig experiments showed that local lesions were reduced in size but not prevented by early (within 10 – 15 minutes) intravenous antivenom administration (Christensen, 1969).

Mozambique spitting cobra envenomation (Table 9-11)

Case E 318, where swelling was progressing slowly, was given 50 ml of antivenom at 35 hours. Swelling continued to progress but was soft, cool and non-tender instead of hot, tender and indurated. The same happened to case E300, a clinically diagnosed but unproven Mozambique spitting cobra bite, when 40 ml was administered at 12 hours.

Iddon *et al.* (1987), after animal experimentation with black-necked spitting cobra venom, suggested that irreversible tissue changes occur too quickly for antivenom to prevent necrosis. This is compatible with the experience in seven cases of proven

Mozambique spitting cobra bites given antivenom, all but one of whom developed necrosis, and of four clinically diagnosed (unproven) cases, three developed necrosis. In these cases, in spite of large quantities of antivenom administered (55 – 100 ml), the area of necrosis increased substantially (Table 9-11).

Gaboon adder envenomation (Table 9-12)

Swelling progressed in two patients receiving antivenom (80 and 100 ml) and both developed areas of minor necrosis (Edwards et al., 1979; McNally et al., 1993), suggesting that the doses were inadequate. Marsh & Whaler (1984) considered that this snake produces the largest amounts of venom of all poisonous snakes. Their largest yield from a single milking was 9,7 ml (2,4g dried venom). Such quantities of venom require large amounts of antivenom for neutralisation, so 200 ml of antivenom would be more appropriate.

Bibron's stiletto snake envenomation

Two patients given antivenom obtained no relief (Rippey et al., 1976). This venom is not used in the antivenom manufacturing process.

9.7.3.2 Effect on bleeding and thrombocytopenia

Aitchison's case (clinically diagnosed puff adder bite) stopped actively bleeding when 40 ml of antivenom was administered at 41 hours, and there was significant improvement in the thromboelastogram performed 15 minutes later (Table 9-10).

9.7.3.3 Indications

Indications for antivenom in various published papers and medical booklets depend of the views of the authors (Tables 7-2 and 7-3) and include: bites by specific snake species (puff adder or Gaboon adder); signs of poisoning from these snakes; swelling involving a whole hand or foot within one hour of the bite, to the elbow or knee within 3 - 6 hours, and to the shoulder or groin within 12 hours; swelling extending proximally with blistering and serosanguinous ooze; swelling to the trunk, swelling affecting the airway; and signs of foetal distress in pregnant patients. Swelling which soon involves a whole limb (especially the leg) leads to an intravascular fluid loss of several litres and may include blood with consequent hypovolaemic shock, anaemia and possible death of the patient (Tables 9-2 and 9-3). Swelling reaching the trunk from an acral bite signifies severe envenomation and is associated with unacceptable complications and possible mortality (Table 9-1). If these degrees of envenomation can be anticipated, the progression of swelling can be stopped with appropriate antivenom use, or its character changed. This degree of severe envenomation is estimated to occur in 3% - 8% of patients with PPS (Blaylock, 2000).

A prerequisite for antivenom treatment is that swelling is actively advancing and not stable.

A. Anticipated severe envenomation

A.1. Swelling of a whole bitten hand or foot within one hour of the bite.

Unidentified and other snake species excepting the puff adder and Gaboon adder (antivenom potentially indicated).

The swelling of bites by the stiletto snake, night adders and other adders, although fulfilling this criterion, uncommonly involves a whole limb and is rarely life threatening. Swelling progression from spitting cobra bites is slow. In this situation this degree of swelling from an unidentified snake should be taken as a warning rather than an indication for antivenom use.

B.   Severe envenomation present

B.1   Distal extremity bites

B.1.1 Swelling of a whole bitten hand or foot within one hour of the bite due to puff adder and Gaboon adder envenomation.

In these-species specific bites the situation denotes severe envenomation with swelling increasing at a rate of 10 - 15 cm per hour or faster. Unless stopped this swelling will reach the trunk with its attendant complications (Table 9 - 1).

B.1.2 Swelling to the elbow or knee by 3 - 4 hours

This degree of envenomation may be reached in puff adder and Gaboon adder bites, but not in spitting cobras or stiletto snake bites. Uncommonly a rhombic night adder may achieve this, especially in children.

B.1.3 Swelling of the whole arm or leg within 12 hours of the bite

Note the potential complications in Table 9-1.

B.2 Incipient or established compartment syndrome

Compartment syndrome can be prevented and in early cases reversed by the use of antivenom and elevation of the bitten limb. Intravenous mannitol is of value (11.5.1.1). Antivenom administration indicated by points in B1 would probably prevent or reverse a compartment syndrome. This is possible in rattlesnake bites (Mubarak & Hargens, 1983).

B.3 Dyspnoea unassociated with fright, oligaemic shock or venom allergy

Anaemia or swelling involving the chest with parietal pleura and lung involvement due to venom spread, by continuity and contiguity, may produce dyspnoea. In the latter circumstance, arterial blood gases are usually maintained at normal levels but it is a frightening situation for both patient and doctor and could potentially lead to oxygen desaturation. Patients with Gaboon adder bites may become dyspnoeic within a few minutes of the bite due to pulmonary oedema or hypotension (Table 9-12; Blaylock, 2000).

B.4 Swelling associated with active bleeding or platelets < 40 x 10^9/l in a peripheral hospital or < 20 x 10^9/l in a critical care setting (see bleeding syndrome, Chapter 14)

B.5 Evidence of cardiotoxicity

This is rare in Southern Africa but has been described in a Gaboon adder bite (Edwards *et al.*, 1979).

C. Swelling threatening the airway

Such swelling is usually due to bites of the head, neck or upper chest and airway obstruction may result if laryngeal oedema occurs.

9.7.3.4 Dose

Table 7-4 shows that various authors recommend a dose between 40 and 200 ml. The Eshowe series demonstrates that 40 - 50 ml can either stop progression of swelling or change its character (Table 9-9).

Unknown snake species and puff adder bites if antivenom is indicated: 50 ml is sufficient in most cases.

Gaboon adder bites (Table 9-12). Two hundred millilitres is recommended.

Algorithm 9-1

Management of painful progressive swelling

|

Intravenous fluids ⎤
    Elevation   ⎬ Sufficient for most bites
    Analgesia   ⎦

|

Antivenom

|

Swelling should be actively progressing.

Potential severe envenomation (a warning that antivenom may be necessary)	Severe envenomation present
Unidentified snakes	**A. Distal extremity bites** A1. Swelling of a whole hand or foot within 1 hour due to an identified puff adder or Gaboon adder bite. A2. Swelling to the elbow or knee by 3 – 4 hours.
	A3. Swelling of a whole limb within 12 hours.
Swelling of whole hand or foot within 1 hour of the bite	B. Swelling threatening the airway. C. Presence of a limb compartment syndrome. D. Unexplained dyspnoea. E. Associated coagulopathy. F. Evidence of cardiotoxicity (rare).

In a critical care unit with snakebite expertise, except for a significant coagulopathy and cardiotoxicity, antivenom may be unnecessary.

Premedication with intra-muscular adrenaline (0,2 – 0,5 ml 1:1 000 solution) for atopic individuals is warranted (Chapter 8).

A sensitivity test is not predicative of the outcome of the main dose (Chapter 8)

A volume of 50 ml intravenously administered as a slow intravenous injection which is as safe as a slow infusion is suggested, except for Gaboon adder bites where 200 ml is recommended.

CHAPTER 10

SURGERY FOR BITE SITE COMPLICATIONS

CONTENTS

10. Surgery for bite site complications

10.1 Abstract

Objective: To make recommendations for the management of complications that may occur at the bite site.

Method: Prospectively studied Eshowe patients with bite site complications are analysed.

Results: Bite site complications occurred 45 times in 42 of 282 patients. Surgery was more commonly performed on fingers and hands than on other parts (P = <0.001). Debridement at 6 days or less usually led to repeat debridement (P = <0.03).

Conclusion: Blisters are best left undisturbed, abscesses treated on merit, haematomas drained or aspirated, and necrotic areas (including fingers) left for 5 - 7 days prior to debridement. Skin cover follows standard surgical principles.

10.2 Introduction

Early surgery during the first few days after a snakebite may be necessary for bite site complications, and includes drainage of abscesses or haematomas, excision of necrotic tissue (debridement), skin closure by means of delayed primary suture, secondary suture or skin grafts (partial or full thickness), or flaps or amputation. Later reconstructive surgery may be necessary for better skin cover, mobilisation of joints or excision/amputation for squamous malignant change in a chronic ulcer.

Compartment syndrome and vessel entrapment syndrome are discussed in Chapter 11.

Table 10-1   Surgery to blisters not overlying necrosis, deep haematomas and abscesses at bite sites

Eshowe No.	Age	Swelling severity	Bite site	Surgery
			Blisters	
X 58	25	Gross	Calf	Nil. Resorbed day 15
60	26	Gross	Foot	Healed spontaneously
79	13	Mild	Finger	Nil
96	24	Moderate	Toe	Nil
97	7	Severe	Foot	Nil
X 114	3	Moderate	Leg	Nil
152	15	Moderate	Foot	Nil
169	8	Gross	Foot	Nil
211	13	Mild	Finger	Deroof day 4
272	7	Severe	Finger	Nil
305	3	Moderate	Foot	Nil
			Deep haematomas	
52	5	Moderate	Foot	Aspirated day 7
188	15	Moderate	Ankle	Drained day 7
			Abscesses	
85	12	Mild	Leg	Drained spontaneously day 6
110	4	Moderate	Shin	Drained spontaneously day 9
295	11	Moderate	Foot	Drained day 8 Skin graft day 12
319	13	Moderate	Toe	Drained day 4
320	60	Moderate	Ankle	Drained day 7
Day 1 is the day of the bite. X: widespread blisters				

Table 10-2   Outcome of necrotic bite sites. 24 Eshowe patients. Compartment syndromes excluded

Eshowe No.	Age	Bite site	Swelling severity	Day(s) of debridement	Day(s) of wound closure
Fingers and hands					
14	7	Finger	Moderate	5	Secondary suture: 11 Skin graft: 18
19	4	Hand	Moderate	11	Healed spontaneously
153	34	Hand	Severe	7, 14	Skin graft: 22
199	42	Finger	Moderate	8	Skin graft: 19
199	42	Hand	Moderate	8	Skin graft: 19 Tensor fascia lata flap: 19
200	8	Finger	Mild	9	Healed spontaneously
232	61	Finger	Moderate	6, 12, 18	Amputation: 23 Skin graft: 31
237	15	Finger	Mild	Absconded	Dead finger
255	39	Finger	Mild	4, 10	Healed spontaneously
281	65	Hand	Moderate	4, 7	Skin graft: 25
286	2	Finger	Severe	Amputated 13	Skin graft: 27 at KEH*
300	18 mths	Two bites same hand	Gross	Day 7 for both bites	Healed spontaneously
318	11	Hand	Severe	7	Delayed primary closure: 9
Elsewhere					
18	18 mths	Ankle	Moderate	Nil	Healed spontaneously
22	70	Foot	Moderate	16	Skin graft: 37
51	25	Foot	Moderate	12	Skin graft: 22
54	19	Ankle	Severe	Nil	Healed spontaneously
68	10	Foot	Mild	Nil	Healed spontaneously
120	18	Foot	Mild	22	Skin graft: 38
122	6	Leg Thigh	Moderate Moderate	11, 11	Skin graft: 36, 36
196	20	Scapula	Mild	Nil	Healed spontaneously
218	5	Ankle	Moderate	Nil	Healed spontaneously
256	19 mths	Foot	Severe	Nil	Healed spontaneously
296	30	Toe	Moderate	Nil	Healed spontaneously
321	50	Shin	Mild	Nil	Healed spontaneously

Surgery to fingers and hands: all 14 bites. Surgery elsewhere: 5 of 13 bites.
$P = 0,0006$. Debridement at ≤ 6 days: 3 of 4 required repeat surgery. Debridement ≥ 7 days: Single debridement in 1 of 13 bites (KEH case excluded) $P = 0,0223$. Day 1 is the day of the bite.
*KEH: King Edward VIII Hospital.

Mozambique spitting cobra bite.   Patient E122.   Left leg

Fig   10 - 1
Day 11

Fig 10 - 2
Day 11
post
debridement
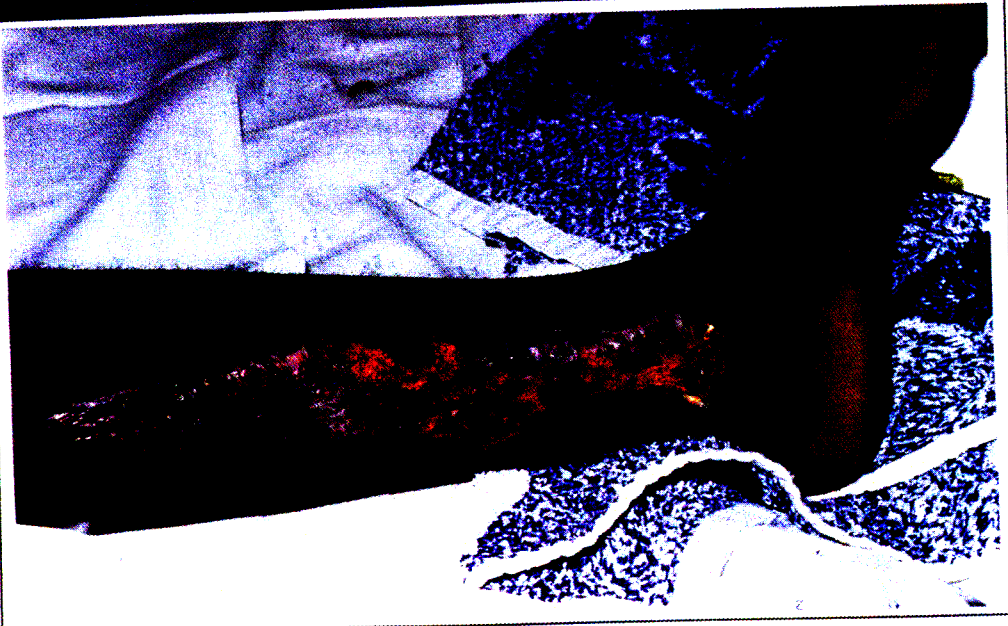
Fig 10 - 3
Wound
closure
with split
skin.
2 months

Mozambique spitting cobra bite.   Patient E122.   Right thigh
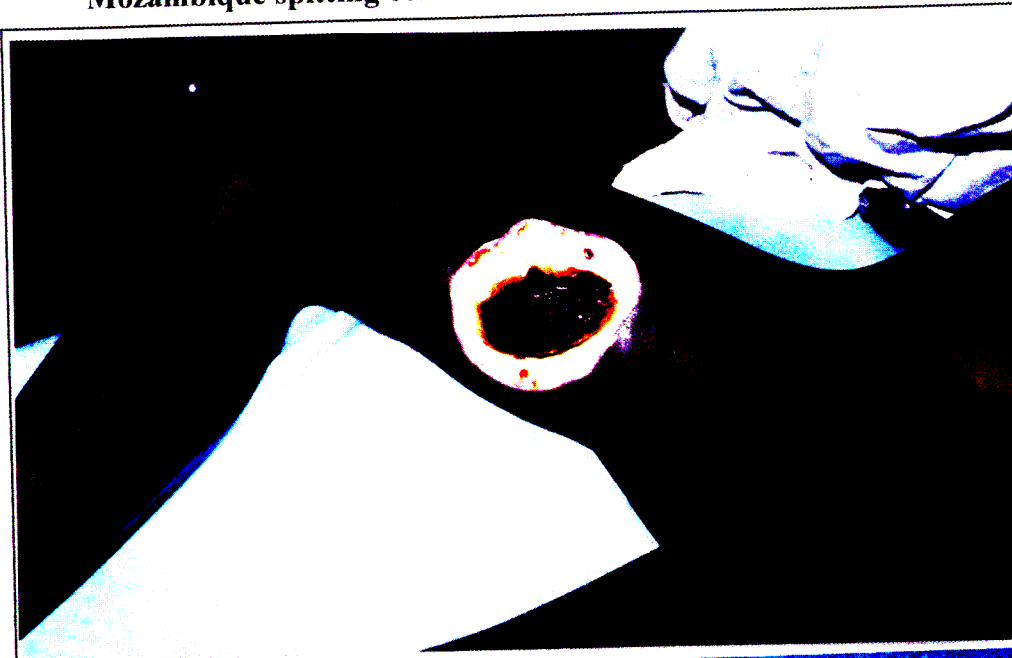
Fig   10 - 4
Day 11

Fig 10 - 5
Day 11
Post
debridment

Fig   10 - 6
Wound
closure
with
split skin.
2 months

Mozambique spitting cobra bite.   Patient E318
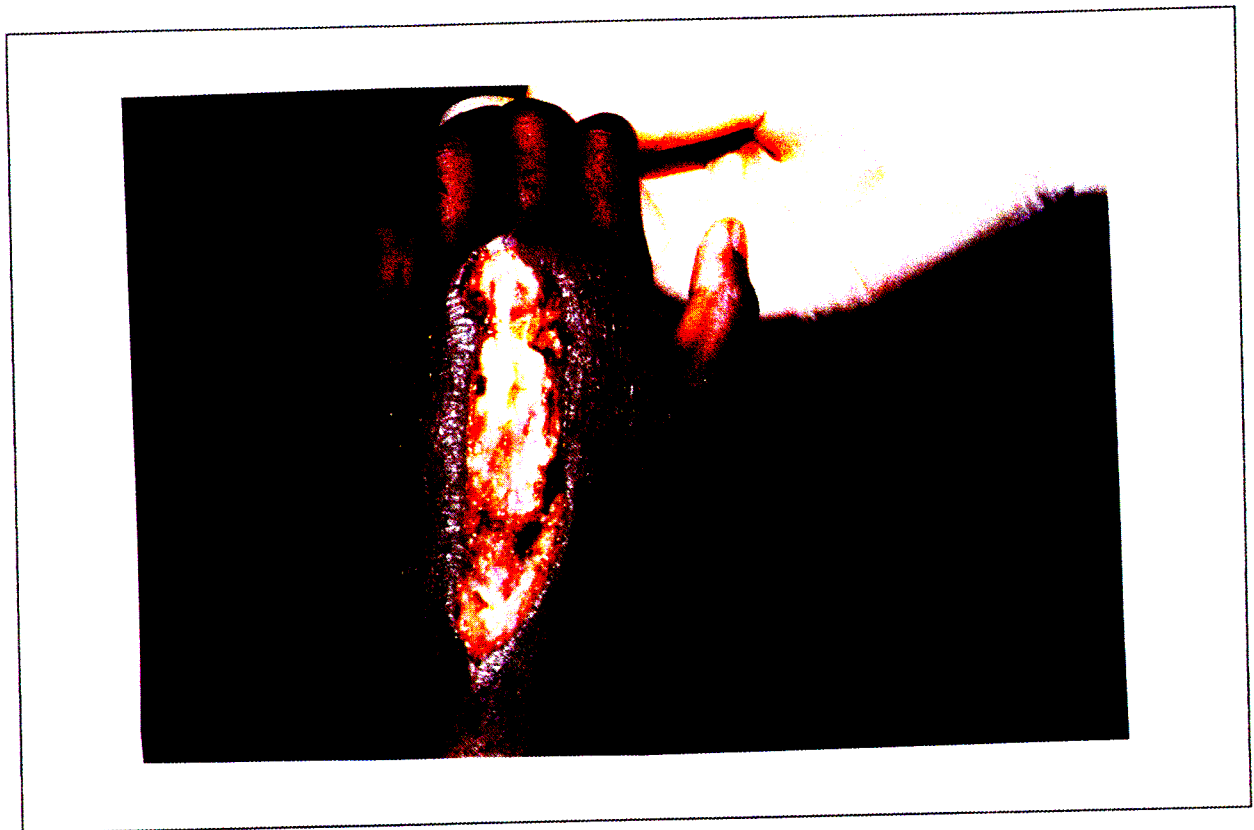
Fig 10 - 7   Debridement day 7

Fig 10 – 8   Day 9. Delayed primary skin closure

Patient E318.   Permanent loss of function
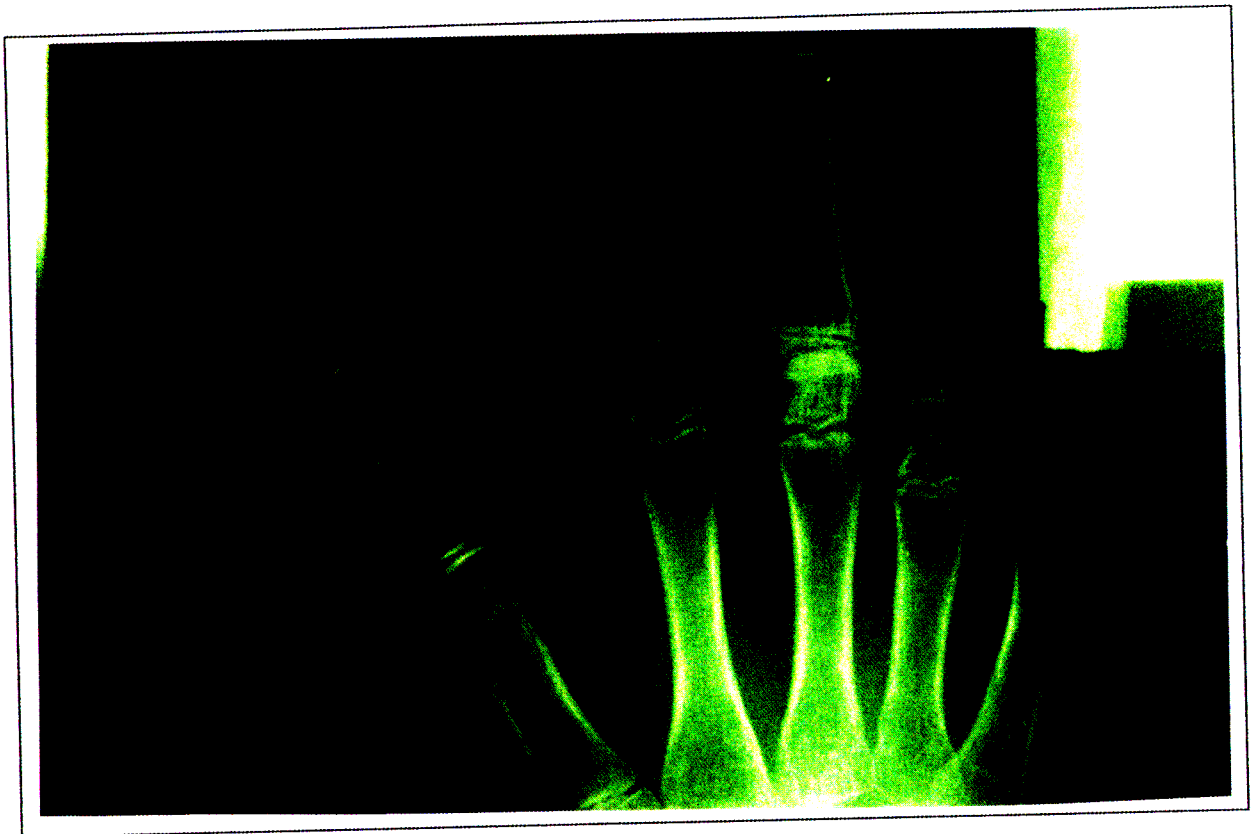
Fig. 10–9   Venom chondrolysis of the metacarpo-phalangeal joint

Fig. 10–10   Permanent loss of function

A Mozambique spitting cobra bite in Swaziland
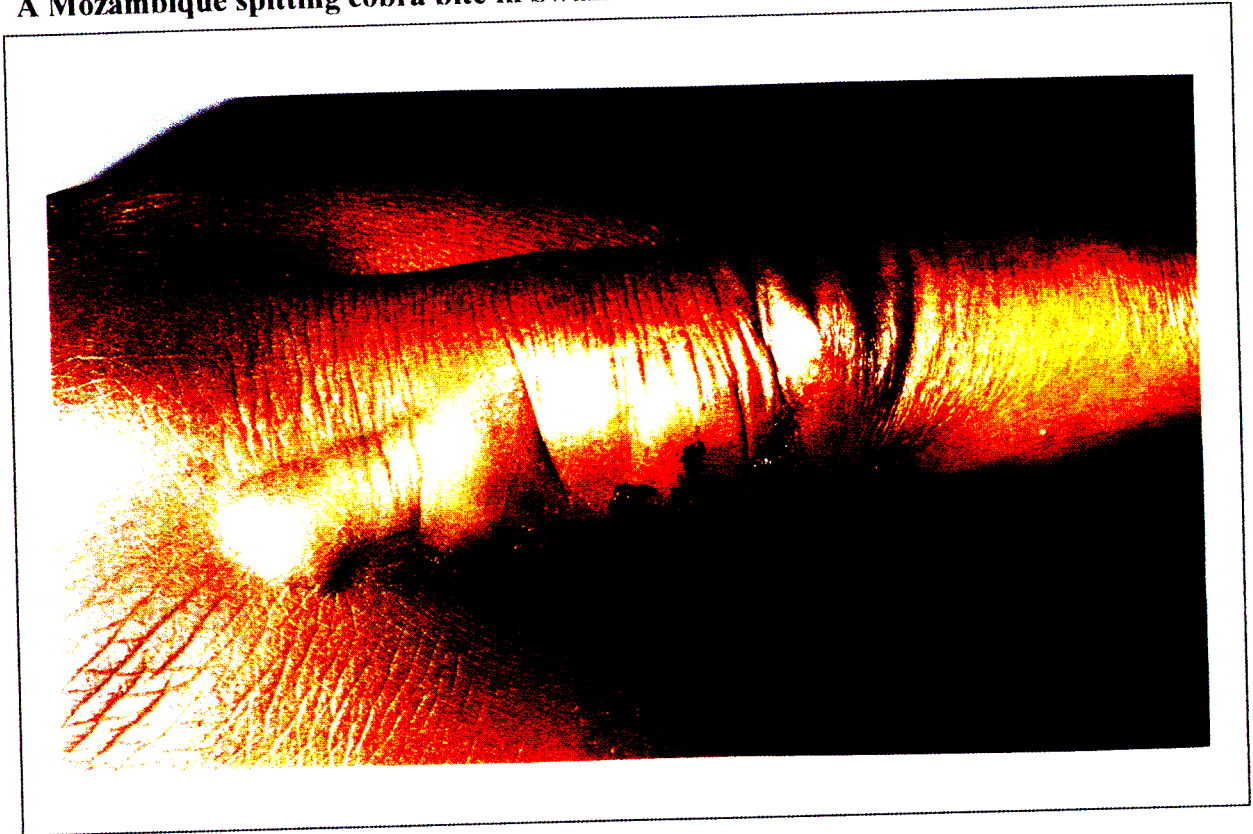
Fig. 10–11   Day 8

Fig 10–12   Day 21. Partial wound closure. Exposed tendons/ligaments
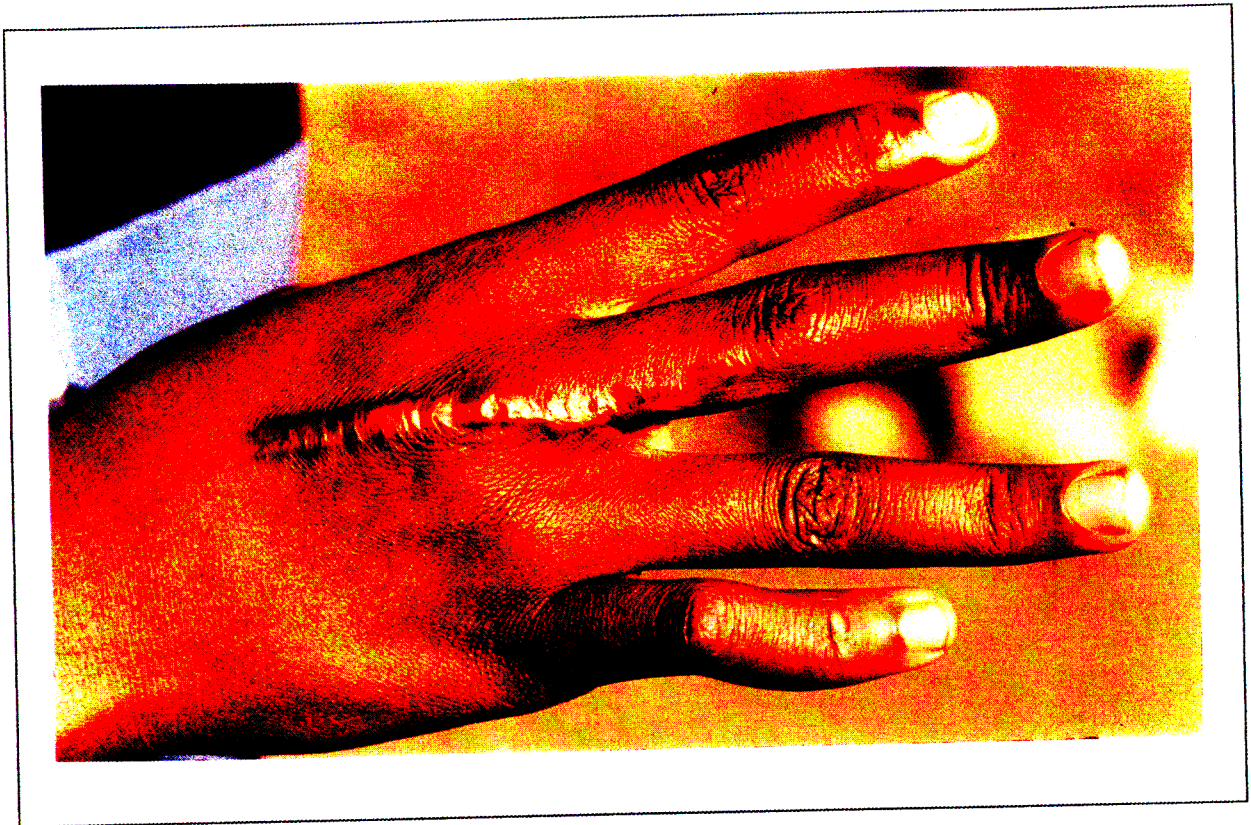
Fig 10 – 13   6 Months
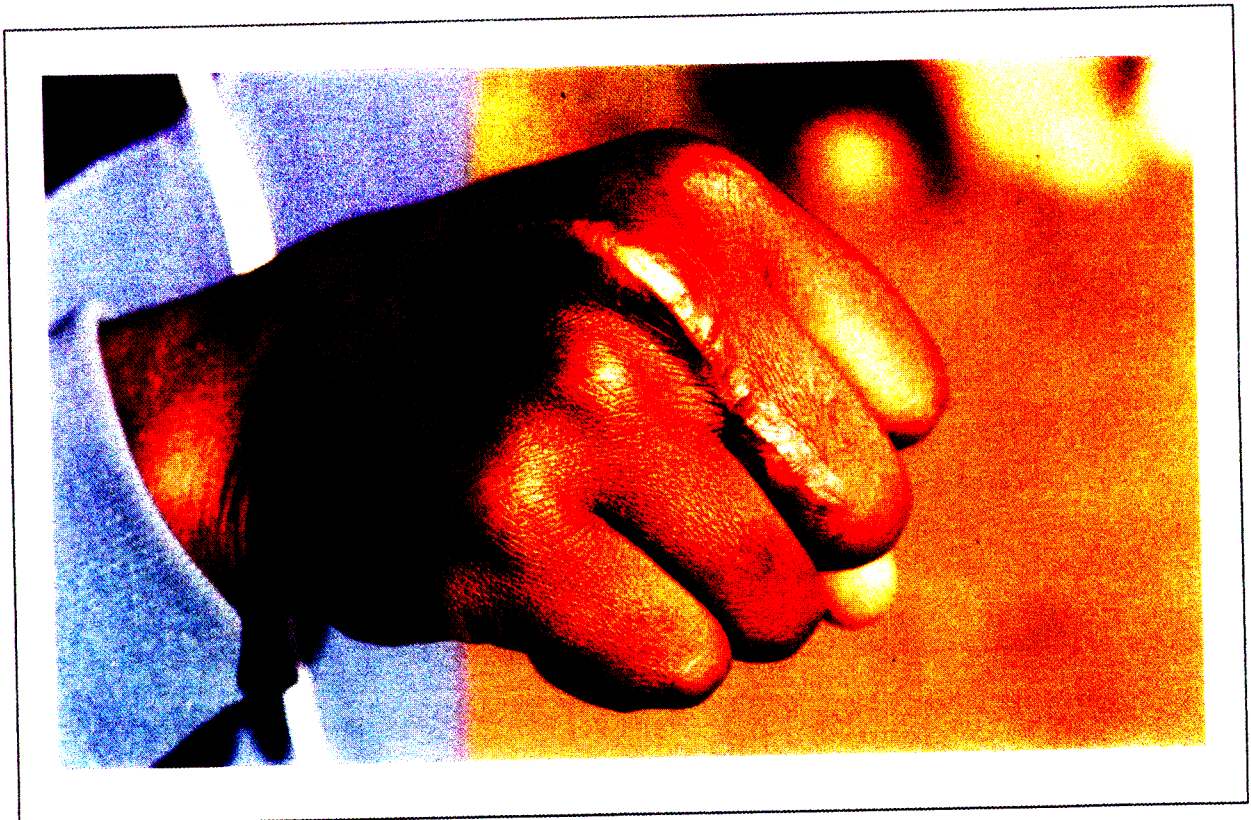
Fig 10 – 14   6 Months. Normal function

Mozambique spitting cobra bite. **Patient E232**

Fig. 10-15 **Day 24** **Debridement at days 6, 12, 18**

Fig. 10-16 **Amputation of index finger day 23. Split skin graft. Day 33**

Patient E 300. Bitten twice on the same hand

Fig. 10–17   Debridement at day 7
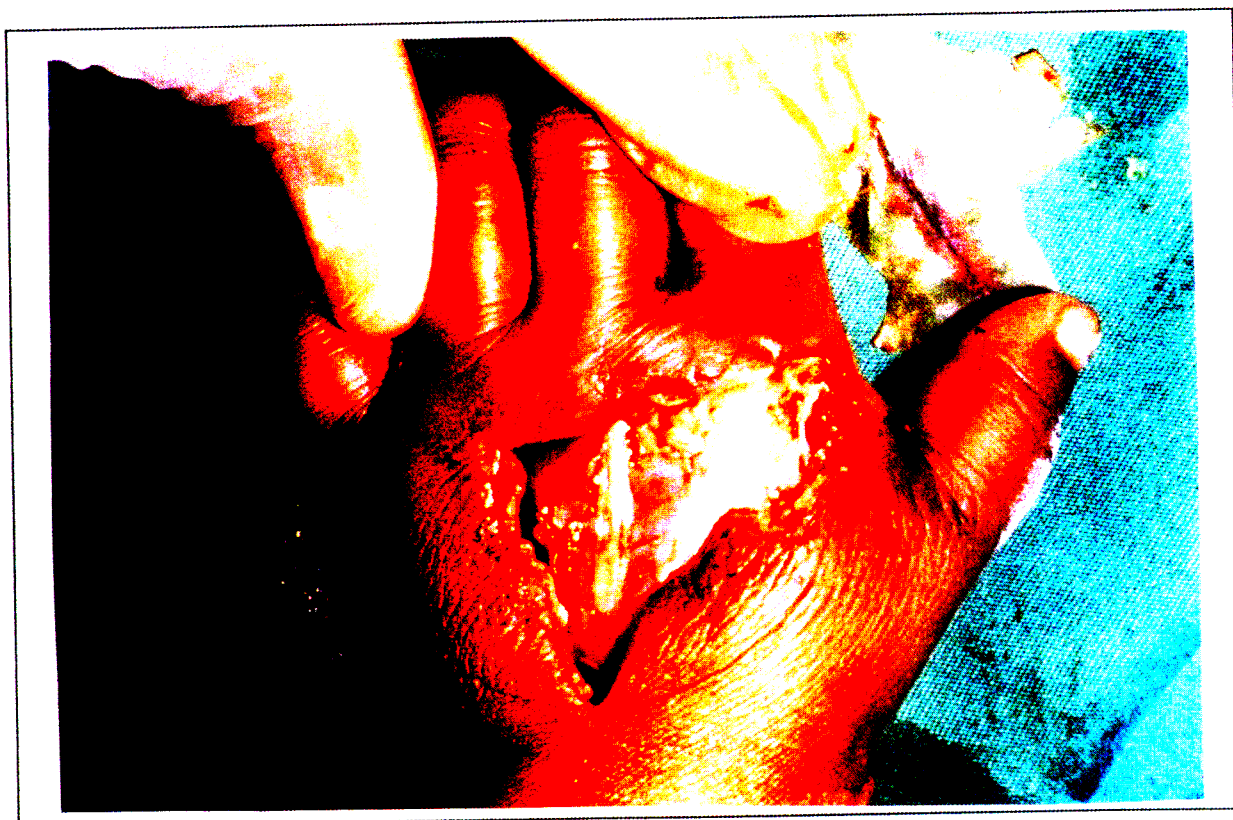
Fig. 10–18   Debridement at day 7

Patient E 300   Spontaneous healing as an outpatient

Fig   10 - 19   Day 36

Fig 10 - 20   Day 36

Mozambique spitting cobra bite. Bitten on both hands.
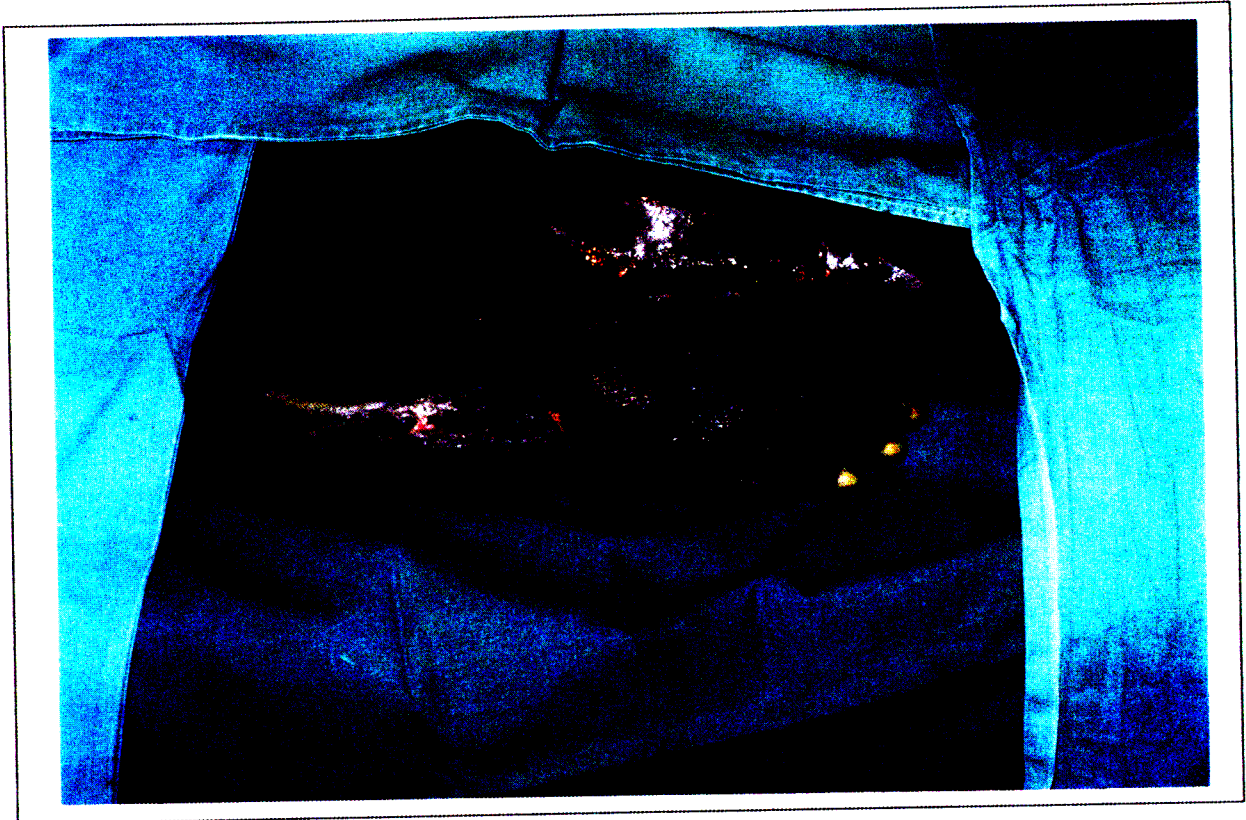
Fig 10 – 21   Patient E199. Tensor fascia lata flap. Day 19.
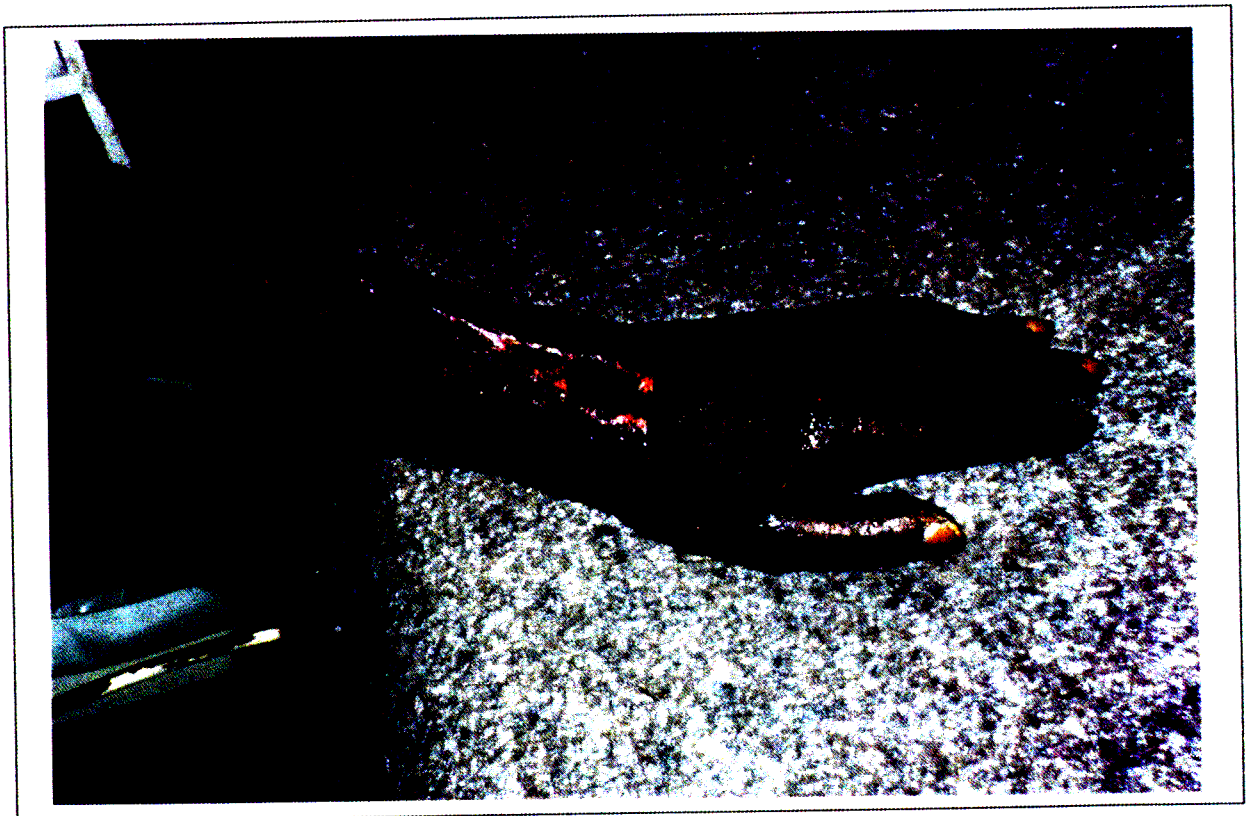
Fig 10 – 22   Patient E199. Flap separated. Day 39.

Puff adder bite
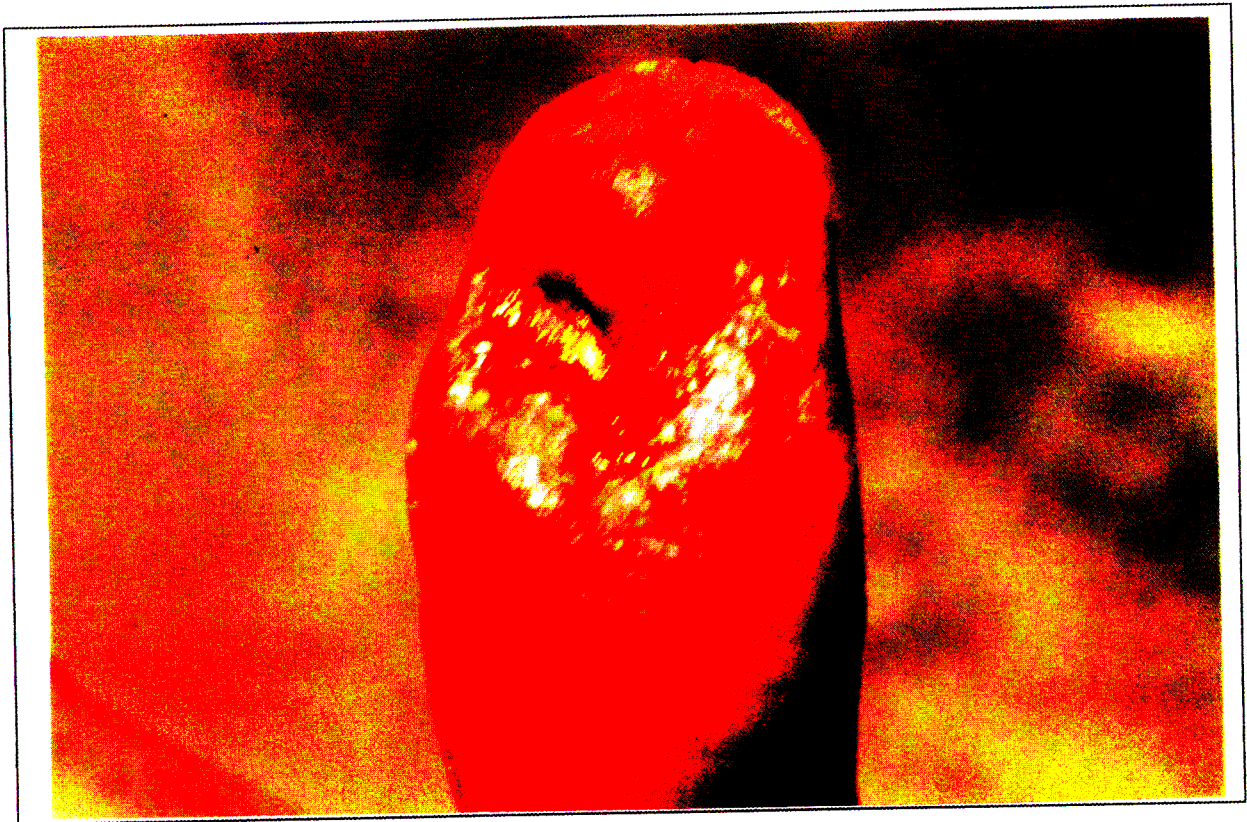
Fig 10 - 23   Day 43. Anaesthetic distal to interphalangeal joint

Fig 10 - 24   Free graft with micro neuro-vascular anastomosis. Day 63

10.5   Discussion

Bite site complications (BSCs) developed in 15% of all recently bitten patients presenting with painful progressive swelling (PPS).

Compartment syndromes and vessel entrapment syndromes are regional complications and are discussed in Chapter 11. Combining bites sites and regional complications gives a complication rate of 18% (50 of 285 bites involving 282 patients presenting with PPS).

10.5.1   Blisters, deep haematomas and abscesses (Table 10-1)

Eleven patients developed bite site blisters without underlying necrosis. They were left intact as recommended by Warrell, (1996), and all except E211 resorbed or burst spontaneously. The blister of patient E211 was deroofed to obtain a pus swab, which was negative for bacteria. The two deep haematomas (E52, E188) that developed were aspirated or drained on day 7. There were no sequelae. Of five minor abscesses (E85, E110, E295, E319, E320) which developed with no concomitant macroscopic necrosis, three were drained on days 4, 7 and 8, two drained spontaneously on days 6 and 9, and one required later skin graft.

10.5.2   Necrosis (Table 10-2)

Minor necrosis of 12 of the 24 patients healed spontaneously. Of the other patients, one absconded (E237) after amputation was offered for a gangrenous finger, and one (E286) was transferred to a tertiary hospital where a finger amputation was performed.

Eleven patients required single debridement for 13 necrotic areas, while in four debridement was repeated prior to skin closure. Three of four patients where debridement was undertaken on day 6 or sooner required repeat debridement, while of 13 necrotic areas debrided after this time, all but one required single surgery ($P = <0.03$ – Table 10-.2). The explanation for repeat debridement being necessary if initial surgery is undertaken too early (excluding patients requiring fasciotomy) is probably that prior to this time, the junction between dead and viable tissue is not well defined, and too little tissue may be excised.

10.5.2.1 Hand, fingers and thumb

Necrosis and permanent disability of bitten fingers and hands is far more common than elsewhere on the body (Blaylock, 2000). Reid et al. (1963b) noted that necrosis caused by Malayan viper bites was most common in toe and finger bites, whilst Grace & Omer (1980) found functional losses due to rattlesnake bites to be most frequent in the upper extremities.

The author has not seen the sequelae of a compartment syndrome involving the hand, foot or associated fingers and toes. Compartment syndromes do occur but these compartments spontaneously decompress as they are not bound by tough fascia (such as fascia lata), and necrosis in this situation is venom induced and involves part of a compartment.

Huang *et al.* (1978) in North America describe early excisional therapy for bites of the hand and fingers. The rationale is that this will eliminate the possibilities of delayed systemic intoxication, further local tissue damage and allergic reactions to antivenom,

which is only administered for systemic toxicity. Of 22 historical controls using this method, 15 (68,2%) developed necrosis of which seven (32%) required amputation. Early excisional therapy was carried out on 61 prospective patients, of whom five (8,2%) developed necrosis and permanent disability. Almost all the patients were bitten by *Viperidae* (rattle snakes, water moccasins and copperheads). Haemorrhagic tissue was excised except tendons, nerves and large vessels. The wounds were closed immediately or closure was delayed until tissue viability had been ascertained. This compares to 41 Eshowe patients with hand and finger bites, 36 of whom developed PPS. Seventeen (41,5%) developed necrosis and six (15%) permanent disability (Blaylock, 2000). These two series are not comparable due to the different snake species involved, and most bites treated at Eshowe did not lead to delineated haemorrhagic tissue. The four snakes in Eshowe responsible for painful progressive swelling are the Mozambique spitting cobra, Bibron's stiletto snake, the puff adder and the rhombic night adder. The necrosis rates for envenomation from spitting cobra bites is about 90%, but it has yet to be described for a night adder bite, with the rates of necrosis from the bites of the other two lying in between..

Haemorrhagic necrosis only occurs with puff adder bites, while the limits of envenomed tissue are not macroscopically visible with the other bites. Snakebite victims in Southern Africa do not reach hospital as early as they do in North America, and if this early surgical regimen were adopted in Southern Africa, many patients would be subjected to unnecessary surgery as envenomed tissue in most cases would be non-haemorrhagic and ill-defined. The long fangs of the puff adder deposit venom deeply, often into important structures, and thrombocytopenia would require prior control.

To maintain or achieve normal finger and hand function, physiotherapy to put all the joints through the full range of movement should be commenced early. This can be achieved with hand and finger bites within 2 - 4 days when pain has subsided. Waiting for 7 days before surgery is carried out does not put the hand at risk of diminished function. The situation is different in septic hands, where delay leads to further tissue destruction and scar formation.

Surgery was required for all 14 fingers or hands and five of 13 necrotic areas in other anatomical locations (P = <0,001). This discrepancy is due to fingers and hands containing many delicate important anatomical structures near the skin, damage to which easily disrupts important functions. The aim in surgery is to disrupt function for the shortest possible time, resulting in the least permanent loss of function.

10.5.3 Skin closure (Table 10-2)

Five areas requiring debridement healed spontaneously (E19, E200, E255, E300). Delayed primary skin closure two days after debridement was successful in the only case where it was attempted (E318), while a secondary skin closure failed and was followed by a split skin graft (E14). In six cases, first-time split skin grafts were successful (E22, E51, E120, E122, E281), while later split skin grafts were carried out in E232 and E286 to the dorsum of the hand following amputations.

Patient E199 was bitten on a finger and the opposite hand while catching a snake that had crawled inside his trousers (he bit its head off!). Both hands were debrided on

day 8 and skin was grafted on day 19, together with an axial tensor fascia lata flap transferred to the right hand for full-thickness skin cover to the dorsal tendons. The pedicle was divided on day 39. Good function was obtained. An axial reverse radial forearm flap would now be preferred as it is less bulky, does not immobilise the patient prior to pedicle division, and allows easier physiotherapy.

Algorithm 10–1

Surgery for bite site complications

Blisters: leave alone

Deep haematomas: aspirate or drain

Necrosis: debridement most common in hand and finger bites

Time of debridement: not before 5 - 7 days

Wound closure: standard surgical procedures

Local physiotherapy: when severe has pain subsided (2 – 4 days)

Late surgery: Reconstruction

Amputation

Excision/amputation for malignancy

CHAPTER 11

SURGERY FOR REGIONAL COMPLICATIONS

CONTENTS

11. Surgery for regional complications

11.1 Abstract

Objective: To assess the prevalence of regional complications in snakebite patients and to suggest management strategies.

Method: Prospectively studied Eshowe snakebite patients were analysed.

Results: Compartment syndromes requiring fasciotomy occurred in four of 333 (1,2%) of Eshowe patients or in 282 (1,4%) patients with the painful progressive swelling syndrome. Femoral vessel entrapment syndrome was noted in a single patient.

Conclusion: Compartment syndromes may be successfully treated with intravenous fluids, elevation, antivenom and mannitol. Failure of medical management warrants open full-length fasciotomy provided there is no coagulopathy. Temporary carpal tunnel syndrome may complicate hand and finger bites. Femoral vessel entrapment syndrome may require division of the inguinal ligament.

11.2 Introduction

Regional complications of snakebite pertain to the bitten limb and are not limited to the bite site. They include compartment and entrapment (vessel or nerve) syndromes and deep haematomas. Compartment syndrome occurs when the pressure in a comparatively inelastic fascial or osseofascial compartment rises to a level that impedes capillary perfusion and threatens the viability of contained tissue. In the case of snakebite the rise in intra-compartmental pressure (ICP) may be due to an increase in compartment fluid content or to externally applied (tourniquet) pressure. Capillary perfusion is directly related to pressure at the arterial end (30 - 35 mmHg) and the

venous end (10 - 15 mmHg) which are in turn related to arterial systolic and venous pressure.

In the case of snakebite these syndromes are confined to the limbs, hands, feet and digits. Acral compartment syndromes may be caused by bites from snakes with short fangs (Mozambique spitting cobras, stiletto snakes and small adders), where compartments are close to skin; while compartment syndrome of the limbs requires long fangs to penetrate deep fascia and are mainly due to bites by the puff adder and Gaboon adder.

Intra-compartmental venom causes inflammation and fluid extravasation, which raises ICP. Venous obstruction, venous hypertension and narrowed capillaries with lumens already reduced by endothelial oedema set the stage for obstruction by macro leukocytes, fibrin and thrombus. Such a situation is usually accompanied by oligaemic hypotension, with the net result of slow or no capillary perfusion.

Uncommon femoral and axillary vessel entrapment deep to the inguinal ligament or in the thoracic outlet respectively, due to the presence of massive ascending swelling in these regions with associated lymphadenopathy, impedes venous return and diminishes arterial input, further diminishing capillary perfusion. Carpal tunnel syndrome is the most common nerve entrapment syndrome encountered.

11.2.1 Diagnosis

Compartment syndrome is normally suspected when there is pain out of proportion to the pathology, pain on passive stretching of muscles, paraesthesia or diminished

sensation of nerves running through the compartment, paresis, palpable tenseness in the compartment and the presence of distal pulses.

These symptoms and signs are easily mimicked by a snakebite without compartment syndrome (Mubarak & Hargens, 1983). In snakebite, pain is frequently out of proportion to the amount of swelling, especially if hands are involved. Hyperalgesia has been shown in rats injected with South American *Bothrops* venom (Texeira *et al.*, 1994; Chacur *et al.*, 2001), and it is a subjective impression that hyperalgesia occurs with Southern African necrotising venoms, which is a justifiable cause of incorrect and excessive diagnoses of compartment syndrome. In snakebite, paraesthesia and hypoaesthesia may be venom induced; paresis is due to pain; muscles are painful on passive stretching; the oedematous thick indurated skin may give a false impression of raised ICP; and pulses are usually present.

With clinical experience finger palpation of ICP is reliable through tender indurated overlying skin. Distant hypoaesthesia in the distribution of nerves travelling through the compartment is additive. Direct measurement of ICP is more accurate using the techniques by Whitesides *et al.* (1975); Matsen *et al.* (1976) or Rorabeck *et al*, (1981) and connecting the needle or catheter to a fluid-filled column (central venous pressure measuring set), micro-processor or arterial pressure monitor.

Fasciotomies are considered when compartment syndrome is suspected or in adults if the ICP is within 20 mmHg of diastolic pressure, and in children if the ICP is within 30 mmHg of the mean arterial pressure (Mars and Hadley, 1998).

11.3 Materials and methods

The Eshowe series of patients is analysed.

11.4 Results. Table 11-1 and figures 11-1 to 11-9

Table 11-1 Eshowe patients with compartment syndromes

Eshowe Number	24	39	48	210
Age years	40	11	11	15
Bite site	Right wrist	Right thigh	Right foot	Above right ankle.
Loss of sensation	?	Below knee	Dorsum of foot	?
Acral pulses	Palpable	Just palpable	?	Not palpable or detected with Doppler.
Compartment pressures	Not measured	Anterior tibial 90 mmHg. Posterior calf 120 mmHg. Anterior thigh 190 mmHg.	Right anterior tibial 140 mmHg. Posterior calf 110 mmHg. Left: Anterior tibial 30 mmHg.	Palpably high.
Time of fasciotomy after bite (hours)	Missed compartment syndrome	43	31	18
Time of fasciotomy after admission to hospital (hours)		26	26	5
Day(s) at debridement	12, 15, 64		29.43	5, 18, 27, 53
Day(s) at wound closure	Skin graft: 29, 78		Skin graft : 50	Closure thigh: 7 Partial closure medial calf: 7 Skin graft: 32
Outcome	Significant necrosis of extensor and flexor forearm muscles.	Died day 4 with Hb 2g/dl. Platelets 17 x 10^9/l (were 5 x 10^9/l).	Necrosis of tendon.	Necrosis of anterior tibial and peroneal muscles and skin dorsum of foot.

Compartment pressures were measured by the Whitesides method using a tubed central venous pressure measuring set.
Patient E24: The compartment syndromes were clinically missed.
Patient E210: Some leg muscle flow was only established after division of the inguinal ligament (vessel entrapment syndrome).
Fasciotomy was considered for patients E300 (gross swelling), 148, 256 (severe swelling) and 21 (moderate swelling).

Patient E64 who was bitten on the foot developed a deep haematoma of the calf which resorbed spontaneously and is considered a regional complication.

11.5 Discussion

11.5.1 Compartment syndrome

Compartment syndrome requiring fasciotomy is uncommon following snakebite, and was present in four (1,4%) of 285 bites of 282 patients with painful progressive swelling. It manifested as painful progressive swelling in the present series.

Of a total of 1 870 cases of snakebites in Southern Africa (Chapman, 1968; Blaylock, 1982a; Coetzer & Tilbury, 1982; Tilbury, 1982; McNally & Reitz, 1987; Tilbury & Branch, 1989; Wilkinson, 1994; Yerzingatsian, 1997), not one patient had a fasciotomy and there is no mention of the specific sequelae of compartment syndrome. In contrast, Scharf & du Plessis (1993) performed forearm fasciotomies (and an arm fasciotomy on one) on all 12 patients bitten on the fingers by puff adders, and all required partial or complete finger amputation. These authors performed fasciotomies on eight of 12 patients with bites of the leg, the results of which are unknown.

North American rattlesnake and puff adder bites present in a similar fashion. Russell *et al.* (1975), in discussing rattlesnake bites, states that "Fasciotomy should be discouraged", and "We have not observed the need for this measure in the early management of more than 500 cases of snake venom poisoning". On the same theme, Glass (1976) advocated surgical exploration of all bites, "If the muscle is oedematous, haemorrhagic or obviously necrotic and bulges through the inspection site, the fascia is opened widely in a longitudinal direction and the necrotic muscle is thoroughly debrided". Grace & Omer (1980) suggested that as functional losses were more frequent in the upper extremities, aggressive treatment was warranted, including

fasciotomy that may turn out to be unnecessary. Roberts *et al.* (1985), performed upper limb fasciotomy only if intracompartmental pressures were raised. Mubarak & Hargens (1983) found only one of 20 patients bitten by rattlesnakes to have an ICP above 30 mmHg, which was their critical level for fasciotomy. Furthermore, their previous canine experimentation showed that fasciotomy did not appear to reverse the venom-induced muscle necrosis, with only immediate treatment of antivenom limiting it. Garfin *et al.* (1979) injected rattlesnake venom subcutaneously and intramuscularly into dogs with and without fasciotomy. When the venom was injected subcutaneously, muscle involvement was minimal, and when injected intramuscularly, fasciotomy decreased ICP but muscle destruction was not prevented. This led them to adopt a primarily medical mode of management for rattlesnake venom poisoning.

These differing views concern the immediate management of rattlesnake bites. There is less controversy if a compartment syndrome occurs later, but it is generally accepted that early antivenom management can prevent such an occurrence, which is similar to the Southern African situation.

In the case of rare vessel entrapment syndrome in snakebite as shown by patient E210, it would be important to know the regional blood pressure of the involved limb as this must be part of the equation when determining whether fasciotomy is warranted.

11.5.1.1 Diuretics

In 40 patients with bites to the lower leg, the anterior tibial compartment pressure decreased by 25% in the group that received diuretics (bendroflumethiazide) in the first 24 hours following the bite, as compared to a pressure increase of 20% in the group given a placebo (Christensen & Wulff, 1985).

Mannitol is an almost inert non-toxic hexose excreted by glomerular filtration alone and acts as an osmotic diuretic. It has been used to manage raised intracranial pressure and acute renal failure due to oligaemia and myoglobinuria, and it may prevent acute tubular necrosis (South African Medicines Formulary, 2000). Two hundred millilitres of a 20% solution administered over 20 min is suggested for snakebites in South East Asia to prevent renal damage should myoglobinuria or haemoglobinuria be present (Warrell, 1999).

Hutton et al., (1982) produced tourniquet ischaemia in the hind legs of dogs for 12 - 14 hours, and after a further 12 hours, their ICPs were raised. After perfusion with mannitol, all treated animals had decreased ICP five minutes after the initial injection, which diminished to zero within two hours. Control animals, which did not receive mannitol, maintained high or slightly increased compartment pressures.

Oredsson et al. (1994) showed, using rabbit hind legs that had been ischaemic for four hours and reperfused for two hours, that mannitol lowered ICP by removing fluid and scavenging free radicals, but was not as effective as fasciotomy in lowering ICP. Energy charge was greater and muscle injury less in mannitol-treated limbs than it was in those perfused with glucose or treated by fasciotomy. The muscle injury was

more likely due to ischaemia/reperfusion and not to the elevation of compartment pressure.

Mannitol has several theoretical advantages in the presence of compartment syndrome due to snakebite. It may prevent or reverse compartment syndrome, limit muscle necrosis and perhaps prevent acute renal failure due to associated hypotension and myoglobinuria.

Puff adder bite and mannitol infusion

No antivenom was administered. A continuous infusion of mannitol 12 g two hourly was continued until day 3 when swelling ceased progressing.

Fig. 11–1   Day 2   Swelling extended to the chest wall but the circumference
of the forearm and arm was less than expected

Fig. 11–2   Day 5

If a compartment syndrome is suspected in *Bothrops* envenomation in Colombia, the intravenous administration of 1 – 2 g/kg mannitol over 20 – 60 minutes can prevent fasciotomy (Otero, 2001).

Three patients with PPS due to snakebite were treated with mannitol. Patient E58, bitten on the calf, was given 500 ml of a 20% solution on day five as a diuretic, due to the development of significant abdominal oedema. Patient E210 (Table 9.2), bitten just above an ankle, presented with swelling up to the chest 15 hours after the bite. There was hypotension and oliguria with palpably tense compartments above and below the knee. Vigorous intravenous fluid resuscitation was commenced, which included 1 000 ml 20% mannitol. Acute renal failure did not develop. A patient (Figures 11-1 and 11-2, Blaylock, 2000), bitten by an adult puff adder on the thumb, developed a platelet count of 28 x 10 ^{9}/l four hours ten minutes post-bite with swelling spreading to the abdomen on day three. Instead of antivenom, in view of hypersensitivity, it was elected to give mannitol 12 g/50 ml (one ampoule) two hourly while swelling was still active. At no time was the circumference of the arm and forearm increased to the extent expected (Figures 11-1 and 11-2).

11.5.1.2 Elevation

Elevation of the bitten limb, although controversial (Mars and Hadley, 1998), is considered important (9.5). Elevation facilitates venous drainage and reduces venous hypertension that occurs in compartment syndrome. Venous drainage indirectly increases arterial inflow (Cywes and Louw, 1962). As elevation has an analgesic effect, this suggests that it lowers intracompartmental pressures, and it has been an

integral part of the management of PPS in this series. If compartment syndrome is suspected or potential, steep elevation is required. In children bitten on a leg, vertical elevation is used, similar to gallows or Bryant's traction, but without lifting the buttocks off the bed.

11-1 Algorithm

Suggested management of a proven or suspected compartment syndrome

|

Book theatre

|

Obtain normovolaemia

|

Treat a coagulopathy if present

|

Steep elevation

Antivenom 50 mg IVI

Mannitol 100 gm (500 ml 20%) IVI over 1 hour

(less mannitol for children)

|

Reassess at 1 - 1½ hours

|

Compartment pressure, still elevated and

no coagulopathy

|
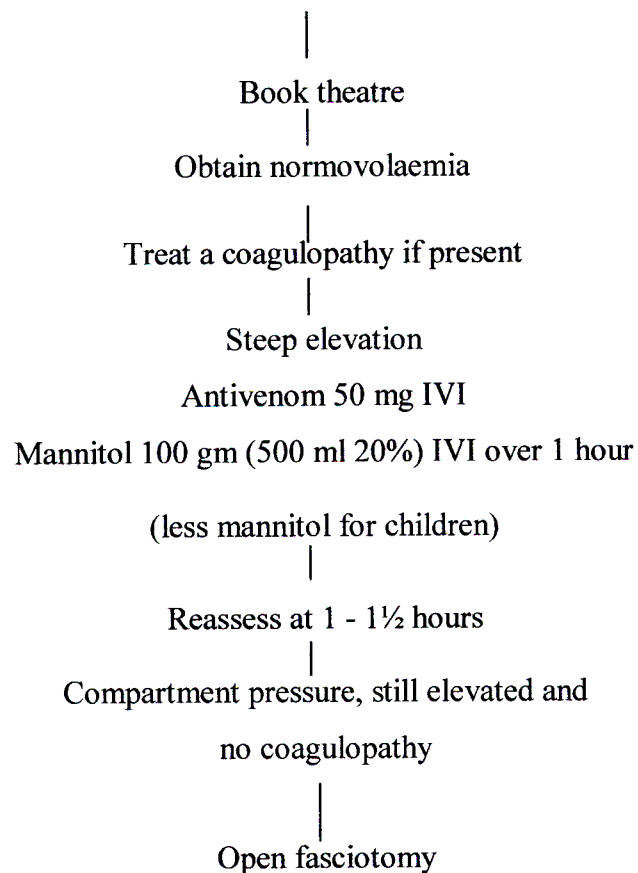
Open fasciotomy

11.5.1.3   Fasciotomy

Wide, open fasciotomy is performed when aggressive conservative management has failed. Skin incisions should be full length with decompression of all affected compartments.

11.5.1.4 Presence of coagulopathy

Patient E39 died of bleeding following a fasciotomy in the presence of a coagulopathy. It cannot be stressed enough that a fasciotomy should not be performed unless and until a coagulopathy has been controlled.

11.5.1.5 Debridement and skin closure

The three surviving patients with compartment syndromes required multiple debridements. Spilt skin grafts were performed on days 29 and 78 (E24) and day 50 (E48). Case E210 with multiple compartment syndromes of a leg and a femoral vessel entrapment syndrome, had a primary closure of the thigh wound and partial closure of the lateral leg fasciotomy wound five days after the fasciotomy. Repeat debridement of the area of muscle necrosis (anterior tibial and peroneal) was required on four occasions, with wound closure achieved by split skin graft on day 85. He subsequently developed a septic arthritis of the ankle, but the eventual outcome is unknown. Scharf & du Plessis (1993) closed their fasciotomies for puff adder bites on the $5^{th} - 7^{th}$ day.

11.5.2 Entrapment syndromes

Entrapment of nerve or vessel by adjacent tissue if it traverses a fibrous or osseofibrinous tunnel presents as a neuropathy, ischaemia or venous hypertension. Venom-induced swelling in these tunnels would be expected to precipitate these syndromes. Usually the patient has significantly more important medical problems and these syndromes are ignored or not diagnosed.

11.5.2.1 Nerve entrapment syndromes

Carpal tunnel syndrome has been described following two puff adder bites (Blaylock, 2000) and one stiletto snake bite (Blaylock, 1982b). Treatment was conservative, with the symptoms subsiding as the swelling resolved. Wilkinson (1994) performed a carpal tunnel release on one patient. Patients with this temporary syndrome are treated conservatively. If a volar forearm fasciotomy is indicated, carpal tunnel release is performed concomitantly.

11.5.2.2 Vessel entrapment syndromes

Femoral vessel entrapment syndrome

Patient E210 (Table 11-1 and figures 11-3 to 11-9) presented with compartment syndromes above and below the knee due to oedema that was present from his foot to the chest wall. He was hypotensive with unilateral absence of foot pulses using a Doppler probe. A four-compartment fasciotomy was performed below the knee together with an anterior thigh fasciotomy. There was no bleeding and restoration of blood flow was achieved by division of the inguinal ligament. The skin of the dorsum of his foot developed necrosis. It is postulated that there was femoral vessel entrapment, as evidenced by the return of arterial blood flow after division of the inguinal ligament and necrosis of skin distant to the bite site. Femoral vessel compression must aggravate or precipitate compartment syndromes in a similar fashion to severe ilio-femoral thrombosis (Qvarfordt *et al.*, 1983).

Thoracic outlet syndrome, popliteal artery entrapment, and other entrapment syndromes have yet to be ascribed to snakebite.

Compartment and femoral vessel entrapment syndrome.

Fig 11 – 3   Patient E210.   15 hours : medial side.
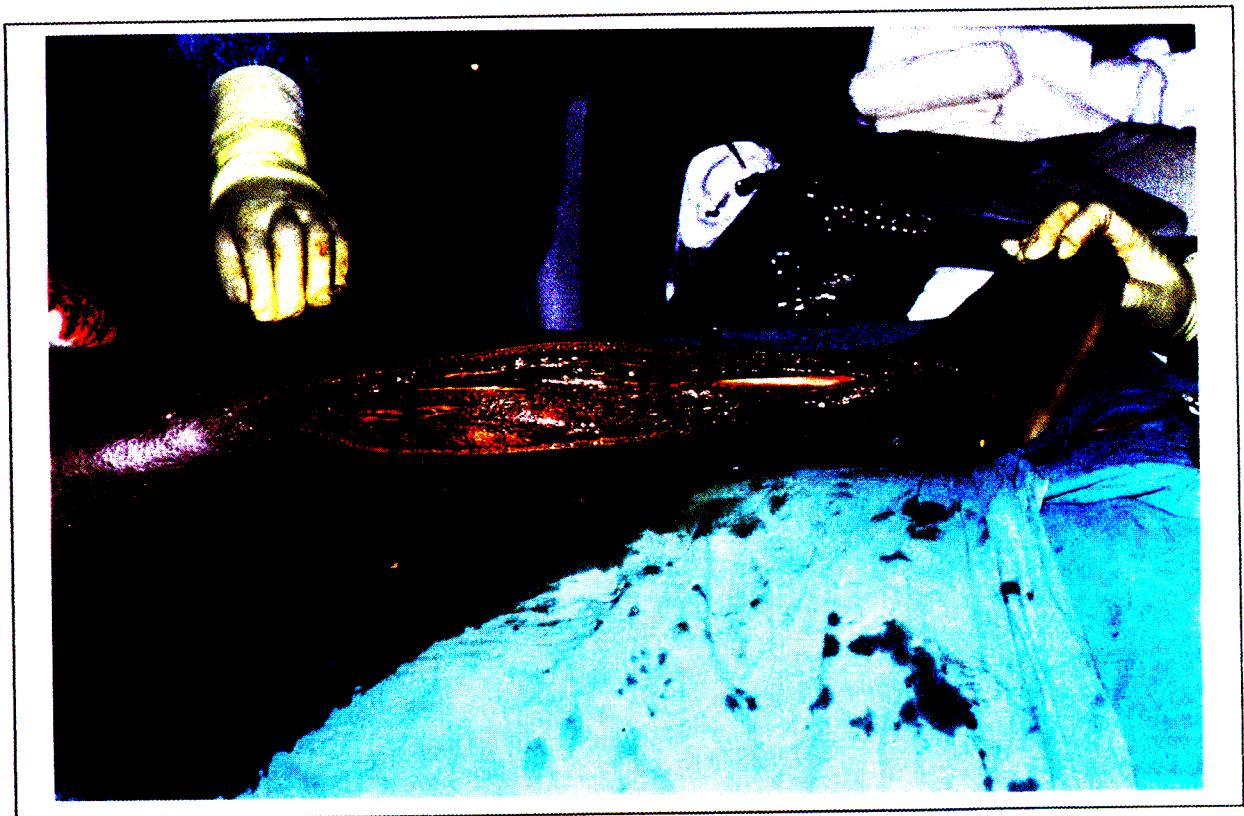
Fig 11 – 4   Patient E210.   15 hours.   Lateral side showing unhealthy muscle

Fig. 11–5 Patient E210. Thigh fasciotomy closure, day 5 (photo day 25 after bite)

Fig. 11–6   Patient E210.   Incomplete calf closure day 5 (photo day 25 after bite)
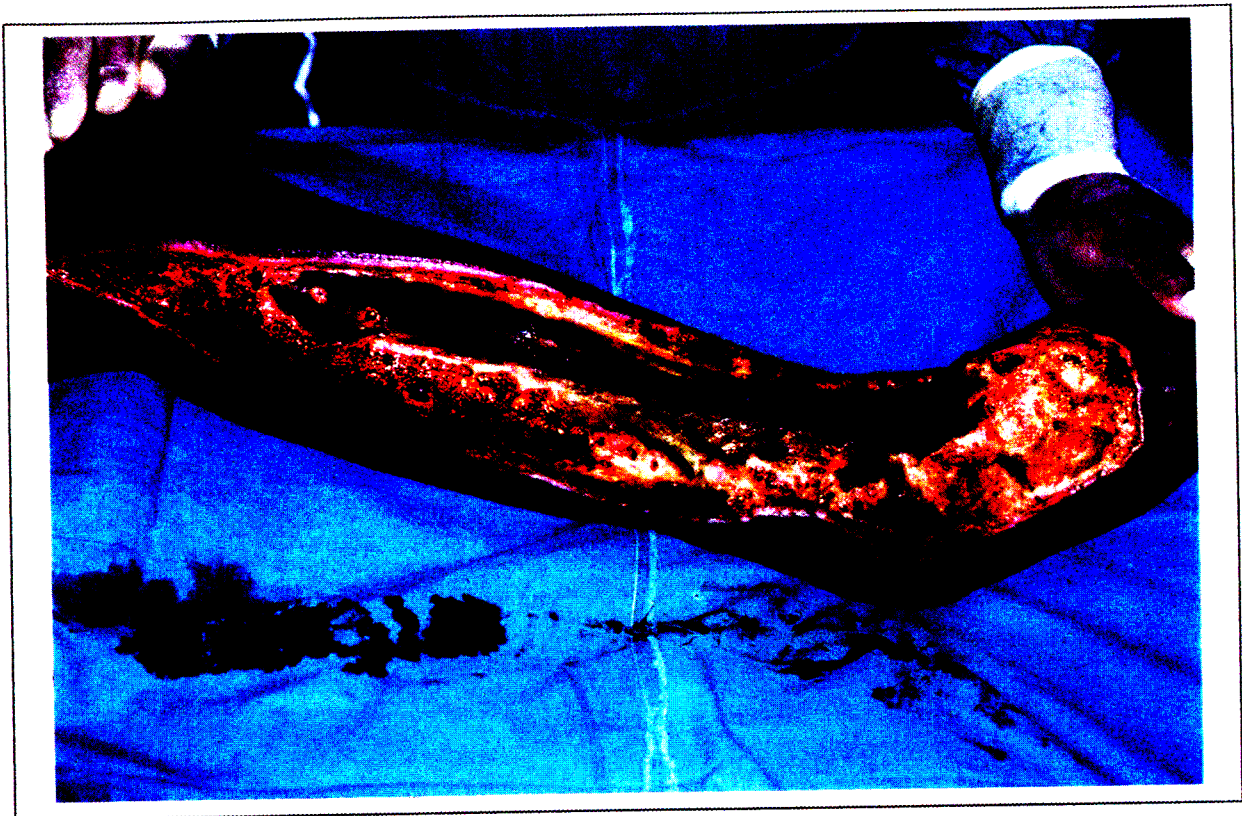
Fig 11 – 7   Patient E210. Day 25

Fig 11 – 8   Patient E210. Day 25 post debridement

Fig 11 – 9   Patient E210. Skin cover achieved. This ankle later became septic
which probably originated from his initial hospital admission.

Algorithm 11–2

Surgery for regional complications

Suspected or proven compartment syndrome

Deep haematoma
Leave /aspirate / drain

Significant entrapment syndrome

Conservative treatment
(IV fluids, elevation, mannitol, antivenom)

Vessel (probably femoral)

Nerve

failed (1 - 1½ hours)

decompression and fasciotomy

conservative treatment

absent coagulopathy

open full-length fasciotomy

CHAPTER 12

PROGRESSIVE WEAKNESS SYNDROME

CONTENTS

12.   Progressive weakness syndrome (PW)

12.1   Abstract

Objective: To analyse the treatment outcome of patients with progressive weakness (PW) and make recommendations on management.

Subjects and methods: Prospectively studied patients at Eshowe Hospital and other case histories of snakebite patients were retrospectively analysed.

Results: Ventilation by itself prevents death. In the majority of patients antivenom can prevent or reverse respiratory failure in the absence of ventilation and, if ventilated, reduce the duration of ventilation.

Conclusions: A minimum of 40 ml (preferably 80 ml) SAIMR polyvalent antivenom is indicated for severe envenomation. This is shown by dyspnoea in the absence of painful progressive swelling (PPS), generalised weakness in the presence of PPS or widespread myalgia, or an inability to swallow saliva.   Sedation is mandatory in ventilated patients, and both antibiotics and analgesics are not commonly required. Muscle relaxants are generally contraindicated.

12.2   Introduction

The term progressive weakness describes the clinical condition of a patient injected with neurotoxic venom.   It generally starts affecting all skeletal muscles to some degree before the patient becomes too weak to breathe, with resulting respiratory failure and possible death.   The time of onset of weakness is dependent on venom constituents mainly depending on snake species, the amount of venom injected and the size of the victim.   The larger the amount of venom and the smaller the patient, the

sooner the progression to weakness. Small amounts of venom, especially in large victims, may not lead to respiratory failure. Such bites may or may not lead to bite site swelling that is neither painful nor tender (mambas), or to swelling that is painful and tender (non-spitting cobras, rinkhals and berg adder).

This syndrome occurs following bites by the black and green mamba *(Dendroaspis spp,* most symptoms being compatible with parasympathetic effects), the non-spitting cobras (the forest cobra - *Naja melanoleuca,* the Cape cobra - *N. nivea,* and the snouted cobra - *N. annulifera)* and the rinkhals *(Hemachatus haemachatus),* which is not a true cobra, with alpha neurotoxic effects. Other snakebites where painful progressive swelling (PPS) is dominant, namely bites by the Berg adder *(Bitis atropos),* shield-nosed snakes *(Aspidelaps spp),* garter snakes *(Elapsoidea spp),* desert mountain adder *(Bitis xeropaga)* and Peringuey's adder *(Bitis peringueyi),* have a component of weakness probably due to beta neurotoxins. Minor neurotoxicity may occur in Gaboon adder bites *(Bitis gabonica),* where PPS and bleeding predominate.

Severe envenomation potentially leading to respiratory failure occurs in 50 – 70% of cases with PW as the primary presentation (Blaylock, 2000).

Most of the data available for analysis are on mamba envenomation, which is quicker in action and of shorter duration than envenomation by non-spitting cobras.

12.3   Materials and methods

Eshowe patients with progressive weakness are analysed for treatment and outcome and, where appropriate, a literature search was undertaken.

12.4 Results. Tables 12-1 to 12-8 and figures 12-1 to 12-4

Table 12-1 SAIMR polyvalent snakebite antivenom administered to Eshowe patients with progressive weakness

Eshowe number	Age of patient Years	Bite site	Condition at time of antivenom administration	Duration of ventilation	Comments
E6	49	Knee	Respiratory failure 5 h 10 min: 10 ml 5 h 40 min: 90 ml 23 h 10 min: 100 ml (Total 200 ml)	From 4 h 40 min for 14 h 35 min From 20 h for 21 h 20 min	Known congestive cardiac failure and asthmatic. Bronchospasm present prior to ventilation
E87	14	Calf	Respiratory failure 3 h 50 min: 100 ml	From 1 h 50 min for 5 h 10 min	Day 2: Normal
E212 Black mamba	3	Calf	Respiratory failure 4 h 30 min: 60 ml	From 3 h 25 min for 2 h 5 min	A small snake (60 cm)
E259	9	Calf	Dyspnoea 2h 30 min: 10 ml 5 h 30 min: 90 ml	Intubated at 2 h 30 min for 5 h 39 min	Not ventilated
E306	19	Leg	Ptosis Lump in throat 1 h 30 min: 90 ml	Nil	Antivenom administered prior to admission.
Antivenom was administered intravenously All patients had no envenomation morbidity on hospital discharge					

Table 12-2 SAIMR polyvalent antivenom administration for progressive weakness due to unidentified elapid species

Author and age of patient	Clinical condition at time of antivenom administration	Amount and time of antivenom administration	Duration of ventilation	Outcome
1. Visser & Chapman, 1978 47 yr (case 6)	Dyspnoea, ptosis, excessive salivation	6 h 15 min - 6 h 45 min 40 ml	Nil	7 h 30 min: Improved. 15 h: asymptomatic
2. Blaylock, 1982a 19 yr	Weak. Slurred speech. Unable to swallow. Drooling of saliva. Dyspnoea.	1 h 45 min: 10 ml IV & 10 ml IM 10 h: 40 ml IV	Nil	32 h: Well.
3. 3 yr	Unable to stand. Cold and sweating. Flaccid limbs. Stertorious respiration. Marked salivation.	1 h: 10 ml IV & 10 ml IM	After cardiac arrest	2 h 20 min: Cardiac arrest. 2 h 35 min: Died.
4. 40 yr	Cold. Sweating. Unable to stand. Unrecordable blood pressure. Unable to swallow saliva.	? time: 10 ml IM & 100 ml IV	Nil	Day 2: Speaking normally Day 3: Able to walk.
5. 38 yr	Profuse sweating. Unable to swallow. Blind. Collapsed.	2 h 12 min: 60 ml IV 2 h 25 min: 40 ml IV	Nil	4 h: Able to talk Day 2: Able to walk.
6. 23 yr	Cold and clammy. Semiconscious. Profuse salivation. Urinary incontinence. Convulsions. Respiratory failure.	3 h 3 min: 100 ml IV	From 3 h 30 min for 1 h 15 min	5 h: Able to walk.
7. 34 yr	Dyspnoea. Difficulty speaking. Sweating. Bilateral ptosis.	2 h 15 min: 60 ml IV	Nil	5 h 15 min: asymptomatic.
8. Naidoo et al., 1987 24 yr	Respiratory distress. Frothing at the mouth. Unable to speak.	2 h 15 min: 80 ml IV	From 7h 10 min following cardiac arrest for 7 days	Day 13: Full recovery
9. Delport et al., 1991 9 yr	Apnoea. Forearm compartment syndrome.	5 h: 60 ml IV	From 5 h for 14 h	13 h: Spontaneous respiratory efforts. 19 h: normal respiration.
10.Oberholzer et al 1991 Adult	Delirious, restless, ptosis, dysphagia, dysarthria, respiratory paresis, sweating, bradycardia.	6 h 15 min: 40 ml IV 9 h 15 min: 20 ml IV	From 6 h 45 min for 23 h 15 min	25 h 15 min: Breathing improved. 30 h: extubated
11. Blaylock & Canter (unpublished) 35 yr	Dyspnoeic. Collapsed. Unable to sit. Profuse sweating. Thick speech, left pin-point pupil, right corneal scar.	1 h 40 min - 2 h: 90 ml IV 4 h 15 min: 50 ml IV 10 h: 10 ml IV	Nil	2 h: deterioration, > 10 h: Able to eat and drink. 24 h: Systemically normal

IM: intramuscular   IV: intravenous

Unpublished patients reported by Visser & Chapman (1978) are used, whilst others previously published are attributed to the original author(s).

Table 12-3   SAIMR polyvalent antivenom administered for black mamba bites

Author, age of patient and snake length (metres)	Clinical condition at time of antivenom administration	Amount and time of antivenom administration	Duration of ventilation	Outcome
(1) Strover, 1967. Adult	Weak. Diaphragmatic respiration only.	1 h 30 min: 20 ml IV	Nil	Died at 4 h 30 min.
(2).Krengel 1967. 34 yr 3,08 m	? Respiratory failure	Soon: 70 ml IM 8 h 30 min: 80 ml IV	From 8 h 30 min for < 10 h	Well day 2
(3) Visser & Chapman, 1978. 24 yr. 2,05 m	Dyspnoea	0 - 4 h 45 min: 14 ml IM & 65 ml IV	Nil CPR at 6 h 30 min	Respiratory failure at 6 h 30 min. Died at 8 h
(4) Saunders, 1980. 35 yr. 2,24 m	Known full black mamba bite.	14 min: 60 ml IV 31 min: 60 ml IV	Nil (Arterial tourniquet)	Local muscle fasciculation for 5 days. Local induration for 2 weeks.
(5) Crisp, 1985. 2 yr. 1,5m	Moribund.	1 h 55 min - 2 h 10 min: 40 ml IV	Nil	2 h 45 min: Responds to commands. 3 h30 min: Able to sit and is alert.
(6) Hilligan, 1987. 14 months 0,45 m	Laboured breathing.	± 40 min - 1 h 25 min: 70 ml IV	Nil	< 1 h: Breathing easier. 1 h 20 min: Vital signs stable.
(7) 34 yr 2,25 m	Dizzy, restless, sweating, constricted throat.	± 40 min -1 h 20 min: 70 ml IV	Nil	After 40 ml antivenom: Asymptomatic but restless and hypotensive for 40 min.
(8) Haagner, 1990. 28 yr 1,92 m	Weak and dyspnoeic.	33 min: 100 ml IV	Nil	3 h 12 min: Breathing easier.
(9) Durrant & Haagner, 1992. 41 yr 3,06 m	Unable to swallow. Profuse sweating, weak, tightness of chest.	70 min: 50 ml IV 1 h 45 min: 20 ml IV 5 h 25 min: 70 ml IV 16 h 55 min: 50 ml IV	From 4 h 5 min. for 39 h50 min	4 h 5 min: Respiratory distress. 44 h: extubated.
(10) Blaylock, 2000. Case 11 13 months 0,65 m	Respiratory and cardiac arrest.	25 - 55 min: 90 ml IV	From 15 min for 1 h 10 min	1 h 25 min: spontaneous respiration. 2 h 10 min: extubated.
IM: intramuscular	IV: intravenous			

Table 12-4   SAIMR trivalent mamba antivenom for progressive weakness due to unidentified elapid bites

Author and age of patient	Clinical condition at time of antivenom administration	Amount and time of antivenom administration	Duration of ventilation	Outcome
Louw, 1967. 1. 45 yr	Dyspnoea, slurred speech, diplopia, bradycardia	3 h 30 min: mamba antivenom 20 ml IV & 20 ml IM	Nil	4 h 30 min: Deteriorated followed by improvement. 16 h: Normal
2. 12 yr	Normal	1 h: 10 ml polyvalent antivenom IV		Deteriorated
	Dyspnoea, paretic, moribund	4 h: mamba antivenom 30 ml IV and 10 ml IM	From 4 h for 1 h	18 h: Normal
Edington, 1973. 3. 9 yr	Dyspnoeic and foaming at mouth	45 min: 10 ml polyvalent antivenom IV and 10 ml mamba antivenom IV	From 45 min for 16 h 45 min	1 h 45 min: Cardiac arrest later repeated.
		3h: 30 ml polyvalent antivenom and 20 ml mamba antivenom IV ? Time: 100 ml polyvalent antivenom IV 6 h 30 min: 100 ml polyvalent antivenom IV		No effect 11 h 30 min: Leg movement. 14 h 20 min: Moving all limbs, 17 h 30 min: Extubated
Visser & Chapman, 1978. 4. 37 yr	Pins and needles. Muscle spasms. Respiratory failure	25 min: 10 – 20 ml^x 1 h: 10 ml^x 2 h 45 min: 10 ml 6 h: 10 ml	Nil	1 h 35 min: much improved. Respiration 30/min. 2 h 45 min: Slightly laboured breathing. 6 h: Worse 7 h: Well
IM: intramuscular IV: intravenous				

Table 12–5   SAIMR polyvalent antivenom administered for specific elapid bites

Author and age of patient	Clinical condition at time of antivenom administration	Amount and time of antivenom administration	Ventilation	Outcome
Eastern green mamba				
1. Visser & Chapman, 1978. 26 yr (case 7)	Unconscious. Laboured breathing	40 min - 1 h 40 min: 90 ml IV	No	Slow improvement. 12 h: asymptomatic
2. Haagner, 1987. 25 yr	Dyspnoeic. Profuse perspiration	1 h 10 min: 40 ml IV	No	3 h 20 min: breathing improved.
Cape cobra				
Blaylock *et al.*, 1985. 3. Case 1: 53 yr	Dry mouth, sweating, ptosis, unsteady on feet Convulsion then flaccid paralysis	1 h: - 10 ml IV 7 h: 90 ml IV 17 h: 90 ml IV	From 4 h to day 6	2 h 15 min: assisted ventilation. 4 h: intubated and ventilated No effect No effect Day 3: opened eyes, moved tongue and left leg. Day 6: moved arms and legs. Day 6: extubated
	20 h: 5 mg prostigmine & 1,2 mg atropine iv. Peripheral stimulation of ulnar nerve changed from no response to post-tetanic facilitation. 40 h: 3/4 response to chain of 4 impulses with post-tetanic facilitation. Prostigmine 2,5 mg: dramatic increase in twitch size and improvement in motor response to command			
4. Case 2: 26 yr	Unknown Flaccid paralysis Flaccid paralysis	2 h: 40 ml IM and 20 ml IV 4 h 30 min: 40 ml IV 11 h 30 min: 60 ml IV Day 5: 40 ml IV	From 2 h 30 min to day 8	2 h 30 min: unconscious and paralysed. Opened eyes, moved legs. Weak No effect Day 2: movement of hands and head. Day 3: opened eyes, moved head and shoulders No effect Day 8: extubated
	11 h 30 min: 5 mg prostigmine iv had no effect			
Rinkhals				
5. Blaylock, 2000.	Swollen hand and forearm. Drowsy, disorientated, shallow respiration and unable to sit up.	15 h: 60 ml IV	No	17 h: Dramatically improved. Minor necrosis
Snouted cobra				
6. Alves, 1960. Repeated by Visser & Chapman, 1978. Case B	6 h 45 min: moribund	1 h 5 min: 10 ml SC and IM 2 h 15 min: 10 ml Sometime: 30 ml	From: 9 h 15 min	Died at 17 h

IM: intramuscular   IV: intravenous   SC: subcutaneous

Table 12-6   Inappropriate volumes of antivenom administered to dyspnoeic patients and progression to ventilation

Author, age of patient and snake length (metres)	Peak illness	Ventilation
BLACK MAMBA		
1. Read & Foster, 1959. Adult 3, 22 m	Dyspnoeic	Nil
2. Blake, 1960. 26 yr 2 m	Dyspnoeic	Nil
3. Strover, 1967. Adult, case 1, Table B2	Respiratory failure	Nil. Died
4. Haagner & Morgan, 1991. 28 yr 1,1 m	Dyspnoeic Unconscious	Nil
Blaylock, 2000. 5. Case 8 16 yr 1,5m	Respiratory failure	From 3 h for 14 h
6. Case 9 14 yr 2,9m	Respiratory failure	From 3 h 30 min for 47 h
7. Case 12 18 yr 2,25m	Respiratory failure	From 45 min for 3 h 35 min
8. Case 20 25 yr Large	Respiratory failure (Arterial tourniquet)	From 2 h 15 min for 41 h 50 min
UNIDENTIFIED ELAPIDS		
9. Blaylock, 1982a. (No. 3, table B1)	Respiratory failure	Nil. Died
10. Harvey, 1985. 50 yr	Respiratory failure	From 4h 30 min for ± 63 h
McNally & Reitz, 1987. 11. 16 yr	Respiratory failure	Nil. Died
12. Unknown age	Presumed respiratory failure	Nil. Died
13. Unknown age	Presumed respiratory failure	Nil. Died
Inappropriate antivenom is defined as less that 40 ml SAIMR polyvalent antivenom or Behringwerke antivenom in Southern African patients		

Table 12-7   Collapsed or dyspnoeic patients. Antivenom and ventilation

Patients from Tables 12-1 to 12-6

	Nil or inappropriate antivenom	Appropriate antivenom	Fisher's exact test P =
	n 13 Patients 1 - 13 (Table G5)	n 26 Patients E87, E212, E259 (Table 12-1), 1, 2, 4, 5, 6, 7, 9,10, 11 (Table G1), 2, 3, 5, 6, 8, 9, 10 (Table G2), 1,2, 3, 4 (Table G3), 1, 2, 5 (Table G4)	
Died	(38%) (5 of 13)	(4%) (1 of 26)	0,0108
Ventilated	(38%) n 5	(38%) n 10	1,0000
Mean duration of ventilation in those ventilated	33 h 53 min n 5	11 h 27 min n 10	> or < 24 h 0,0769
Range of ventilation	3 h 35 min - 63 h	45 min - 39 h 50 min	
Ventilated and survived	n 5 100%	n 10 100%	
Not ventilated and survived	38% (3 of 8)	94% (15 of 16)	0.0069

n: number
Exclusions: E6: Known asthmatic with congestive cardiac failure.
Case 8, Table G1: Ventilated after cardiac arrest and suffered a myocardial infarction.
Cape cobra bites, Table G4: No response to antivenom once paralysed.
Snouted cobra bite, Table G4: Ventilated late and unknown time of final 30 ml antivenom administration.

Table 12-8 Volume of SAIMR polyvalent antivenom administered to dyspnoeic or collapsed patients who were not ventilated (Tables 12-1 to 12-6)

Amount of antivenom	Patients Number and Table	Outcome	Death
10 -30 ml	3, Table 12-2 1, Table 12-3 (black mamba) McNally & Reitz, 1987 11, 12, 13 Table 12-6	Died at 2 h 35 min Died at 4 h 30 min All died the same day	All 5
40 ml	1, Table 12-2 5, Table 12-3 (black mamba) 1, Table 12-4 2, Table 12-5 (green mamba)	Improved at 7 h 30 min Responded to commands at 2 h 45 min Normal at 16 h Breathing improved at 3 h 20 min	0 of 4
60 - 79 ml	E212, Table 12-1 2, Table 12-2 7, Table 12-2 3, Table 12-3 (black mamba) 6, Table 12-3 (black mamba) 7, Table 12-3 (black mamba) 5, Table 12-5 (rinkhals)	Ventilated for 2 h 5 min Well at 32 h Asymptomatic at 5 h 15 min Died at 8 h Vital signs stable at 1 h 20 min Survived Dramatically improved at 17 h	1 of 7
80 ml or more	E87, Table 12-1 E259, Table 12-1 4, Table 12-2 5, Table 12-2 11, Table 12-2 8, Table 12-3 (black mamba) 1, Table 12-5 (green mamba)	Normal day 2 Intubated but not ventilated Spoke normally on day 2 Able to talk at 4 h Able to eat and drink at 10 h Breathing easier at 3 h 12 min Asymptomatic at 12 h	0 of 7

All patients were dyspnoeic or collapsed but did not necessarily have the same degree of envenomation.
Patient 3 (Table 12-2) was severely envenomed following 3 bites by a 205-cm black mamba.
In view of these results, the appropriate antivenom volume is defined as 40 ml or more.

12.5   Discussion

12.5.1 General

Respiratory failure due to progressive weakness is mainly due to temporary restrictive lung diseases ("pump failure") with possible components from excessive lung secretions, pulmonary oedema and ineffective or absent coughing. Excessive oral secretions and an inability to swallow may lead to aspiration.

Management aims to combat this. Excessive oral secretions may be managed by placing the patient on the side, oral suction, endotracheal intubation or tracheostomy. Respiratory drive is PCO_2 and pH stimulated, with respiratory failure managed by ventilation should oxygen supplied by face mask fail.

Dyspnoea suggests impending respiratory failure. There is an increase in the breathing rate, falling tidal volume and associated tachycardia. The ability to inhale is more important than exhalation. Breathing that is solely diaphragmatic with a bradycardia signifies significant hypoxia and a preterminal state.

The necessity for ventilation is easily clinically assessed. Repeated special investigations are helpful in determining whether a patient is improving or deteriorating. These include measurement of forced vital capacity or forced expiratory volume in one second using flow volume loop spirometry, peak expiratory flow rate using a Wright's spirometer, pulse oximetry or arterial blood gas estimations.

Once a decision to ventilate is made, it can be done by mouth-to-mouth or nose, mask and bag, or intubation and mechanical ventilation.

12.5.2   Ventilation

All ventilated patients survived whether or not they received antivenom (Table 12-7). This reiterates the importance of ventilation over any other treatment.

12.5.3   Muscle relaxants

These are not recommended.   Unusually, a short-acting muscle relaxant such as suxamethonium chloride may aid intubation in struggling, restless or hypoxic patients.

12.5.4   Sedation

Sedation is extremely important during ventilation. After recovery following ventilation, several patients have complained that although they were totally paralysed, they could hear and understand what was said. This included doctors' conversations concerning their ignorance of treatment and prognosis and, in one case, a conversation concerning the switching off of the ventilator in view of the "hopeless prognosis". All recovered fully to tell the story.

12.5.5 Antibiotics

In the absence of local bite site interference and necrosis, infection does not occur. Antibiotics may be indicated for aspiration or ventilation-induced pneumonia.

12.5.6 Analgesics

In the case of mamba bites, bite site pain is minimal. However, non-spitting cobra bites and adder bites result in painful progressive swelling which, as the name implies, is painful.

12.5.7 Antivenom

The outcome of patients given appropriate antivenom is compared to those who received inappropriate antivenom. In view of the response of patients in Table 12–8, appropriate antivenom is defined as 40 ml or more of polyvalent antivenom or, in the case of clinically suspected black mamba bites, 40 ml or more of specific mamba antivenom (no longer manufactured) or a combination of these antivenoms. Inappropriate antivenom is defined as less than 40 ml or antivenom manufactured from venom obtained from outside Southern Africa in view of the geographical variation of snake venom.

Patients who were dyspnoeic or collapsed due to progressive weakness are included in this analysis. Excluded patients are listed in Table 12–7. The majority of patients analysed will have been bitten by black mambas due to the prevalence of this snake species in the geographical areas where they were bitten.

12.5.7.1 Prevention of death

In the group of non-ventilated dyspnoeic patients receiving inappropriate and appropriate antivenom respectively (Table 12-7), five of eight and one of 16 died ($P = 0{,}007$). Clearly, antivenom in the appropriate dosage can reverse dyspnoea or respiratory failure in the absence of ventilation.

12.5.7.2 Reduction of the period of ventilation

The mean duration of ventilation in the inappropriate and appropriate antivenom groups is 33 h 53 min (range: 3 h 35 min to 63 h) and 11 h 27 min (range: 1 h 10 min to 39 h 50 min) respectively. This strongly suggests that appropriate antivenom can reduce the time necessary for ventilation. The shortest periods of ventilation are achieved by a responsible doctor remaining at the bedside (cases E212, Table 12-1; and 10, Table12-3). Longer periods result from overnight ventilation in the absence of expert care, and especially when muscle relaxants are used.

12.5.7.3 Specific snakes

Black mamba envenomation (Tables 12-1 and 12-3, Figs 12–1 to 12–4)

Almost all these cases are probable black mamba bites in view of the evolving history of envenomation and the prevalence of black mambas in the geographical areas where the bites occurred. Probable exceptions include those stated and the case reported by Delport *et al.* (1991) with compartment syndrome, and that by Oberholzer *et al.* (1991). These two cases are compatible with a snouted cobra or rinkhals bite.

Eastern green mamba envenomation (Table 12-4)

Green mamba envenomation appears to be less severe than black mamba envenomation, based on seven green mamba bites (Blaylock, 2000). Two patients with dyspnoea did not require ventilation after antivenom administration.

Cape cobra envenomation (Table 12-4)

While both cases were being ventilated, doses of 190 ml and 180 ml were of no clinical benefit, and ventilation was required until days 6 and 8 respectively. Antivenom may be of value prior to respiratory failure only if the venom can be neutralised before it is fixed to its post-synaptic receptor, but once established, the antivenom doses used were of no value, perhaps due to stable toxin binding. This is compatible with Christensen's (1969) findings that, in comparison to the amount of antivenom in an injected admixture of venom and antivenom, only moderately larger amounts of intravenous antivenom could save Cape cobra envenomed mice at 30 minutes. There was no increased chance of survival with larger amounts of antivenom after 40 minutes. $F(ab^1)_2$ antivenom in doses up to 450 ml is often necessary to reverse or eliminate the symptoms of *Naja kouthia* envenomation (Far Eastern monocled cobra, Viravan *et al.*, 1986).

Black mamba bite.   Patient E212

Fig. 12–1   Face mask-bag ventilation 3½ h after the bite
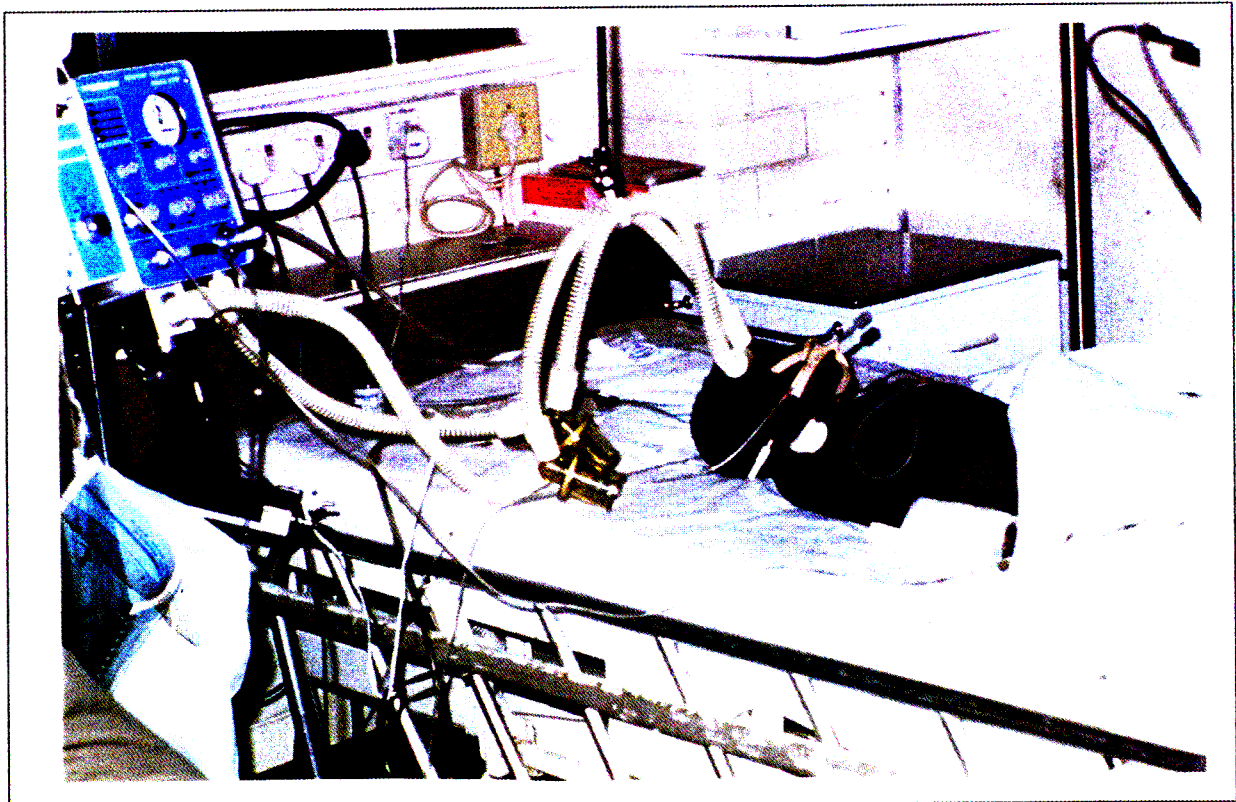
**Fig. 12–2   60 ml SAIMR polyvalent antivenom administered intravenously.
Mechanically ventilated for 2 h 5 min**

Patient E 212

Fig. 12–3   Tissue oxygen saturation 100%, pulse rate 147/min

Fig 12–4   Offending immature snake. Day 2, waiting to go home.

Snouted cobra envenomation

There are too few published cases from which to draw conclusions on the efficacy of antivenom.

12.5.7.4 Indications

Indications for antivenom administration for neurotoxic bites suggested in published papers and medical booklets (Tables 7-2, 7-3) vary, and include bites by specific snake species without clinical envenomation (cobras, mambas, black mambas), signs of poisoning, cranial nerve palsies with or without paresis, diminishing peak expiratory flow rate, dyspnoea, cyanosis or shock, depending on the author. Bites by these snakes may lead to envenomation not being clinically evident or falling short of respiratory failure.

Antivenom is best administered at the onset of dyspnoea (if it occurs) to prevent respiratory failure. Flaccid paralysis caused by a Cape cobra bite cannot be reversed with SAIMR antivenom in doses up to 190 ml, but antivenom may be of value at the onset of paresis prior to dyspnoea. This is accounted for by the recommended indications for antivenom.

Bites by the berg adder, desert mountain adder, Peringuey's adder and rinkhals usually cause the development of cranial nerve dysfunction, with paresis uncommonly progressing to respiratory failure. Cranial nerve dysfunction is not automatically associated with later respiratory failure and, for this reason, cranial nerve palsies per se are not an indication for antivenom use.

A.   Dyspnoea (non-tender swelling may be present around the bite)

In the majority of patients with dyspnoea, the progression to respiratory failure can be prevented.

B.   Generalised paresis with painful progressive swelling or generalised myalgia

The former accounts for patients who, when paralysed, may not benefit from antivenom (e.g. Cape cobra bites), while in the latter, sea snake bites (uncommon) may be considered.

C. Reduction of the period of ventilation

In most cases the duration of ventilation can be shortened by antivenom except for Cape cobra bites, where the standard dose of antivenom appears to be of no value.

12.5.7.5 Dose of antivenom

Table 12-8 shows that all five patients receiving antivenom in a dose of 10 to 30 ml in the absence of ventilation died, whilst one of seven patients receiving between 60 - 79 ml died. It may be that this single latter death was due to antivenom administered in the presence of irreversible anoxic damage, or a huge amount of venom was injected. All seven patients receiving 80 ml or more of antivenom survived. It is suggested that 40 ml is the minimum effective dose and that 80 ml should be used if antivenom is

freely available. Further doses of antivenom may be necessary if there is no improvement within 30 minutes to an hour.

12.5.7.6 Route of administration (see 7.5.3)

Antivenom is maximally effective when given intravenously. Should this be impossible, the intramuscular route is the next best. By the time antivenom is indicated, it is too late for local infiltration around the bite site.

Algorithm 12-1

Management of progressive weakness

|

Maintain oxygenation

|

If necessary: Clear airway
Coma position
Ventilate, sedate, do not paralyse

|

Suggested indications for antivenom

Dyspnoea due to generalised paresis in the absence of painful progressive swelling (mambas)

Generalised paresis in the presence of

a) painful progressive swelling (non-spitting cobras)

b) widespread myalgia (sea snakes)

Inability to swallow saliva

Electrocardiogram evidence of cardiotoxicity (extremely rare).

Cranial nerve palsies per se may not be followed by respiratory failure.

40 ml of SAIMR polyvalent snakebite antivenom is the minimum effective dose. 80 ml is suggested and may need to be repeated.

All antivenom is given as a slow intravenous injection without prior sensitivity testing.

CHAPTER 13

THE EFFECT OF ATROPINE, CHOLINESTERASE REACTIVATORS AND NEOSTIGMINE ON BLACK MAMBA-INDUCED RESPIRATORY FAILURE IN MICE

CONTENTS

13. THE EFFECT OF ATROPINE, CHOLINESTERASE REACTIVATORS AND NEOSTIGMINE ON BLACK MAMBA-INDUCED RESPIRATORY FAILURE IN MICE

13.1 Abstract

Objective: To assess whether atropine, obidoxime or neostigmine could delay the onset of apnoea in black mamba-envenomed mice.

Materials: Black mamba venom (BMV) 2 x $LD_{50}/0,1$ ml normal saline solution, atropine sulphate, obidoxime chloride, neostigmine, ketamine and specified pathogen-free NMRI mice.

Method: Study 1: Thirty-six mice were injected with ketamine intramuscularly (IMI), followed by 15 µg BMV subcutaneously (SCI) 15 minutes later. After the anaesthetic, three groups of three mice each were immediately injected with atropine 0,25, 0,5 or 1 mg/kg intraperitoneally (IPI). Six groups of three mice were either injected with obidoxime (1, 4 or 8 mg/kg) intravenously (IVI) or neostigmine (0,02, 0,06 or 0,2 mg/kg) IVI 4 – 5 minutes after BMV. A second study used combinations of atropine 0,25 and 0,5 mg/kg, and obidoxime 4 and 8 mg/kg following BMV in groups of three mice. The time to apnoea after BMV was recorded.

Results: Preliminary study: The mean times to apnoea after BMV were: BMV alone, 45 min; atropine 0,25, 0.5 and 1 mg/kg, 35, 37 and 35 min respectively; obidoxime 1, 4 and 8 mg/kg, 33, 39 and 37 min respectively; neostigmine 0,02, 0,06 and 0,2 mg/kg, 31, 23 and 21 min respectively. The second study showed mean times to apnoea after BMV of: BMV alone 32 min; atropine 0,25 mg/kg and obidoxime 4 mg/kg, 32 min; atropine 0,25 mg/kg and obidoxime 8 mg/kg, 31 min; atropine 0,5 mg/kg and obidoxime 4 mg/kg, 21 min; atropine 0,5 mg/kg and obidoxime 8 mg/kg, 21 min.

Conclusion: The onset of apnoea was accelerated by atropine, obidoxime and neostigmine injected alone with the drug doses used in this study design. Survival time was adversely affected by the large dose combination of atropine and obidoxime, whilst it was unaffected by the low-dose combination. Elevated acetylcholine levels may be the cause of paresis, while a non-depolarising neuromuscular block is unlikely.

13.2 Introduction

Blaylock (2000) noted that the symptoms and signs of black mamba *(Dendroaspis polylepis)* envenomed patients are compatible with parasympathetic muscarinic, nicotinic and CNS effects. These include nausea, vomiting, abdominal cramps, diarrhoea, faecal incontinence, sweating, ptyalism, miosis, blurred vision, bradycardia, hypotension, increased bronchial secretions, fasciculation, muscle weakness, hypoventilation, pulmonary oedema, respiratory failure, tachycardia, anxiety, confusion, headache, convulsions and coma. Lacrimation, cardiac conduction blocks and urinary incontinence were not noted. The early paraesthesia frequently experienced is unexplained. Cape cobra bites produce a flaccid areflexic paralysis due to a non-depolarising muscle block (Blaylock *et al.,* 1985). This is unlike black mamba paralysis where flaccidity, normal muscle tone or spasticity, with retention of tendon reflexes, may occur. There may be associated muscle fasciculation especially of the legs (Blaylock, 2000). This is compatible with depolarising muscle activity.

Black mamba venom contains components that elevate acetylcholine levels, namely fasciculins (anti-acetylcholinesterase) that prevent acetylcholine degradation and dendrotoxins that facilitate acetylcholine release at nerve endings, and the venom also

contains acetylcholine (ACh) (Červeňanský *et al.*, 1991; Harvey & Anderson., 1991; Mebs & Claus, 1991). Known named toxins include calciseptine, which affects L-type calcium channels and blocks atrial muscle contraction; dendroaspin which inhibits platelet adhesion to fibrinogen by blocking the G 11b/111a fibrinogen receptor and weakly inhibits platelet binding to fibrinonectin; dendrotoxin 1 (DXT_1) which comprises 20% of whole venom by weight and blocks K^+ and Ca^{2+}-activated K^+ channels ; dendrotoxin K, a specific blocker on non-inactivating Kv1.1 voltage gated K^+ channels ; fasciculin 1 which inhibits acetylcholinesterase; DpMTx which selectively binds to muscarinic acetylcholine receptors (M1, M3); MT alpha which binds to muscarinic ACh receptors in a one-step reversible process; and MT beta which is similar to the last mentioned but binds in a more complex fashion involving at least two consecutive steps (Theakston & Kamiguti, 2002). Mamba prey is essentially paralysed by flooding synapses with acetylcholine (Aird, 2002), which is not unlike organophosphate poisoning. However, the muscarinic toxins may affect ACh action at muscarinic receptors and low concentrations of alpha neurotoxins competitively bind to acetylcholine receptors (Aird, 2002), which theoretically prevent acetylcholine action at neuromuscular junctions.

Atropine 50 mg/kg administered intraperitoneally protected mice against respiratory failure induced by toxin F7 isolated from eastern green mamba (*Dendroaspis angusticeps*) venom. This respiratory failure was considered to be peripheral in origin, chiefly, if not entirely, due to its anticholinesterase activity (Lee *et al.*, 1986).

Atropine has been given to patients in Southern Africa for snake venom-induced progressive weakness either for bradycardia or, together with neostigmine, to reverse

neurotoxicity (Crisp, 1985; Harvey, 1985; Canter, unpublished; Blaylock, 2000). It is unknown whether it was of benefit. Anticholinesterase agents have been successfully administered to patients bitten by the Philippine cobra (Watt *et al.*, 1986) and Malayan krait (Warrell *et al.*, 1983), which reversed the post-synaptic neuromuscular block.

The possibility of using drugs to prevent and reverse black mamba-induced respiratory failure in mice was considered. Drugs tested included atropine, obidoxime and neostigmine. Atropine is a competitive antagonist of ACh (acetylcholine) at muscarinic receptors, obidoxime is a cholinesterase reactivator which acts by reversing phosphorylation of the enzyme and neostigmine is an anticholinesterase that reverses a non-depolarising neuromuscular block. It is recommended that neostigmine be used in conjunction with atropine to prevent unwanted muscarinic effects and that patients be given atropine IVI about 5 min prior to administration of cholinesterase reactivators (obidoxime), with continued doses until atropinisation is reached (SA Med Formulary, 2000).

Figure 13–1   Some known actions of black mamba venom
ACh: Acetylcholine

Stimulation
of muscarinic
receptors
(action of muscarinic
receptor toxins ?)

Stimulation
of nicotinic
receptors

Rich in ACh

**Mamba
Venom**

**Dendrotoxin
(facilitates ACh release
at the neuromuscular
junction)
(20% of venom by weight)**

ACh ⟶ Increased
systemic
ACh levels

**Fasciculin
(anti-ACh esterase)**

digests
ACh esterase
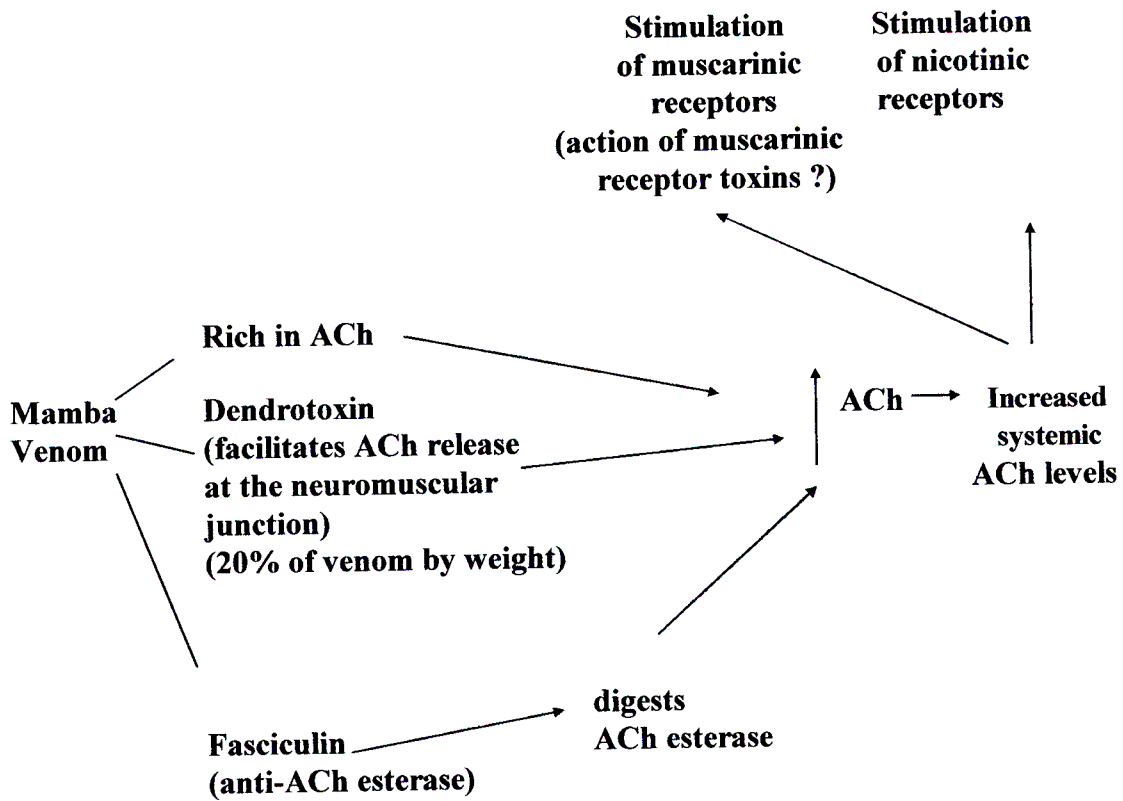
Figure 13–2   Neuromuscular junction and alpha neurotoxins
(low concentrations in mamba venom)

Motor neurone

O   Alpha neurotoxins

O   Competitive antagonist of ACh at ACh receptors

O   **muscle**
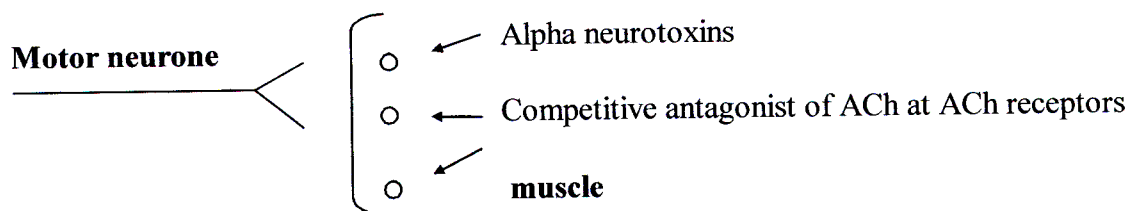
Figure 13-3

Action of ACh (acetylcholine)

```
                              ↑ Secretions of        (Salivation,
                              │ glands                bronchial
                             ╱                        secretions,
                            ╱                          sweating)
                           ╱
                          ╱
              Muscarinic  ──── Acts on              (cramps,
             ╱ receptors        smooth muscle         diarrhoea,
            ╱                                          hypotension)
           ╱
    ACh   ╱
stimulates╲
           ╲
            ╲ Nicotinic    ──── Neuromuscular        (weakness)
              receptors          junction
                                 dysfunction
```
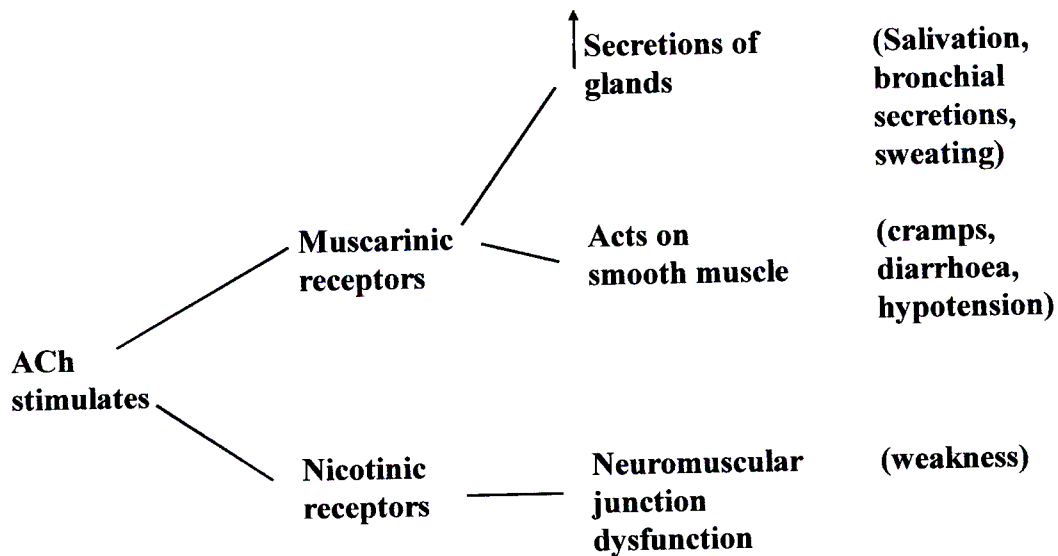
Atropine combats the muscarinic effects of ACh. Obidoxime (Toxogonin®) is an enzyme reactivator antagonistic to anti-ACh esterase (fasciculin) and neostigmine increases ACh at the neuromuscular junction.

13.3 Materials

Fifty one mice (± 20 g specified pathogen-free NMRI) were anaesthetised with ketamine (Bayer Animal Health Division, Isando, South Africa) 1,5 mg in 0,015 ml solution by intramuscular injection (IMI). Black mamba venom (batch BM5, 1990) was obtained from the National Health Laboratory Service Antivenom Unit, Edenvale, Johannesburg, and supplied as 15 μg in 0,1 ml water for injection (IV LD_{50} dose 7,78 μg). Other drugs used include atropine sulphate and neostigmine (Intramed, Port Elizabeth, South Africa) and obidoxime chloride (Merck, South Africa).

13.4 Methods

All mice were anaesthetised with 1,5 mg ketamine in 0,015 ml by thigh IMI. In the preliminary study BMV was administered 15 minutes after the anaesthetic to 27 mice in groups of 3, and after a further 4 – 5 minutes no drug, obidoxime or neostigmine were administered intravenously. Three groups of 3 mice were anaesthetised followed by intraperitoneal administration of atropine in doses of 0,25, 0,5 and 1 mg/kg and, after 15 minutes to allow systemic absorption of the atropine, 15 µg black mamba venom (BMV) was administered subcutaneously. A second study used 15 µg BMV (SCI), and combinations of atropine 0,25 and 0,5 mg/kg and obidoxime 4 and 8 mg/kg, in 5 groups of 3 mice. The time to apnoea after BMV SCI was recorded.

13.5 Results

Studies of black mamba-envenomed mice - atropine, obidoxime and neostigmine. Time to apnoea after BMV is taken to the nearest minute. BMV: black mamba venom. SCI: subcutaneous injection. IPI: intraperitoneal injection. IVI: intravenous injection.

The experiments in Tables 13-1 to 13-5 were performed using the same batch of venom (BM5), but the venom used in Table 13-5 was weighed and diluted separately on a different day.

Table 13-1   Black mamba venom (15 µg SCI) 15 min after the anaesthetic and time to apnoea

Mouse number	Weight: g	Gender	Time to apnoea: min (after BMV SCI)
1	20,4	Female	45
2	20,0	Female	55
3	20,1	Female	42
4	20,1	Male	43
5	19,1	Female	42
6	20,3	Male	54
7	19,8	Male	43
8	21,5	Male	42
9	21,7	Male	44
Mean	**20,3**		**45**

All salivated for a few minutes prior to death. Micturition signified death.

Table 13-2   Anaesthetic. Atropine IPI. BMV 15 µg SCI 15 min later and time to apnoea

Mouse number	Weight: g	Gender	Atropine mg/kg	Time to apnoea: min (after BMV SCI)
1	20,4	Male	1	37
2	21,1	Female	1	34
3	21,2	Female	1	35
Mean	**20,9**			**35**
1	20,1	Female	0.5	41
2	20,6	Female	0.5	45
3	20,2	Male	0.5	37
Mean	**20,3**			**41**
1	20,1	Female	0.25	42
2	19,4	Female	0.25	48
3	19,5	Male	0.25	35
Mean	**19,7**			**42**

Salivation and micturition were not noted.

Table 13-3 **Anaesthetic: BMV 15 µg SCI at 15 min, followed by obidoxime IVI 4 – 5 min later and time to apnoea**

Mouse number	Weight: g	Gender	Obidoxme mg/kg	Time to apnoea: min (after BMV SCI)
1	19,1	Female	1	33
2	19,0	Male	1	33
3	19,4	Female	1	33
Mean	**19,2**			**33**
1	20,4	Female	4	31
2	19,7	Female	4	31
3	20,0	Female	4	39
Mean	**20,0**			**34**
1	19,1	Female	8	39
2	19,4	Female	8	39
3	19,8	Female	8	31
Mean	**19,4**			**37**
Salivation was infrequent and micturition did not occur				

Table 13-4 **Anaesthetic: BMV 15 µg SCI at 15 min followed by neostigmine IVI 4 – 5 min later and time to apnoea**

Mouse number	Weight: g	Gender	Neostigmine mg/kg	Time to apnoea: min (after BMV SCI)
1	18,7	Female	0,02	28
2	19,9	Female	0,02	34
3	19,3	Male	0,02	29
Mean	**19,3**			**31**
1	18,9	Male	0,06	34
2	18,7	Male	0,06	37
3	19,4	Female	0,06	23
Mean	**19,0**			**32**
1	19,0	Male	0,2	9
2	20,1	Female	0,2	31
3	19,0	Male	0,2	22
Mean	**19,4**			**21**
Salivation was infrequent and micturition did not occur				

Table 13-5 **Anaesthetic: Atropine IPI. BMV 15 μg SCI at 15 min followed by obidoxime IVI 4 min later and time to apnoea**

Mouse number	Weight: g	Gender	Atropine mg/kg IPI	Obidoxime mg/kg IVI	Time to apnoea: min (after BMV SCI)
1	19,7	Male	Nil	Nil	30
2	20,2	Male	Nil	Nil	32
3	19,8	Female	Nil	Nil	35
Mean	19,9				32
4	19,3	Female	0,25	4	29
5	19,5	Female	0,25	4	35
6	19,3	Male	0,25	4	34
Mean	19,4				32
7	18,8	Male	0,25	8	31
8	18,4	Female	0,25	8	26
9	18,9	Female	0,25	8	37
Mean	18,7				31
10	17,8	Male	0,5	4	18
11	18,8	Female	0,5	4	22
12	19,0	Female	0,5	4	24
Mean	18,5				21
13	18,1	Male	0,5	8	16
14	175	Female	0,5	8	24
15	18,4	Female	0,5	8	33
Mean	18,0				21

13.6 Discussion

Atropine 1 mg/kg but not in lower doses was found to protect mice against respiratory failure induced by toxin F_7 from eastern green mamba venom (Lee *et al.*, 1986). This and lower doses were chosen for the study. One mg/kg is difficult to administer to 20 g mice except by the intraperitoneal route. Fifteen minutes were allowed to elapse, to allow systemic absorption of atropine prior to BMV injection. The doses of obidoxime and neostigmine are above and below those suggested for humans and were administered 4 – 5 minutes after BMV was given. The latter is soon absorbed into the circulation and the SCI LD_{50} dose is only slightly higher than the LD_{50} IV dose

(Christensen & Anderson, 1967). It was elected to wait 4 – 5 minutes after BMV SCI before administration of obidoxime or neostigmine to allow time for the venom to act. BMV was administered 15 minutes after the anaesthetic (ketamine) as preliminary studies showed that if administered soon after the anaesthetic, the time to apnoea after BMV injection was reduced by as much as 10 minutes, which suggests that ketamine contributed to early death. A better indication of time to apnoea is obtained without the anaesthetic, which is ethically unacceptable.

The results clearly demonstrate that atropine, obidoxime and neostigmine alone accelerated the time to apnoea. The high-dose atropine and obidoxime combination adversely affected survival times, but they were unaffected by the low-dose combination. The results may be false in view of the study design and choice of animal.

This does not prove that the cause of apnoea in BMV-injected mice is solely due to excessive circulating levels of acetylcholine, but this hypothesis is supported by neostigmine contributing to an earlier death. The latter suggests that death is not caused by a non-depolarising neuromuscular block.

Algorithm 13–1   Black mamba envenomation

Venom

Muscarinic toxins

**Venom ACh
Fasciculins
Dendrotoxins**

**? block action
of ACh**

Alpha neurotoxins   **Other toxins?**

**Non-depolarising
neuromuscular block**

**?
overcomes**

Increase ACh levels

Stimulation

**muscarinic   nicotinic
receptors**
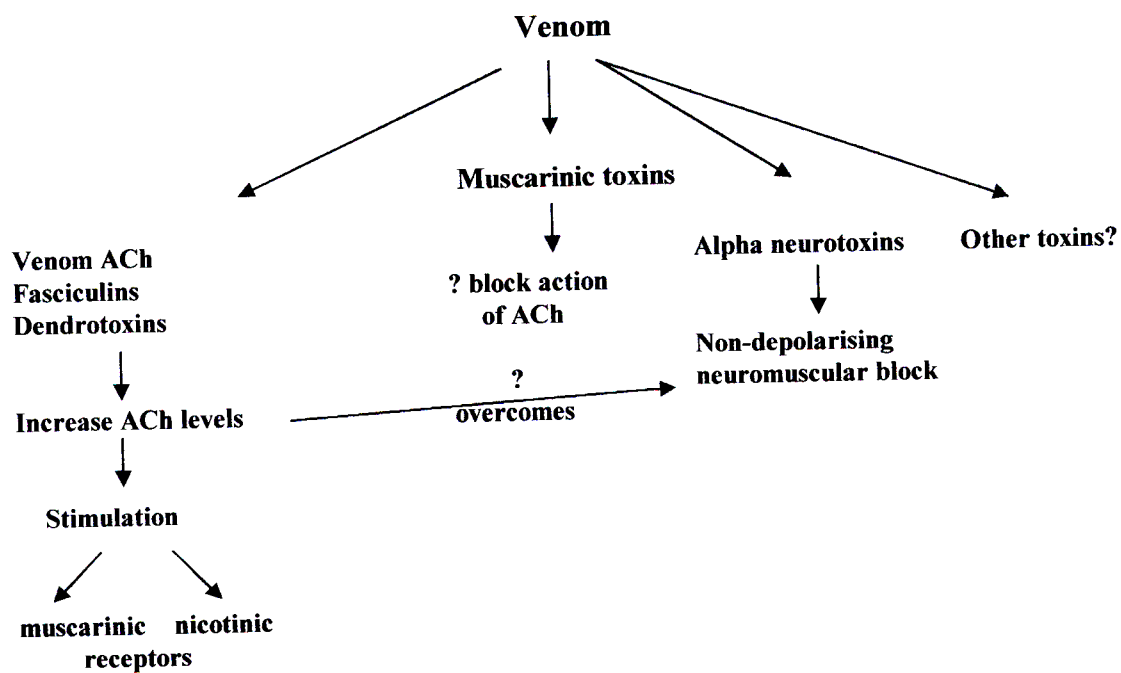
Synergism occurs with toxins. In the present study the time to apnoea in mice was accelerated by atropine, obidoxime and neostigmine individually, but was unaffected by the low-dose atropine/obidoxime combination.

CHAPTER 14

BLEEDING SYNDROME

CONTENTS

14. BLEEDING SYNDROME

14.1 Abstract

Objective: To determine which Southern African snakes are responsible for the bleeding syndrome and suggest a management strategy.

Method: Prospectively studied Eshowe patients and published patients with the bleeding syndrome are analysed.

Results: A coagulopathy or active bleeding may occur in bites by the puff adder *(Bitis arietans)* (thrombocytopenia), boomslang *(Dispholidus typus)* and vine snake *(Thelotornis spp)* (DIC by activation of factors II & X), and Gaboon viper *(Bitis gabonica)* (inhibitor of platelet aggregation, and conversion of fibrinogen to fibrin). With all these bites fenestration of capillaries by haemorrhagins facilitates bleeding. Treatment is with blood component therapy and antivenom. The latter is inappropriate for vine snake bites.

Conclusions: Indications for antivenom include active systemic bleeding, non-clotting blood or laboratory evidence of a significant coagulopathy. Suggested volumes of polyvalent antivenom, if bleeding is associated with painful progressive swelling, are 50 ml for an unknown snake or a puff adder bite, and 200 ml for a Gaboon adder bite. Twenty millilitres of monospecific antivenom is usually adequate for boomslang venom-induced coagulopathy. Blood component therapy is usually required. Heparin, thrombolytics or fibrin stabilising drugs are of no value.

14.2   Introduction

The bleeding syndrome is characterised clinically by internal and external bleeding, or by laboratory evidence of a coagulopathy. A haemostatic disturbance and capillary leaks are toxin induced. External bleeding may be manifested by purpura, ecchymosis, subconjunctival haemorrhage, epistaxis, bleeding gums, haemoptysis, haematemesis, haematuria and bleeding from the anal canal, fang wounds, recent traumatic wounds or vene puncture sites. Acute myocardial infarction and cerebrovascular accident were reported after a viper bite in Greece (Aravanis *et al.*, 1982), cerebrovascular accidents after bites by the Australian tiger snake and taipan (Tibballs *et al.*, 1991; McGarity *et al.*, 1991; Trevett *et al.*, 1994), intracranial haemorrhage from Brazilian snake bites (Caiaffa *et al.*, 1994), cerebral infarction, myocardial infarction, pulmonary embolism and femoral thrombosis in South America (Thomas *et al.*, 1995) and ileocolic vessel thrombosis in a bite by a European adder (Beer & Musiani, 1998). Such distant haemostatic complications have not been described in Southern Africa. Snakes responsible for the bleeding syndrome include the puff adder, boomslang, vine snake and Gaboon adder. Active bleeding occurs in less than 1% of snakebite in Southern Africa, although a minor coagulopathy, manifest as ecchymosis, commonly occurs in puff adder bites.

The dominant presentation of puff adder envenomation is painful progressive swelling. A venom platelet aggregating factor initiates thrombocytopenia (Phillips *et al.*, 1973, Brink & Steytler, 1974; Warrell *et al.*, 1975). More than half of envenomed patients will develop ecchymosis of the bitten limb, most commonly around the proximal draining lymphatics (medial thigh or arm). Active bleeding is unusual. Blood loss into

the bitten limb leads to early anaemia, hypoalbuminaemia, hypofibrinogenaemia and contributes to platelet loss. Simon & Grace (1981) demonstrated sequestration of platelets in the damaged tissue at the site of pit viper bites in rabbits. Initially, the presence of fibrin degradation products (FDPs) is a regional effect and not due to disseminated intravascular coagulation. Fibrino(geno)lysins play a lesser role.

Bites by the boomslang and vine snake share a similar consumption coagulopathy. A procoagulant enzyme converts prothrombin to a thrombin-like enzyme and there is activation of factor X (Atkinson, 1980; Atkinson *et al.*, 1980). Relatively early platelet sparing occurs as the thrombin-like substance does not activate platelets to the same extent as physiological thrombin (Atkinson, 1980). Excessive fibrinolysis is due to activation of the patient's own plasminogen-plasmin system (Mackay *et al.*, 1969).

Gaboon adder venom contains gabonase which cleaves fibrinopeptides A and B from fibrinogen and activates factor XIII (Pirkle *et al.*, 1986). A further component, gabonin, inhibits platelet aggregation (Huang *et al.*, 1992). The major presentation is painful progressive swelling and bleeding, with minor cranial nerve dysfunction and cardiotoxicity sometimes occurring.

Bleeding due to bites by the black-necked spitting cobra *(Naja nigricollis nigricollis)* has not been described in Southern Africa, but has been in Nigeria, and is considered to be due to a platelet defect (Warrell *et al.*, 1976a).

14.3   Material and methods

Eshowe patients with the bleeding syndrome were analysed and a literature search was

undertaken.

14.4   Results

Table 14-1   Haematology of two Eshowe patients bitten by unidentified snakes. Both had clinical signs of puff adder bites

Clinical presentation	Hb g/dl	Platelets 10^9/l	Fibrinogen	INR	PTT Seconds	FDPs N<10 µg/ml	Albumin g/l
E39 PPS with compartment syndromes Day 4: Died	2,4	5	N	2.09	49	>40	19
E210 PPS with compartment syndromes and vessel entrapment syndrome Day 1	3,3	127	Undetectable	2.45	118	>40	12
Patient E39 bled to death following fasciotomy							

Of five patients accompanied by the offending dead puff adder (E56, E60, E214, E313, E317), four developed ecchymosis of the bitten limb, three around the proximal draining lymphatics and one around the bite site. There was no evidence of bleeding or severe haematological abnormality in other patients accompanied by the dead snake, including those bitten by the Mozambique spitting cobra (E90, E122, E153, E196, E232, E318, E321).

Table 14-2 SAIMR polyvalent antivenom administered to patients with painful progressive swelling and active bleeding (not ecchymosis)

Author and age of patient	Bite site	Condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
PUFF ADDER				
Blaylock, 2000 Case 7 26 yr	Distal shin	Petechial haemorrhages of face, neck, upper trunk. Subconjunctival haemorrhage. Active bleeding from old lacerations. Haematemesis	2 h: 10 ml 3 h 30 min: 10 ml	4 h: Hb 12,1 g/dl Platelets 86 x 10^9/l P.I. 59% PTT 57/31 s 17 h 20 min: Hb 12,1g/dl Platelets 172 x 10^9/l P.I. 76% PTT 31.7/31 s
Aitchison (Unpublished) 21 yr	Ankle	Bleeding from gums, haemoptysis, haematemesis, haematuria, periorbital haematoma, subconjunctival haemorrhage, purpura chest wall. 5 h: Hb 19,7g/dl INR 2,7 PTT 133 s 37 h: Hb 5,1g/dl Platelets 26 x 10^9/l INR 1,79 PTT 52 Fibrinogen normal	41 h: 40 ml	No evidence of further bleeding. 41 h 15 min: Significant improvement in thromboelastogram 44 h: INR 1,2 PTT 35 s
GABOON ADDER				
McNally *et al.*, 1993 35 yr	Wrist	30 min: Swelling of wrist to shoulder. Dyspnoeic	<1h: 100 ml	Day 2: Swelling progressed to abdomen. Pulmonary oedema. Ecchymosis from cubital fossa to trunk. Day 3: Falling fibrinogen and factor XIII. Raised D-dimers
		Day 4: Thrombin time > 100 s	Day 4: 100 ml	Resolution of haemostatic abnormalities. Minor local necrosis

Antivenom was administered intravenously unless otherwise stated. HBD - Alpha-hydroxybutyrate dehyrogenase

Table 14- 3   SAIMR monovalent antivenom administered to patients with boomslang bites

Author and age of patient	Bite site	Condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
1. Mackay *et al.*, 1969 51 yr (Nairobi)	Thumb	Bleeding gums. Scattered ecchymosis. Whole blood clotting time 5 min. Thromboplastin generation test - accelerated. WCLA – shortened (3,25 h) Fibrinogen 117 mg/dl Platelets 140 x 10^9/l	Day $5\frac{1}{2}$: 30ml	No evidence of fresh bleeding. Immediate: Clotting time 10 min. Thromboplastin generation test normal. WCLA > 72 h Fibrinogen and platelets increased slowly.
2. Lakier & Fritz, 1969. 26 yr	Finger	Haematemesis, bleeding gums and fever blister, haematuria, haemoptysis. Blood failed to clot. Prolonged bleeding time. Fibrinogen 10 mg/100 ml. Platelets 10 x 10^9/l. Euglobulin lysis time normal.	? time: 40 ml	Improved haematological profile over hours.
3. Nicolson *et al.*, 1974. 24 yr	Web space hand	Epistaxis, haematoma vene puncture site, haematuria and haemoglobinuria. Blood incoagulable. Platelets <10 000/µl Afribrinogenaemia.	Day 5: 40 ml	Day 6: Haematuria ceased. Whole blood clotting time normal. Thrombin time normal. Platelets increasing. "Rapid response to specific antivenom".
4. Gomperts & Demetriou, 1977. 22 yr	Finger	Haemoptysis. Bleeding from vene puncture sites PT and APPT blood failed to clot. Fibrinogen unrecordable. Factor V 5% Factor VIII < 1% Fibrin monomers positive. Increased FDPs. Normal platelets	± 19 h: 15 ml	± 20 h: PT 75 s APPT 119 s Fibrinogen 13 mg/l 27 h 30 min: PI 87% 37 h 30 min: PI 86% APPT 47,3 sec Fibrinogen normal. 48 h: Haemoptysis ceased.
5. Gerber & Adendorff, 1980. Adult	Thumb	Haemoptysis, haematemesis, epistaxis, haematuria, rectal bleeding.	32 h: ? 10 ml	Day 3: Bleeding ceased.

Author and age of patient	Bite site	Condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
6. Du Toit, 1980 25 yr	Web space hand	Semi comatose, bleeding from mouth, fang wounds, eyes and nose. Bruises at injection sites. Blood incoagulable. Oliguric.	86 h: 20 ml	86 h: no fresh bleeding. 87 h: Clotting time 7 min. 72 h: Clotting time 15 min. 96 h: P.I. 70% 98 h: Normal urine output.
7. Geddes & Thomas, 1985, 30 yr	Shoulder	Blood oozing from mouth and ear. Local ecchymosis. Bleeding vene punctures. P.I. $\leq$ 11%. PTT 300/32,8 s. FDPs $\geq$ 1 280. Platelets normal.	30 h 45 min: 20 ml	30 h 45 min: Immediate cessation of bleeding. 38 h 45 min: Haematological profile normal.
8. Branch & McCartney, 1986. 24 yr	Finger	PTT > 120 s PT 29/12,7 s. Platelets normal. F.T. < 1:2	16 h: 20 ml	17 h: PT and PTT vastly improved. F.T. 1:64. Platelets normal.
9. Haagner & Smit, 1987. (unpublished) 34 yr	Finger	Blood oozing from needle punctures and scratches. P.I. 0%	10 h 15 min: 10 ml 12 h 15 min: 10 ml	12 h 15 min: P.I. 0% 26 h 15 min: P.I. 0% Day 3: P.I. 11% Day 4: P.I. 25% Day 7: P.I. 70% Day 9: P.I. 89%
10. Aitchison, 1990. Case 1 10 yr	Foot	Frank haematuria. Thromboelastograph: severe hypocoagulability.	48 h: 10 ml 51 h: 10 ml	49 h: No further active bleeding. Improved thromboelastogram. 67 h: Near normal thromboelastogram
11. Case 2 3 yr	Foot	Gastrointestinal bleeding.	48 h 15 min: 10 ml	66 h: Coagulation screen and thromboelastogram normal except slightly decreased fibrinogen.
12. Vaughan-Scott & Lobetti, 1995. 8-month DOG	Lip	Continuous ooze of blood from lip wounds.	Day 2: 10 ml	1 h after antivenom: Bleeding ceased.

Author and age of patient	Bite site	Condition at time of antivenom administration	Amount and time of antivenom administration	Outcome
13. Blaylock, 2000. Case 9.2.1.1	Finger	Ecchymosis, bleeding drip and injection sites. Haematuria, haematemesis, haemoptysis, melaena. INR > 10 PTT > 200 s FDPs >160 Platelets 143 x 10^9/l Fibrinogen 0.1g/dl	21 h: 20 ml 27 h: 20 ml	Within 6 h antivenom administration: INR 1.1 PTT 22 s Fibrinogen 1.2 Platelets 108 x 10^9/l
14. Case 9.2.1.2 70 yr	Finger	Bleeding from gums, petechiae of tongue, ecchymosis thigh. Bleeding already diminishing. PTT 204/37 s INR 3.53 Platelets 107 x 10^9/L	Day 3: 10 ml	Day 4: No further bleeding PTT 49/36 sec INR 1.6 Platelets 65 x 10^9/L

WCLA - whole clot lysis activity. PT - prothrombin time. APPT - activated partial thromboplastin time. FDPs – fibrin degradation products. P.I. - prothrombin index. INR - international normalised ratio. PTT – partial thromboplastin time. F.T. – fibrinogen titre.

14.5   Discussion

14.5.1   Antivenom

14.5.1.1   Puff adder bites

Aitchison's case (Table 14-2) stopped actively bleeding when 40 ml polyvalent antivenom was administered at 41 hours, with significant improvement in the thromboelastogram performed 15 minutes later.

Most patients with active bleeding have passed the nadir of thrombocytopenia at the time of hospital presentation. A platelet count of less than $40 \times 10^9/l$ in a peripheral hospital is an indication for antivenom administration if platelet transfusion is not immediately available. In a critical care setting, $<20 \times 10^9/l$ platelets would be a reasonable indication as lethal bleeding could occur in spite of the availability of platelet transfusion.

14.5.1.2   Boomslang bites   (Table 14-3)

In five cases (Mackay *et al.*, 1969; Du Toit, 1980; Geddes & Thomas, 1985; Aitchison, 1990; Vaughan-Scott & Lobetti, 1995), active bleeding stopped immediately or within an hour of antivenom administration. The haematological profile improved and bleeding stopped within hours in the other nine cases. Furthermore, in seven cases not given antivenom, the mortality rate was 43% ,whereas there were no deaths in the antivenom-treated group of 13 patients (Blaylock, 2000), which may also have been aided by the better supportive care that this group received in more recent times.

14.5.1.3   Gaboon adder bites

The haemostatic abnormalities caused by a Gaboon adder bite (Table 14-2) resolved

after 200 ml antivenom was administered (McNally *et al.*, 1993).

14.5.1.4   Vine snake bites

There is no effective antivenom or cross-sensitivity to boomslang antivenom (Atkinson

et al., 1980).

14.5.2   Other modalities of treatment

14.5.2.1 Blood component therapy

Blood component therapy is essential if low blood factor levels are responsible for

potential or active bleeding. It has been suggested that this could worsen consumption

coagulopathy, which would be deleterious, but is unproven.

14.5.2.2   Heparin

The rationale for using heparin is its stimulatory activity of antithrombin III, which is

the major inhibitor of thrombin and activated clotting factors IX, X, XI and XII.

Boomslang bites *(Dispholidus typus)*

Heparin has been advocated for boomslang bite patients with venom-induced coagulopathy. Van der Merwe (1992) suggests that an attempt should be made to prevent thrombin from entering the circulation by using a low dosage of heparin, and gives a case report where heparin and specific antivenom were used. Gomperts & Demetriou (1977) describe a case in which supportive therapy consisting of heparin and fresh-frozen plasma may have contributed to the clinical improvement of their patient. Nicolson *et al.* (1974), when discussing their patient, said that heparin had produced little obvious improvement but there had been a rapid response to specific antivenom. Heparin was found to be without effect against boomslang venom in mice (Mason *et al.*, 1961). In vitro studies by Mackay *et al.* (1969) showed that increasing concentrations of heparin lead to progressive inhibition of the coagulant action of the venom. Atkinson *et al.* (1981) showed that boomslang venom displays heparin resistance, in that more heparin is required to prevent coagulation due to this particular venom than coagulation due to either Russell's viper *(Daboia russelli)* venom or activation of the intrinsic pathway. This is probably due to venom-induced thrombin not being identical to physiological thrombin (Warrell, 1996).

Exotic snakes

A trial of heparin for disseminated intravascular coagulation caused by a carpet viper *(Echis carinatus)* bite where there is activation of factors II, IX and X, using low-dose heparin (50 units/kg body weight by intravenous injection, followed by 10 units/kg/h by intravenous infusion for 22 hours) in patients receiving antivenom, showed no

difference in outcome between the heparin and non-heparin groups of patients (Warrell et al., 1976b). A similar controlled trial in Russell's viper bite victims (activation of factors V and X) with impending DIC, using monovalent antivenom and either heparin (as above) or normal saline solution, showed the recovery rate from the clotting defect to be similar in the two groups, but in patients with initially very low fibrinogen levels there was a tendency for heparin to restore fibrinogen faster (Myint-Lwin et al., 1989).

Calcium nadroparine (Fraxiparine®) failed to prevent thrombosis in Martinique patients bitten by Bothrops lanceolatus snakes, whereas monospecific antivenom did (Thomas et al., 1995).

Heparin should not be used because it may exacerbate haemostatic disturbances and does not neutralise the thrombin generated by most snake venoms (Warrell, 1996).

14.5.2.3 Antithrombin III

Nontprasert et al. (1993), using rats envenomed with Thai Russell's viper venom, showed that antivenom is effective in the prevention of a coagulopathy and is potentiated with antithrombin III supplementation. There was progressive diminishing antithrombin III activity in all rats which developed non-clotting blood.

Using Malayan pit viper (Calloselasma rhodostoma) venom on rats, antivenom was shown to be essential as a specific treatment, but the dose could be reduced if antithrombin III was administered to restore normal antithrombin III levels (Clemens et al., 1993).

The effects of antithrombin III administration to boomslang or vine snake envenomed patients are unknown, but as venom-induced thrombin is relatively heparin resistant, it may not be effective.

14.5.2.4 Antifibrinolytic agents

Antifibrinolytic agents such as trasylol and epsilon-amino-caproic acid have not proved clinically effective and should not be used (Warrell, 1996).

14.5.2.5 Thrombolytics

Urokinase given to Martinique patients bitten by *Bothrops lanceolatus* snakes did not prevent thrombotic complications, whereas monospecific antivenom did (Thomas *et al.*, 1995).

Algorithm 14–1

Management of the bleeding syndrome

in the acute phase

Great value	**Unproven value**	**Of no value**
Blood component therapy	Antithrombin III	Heparin
		Antifibrinolytics
Antivenom		Thrombolytics

Indications

Active systemic bleeding (not ecchymosis alone).

Non-clotting blood after 20 min in an undisturbed new clean, dry test tube. Use blood from a healthy person as a control.

Significant laboratory evidence of a coagulopathy.

Pregnancy: Antivenom is administered more liberally, due to high foetal wastage. This includes ecchymosis, slow-clotting blood in a test tube or moderate laboratory evidence of a coagulopathy.

Boomslang-induced coagulopathy: 20 ml SAIMR monospecific boomslang antivenom. May be repeated at 4 - 6 hours if necessary.

Unknown snake or puff adder-induced bleeding (thrombocytopenia): 50 ml SAIMR polyvalent snakebite antivenom.

Gaboon adder coagulopathy: 200 ml SAIMR polyvalent snakebite antivenom.

SECTION V

ASPECTS OF CLINICAL SIGNIFICANCE

V. Aspects of clinical significance

Preamble

This section includes snakebite during pregnancy, where mother and fetus are involved, venom ophthalmia due to spitting snakes and commonly used treatment modalities which are not evidence based.

CHAPTER 15

SNAKEBITE AND PREGNANCY

CONTENTS

15. Snakebite and pregnancy

15.1 Abstract

Objectives: To relate pregnancy outcome to clinical snakebite envenomation syndromes, explore the extent of the problem in Southern Africa and suggest management strategies.

Subjects and methods: Four prospectively studied pregnant snakebite patients are presented and a literature review is undertaken.

Results: Of the four patients reviewed, pregnancy was unaffected. The English literature shows that of the envenomation syndromes comprising non-envenomation, painful progressive swelling, progressive weakness and bleeding, the latter is responsible for most fetal wastage.

Conclusion: Adequate maternal support, including resuscitation, oxygenation and appropriate antivenom use, are essential. Antivenom-induced anaphylaxis is preferably treated with ephedrine and not adrenaline. Unless the life of the envenomed mother is threatened or a coagulopathy exists, pregnancy is unlikely to be affected. Significant venom-induced coagulopathy is not common in Southern Africa and the extent of envenomation-induced fetal abnormalities is unknown.

15.2 Introduction

Snake envenomation may affect pregnancy by interfering with maternal health by producing pyrexia, anaemia, hypoxia, hypotension or bleeding; interfering with the utero-placental junction (disseminated intra-vascular coagulation and bleeding); inducing uterine contractions or by direct envenomation of the fetus with possible teratogenesis, growth retardation and mutagenesis. This may result in possible maternal and fetal death, abortion or prematurity and congenital abnormalities.

Dunnihoo, *et al.* (1992) noted that bites of pregnant patients by the *Crotalidae* family (rattlesnakes, water moccasins, copperheads), resulted in a maternal mortality rate of 10% and fetal wastage of 43%, although not all the patients analysed were bitten by *Crotaline* snakes. In the Southern African literature four cases of snakebite in pregnancy are reported (McNally & Reitz, 1987; Pantanowitz & Guidozzi, 1996), one of whom delivered prematurely.

Crude puff adder *(Bitis arietans)* venom increased the frequency and amplitude of the spontaneously contracting rat uterus, which was partially blocked by indomethacin (Osman & Gumaa, 1974). This suggests that venom could potentially induce abortion or labour.

Experiments on pregnant mice have shown that venom or venom components can cross the utero-placental barrier. European viper *(Vipera aspis)* venom produced fetuses with exencephaly, cleft palate and face deformities (Gabriel-Robez & Clavert, 1969; Clavert & Gabriel-Robez, 1971). North African spitting cobra *(Naja nigricollis)* venom affected developing fetal tissue including the kidney, liver, heart, aorta and

blood vessels (Mohamed *et al.*, 1974), and produced dysmelia (Mohamed & Nawar, 1975). Egyptian cobra *(Naja haje* from north Africa) venom produced an increase in size of the fetal ventricular system, with chromolytic changes in the anterior and posterior horns of the spinal cord and posterior root ganglia considered to be due to overgrowth of the choroid plexus and other vascular effects (Nawar, 1980). Cobra *(Naja naja)* venom incubated with early chick embryos in vitro for 24 hours resulted in failure to efficiently form the optic vesicles and incomplete closure of the neural tube (Ahmed *et al.*, 1974). In these experiments, maternal envenomation in early pregnancy resulted in fetal abnormalities, while in late pregnancy there was direct injury to fetal tissue.

The object of this analysis is to relate pregnancy outcome with the three clinical envenomation syndromes and explore the extent of the problem in Southern Africa.

15.3   Subjects and results

In the Eshowe series of 333 snakebite patients in KwaZulu-Natal there were three pregnant patients. One was 28 weeks pregnant (E53) with mild swelling and no necrosis and was discharged on day eight. Another was nine months pregnant (E249) with minimal swelling and no necrosis and was discharged on day two. Both were treated with elevation and analgesia only. The third (E239) was 30 weeks pregnant with no signs of envenomation. She was discharged on the following day. All were bitten on a toe, foot or ankle. A fourth Swaziland patient, not in this series but handled by the author, was bitten by a Mozambique spitting cobra on the right ankle while sleeping. She was 20 weeks pregnant and developed an area of necrosis

measuring 7 - 8 cm x 5cm, which was debrided on day five. No antivenom was administered. At six months follow-up, she was seen with her healthy infant that had been a normal home vaginal delivery. During hospitalisation fetal distress did not occur in the patients.

15.4 Discussion

Pyrexia, anaemia and oligaemic hypotension may occur with the clinical envenomation syndrome of painful progressive swelling (PPS). The hypervolaemia of late pregnancy, together with uterine vasoconstriction, delays maternal signs of oligaemic shock, whilst the fetus may be subject to severe hypoxia (American College of Surgeons Committee on Trauma, 1997). Early aggressive fluid replacement with monitoring is essential. Hypoxia due to progressive weakness (PW) may render the fetus severely hypoxic when maternal hypoxia is minimal (Strauch, 1986). Generous oxygenation of the mother should be provided. Bleeding due to bites by the puff adder (thrombocytopenia), Gaboon viper (formation of fibrin and inhibition of platelet aggregation), and the boomslang and vine snake (activation of factors II and X) may lead to utero-placental dysfunction.

The supine hypotensive syndrome of pregnancy was thought to be a contributing factor in the death of a mildly envenomed patient bitten by an immature brown snake in Australia (Sutherland *et al.,* 1982). The left lateral decubitus position, or elevation of the right hemipelvis with manual displacement of the uterus to the left, or sitting upright is recommended during resuscitation of patients in the third trimester of pregnancy.

Suggested indications for antivenom are the envenomation status of the mother (Parrish & Khan, 1966; Dunnihoo *et al.,* 1992), slowing of fetal movement (James, 1985) and symptomatic mothers or a distressed fetus (Pantanowitz & Guidozzi, 1996). If future epidemiological studies show a link between snake envenomation during pregnancy and fetal congenital abnormalities, antivenom may then be warranted for asymptomatic patients. Adverse prognostic indicators include delayed treatment, early gestation and severe envenomation (Parrish & Khan, 1966). Careful monitoring of a patient given antivenom is essential, as anaphylaxis may result in hypotension and diminished uteroplacental perfusion. Ephedrine is preferred to adrenaline in the treatment of this condition. The former is essentially a beta agonist except in large doses, while the latter is an alpha agonist causing uterine vasoconstriction. It is believed that ephedrine in clinically useful doses of 25 – 50 mg by slow intravenous injection spares uterine blood flow (Entman & Moise, 1984).

No attempts have been made in Southern Africa or elsewhere to correlate the outcome of pregnant patients with the three envenomation syndromes. There is a paucity of cases in the world literature (Pantanowitz & Guidozzi, 1996). The Eshowe patients and the literature search revealed that non-envenomation occurred in six cases (E239, James, 1985; Dunnihoo *et al.,* 1992; Parrish & Khan, 1996) with no morbidity. Of 15 cases with painful progressive swelling, one who was bitten while three months pregnant delivered a child with multiple malformations (Malz, 1967). There was a good obstetric outcome in the other 14 patients (E53, E249, Swaziland case; Malz, 1967; Parrish & Khan, 1996). There are no case reports of pregnant patients with severe progressive weakness (neurotoxic venom). However, in three cases in Sri

Lanka described by James (1985), two were clinically non-envenomed patients and one had prolonged clotting time and mild bilateral ptosis. In all three there was an absence of fetal movement and no fetal heart sounds could be detected, but the obstetric outcome was normal. The reason may be that neurotoxins crossed the placental barrier, causing fetal paralysis and physiologically reduced cardiac output, which is why heart sounds could not be detected during auscultation. In patients who required blood transfusion during resuscitation or were actively bleeding (bleeding syndrome), the outcome was different. In 11 cases, two of whom developed abruptio placentae, there were two maternal deaths, ten spontaneous abortions or stillbirths and one elective abortion (Singh, 1925; Malz, 1967; Bhat, 1974; Chugh *et al.*, 1983; James, 1985; Zugaib *et al.*, 1985; Parrish & Khan, 1996). Reid *et al.* (1963a), when discussing Malayan viper bites, were struck by the general well being of pregnant patients despite non-clotting blood. One of five pregnant patients aborted without excessive blood loss. In Southern Africa a mild coagulopathy not requiring immediate blood transfusion, and manifesting as purpura of the bitten limb, is common in puff adder bites. Occasionally, active bleeding or the requirement for early blood transfusion occurs (Blaylock, 2000).

In-depth studies of five rural series of snakebites have been published, and it is estimated that about 255 out of 1 079 were females of child-bearing age (this series; Blaylock, 1982; Coetzer & Tilbury, 1982; McNally & Reitz, 1987; Wilkinson, 1994). About 25 (10%) would be expected to be pregnant, of which only four were diagnosed. One, a 17-year-old with a mild to moderate cytotoxic reaction to a snakebite, delivered a healthy premature infant during the same admission (McNally & Reitz, 1987), although this may have been coincidental.

Most publications on snakebite in the Southern African region do not mention pregnancy (Fitzsimons, 1912; Schmid, 1966; Chapman, 1968; Wapnick *et al.,* 1972; Rippey *et al.,* 1976; Visser & Chapman, 1978; Christensen, 1983: Auerbach, 1989; Kasilo & Nhachi, 1993; Spawls & Branch, 1995; Yerzingatsian, 1997). This strongly suggests that snakebite in pregnancy in Southern Africa rarely leads to abortion or premature delivery, as active bleeding or a significant coagulopathy are uncommon. Should a pregnant patient have a coagulopathy, antivenom is strongly indicated and it would be prudent to exclude a separation of the placenta (Pantanowitz & Guidozzi, 1996). Ephedrine instead of adrenaline is suggested for antivenom-induced anaphylaxis in order to preserve utero-placental perfusion (Entman & Moise, 1984).

An epidemiological study on abnormal fetuses has not been performed in areas of high human-snake encounters. If a person in early pregnancy suffers a snakebite, follow-up to exclude congenital abnormalities is advised.

Algorithm 15–1

Envenomation in pregnancy

Early pregnancy and
survival

Any stage of pregnancy

|

Any coagulopathy

|

Follow-up for congenital
abnormalities

PW or PPS

Treat the mother on
merit. Ensure
adequate oxygenation
and fluid resuscitation.

Antivenom to prevent
abruptio placenta, abortion or
still birth
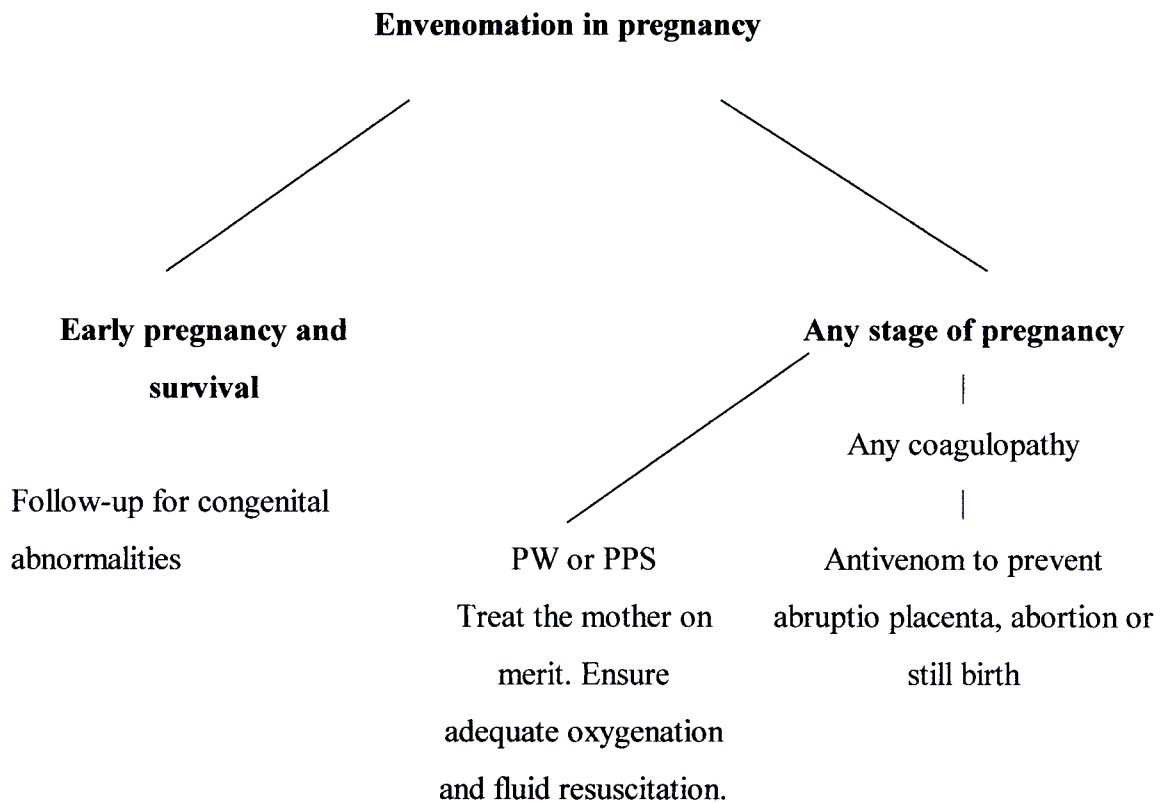
The indications for antivenom in non-pregnant patients with bleeding syndrome include active bleeding (clinical), non-clotting blood (bedside test) or a significant coagulopathy (laboratory). A minor coagulopathy (ecchymosis, slow-clotting blood or laboratory determined) is an indication in pregnant patients. Ephedrine instead of adrenaline is suggested for antivenom-induced anaphylaxis in order to preserve uteroplacental perfusion (Entman & Moise, 1984).

CHAPTER 16

VENOM OPHTHALMIA

CONTENTS

16.   VENOM OPHTHALMIA

16.1   Abstract

Objective: To assess complications and best treatment of venom ophthalmia. *Material and methods:* Analysis of recent personally managed and prospectively studied cases.

Results: Of five cases of venom ophthalmia *(Naja mossambica, Hemachatus haemachatus)*, one had punctate corneal erosions and all affected eyes were normal at 24 – 48 hours.

Conclusions: Venom ophthalmia is an immediate acute conjunctivitis with possible corneal erosion. A single instillation of local anaesthetic eye drops allows bland fluid eye irrigation. The application of antibiotic eye ointment and a pad leads to normality in 24 – 48 hours, even in the presence of corneal erosions.

16.2   Introduction

Venom ophthalmia occurs when squirted venom comes into contact with the eyes. It may be unilateral or bilateral and is due to spitting by the rinkhals *(Hemachatus haemachatus)* or one of the spitting cobras, which comprise the Mozambique spitting cobra *(Naja mossambica)*, black-necked spitting cobra *(Naja n nigricollis)*, zebra spitting cobra *(Naja nigricollis nigricinta)*, and the South-western black cobra *(Naja nigricollis wood)*. The rinkhals is mainly a resident of the Southern African highveld, the spitting cobras are most commonly found in the lowveld, the *Naja nigricollis* species are found in the west and the Mozambique spitting cobra occurs in the northern and eastern parts of the region.

Venom in the eyes is intensely painful with associated blepharospasm and epiphora. Hyperaemia, chemosis, corneal oedema, and possible corneal epithelial erosions and iritis may occur. If an erosion becomes infected and results in perforation, endophthalmitis can occur with loss of the eye. It is a relatively benign condition unless it remains untreated or is aggravated by the topical application of certain folk medicines.

There are no substantiated reports on eye venom absorption resulting in death in humans. An unsubstantiated report by Strover (1961) mentions a dog with venom ophthalmia which developed paralysis of the lower jaw.

16.3 Materials and methods

Two cases of Mozambique spitting cobra venom ophthalmia from the Eshowe series and three cases of rinkhals ophthalmia managed by the author while resident in Gauteng are presented.

16.4 Results

Table 16-1   Patients with venom ophthalmia

Patient and age (years)	Time and clinical findings	First aid	Treatment	Outcome
Mozambique spitting cobra				
E9 (19)	Same day: bilateral conjunctivitis, no corneal erosions.		Chloramphenicol drops. Oral analgesia. Eye pad.	Normal within 48 hours.
E235 (3)	Same day: blepharospasm, conjunctivitis, chemosis. No corneal erosions.	Immediate irrigation with milk.	Eye pad.	Discharged within 24 hours.
Rinkhals				
J.V (35)	Same day: bilateral conjunctivitis, mild punctate fluorescein staining inferomedially left.	Immediate milk irrigation.	Saline irrigation. Topical chloramphenicol ointment 6 hourly. Eye pad.	Not admitted.
A.B (46)	20 minutes: blepharospasm, epiphora, conjunctival hyperaemia, chemosis. Normal pupils. No corneal erosions.	Water irrigation.	Topical chloramphenicol. Eye pad.	Not admitted. Normal at 24 hours.
B.B (36)	Three minutes: blepharospasm, conjunctivitis. No corneal erosions.	Near immediate water irrigation.	Topical antibiotic. Eye pad.	Not admitted. Near normal within 24 hours.
J.S (32)	30 minutes: unilateral conjunctivitis with palpable oedema. No corneal erosions	Near immediate water irrigation followed by milk irrigation.	Local anaesthetic eye drops. Water irrigation. Tobramycin drops. Topical chloramphenicol. Eye pad.	Not admitted. 2 weeks follow-up: normal.
All patients were tested for fluorescein staining of the cornea. Slit lamp was used for J.V. No patient developed later complications.				

16.5 Discussion

Fitzsimons (1929) noted that venom in the eyes causes congestion and inflammation, resulting in blindness without correct treatment, or death if the venom is absorbed through the mucous surfaces of the eye. His suggested treatment included thoroughly washing the eyes either with plain water or a pint of water in which a teaspoon of bicarbonate of soda or a pinch of permanganate of potash had been dissolved. Other suggestions included using cow's milk, warm tea, soda water or lemonade. The eyes were bandaged and the patient placed in a darkened room. "Should any pus or matter gather in the eyes, or if there be a discharge of any kind, the affected organs should be bathed frequently with warm water, in which a little boracic powder has been dissolved....".

Treatment has since changed. There are no substantiated reports of eye venom absorption resulting in death in humans. An editorial in the Central African Journal of Medicine (1956) suggested using milk as an irrigant with permanganate of potash and a few drops of antivenom. Local dilute antivenom irrigation was suggested by Strover (1961), Mason (1963), White (1984), van der Merwe (1992) and Schrire *et al.* (1996). Authors not advocating local antivenom irrigation include Chapman (1968), Warrell & Ormerod (1976), Blaylock (1982a, 1982b), Lath & Patel (1984) and White (1985).

Warrell & Omerod (1976) noted 11 cases *(Naja spp.)* of venom ophthalmia from Nigeria of which five developed corneal ulceration. Lath and Patel (1984) noted superficial keratitis (erosions of the corneal epithelium) in 32%, iritis with mydriasis in 6%, and iritis with miosis in 3% of 34 patients with *Naja spp.* induced ophthalmia.

Nevertheless, they considered it a benign condition if treated timeously, with no late complications. Blaylock (1982a) mentioned 36 cases due to *Naja mossambica*, all with conjunctivitis and none with corneal erosions, as shown by fluorescein staining. Corneal erosions did not apparently occur in the case reported by Coetzer & Tilbury (1982) or the three cases reported by McNally & Reitz (1987).

Of five cases (Table 16-1), one developed mild punctate ulcers (rinkhals). If slit lamp examination were routine in all cases, the reported incidence of corneal erosions would increase. These erosions of the corneal epithelium heal quickly with correct treatment but may become infected with resultant serious sequelae, especially if traditional topical applications are used.

With early treatment, venom ophthalmia is a benign condition.

Algorithm 16-1   **Management of venom ophthalmia**

First aid: Immediate irrigation with water or other bland

solution (open and close the eyes under water)

|

Medical practitioner : A single application of local anaesthetic

eye drops to overcome blepharospasm

facilitates irrigation. Fluorescein staining.

|

Slit lamp

|

Corneal erosions

Absent   Present

Antibiotic eye ointment   Antiobiotic eye drops

Eye pad   Mydriatic

Resolution within   Eye pad

24 - 48 hours   Daily slit lamp

            examination until cured

Antivenom topically (dilute) or systemically not indicated.

Steroids (topical or systemic) are contra-indicated.

CHAPTER 17

OTHER TREATMENT MODALITIES

CONTENTS

17. OTHER TREATMENT MODALITIES

17.1 Abstract

Objective: To assess the efficacy of glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamines in the treatment of snakebite.

Method: Published human and animal trials were assessed.

Results: Most trials and experimentations view the use of glucocorticosteroids unfavourably, there is evidence that NSAIDs are potentially detrimental, and there is no support for antihistaminics.

Conclusions: There is little or no evidence to support the administration of these drugs in the management of snakebite. The potential side effects of glucocorticosteroids and NSAIDs negate their use.

17.2 Introduction

It is important that any therapy used in medical management should be thoroughly evaluated before it is used routinely. NSAIDs, glucocorticosteroids and cytotoxic drugs in that order have increasing anti-inflammatory properties. One of the indications for use is to diminish deleterious non-infective inflammation as seen in the inflammatory arthropathies and immune disorders. The former two, together with antihistamines, are popularly used for snakebite without evidence of efficacy.

17.3 Glucocorticosteroids

The principal reactions of glucocorticosteroids involve anti-inflammatory, immuno-suppressant and metabolic effects. Hydrocortisone (cortisol) is the body's natural glucocorticosteroid and is short acting. Prednisolone, prednisone, methylprednisolone and triamcinolone are intermediate acting, while dexamethasone and betamethasone are long acting. The longer the action, the greater the anti-inflammatory potency (South African Medicines Formulary, 2000). Glucocorticosteroids are used in snakebite in the hope of negating the local and systemic effects of venom. There are numerous anecdotal reports of these drugs improving the clinical outcome of snakebite patients, especially in the older literature (Hoback & Green, 1953; Ariff, 1955; Glass, 1976).

Dexamethasone attenuated the hyperalgesic effect but not oedema produced by *Bothrops jararaca* and *Bothrops asper* venom injected into the foot pad of rats (Texeira *et al.*, 1994; Chacur *et al.*, 2001). Both effects are known to be partly produced by phospholipase A_2 enzymes, of which dexamethasone is a part inhibitor (Chacur *et al.*, 2001). Phospholipase A_2 enzymes, together with metalloproteinases and other cytotoxins, are responsible for bite site inflammation and necrosis.

17.3.1 South African literature

Christensen (1961) reported on the use of prednisolone 0,5 mg intravenously prior to, or half an hour after, subcutaneous injection of snake venom in mice. A slight but significant reduction in toxicity could be demonstrated for the venom of the Cape cobra *(Naja nivea)*, forest cobra *(Naja melanoleuca)* and black-necked spitting cobra

(Naja nigricollis), but not for the venom of the snouted cobra *(Naja annulifera)*, rinkhals *(Hemachatus haemachatus)*, black mamba *(Dendroaspis polylepis)*, eastern green mamba *(Dendroaspis angusticeps)* or puff adder *(Bitis arietans)*. Christensen (1969), of the SAIMR Antivenom Unit, stated that steroids had no proven beneficial effect on local or systemic snakebite poisoning, while Visser & Chapman (1978) felt that on the evidence available, no benefits are derived from steroids.

17.3.2   Non-South African literature

17.3.2.1 North America

Hoback & Green (1953) and Gowdy (1954) reported on human snakebite victims responding favourably to cortisone. Schöttler (1954) points out that it was only the personal impressions of the authors that supported the favourable opinion of cortisone being of benefit.

Allam *et al.* (1956), using dogs subcutaneously envenomed with *Crotalus adamanteus* or *Crotalus atrox* venom, and treated with cortisone 50 – 100 mg/kg IMI. one or two hours post-venom injection, found no benefit of cortisone as the sole treatment. Deichmann *et al.* (1958) injected (IMI.) *Crotalus adamanteus* venom into dogs and gave an initial 100 mg hydrocortisone intravenously, either immediately or at two or four hours after venom injection, followed by 50 mg daily. The survival of subjects given cortisone was significant in comparison to controls. Grace & Omer (1980), using rabbits injected with *Crotalus atrox* venom, found that dexamethasone sodium phosphate 5 mg/kg/24 h IVI did not alter local swelling and haemorrhage in comparison to controls. Russell & Emery (1961) noted that single injections of

methylprednisolone (5 - 100 mg/kg) in mice did not suppress the lethal activity of *Ancistrodon contortrix* (moccasin snake) venom. Likewise, single intravenous injections of hydrocortisone (5 - 500 mg/kg) failed to benefit, with the possible exception of the dose of 100 mg/kg. Russell (1966) also noted that corticosteroids did not alter the mean arterial blood pressure in patients with shock following rattlesnake poisoning. Arnold (1976), in a letter of response to the article by Glass (1976) on the use of cortisone in pit viper bites, points out that Glass's mortality of 1 - 2 per 200 patients should be compared to that of the USA as a whole at 1 per 1 000 patients.

17.3.2.2 South America

Schöttler (1954) experimented with mice and guinea pigs which he injected subcutaneously with *Crotalus durissus terrificus* or *Bothrops jararaca* venom. ACTH in doses of 2,5 or 25 mg/kg, cortisone 2,5 or 25 mg/kg, or hydrocortisone 2 mg/kg were immediately injected subcutaneously at a different site. There was no evidence of beneficial effects.

17.3.2.3 Asia

Reid *et al.* (1963c) conducted a double-blind therapeutic trial on patients with Malayan pit viper bites. One hundred patients were randomised to antivenom alone, prednisone (120 mg orally in divided doses within three days of the bite) or placebo. All were treated within six hours of the bite and prednisone seemed to benefit neither systemic nor local poisoning.

Prednisone 1 mg/kg/day in children bitten by green pit vipers in Thailand may have reduced local swelling (Lekagul & Nuchprayoon, 2001).

17.3.3 Effect on antivenom-venom reaction

Chang & Weinstein (1957) demonstrated that cortisone not only enhances the lethal effect of tetanus toxin in unprotected mice, but also interferes with the therapeutic activity of tetanus antitoxin. There is reason to believe that glucocorticosteroids interfere with the action of snake antivenom (Ward, 1976).

Recent literature does not advocate steroid use in snakebite (Warrell, 1996; Russell *et al.*, 1997).

17.4 Non-steroidal anti-inflammatory drugs

Acute inflammation is a prerequisite for healing and countering local infection, but anti-inflammatory drugs counteract or suppress inflammation. There is a relatively poor relationship between analgesic effects and the anti-inflammatory potency of NSAIDs (Yaksh *et al.*, 1998). There are, however, reports of anti-inflammatory complications occurring where the analgesic effect is required. Neutrophil chemotaxis and, to a lesser extent, monocyte chemotaxis are inhibited by piroxicam (Scheinberg *et al.*, 1983). Solberg *et al.* (1978) noted reduced killing of *Staphylococcus aureus* and *Streptococcus* group B by granulocytes incubated with phenylbutazone. Krige *et al.* (1985) showed that the lymphocytes of a previously healthy patient incubated with aspirin or indomethacin had depressed function and transformation to phytohaemagglutinin. Similarly, a patient on ibuprofen was shown to have an abnormal reaction of neutrophil chemotaxis, chemiluminescence and lymphocyte transformation on phytohaemagglutinin (Espersen & Larsen, 1987).

Seventy-seven per cent of rural snakebite patients present at hospital with inflamed snakebite wounds, which is the aetiological basis for the painful progressive swelling syndrome. No trials have been done on the use of NSAIDs in snakebite.

17.4.1 Delayed wound healing

There are numerous reports of delayed wound healing due to NSAIDs, with harmful effects on the healing of fractures (Ro *et al.,* 1976; Allen *et al.,* 1980; Mizuno *et al.,* 1990; Altman *et al.,* 1995), spinal fusion (Dimar *et al.,* 1996), cartilage (Dingle, 1993) and muscle (Almekinders & Gilbert, 1986). NSAIDs responsible for delayed healing in these studies include aspirin, indomethacin, ibuprofen, naproxen, mefenamic acid, diclofenac and piroxicam. In a human double-blind placebo controlled trial, severe hamstring injury cases had less pain at seven days on placebo than those on meclofenamate or diclofenac (Reynolds *et al.,* 1995). This property of bone healing has an advantage in that NSAIDs have become the treatment of choice in the prophylaxis of periarticular heterotopic ossification after total hip arthroplasty (Dimar *et al.,* 1996).

17.4.2 Infection

Solomon (1966) reported on three cases where latent infection was believed to have been activated by indomethacin.

Reports on necrotising fasciitis following the use of NSAIDs after caesarean section (Van Ammers *et al.,* 1991) and minor trauma (Krige *et al.,* 1985) have emanated from

South Africa. There are similar non-South African reports (Brun-Buisson *et al.*, 1985; Rimailho *et al.*, 1987; Esperson & Larsen, 1987; Smith & Berk, 1991) on cases in which NSAIDs were used for various maladies and were followed by the onset of necrotising fasciitis. Implicated NSAIDs include aspirin, diflunisal, indomethacin, oxyphenbutazone, ibuprofen, flubiprofen, niflumic acid, piroxicam and diclofenac. The aforementioned NSAIDs are Cox 1 and Cox 2 inhibitors, but it is unlikely that Cox 2 variants affect acute inflammation differently. The reduction of granulocyte, monocyte and lymphocyte functions, with or without the human immunodeficiency virus, is potentially disastrous.

Until convincing evidence is available on the benefit of NSAIDS in snakebite they should be avoided.

17.5 Antihistamines

Feldberg & Kellaway (1938) and Dutta & Narayanan (1952) showed that cobra venom led to histamine release in vitro. Dragstedt *et al.* (1938) showed histamine release in vivo in 2 of 5 dogs injected with rattlesnake venom *(Crotalus atrox)*, which was thought to be inadequate to account for the degree of vascular reaction. Nevertheless, the possibility of antihistamines being beneficial in snakebite was considered. Schöttler (1954), using the antihistamine promethazine (Phenergan®) in doses of 0,1, 1, 10, 20 and 50 mg/kg in mice envenomed with *Bothrops jararaca* venom and doses of 1, 20 and 50 mg/kg in mice envenomed with *Crotalus durissus terrificus* venom, showed it to be of no benefit.

Algorithm 17–1

Other drugs for snakebite

Glucocorticosteroids	**NSAIDS**	**Antihistamines**
No good evidence of efficacy for diminishing local and systemic effects of envenomation	No trial for efficacy	No effect on envenomation outcome
Interferes with antivenom-venom reactions	Delays wound healing	Does not reduce the incidence of acute adverse reactions to antivenom (Chapter 8)
Delays wound healing	Predisposes to necrotising fasciitis	
A course prevents delayed reactions (serum sickness) to antivenom (Chapter 8)		

SECTION VI

SUMMARY, APPENDICES, REFERENCES

18. Summary

The prevalence of snakebite in eastern South Africa and Zimbabwe is 23 – 81 per 100 000 population. Snakebite in humans presents as a combination of minor trauma at the bite site, a fearful or uncommonly hysterical psychological reaction, a venom-induced acute allergic reaction in atopic individuals or, most commonly, as an envenomation syndrome.

An analysis of four rural snakebite series showed that painful progressive swelling (PPS) is the most common presentation, at 77% or 92% of envenomations. Here death can be potentially caused by hypovolaemia, early bleeding or later multiple organ failure. Progressive weakness (PW) with or without painful progressive swelling comprised 7% of cases, with possible death due to respiratory failure. Bleeding comprised 0,3% of patients, and other unclassifiable presentations due to minimal envenomation were limited to 1%. Potentially lethal bites were most common above ankle level in standing victims, as large adders and elapids most commonly strike here.

Many of these bites could have been prevented by being sensible, not handling dead snakes and, at night, wearing shoes, using a light or sleeping in a dwelling with measures to keep snakes out. Clothing only has protective value if it prevents fang penetration. There is no good first-aid measure for all snakebites. The most common traditional measures comprise the proximal application of a tourniquet and ingestion of various "medicines". Painful progressive swelling (PPS) commencing at the bite site is aggravated by tourniquets regardless of tourniquet type. Other pre-hospital measures to remove venom, degrade it or slow its absorption do not work as, in potentially severely envenomed patients, venom is either deposited deeply (large adders) or absorbed quickly (mambas). The priority is to get the patient to competent medical help. Necrosis is most common following bites of the hand or fingers. This is postulated to be due to venom remaining at the depot injection site for

longer periods of time than in other anatomical areas, due to the comparative inactivity of venous and lymphatic pumps, as bitten hands tend to be cradled and not used, especially by adults. This finding is strongly supported by the outcome of mice injected with the necrotising venoms of the puff adder and Mozambique spitting cobra. Immediate active mouse movement either prevented or reduced the area of necrosis in comparison to anaesthetised mice. It is suggested that if bitten on a hand or finger in Southern Africa, consideration should be given to raising the arm and flexing and extending the fingers for 5 – 10 minutes to spread the venom proximally. This was not found to increase mortality, and further epidemiological and experimental studies should be done.

Bacterial infection may occur at the bite site if there are local complications that supply conditions favourable for bacterial growth. Bite site complications include blistering, necrosis or haematoma. In this situation, bacterial infections are possible but not certain due to low numbers of bacteria in snake mouths, their low pathogenicity in this situation and the antibacterial properties of snake venom. Snake mouths are the source of the bacteria, as mouth bacterial species are identical to the bacterial species found in infected snakebite wounds - they comprise mainly the *Enterobacteriacea* with some *Staphylococcal* and *Streptococcal* species. Anaerobes are decidedly uncommon. A trial of snakebite patients without bite site complications not receiving "prophylactic" antibiotics in comparison to patients inadvertently given antibiotics, showed no difference in the length of hospital stay between the two groups. The duration of hospitalisation was longer in patients with necrosis to whom antibiotics were administered in comparison to patients with necrosis who were not given antibiotics. This is not a measure of the efficacy of not using antibiotics, but rather a measure of more severe necrosis in those receiving antibiotics. A study of bacterial species in healthy snake mouths showed them to be transient colonisers with no species consistency geographically, in the same snake with time, the same snake species or the same

serpentarium. The mouths of non-venomous snakes are more commonly bacteriologically sterile than those of venomous snakes, with greater bacterial numbers and more species occurring in winter. The venom of South African snakes is antibacterial, the degree of which depends on venom type. This property coincidentally reduces bite site sepsis and functions as part of the self-cleansing mechanism of the snake's mouth, protects the snake against ingested microbes and prevents prey putrefaction prior to digestion. Antibiotics should not be routinely administered in cases of snakebite, but restricted to the few cases with bite site haematoma, blisters, abscess or necrosis.

Polyvalent antivenom is manufactured by immunising horses against multiple venoms. The resulting hyperimmune serum is refined to produce $F(ab^1)_2$ antibodies, which is the final product. Monospecific boomslang antivenom is obtained from a horse immunised against the single venom. Antivenom is supplied in 10 ml ampoules with a shelf life of three years. Indications for antivenom are severe envenomation that is life or limb threatening (less than 10% of snakebites). There is no standard antivenom dose, the same volume being administered regardless of patient size. All should be administered as a slow intravenous injection (which is as safe as a slow infusion), without prior sensitivity testing (non-predictive of reactions to the main dose). Repeat administration may occasionally be necessary and is of value, if indicated, while the venom is still active, which may be for several days.

Acute adverse reactions to antivenom are known to be associated with individual susceptibility, species protein, protein size and the presence of molecular aggregates or their fragments. This study also relates these reactions to the acute phase response of the envenomation syndrome involved and the delay in antivenom administration. Acute adverse reactions occurred in 21, 56 and 60% of patients treated with the same polyvalent antivenom

for the syndromes of PW, PPS and bleeding respectively, which correlated with the increased time period from the bite to antivenom administration and was not related to protein load. The envenomation syndrome is thought to be more important than the time of antivenom administration for the development of acute adverse reactions. Premedication with adrenaline prior to antivenom administration is suggested if the individual is atopic, if antivenom is administered for boomslang venom-induced coagulopathy, if there is swelling of a whole limb, or if more than ten hours have elapsed after the bite. . Late antivenom reactions (serum sickness) are related to the amount of antivenom administered and may be prevented and treated with a course of glucocorticosteroids. It is suggested that a prophylactic course of glucocorticosteroids be given if administered antivenom exceeds 100 ml (10 ampoules).

Snakes responsible for painful progressive swelling include the puff adder *(Bitis arietans)*, Mozambique spitting cobra *(Naja mossambica)*, stiletto snake *(Actractaspis spp.)*, the night adders *(Causus spp.)* and the small adders *(Bitis and Proatheris spp.)*. The majority of deaths in the painful progressive swelling syndrome are due to hypovolaemic shock. The faster and greater the extent of swelling, the more important is intravenous fluid resuscitation. Albumin and blood component therapy, apart from crystalloids, may be necessary. Central venous pressure and hourly urine monitoring are helpful adjuncts. Elevation is important in facilitating venous return, diminishing swelling, assisting arterial inflow and facilitating the return to normovolaemia, and has the added benefit of diminishing pain. Pain is proportional to the degree of swelling that eventually develops, the presence of bite site complications, the first 24 hours of admission to hospital and bites of a finger, thumb or hand. Antivenom prevents swelling extension or alters its character. Indications for antivenom include potential or established severe envenomation, as warned by swelling of a whole bitten hand or foot within one hour of the bite, or shown by the same amount of

swelling due to a known puff adder or Gaboon adder bite, swelling to the knee or elbow within 3 – 4 hours, swelling of a whole limb within 12 hours, swelling threatening the airway, unexplained dyspnoea and an associated coagulopathy. The amount of antivenom to be administered intravenously is 50 ml for the bite of an unknown snake, spitting cobra, or puff adder, and 200 ml for a known Gaboon adder bite.

Surgery may be necessary for bite site or regional complications which occur in approximately 18% of cases. Blisters are best left undisturbed, abscesses treated on merit, haematomas drained or aspirated and necrotic areas, including fingers, left for 5 to 7 days prior to debridement. Dead tissue is not well defined prior to this time and too much or too little tissue may be excised. Waiting this long does not prejudice the recovery of bitten fingers. Compartment syndromes requiring fasciotomy occur in about 2% of cases and may be diagnosed by finger palpation, or more accurately by measurement of intra-compartmental pressure. These syndromes are too frequently diagnosed, as significant PPS presents in a similar fashion to compartment syndrome and pain is frequently excessive. Hands, feet or digits with compartment syndromes decompress spontaneously as these structures are not bound by tough fascia. Compartment syndromes of limbs may be aggressively treated medically by restoration of normovolaemia, steep elevation, intravenous administration of 50 ml polyvalent antivenom and 500 ml 20% mannitol (in adults) over one hour. Should conservative treatment fail, open, full-length fasciotomy should be carried out, but is contraindicated in the presence of a coagulopathy. Femoral vessel entrapment syndrome is rare and is associated with distal compartment syndromes. It requires fasciotomy and division of the inguinal ligament. The most common nerve entrapment syndrome encountered is temporary carpal tunnel syndrome, best treated by elevation alone. If a volar forearm fasciotomy is required, carpal tunnel release is performed concomitantly.

The term progressive weakness describes the clinical condition of a patient injected with neurotoxic venom. It generally affects all skeletal muscles to some degree before the patient becomes too weak to breathe, with resulting respiratory failure and possible death. The time of the onset of weakness depends on the venom constituents (mainly determined by the particular snake species), the amount of venom injected and the size of the victim. The larger the amount of venom and the smaller the patient, the sooner the progression to weakness. Small amounts, especially in large victims, may lead to weakness falling short of respiratory failure. Such bites may or may not lead to bite site swelling that is neither painful nor tender (mambas), or to bites that are painful and tender (non-spitting cobras, rinkhals and berg adder).

This syndrome occurs following bites by the black and green mamba *(Dendroaspis spp.,* most symptoms being compatible with parasympathetic effects), the non-spitting cobras (forest cobra - *Naja melanoleuca,* Cape cobra - *N. nivea* and snouted cobra - *N. annulifera),* and the rinkhals *(Hemachatus haemachatus),* which is not a true cobra, with alpha neurotoxic effects. In other snakebites where painful progressive swelling (PPS) is dominant, namely bites by the Berg adder *(Bitis atropos),* shield-nosed snake *(Aspidelaps spp.),* garter snakes *(Elapsoidea spp),* desert mountain adder *(Bitis xeropaga)* and Peringuey's adder *(Bitis peringueyi),* there is a component of weakness probably due to beta neurotoxins. Minor neurotoxicity may occur in Gaboon adder bites *(Bitis gabonica),* where PPS and bleeding predominate.

An adequate dose of antivenom can prevent or reverse respiratory failure (except in Cape cobra bites), and reduce the period of ventilation. Indications for antivenom include dyspnoea due to weakness in the absence of PPS (mambas), generalised weakness in the presence of PPS (non-spitting cobras), or generalised myalgia (sea snakes), or an inability to

swallow saliva. The suggested minimum antivenom dose is 40 ml, but preferably 80 ml if antivenom is freely available. Ventilation alone will return an anoxic non-brain-damaged patient to normality. Concomitant sedation is mandatory as these patients are fully conscious with normal senses. Ventilation is required for a few hours in the case of a mamba bite and for several days in the case of a Cape cobra bite.

In the experiments performed, black mamba envenomed mice did not respond to atropine or obidoxime, whether given alone or in combination. This does not prove that paresis is solely due to excessive systemic acetylcholine levels. The response to neostigmine suggests that death is not due to a non-depolarising neuromuscular block.

The bleeding syndrome is characterised clinically by internal or external bleeding. A coagulopathy or active bleeding may occur in bites by the puff adder *(Bitis arietans)* (thrombocytopenia), boomslang *(Dispholidus typus)* and vine snake *(Thelotornis spp.)* (DIC by activation of factors II and X), and Gaboon adder *(Bitis gabonica)* (inhibition of platelet aggregation and conversion of fibrinogen to fibrin). With all these bites fenestration of capillaries due to haemorrhagins facilitates bleeding. Treatment is with blood component therapy and antivenom, but the latter is inappropriate for vine snake bites. Indications for antivenom include active systemic bleeding, non-clotting blood or laboratory evidence of a significant coagulopathy. Suggested volumes of polyvalent antivenom are 50 ml for a puff adder and 200 ml for a Gaboon adder bite. Twenty millilitres of monospecific antivenom is adequate for boomslang-induced coagulopathy.

Little has been written about snakebite occurring during pregnancy. Three of four patients with PPS, managed without antivenom, had uneventful pregnancies. The fourth patient was not envenomed. Animal experimentation has shown that some venoms can cross the utero-

placental barrier which, in early pregnancy, leads to congenital abnormalities, while in late pregnancy there may be destruction of fetal tissue. Maternal and fetal health may be affected by hypotension and anaemia due to PPS, anoxia due to PW, and a coagulopathy in the bleeding syndromes. Unless the life of the mother is threatened by PPS or PW, pregnancy is unlikely to be affected. A coagulopathy, however, is firmly associated with abortion, prematurity, abruptio placenta, and maternal and fetal death. Even with minor coagulopathy antivenom is indicated.

Venom ophthalmia is caused by venom squirted into the eyes by the spitting cobras *(Naja mossambica, N. nigricollis spp.)* and the rinkhals *(Hemachatus haemachatus).* Venom ophthalmia is a relatively benign condition if the eyes are promptly irrigated and traditional medicine is not applied topically. The condition presents with intense blepharospasm and epiphora due to acute conjunctival inflammation. A single instillation of local anaesthetic eye drops allows bland fluid irrigation of the eyes. Fluorescein staining does not commonly show corneal ulceration unless a slit lamp is utilised. Treatment is with a topical antibiotic eye ointment and pad. A local mydriatic is used to prevent synechiae formation if macroscopic corneal ulcers are present.. With early treatment most eyes regain normality the next day. Late treatment or traditional topical applications may be associated with penetrating corneal ulcers with attendant complications, including eye loss.

Tables 18-1, 18-2 and algorithm 18-1 summarise poisonous snake species, envenomation syndromes, complications and management.

Table 18-1   Clinical envenomation syndromes due to specific snake species and threat to life in the absence of treatment

	Clinical envenomation syndromes		
Threat to life ↑	**Bleeding**	**Painful progressive swelling**	**Progressive weakness**
			← Black mamba →
	← Gaboon adder →		
		← Non-	spitting cobras →
	← Puff adder →		
			← Green mamba →
	← Boomslang →		
	← Vine snake →		
		← Black-necked, Mozambique and South-western black spitting cobras →	
		← Rinkhals →	
		← Berg adder →	
		← Shield-nosed snake →	
		← Peringuey's and desert mountain adders →	
		← Proatheris superciliaris →	
		← Stiletto snakes →	
		← Horned adders →	
		← Garter snakes →	

Arrows denote the spectrum of symptomatology. Their encroachment on a syndromic block denotes the amount of that clinical presentation. Swelling induced by the black mamba and vine snake is neither painful nor tender.

Table 18-1 gives a rough indication of the clinical presentations associated with snake bites and the threat to life. It is stressed that it is a rough guide as many factors are involved.

Table 18-2   Summary of envenomation syndromes, complications and management

SNAKE ENVENOMATION SYNDROMES		
Bleeding	Painful progressive swelling	Progressive weakness
There may be overlap of syndromes depending on		snake species

Presentation		
Ecchymosis Internal and external bleeding	Swelling extends proximally and is painful, hot, tender and indurated, ± regional lymphadenopathy	Generalised progressive paresis or cranial nerve palsies ± generalised Paresis
Complications Internal and external bleeding	Hypovolaemic shock Anaemia Necrosis Compartment syndrome Entrapment syndrome	Aspiration Respiratory failure
First-aid – get the patient to hospital Nil special	Get the patient to hospital Nil special	Get the patient to hospital Unable to swallow saliva: place patient on side Artificial respiration if necessary
Treatment Blood component therapy Antivenom Heparin, antifibrinolytics and thrombolytics of no value	Intravenous fluids Elevation Analgesics Antibiotics if necrosis present Excision of necrotic areas at 5 – 7 days Compartment syndrome: Conservative treatment or fasciotomy Antivenom	Respiratory failure: ventilation with sedation Antivenom

Compartment syndromes

- Conservative treatment. Steep elevation ± mannitol 100 gm over 1 hour ± antivenom. Reassess at 1½ hours.
- Open fasciotomy for failure of conservative treatment.
- Control a coagulopathy prior to fasciotomy.

Algorithm 18-1

Indications for antivenom

Clinical syndromes of envenomation

There may be overlap between syndromes

Antivenom not absolutely indicated

Antivenom may be life saving

Painful progressive swelling (PPS)

1. Distal extremity bites
- swelling of a whole hand or foot within 1 hour of the bite is a warning.

- swelling to the elbow or knee by 3 - 4 hours.

- swelling of a whole limb within 12 hours.

2. Swelling threatening the airway.

3. Associated unexplained dyspnoea.

4. Associated coagulopathy.

3 – 8 % of patients

50ml polyvalent antivenom. 200 ml for Gaboon adder bite

Progressive weakness (PW)

1. Dyspnoea due to weakness in the absence of PPS.

2. Inability to swallow saliva.

3. Generalised paresis in the presence of PPS or generalised myalgia.

The latter indication accounts for some patients who, when paralysed, will not respond to antivenom.

Cranial nerve palsies per se may not be followed by respiratory failure.

50 – 70% of patients

80 ml polyvalent antivenom Repeat 1 h if necessary.

Bleeding

1. Active systemic bleeding (not ecchymosis of the bitten limb alone).

2. Non-clotting blood after 20 minutes in an undisturbed new dry clean test tube. Use blood from a healthy person as a control.

3. Significant laboratory evidence of a coagulopathy.

80 – 100% of patients

20 ml monovalent boomslang antivenom. Nil for vine snake

Pregnant patients : Antivenom is administered more readily in the bleeding syndrome. Beware of a separated placenta.
Babies, children and adults: The same indications apply and the same amount of antivenom is administered.
Antivenom: A test dose is not predictive of adverse reactions to the main dose.
A slow intravenous injection is as safe as an infusion.
Premedication with 0,25 - 0,5ml 1:1 000 adrenaline is recommended (adults) for atopic individuals.

APPENDIX A   Summary of Eshowe patients

Key
Nil - no clinical envenomation
Minimal, mild, moderate, severe and gross - degree of painful progressive swelling
PW - progressive weakness
VO - venom ophthalmia
BSCs – bite site complications
Analgesics listed are those prescribed within 48 hours of hospital admission. Post-operative analgesia is not considered

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
1	16	Toe	Mild		No	AP Cods® Pethidine	2	2
2	21	Leg	Mild		Penicillin V		2	3
3	15	Hallux	Minimal		No	AP Cods®	6	7
4	62	Shoulder	Mild		Ampicillin	Codis®	2	3
5	8	Ankle	Moderate		No	Paracetamol	6	11
6	49	Knee	PW Ventilated		No	Nil	5	5
7	18	Foot	Mild		No	Paracetamol	3	3
8	25	Foot	Moderate		No	Paracetamol	7	7
9	19		VO		Occ. Chloramphenicol	Codis® Diclofenac	4	4
10	47	Ankle	Minimal		No	AP Cods®	2	2
11	21	Foot	Mild		No	Nil	3	4
12	6	Knee	Gross		Ampicillin	Tilidine	15	15
13	14	Foot	Minimal		No	AP Cods®	3	3
14	7	Finger	Moderate	Necrosis	Cotrimoxazole	Paracetamol Pethidine	30	30
15		Foot	Mild		Ampicillin	Codis®	4	5
16	24	Foot	Mild		No	Codis®	3	4
17	6	Foot	Moderate		No	Paracetamol	19	19
18	18 mths	Ankle	Moderate	Necrosis	No	Paracetamol	7	7
19	4	Hand	Moderate	Necrosis	No	Paracetamol	16	16
20	50	Shin	Nil		No	Codis®	2	2
21	5	Ankle	Moderate		Penicillin V	Paracetamol	2	3
22	70	Foot	Moderate	Necrosis	Chloramphenicol		48	4
23	28	Foot	Nil		Benzathine Pencillin	Paracetamol	2	2

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
24	40	Wrist	Moderate	Necrosis Widespread blisters Compartment syndrome	Benzyl Penicillin Metronidazole Gentamicin	Pethidine	83	84
25	6	Jaw	Nil		No	Paracetamol	2	2
26	16	Foot	Minimal		Penicillin V	Nil	2	3
27	34	Foot	Minimal		No	Codis®	2	5
28	12	Hallux	Mild		No	Codis®	3	3
29	9	Iliac crest	Minimal		No	Codis®	2	3
30	11	Foot	Mild		No	Codis®	5	5
31	21	Foot	Moderate		Penicillin V	Paracetamol	3	3
32	43	Calf	Local tenderness	Known CCF. Died D2	No	AP Cods®	2	2
33	22	Foot	Minimal		No	Codis®	5	5
34	18	Foot	Mild		No	Codis®	6	6
35	12	Foot	Moderate		No	Paracetamol	8	8
36	22	Hallux	Mild		No	Codis® Pethidine	5	5
37	14		Minimal		Penicillin V	Paracetamol	4	4
38	8	Ankle	Minimal	Scabies	Erthromycin	Nil	5	6
39	11	Thigh	Gross	Necrosis widespread blisters Compartment syndrome	Ampicillin Cloxacillin	Nil	Died 3	4
40	14	Toe	Minimal		No	Paracetamol	4	4
41	13	Shin	Minimal		No	Codis®	3	3
42	9	Foot	Moderate		Benzathine Penicillin	Aspirin	8	8
43	12	Foot	Moderate		No	Codis®	4	4
44	15	Foot	Mild		No	Codis®	4	4
45	4	Foot	Mild	Coryza	Amoxicillin		9	9
46	15	Foot	Mild		No	Codis®	3	4
47	36	Foot	Mild		No	Codis®	6	6
48	11	Foot	Gross	Necrosis Widespread blisters Compartment syndrome	Ampicillin Metronidazole	Pethidine	60	60
49	16	Foot	Moderate		Ampicillin	Codis®	4	5
50	18	Forearm	Nil		No	Codis®	2	2
51	25	Foot	Moderate	Necrosis	Ampicillin	Codis® Pethidine	38	48

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
52	5	Foot	Moderate	Deep haematoma	No	Paracetamol	7	7
53	22	Below knee	Moderate		No	Codis®	8	9
54	19	Ankle	Severe	Necrosis blister	No	Diclofenac Pethidine	6	7
55		Ankle	Nil		No	Paracetamol	2	2
56 Puff adder		Foot	Moderate		No	Codis®	8	8
57		Foot	Mild		No	Codis®	4	5
58	25	Calf	Gross	Widespread blisters	No	Codis® Pethidine	18	18
59	42	Toe	Mild		No	Paracetamol	4	5
60 Puff adder	26	Foot	Gross	Blister	No	Codis®	14	14
61	47	Foot	Mild		No	Paracetamol	3	3
62	14	Foot	Nil		Penicillin V	Nil	3	3
63	10	Ankle	Severe		No	Codis®	6	7
64	27	Foot	Moderate	Haematoma calf	No Readmitted later	Codis® Diclofenac	9	9
65	12	Hand	Nil		No	Nil	3	3
66	51		Minimal		Ampicillin	Nil	5	6
67	8	Foot	Minimal		Penicillin V	Paracetamol	4	4
68	10	Foot	Mild	Necrosis	No	Paracetamol Pethidine	5	5
69	28	Ankle	Nil		No	Nil	5	?
70	36	Foot	Nil		No		?	?
71	31	Foot	Moderate		No	Codis®	4	5
72	11	Finger	Moderate		No	Paracetamol	3	3
73	28	Hand	Nil		Ampicillin	Codis® Diclofenac	2	2
74	30	Hand	Mild		No	Pethidine	3	3
75	18	Hallux	Mild		No	Codis®	3	3
76	15	Hallux	Minimal		No	Codis®	4	5
77	3	Foot	Moderate		Ampicillin	Paracetamol	4	4
78	10	Foot	Mild		No	Codis®	6	7
79	13	Finger	Mild	Local blister	No	Paracetamol	8	8
80	7	Foot	Mild		No	Codis®	9	9
81	22	Hallux	Nil		No	Codis®	3	3
82	15	Thumb	Minimal		No	Paracetamol	4	4
83	13	Foot	Moderate		No	Paracetamol	2	3
84	54	Foot	Mild		No	Codis®	3	4
85	12	Leg	Mild	Abscess	No	Paracetamol	7	7
86	12	Foot	Minimal		No		4	4
87	14	Calf	PW Ventilated		No	Nil	3	3

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
88 Night adder		Finger	Moderate		No	Codis® Diclofenac	7	7
89		Foot	Minimal		No	Codis®	2	2
90 Mfezi.	20	Thigh x 2	Mild		No	Codis®	3	3
91	12	Foot	Mild		No	Codis®	3	3
92	9	Ankle	Mild		No	Nil	3	3
93	5	Foot	Moderate		No	Nil	?	?
94	8	Foot	Moderate		No	Paracetamol	?	?
95	5	Foot	Moderate		No	Codis®	6	7
96	24	Toe	Moderate	Local blister	No	Codis®	7	7
97	7	Foot	Severe	Local blister	No	Paracetamol	8	10
98	14	Foot	Moderate		No	Codis®	5	6
99	16 mths	Finger	Mild		Ampicillin	Nil	1	2
100	11	Toe	Moderate		No	Nil	3	4
101	9	Foot	Moderate		No	Codis®	5	6
102	25	Foot	Mild		No	Paracetamol	2	2
103	35	Foot	Moderate		No	Paracetamol	4	5
104	13	Ankle	Moderate		No	Paracetamol	4	5
105	14	Foot	Moderate		No	Nil	6	6
106	14	Foot	Mild		Penicillin V	Paracetamol	3	4
107	5	Thumb	Moderate		Penicillin V	Codis® Pethidine	4	5
108	10	Foot	Mild		No	Paracetamol	3	4
109	13	Toe	Moderate		No	Paracetamol	4	5
110	4	Shin	Moderate	Abscess	No	Codis®	22	22
111	4	Leg	Nil		No	Paracetamol	4	4
112	4	Neck	Minimal		No	Paracetamol	4	4
113	5	Leg	Moderate		No	Paracetamol	5	6
114	3	Leg	Moderate	Widespread blisters	Cloxacillin	Nil	4	5
115	60	Foot	Nil		No	Nil	2	2
116	11	Foot	Moderate		No	Nil	3	4
117	10	Foot	Moderate		No	Codis®	5	5
118	10	Knee	Mild		No	Codis®	3	3
119	32	Foot	Mild		No	Codis®	2	3
120	18	Foot	Mild	Necrosis	No Readmitted for deslough	Paracetamol Pethidine	3	3
121	19	Hallux	Moderate		No	Codis® Pethidine	4	
122 Mfezi	6	Calf + opp thigh	Moderate x 2	Necrosis Necrosis	Erythromycin	Paracetamol Tilidine Pethidine	60	61

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
123	62	Foot	Mild		No	Paracetamol	3	3
124	16	Foot	Mild		No	Paracetamol	3	3
125	45	Hallux	Nil		No	Codis®	2	2
126	15	Foot	Mild		No	Paracetamol	4	4
127	36	Hip	Mild		No	Codis®	2	3
128	15	Hallux	Mild		Penicillin V	Codis®	5	6
129	23	Foot	Moderate		No	Codis® Pethidine	8	9
130	42	Foot	Mild		No	Codis®	2	2
131	42	Ankle	Mild		No	Codis®	3	4
132	13	Foot	Mild		No	Codis®	4	4
133	12	Ankle	Moderate		No	Codis® Paracetamol	6	6
134	8	Foot	Moderate		No	Paracetamol Codis® Pethidine	4	5
135	13	Foot	Mild		Ampicillin Cloxacillin	Codis®	3	4
136	15	Toe	Mild		No	Aspirin Paracetamol	3	3
137	8	Forehead	Mild		No	Paracetamol	1	2
138	13	Toe	Mild		No	Paracetamol	2	2
139	10	Foot	Mild		Penicillin V	Paracetamol	4	5
140	9	Toe	Moderate		No	Paracetamol Diclofenac	6	6
141	36	Foot	Nil		No	Paracetamol	3	3
142	14	Foot	Mild		No	Codis®	5	5
143	45	Foot	Mild		Ampicillin	Paracetamol	3	5
144	48	Foot	Mild		No	Codis® Diclofenac	2	3
145	35	Foot	Mild		Tetracycline	Paracetamol	4	5
146	14	Ankle	Minimal		No	Nil	3	3
147	15	Finger	Severe		No	Nil	5	5
148	12	Calf	Severe		No	Codis® Diclofenac	9	9
149	35	Ankle	Moderate		No	Codis®	8	8
150	10	Foot	Moderate		No	Paracetamol	3	4
151	4	Foot	Moderate		No	Paracetamol	5	5
152	15	Foot	Moderate	Local blister	?	Indomethacin	2	11
153 Mfezi	34	Hand	Severe	Necrosis	Ampicillin	Pethidine	25	25
154	45	Foot	Mild		No	Codis® Diclofenac	2	3
155	10	Foot	Mild		No	Paracetamol Diclofenac	6	7
155A	17	Foot	Moderate		No	Codis® Pethidine	5	5
156	6	Foot	Mild		No	Paracetamol	3	3

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
157	70	Cheek	Mild		No	Codis® Diclofenac	3	4
158	39	Buttock	Nil		No	Pethidine	1	1
159	60	Foot	Moderate		No	Codis®	6	7
160	26	Forearm	Locally red		No	Paracetamol	2	2
161	8	Hand	Mild		No	Paracetamol	3	3
162	9	Shin	Mild		No	Paracetamol	2	2
163	11	Shin	Nil		No		4	4
164	34	Calf	PW Not ventilated		Penicillin V	Codis®	5	5
165	22	Hallux	Mild		No	Codis® Pethidine	3	3
166	11	Foot	Moderate		No	Paracetamol	8	9
167	25	Finger	Moderate		No	Codis® Diclofenac	8	8
168	7	Foot	Moderate		No	Paracetamol Diclofenac	4	5
169	8	Foot	Gross	Local blister	No	Paracetamol Pethidine	21	21
170	18	Hand	Moderate		No	Paracetamol	2	3
171 Night adder	4	Foot	Mild		No	Tilidine	5	5
172	12	Toe	Moderate		No	Nil	4	4
173	19	Foot	Moderate		No	Nil	4	5
174	3	Calf	Severe		No	Tilidine	13	13
175	2	Foot	Mild		No	Paracetamol	4	4
176	1	Foot	Moderate	Pharyngitis	Amoxicillin	Tilidine	8	9
177	14	Foot	Moderate		No	Codis®	4	5
178	6	Foot	Moderate		No	Nil	6	6
179	15	Foot	Moderate		No	Codis®	7	7
180	26	Foot	Moderate		No	Codis®	3	3
181 Atractaspis	12	Foot	Moderate		No	Paracetamol Pethidine	5	5
182	24	Foot	Severe		No	Pethidine	6	6
183	24	Foot	Moderate		No	Nil	4	4
184	15	Toe	Moderate		No	Codeine Pethidine	6	6
185	29	Foot	Moderate		No	Codis®	4	5
186	26	Foot	Moderate		No	Paracetamol	5	5
187	9	Hallux	Mild		No	Nil	5	5
188	15	Ankle	Moderate	Haematoma	No	Paracetamol Pethidine	21	21
189	22	Toe	Moderate		No	Paracetamol	3	4
190	10	Foot	Moderate		No	Aspirin	?	?
191	20	Toe	Moderate		No	Codis®	5	5

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
192	10	Foot	Mild		No	Paracetamol	7	7
193	12	Foot	Moderate		No	Paracetamol	4	4
194	8	Hand	Mild		No	Nil	2	2
195	13	Foot	Moderate		No	Nil	5	5
196 Mfezi	20	Scapula	Mild	Necrosis	No	Nil	4	5
197	7	Foot	Nil		No	Nil	1	1
198	15	Ankle	Nil		No	Nil	2	2
199	42	Finger Hand	Moderate Moderate	Necrosis Necrosis	Ampicillin Gentamicin	Paracetamol Pethidine	78	79
200	8	Finger	Mild	Necrosis	No	Paracetamol Tilidine	12	13
201	24	Foot	Moderate		No	Paracetamol	3	3
202	31	Ankle	Moderate		No	Nil	4	4
203	20	Ankle	Nil		No	Nil	3	3
204	20	Ankle	Moderate		No	Nil	6	6
205	5	Foot	Severe		No	Tilidine	6	6
206	13	Hallux	Moderate		Amoxicillin	Paracetamol	5	6
207	11	Toe	Mild		No	Paracetamol	3	3
208	5	Foot	Mild	Established skin pustules	Erythromycin	Paracetamol	9	10
209	27	Finger	Mild		No	Codis®	5	5
210	15	Ankle	Gross	Necrosis Widespread blisters Compartment syndrome	Ampicillin Gentamicin	Nil	123	124
211 Night adder	13	Finger	Mild	Local blister	No	Pethidine	7	7
212 Black mamba	3	Calf	PW Ventilated		No	Nil	4	4
213	27	Ankle	Nil		No	Paracetamol	2	2
214 Puff adder	39	Finger	Moderate		No	Paracetamol	5	5
215	54	Foot	Moderate		No	Nil	8	9
216	30	Foot	Nil		No	Nil	2	2
217	15	Foot	Mild		No	Nil	3	3
218	5	Ankle	Moderate	Necrosis	No	Tilidine	14	15
219	11	Finger	Moderate		No	Paracetamol	4	5
220	25	Thumb	Moderate		No	Codis® Diclofenac	7	8
221	8	Foot	Mild		No	Paracetamol	4	5
222	25	Ankle	Moderate		No	Nil	6	6
223	4	Foot	Moderate		No	Paracetamol	7	8

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
224	22	Foot Wrist	Minimal Minimal		No	Codis®	4	4
225	40	Ankle	Moderate		No	Codis®	3	3
226	7	Hallux	Mild		No	Paracetamol	4	4
227	7	Toe	Mild		Penicillin	Paracetamol	2	2
228	14	Foot	Mild		No	Codis®	4	4
229	32	Thumb	Moderate		No	Paracetamol	5	5
230	15	Ankle	Nil		No	Paracetamol	3	4
231	12	Foot	Minimal		No	Paracetamol	?	5
232 Mfezi.	61	Finger	Moderate	Necrosis	Cotrimoxazole Metronidazole	Codis® Pethidine	95	95
233	22	Hand	Nil		No	Codis®	?	2
234	15	Ankle	Mild		No	Codis®	5	6
235	3		VO		No	Nil	2	2
236	4	Arm	Mild		No	Paracetamol	5	5
237	15	Finger	Mild	Necrosis	Absconded No	Codis®	5	5
238	36	Iliac crest	Nil		No	Paracetamol	2	2
239	24	Ankle	Nil		No	Nil	2	2
240	16	Shin	Mild		No	Paracetamol	2	2
241	9	Foot	Nil		No	Codis®	3	3
242	17	Foot	Moderate		No	Paracetamol	4	5
243	25	Foot	Nil		No	Nil	1	1
244	10	Foot	Moderate		No	Paracetamol	4	4
245	7	Ankle	Minimal		No	Paracetamol	2	2
246	15	Ankle	Tender groin gland		No		2	2
247	5	Ankle	Severe		No	Paracetamol	7	7
248	17	Foot	Moderate		No	Nil	6	6
249	30	Toe	Minimal		No	Codis®	2	2
250	4	Foot	Moderate	Pneumonia	Cotrimoxazole	Nil	11	11
251	60	Toe	Mild		No		3	3
252	19	Shin	PW		No	Codis®	2	2
253	12	Foot	Nil		No	Nil	2	2
254	21	Thigh	Nil		No	Paracetamol	3	3
255 Atractaspis	39	Finger	Mild	Necrosis Blister	Yes Unknown	Paracetamol	4	5
256	19 mths	Foot	Severe	Necrosis Blister	Ampicillin	Tilidine	27	28
257	10	Toe	Moderate		No	Paracetamol	4	5
258	15	Ankle	Mild		No	Nil	5	5

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesia	Days in hospital	Discharge day after bite
259	9	Calf	PW Intubated		No	Nil	2	2
260	10	Ankle	Moderate		No	Nil	6	6
261	12	Foot	Moderate		No	Nil	4	5
262	17	Thigh	Mild		No		3	3
263	2	Heel	Moderate		No	Paracetamol	3	3
264	4	Toe	Severe		No	Paracetamol	7	7
265	12	Toe	Moderate		No	Codis®	4	4
266	7	Calf	Nil		No	Nil	2	2
267	2	Hallux and toe	Nil Nil		No	Paracetamol	2	2
268	12	Ankle	Minimal		No	Paracetamol	3	3
269	Admitted with chronic ulcer due to snake bite in 1997					Nil		
270	31	Foot	Moderate		No	Nil	4	5
271	11	Hallux	Mild		No	Paracetamol	4	4
272	7	Finger	Severe	Local blisters	No	Codis®	5	7
273	4	Hallux	Moderate		No	Paracetamol	4	5
274 Unidentified snake	18	Hand	Mild		No	Paracetamol	1	1
275	15	Foot	Moderate		No	Paracetamol	5	5
276	15	Toe	Mild		No		4	4
277	23	Shin	Mild		No		3	3
278	17	Ankle	Minimal		No	Paracetamol	3	3
279	12	Foot	Moderate		No	Codis®	4	4
280	10	Hallux	Moderate		No	Nil	3	4
281	65	Hand	Moderate	Necrosis Blister	Ampicillin Gentamicin	Pethidine	14	15
282	23	Ankle	Moderate		No	Codis®	4	4
283	16	Ankle	Minimal		No		3	3
284	42	Finger	Nil		No	Paracetamol	3	3
285		Ankle	Nil		No	Paracetamol Codis®	3	
286	2	Finger	Severe	Necrosis	Cefradine Later amputation	Paracetamol Tilidine	3	3
287	11	Foot	Mild		No	Paracetamol	3	3
287A	20	Foot	Moderate		No	Paracetamol	3	4
288	10	Hallux	Mild		No	Paracetamol	4	4
289 Unidentified snake	19	Ankle	Mild		No	Paracetamol	3	3

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day After bite
290	34	Ankle	Nil		No	Paracetamol	4	4
291	12	Hallux	Moderate		Amoxicillin	Nil	4	4
292	40	Hallux Opposite heel	Mild Moderate		No	Paracetamol	5	6
293	10	Hallux	Mild		No	Codis®	4	5
294	11	Foot	Minimal		No	Paracetamol	3	3
295	11	Foot	Moderate	Abscess	No	Paracetamol	4	4
296	30	Toe	Moderate	Necrosis	Erythromycin	Nil	9	10
297	6	Ankle	Mild		Amoxicillin	Paracetamol	16	17
298	34	Shin	Nil		No	Paracetamol	4	5
299	3	Ankle	Mild		No	Paracetamol	3	3
300	18/12	Hand x 2	Gross	Necrosis Necrosis	Ampicillin Gentamicin	Nil	21	21
301	28	Foot	Moderate		No	Paracetamol	4	5
302	11	Foot	Moderate		No		5	5
303	25	Foot	Moderate		No		3	4
304	11	Foot	Moderate		No	Paracetamol	5	5
305	3	Foot	Moderate	Local blister	No	Paracetamol	11	12
306	19	Leg	PW Not ventilated		No	Paracetamol	3	3
307	15	Foot	Moderate		No	Paracetamol	4	5
308	9	Foot	Nil		No	Paracetamol	1	3
309	24	Knee	Nil		No	Paracetamol	4	4
310	2	Heel	Moderate		No	Paracetamol	8	8
311	12	Foot	Moderate		No	Codis®	5	5
312	12	Foot	Moderate		No	Paracetamol	5	5
313 Puff adder	10	Heel	Moderate		No	Paracetamol	3	3
314	15	Finger	Moderate		No	Paracetamol	4	4
315	17	Foot	Moderate		No	Paracetamol	6	6
316	7	Finger	Mild		No	Paracetamol	2	2
317 Puff adder	40	Toe	Moderate		No	Paracetamol	12	13
318 Mfezi	11	Hand	Severe	Necrosis	Ampicillin Gentamicin	Paracetamol Tilidine	26	26
319	13	Toe	Moderate	Abscess	No	Paracetamol	8	8
320 Night adder	60	Ankle	Moderate	Abscess	No	Paracetamol	8	9
321 Mfezi	50	Shin	Mild	Necrosis	Chloramphenicol	Paracetamol	11	12
322	53	Ankle	Moderate		No	Paracetamol	5	5
323	15	Foot	Nil		No	Nil	3	3

Eshowe No.	Age	Bite site	Clinical presentation	BSCs/Other	Antibiotics	Analgesics	Days in hospital	Discharge day after bite
324	20	Arm	Nil		No	Nil	3	3
325	53	Ankle	Moderate		No	?	5	5
326	14	Foot	Mild		No	Paracetamol	2	2
327	4	Foot	Moderate		No	Paracetamol	6	6
328	74	Toe	Moderate		Cotrimoxazole	Paracetamol	7	9
329 Herald snake	20	Knuckle	Nil		No	Nil	2	2
330	50	Ankle	Moderate		No	Paracetamol	6	7
331	19	Foot	Mild		No	Codis® Pethidine	5	5
332	10	Ankle	Mild		No	Codis®	3	4
333	18	Ankle	Mild		No	Paracetamol	5	6
334	18	Foot	Mild		No	Nil	2	2

REFERENCES

Adogu, A.A., Abbas, M., Ishaku, D., (1992). Hysterical paralysis as a complication of snakebite. *Trop Geogr Med* **44**, 167 – 169.

Ahmed, Y.Y., Noor El-Din, M., Mohamed, A.H., Moustafa, F.A., (1974). Effect of cobra venom on the chick embryo. *Toxicon* **12**, 325 – 326.

Aird, S.D., (2002). Ophidian envenomation strategies and the role of purines. *Toxicon* **40** (4), 335 – 393.

Aitchison, J.M., (1990). Boomslang bite - diagnosis and management. A report of two cases. *S Afr Med J* **78**, 39 – 42.

Allam, M.W., Weiner, D., Lukens, F.D.W., (1956). Comparison of cortisone and antivenom in the treatment of Crotaline envenomation. *Am Assoc Adv Sci* 393 – 397.

Allen, H.L., Wase, A., Bear, W.T., (1980). Indomethacin and aspirin: effect of nonsteroidal anti-inflammatory agents on the rate of fracture repair in the rat. *Acta Orthop Scand* **51**, 595 – 600.

Almekinders, L.C., Gilbert, J.A., (1986). Healing of experimental muscle strains and the effects on nonsteroidal anti-inflammatory medication. *Am J Sports Med* **14** (4), 303 – 308.

Aloof-Hirsch, S., Devries, A., Berger, A., (1968). The direct lytic factor of cobra venom: purification and chemical characterization. *Biochim Biophys Acta* **154**, 53 – 60.

Altman, R.D., Latta, L.L., Keer, R., Renfree, K., Hornicek, F.J., Banovac, K., (1995). Effect of nonsteroidal anti-inflammatory drugs on fracture healing: a laboratory study in rats. *J Orth Trauma* **9** (5), 392 – 400.

Alves, R., (1960). Some case histories of snake bites in Southern Rhodesia. *J Herp Assoc Rhod* **9/10**, 15 –17.

Amaral, C.F.S., Dias, M.B., Campolina, D., Proietti, F.A., De Rezende, N.A., (1994). Children with adrenergic manifestations of envenomation after *Tityus serrulatus* scorpion sting are protected from early anaphylactic antivenom reactions. *Toxicon* **32** (2), 211 – 215.

American College of Surgeons Committee on Trauma (1997). In: Weigelt, J.A. and Committee (Eds.), Advanced Trauma Life Support for Doctors. Sixth edition, Chicago, pp. 313 – 323.

Anker, R.L., Straffon, W.G., Loiselle, D.S., Anker, K.M., (1982). Retarding the uptake of "mock venom" in humans. Comparison of three first-aid treatments. *Med J Aus* **1**, 212 – 214.

Aravanis, C., Joannidis, P.J., Ktenas, J., (1982). Acute myocardial infarction and cerebrovascular accident in a young girl after a viper bite. *Br Heart J* **47**, 500 – 503.

Ariff, A.W., (1955). Cortigen for snake-bite (correspondence). *Br Med J* 204 – 220.

Arnold, R.E., (1976). Treatment of snakebite (correspondence). *J Am Med Assoc* **236** (16), 1843.

Arroyo, O., Bolaños, R., Muñoz, G., (1980). The bacterial flora of venoms and mouth cavities of Costa Rican snakes. *Bull Pan Am Health Organ* **14** (3), 280 - 285.

Atkinson, P.M., (1980). The coagulant action of *Dispholidus typus* (boomslang) venom. PhD thesis, University of the Witwatersrand, Johannesburg.

Atkinson, P.M., Bradlow, B.A., White, J.A.M., Grieg, H.B.W., Gaillard, M.C., (1980). Clinical features of Twig snake *(Thelotornis capensis)* envenomation. *S Afr Med J* **58**, 1007-1011.

Atkinson, P.M., Rebello, M., Gaillard, M.C., Bradlow, B.A., (1981). The role of heparin in *Dispholidus typus* envenomation: an experimental study. *Thromb Res* **23**, 355 – 363.

Auerbach, R.D., (1989). Snake envenomation in Botswana. *Botshelo* **19** (2), 1 - 14.

Balarin, L., (1960). Case history of a Puff Adder *(Bitis arietans)* bite. *J Herp Assoc Rhod* **11,** 4 – 6.

Barraviera, B., (1994). Acute-phase response in snakebite (correspondence). *Toxicon* **32** (8), 861 – 862.

Barraviera, B., Lomonte, B., Tarkowski, A., Hansen, L.A., Meira, D.A., (1995). Acute-phase reactions including cytokines in patients bitten by *Bothrops* and *Crotalus* snakes in Brazil. *J Venom Anim Toxins* **1,** 11 – 22.

Barros, S.F., Friedlanskaia, I., Petricevich, V.L., Kipnis, T.L., (1998). Local inflammation, lethality and cytokine release in mice injected with *Bothrops atrox* venom. *Mediat Inflam* **7,** 339 – 346.

Beer, E., Musiani, R., (1998). A case of intestinal infarction following *Vipera aspis* bite. *Toxicon* **36** (5), 729 – 733.

Bhat, R.N., (1974). Viperine snake bite poisoning in Jammu. *J Indian Med Assoc* **63** (12), 383 – 392.

Bielory, L., Gascon, P., Lawley, T.J., Young, N.S., Frank, M.M., (1988). Human serum sickness: a prospective analysis of 35 patients treated with equine anti-thymocyte globulin for bone marrow failure. *Med* **67**(1), 40 – 57.

Black, A.J.G., (2000). A practical approach to the management of snakebite in Southern Africa. *Cont Med Educ* **18** (8), 684 – 692.

Black, R.E., Gunn, R.A., (1980). Hypersensitivity reactions associated with botulinal antitoxin. *Am J Med* **69,** 567 – 570.

Blake, D.K., (1960). Case of a brown mamba bite. *J Herp Assoc Rhod* **9/10,** 17 – 18.

Blaylock R.S.M., (1960). Case history of a bite from *Bitis a. arietans* in Bulawayo. *J Herp Assoc Rhod* **13,** 9.

Blaylock, R.S.M., (1982a). Snake bites at Triangle Hospital, January 1975 to June 1981. *Cent Afr J Med* **28** (1), 1 - 10.

Blaylock, R.S.M., (1982b). The treatment of snakebite in Zimbabwe. *Cent Afr J Med* **28** (10), 237 – 246.

Blaylock, R.S., (1983). Time of onset of clinical envenomation following snakebite. *S Afr Med J* **64**, 357 – 360.

Blaylock, R.S.M., (1994). Pressure immobilisation for snakebite in southern Africa remains speculative. *S Afr Med J* **84** (12), 826 – 827.

Blaylock, R.S., (1999). Antibiotic use and infection in snakebite victims. *S Afr Med J* **89** (8), 874 – 876.

Blaylock, R., (2000). The clinical natural history of snakebite victims in Southern Africa. MMedSc thesis 2000, University of Natal.

Blaylock, R.S., Lichtman, A.R., Potgieter, P.D., (1985). Clinical manifestations of Cape cobra *(Naja nivea)* bites: a report of two cases. *S Afr Med J* **68**, 342 – 344.

Boyer, L.V., Seifert, S.A., Clark, R.F., McNally, J.T., Williams, S.R., Nordt, S.P., Walter, F.G., Dart, R.C., (1999). Recurrent and persistent coagulopathy following pit viper envenomation. *Arch Intern Med* **159**, 706 – 710.

Branch, W.R., McCartney, C.J., (1986). *Dispholidus typus* boomslang: envenomation. *J Herp Assoc Afr* **32**, 34 – 35.

Brian, M.J., Vince, J.D., (1987). Treatment and outcome of venomous snake bite in children at Port Moresby General Hospital, Papua New Guinea. *Trans Roy Soc Trop Med Hyg* **81**, 850 – 852.

Brink, S., Steytler, J.G., (1974). Effects of puff-adder venom on coagulation, fibrinolysis and platelet aggregation in the baboon. *S Afr Med J* **48**, 1205 – 1213.

Broadley, D.G., (1983). Warning, defensive and aggressive behaviour. In: Broadley, D.G. (Ed.). *Fitzsimons Snakes of Southern Africa.* Delta Books, Johannesburg, p 17.

Brossy, J., (1977). The treatment of snakebite. *S Afr Med J* **51**, 390 – 391.

Brun-Buisson, C.J.L, Saada, M., Trunet, P., Rapin, M., Roujeau, J-C., Revuz, J., (1985). Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs. *Br Med J* **290**, 1786.

Bucknall, N.C., (1991). Electrical treatment of venomous bites and stings. *Toxicon* **29** (4/5), 397 – 400.

Caiaffa, W.T., Vlahov, D., Antunes, C.M.F., de Oliveira, H.R., Diniz, C.R., (1994). Snake bite and antivenom complications in Belo Horizonte, Brazil. *Trans Roy Soc Trop Med Hyg* **88**, 81 – 85.

Cardosa, J.LC., Fan, H.W., França, F.O.S., Jorge, M.T., Leite, R.P., Nishioka, S.A., Avila, A., Sano-Martins, I.S., Tomy, S.C., Santoro, M.L., Chudzinski, A.M., Castro, S.C.B., Kamiguti, A.S., Kelen, E.M.A., Hirata, M.H., Mirandola, R.M.S., Theakston, R.D.G., Warrell, D.A., (1993). Randomised comparative trial of three antivenoms in the treatment of envenomation by lance-headed vipers (*Bothrops jararaca*) in Sao Paulo, Brazil. *Quart J Med* **86**, 315 – 325.

Cavinato, R.A., Remold, H., Kipnis, T.L., (1998). Purification and variability in thrombin-like activity of *Bothrops* atrox venom from different geographic regions. *Toxicon* **36** (2), 257 – 267.

Červeňanský, C., Dajas, F., Harvey, A.L., Karlsson, E., (1991). Fasciculins, anticholinesterase toxins from mamba venoms: biochemistry and pharmacology. In: Harvey A.L. (Ed.), *Snake Toxins,* Pergamon Press, New York, pp 303 – 321.

Chacur, M., Picolo, G., Gutiérrez, J.M., Texeira, C.F.P., Cury, Y., (2001) Pharmacological modulation of hyperalgesia induced by *Bothrops* asper (terciopelo) snake venom. *Toxicon* **39** (8), 1173 – 1181.

Chajek, T., Rubinger, D., Alkan, M., Melmed, R.M., Gunders, A.E., (1974). Anaphylactoid reaction and tissue damage following bite by *Atractaspis engaddensis. Trans R Soc Trop Med Hyg* **68** (4), 333 - 337.

Chang, T-W., Weinstein, L., (1957). Effect of cortisone on treatment of tetanus with antitoxin. *Proc Soc Exper Biol Med* **94**, 431 – 433.

Chapman, D.S., (1968). The symptomatology, pathology, and treatment of the bites of venomous snakes of Central and Southern Africa. In: Bücherl, W., Buckley, E., Deulofeu, V. (Eds.). *Venomous Animals and Their Venoms.* Academic Press, London, pp 463 – 527.

Chen, J.C., Bullard, M.J., Chiu, T.F., Ng, C.J., Liaw, S.J., (2000). Risk of immediate effects from F(ab)$_2$ bivalent antivenom in Taiwan. *Wilderness Environ Med* **11** (3), 163 – 167.

Christensen, P.A., (1955). In: Christensen, P.A. (Ed.). *South African Snake Venoms and Antivenoms*. SA Inst Med Res, Johannesburg.

Christensen, P.A., (1961). In: Annual Report of the South African Institute for Medical Research, Johannesburg, pp 132 – 133.

Christensen, P.A., (1966). Venom and antivenom potency estimation. *Mem Inst But* **33** (1), 305 – 326.

Christensen, P.A., (1969). The treatment of snakebite. *S Afr Med J* **43**, 1253 – 1258.

Christensen, P.A., (1977). African snake venoms. In: Gear, J.H.S. (Ed). *Medicine in a Tropical Environment*: Proceedings of the International Symposium, South Africa. A.A. Balkema, Cape Town, pp 310 – 317.

Christensen, P.A., (1983). Snake venoms and the treatment of snake-bite. In: Broadley, D.G. (Ed.), *Fitzsimons Snakes of Southern Africa*, Delta Books, Johannesburg, pp 18 – 23.

Christensen, P.A., Anderson, C.G., (1967). Observations on *Dendroaspis* venoms. In: Russell F.E., Saunders, P.R. (Eds.). *Animal Toxins*. Pergamon Press, New York, pp 223 – 234.

Christensen, J.T., Wulff, K., (1985). Compartment pressure following leg injury: the effect of diuretic treatment. *Injury* **16**, 591 – 594.

Chugh, K.S., Singhal, P.C., Kher, V.K., Gupta, V.K., Malik, G.H., Narayan, G., Datta, B.N., (1983). Spectrum of acute cortical necrosis in Indian patients. *Am J Med Sci* **286** (1), 10 – 20.

Clark, R.F., Selden, B.S., Furbee, B., (1993). The incidence of wound infection following Crotalid envenomation. *J Emerg Med* **11**, 583 – 586.

Clavert, J., Gabriel-Robez, O., (1971). Anomalies de la face déterminées chez l'embryon de souris par l'injection de venin de vipère *(Vipera aspis)* à la femelle gestante. *Bull Ass Anat* **151**, 289.

Clemens, R., Pukrittayakamee, S., Nonprasert, A., Charoenlap, P., Bunnag, D., White, N.J., (1993). AT-III concentrate in combination with antivenom can reduce late coagulopathy in experimentally induced MPV envenoming (Abstract). *Toxicon* **31**, 938.

Coetzer, P.W.W., Tilbury, C.R., (1982). The epidemiology of snakebite in Northern Natal. *S Afr Med J* **62**, 206 - 212.

Corrigan, P., Russell, F.E., Wainchell, J., (1978). Clinical reactions to antivenom. *Toxicon* **1**, *(Supp)*, 457 – 465.

Crisp, N.G., (1985). Black mamba envenomation (correspondence). *S Afr Med J* **68**, 293 – 294.

Cywes, S., Louw, J.H., (1962). Phlegmasia caerulea dolens: successful treatment by relieving fasciotomy. *Surgery* **51** (2), 169 – 176.

Dart, R.C., Gustafson, R.A., (1991). Failure of electric shock treatment for rattlesnake envenomation (correspondence). *Ann Emerg Med* **20**, 659 – 661.

Dart, R.C., Hurlbut, K.M., Garcia, R., Boren, J., (1996). Validation of a severity score for the assessment of *Crotalid* snakebite. *Ann Emerg Med* **27** (3), 321 – 326.

Dart, R.C., McNally, J., (2001). Efficacy, safety, and use of snake antivenoms in the United States. *Ann Emerg Med* **37** (2), 181 – 188.

Deichmann, W.B., Radomski, J.L., Farrell, J.J., MacDonald, W.E., Keplinger, M.L., (1958). Acute toxicity and treatment of intoxications due to *Crotalus adamanteus* (rattlesnake venom). *Am J Med Sci* **236**, 204 – 207.

Delport, S.D., Schmid, E.U., Farrant, P.J., (1991). Delayed neurotoxic and cytotoxic complications after snake envenomation (correspondence). *S Afr Med J* **79**, 169.

Dimar, J.T., Ante, W.A., Zhang, Y.P., Glassman, S.D., (1996). The effects on nonsteroidal anti-inflammatory drugs on posterior spinal fusions in the rat. *Spine* **21** (16), 1870 – 1876.

Dingle, J.T., (1993). Prostaglandins in human cartilage metabolism. *J Lipid Mediat* **6**, 303 – 312.

Dragstedt, C.A., Mead, F.B., Eyer, S.W., (1938). Role of histamine in circulatory effects of rattlesnake venom (Crotalin). *Proc Soc Exp Biol Med* **37**, 709 – 710.

Du, X.-Y., Clemetson, K.J., (2002). Snake venom L-amino acid oxidases. *Toxicon* **40** (6), 659 – 665.

Dunnihoo, D.R., Rush, B.M., Wise, R.B., Brooks, G.G., Otterson, W.N., (1992). Snake bite poisoning in pregnancy: a review of the literature. *J Reprod Med* **37**, 653 - 658.

Durrant, S., Haagner, G.V., (1992). Dendroaspis polylepis black mamba envenomation. *J Herp Assoc Afr* **41**, 46.

Du Toit, D.M., (1980). Boomslang *(Dispholidus typus)* bite. A case report and a review of diagnosis and management. *S Afr Med J* **57**, 507 – 510.

Dutta, N.K., Narayanan, K.G.A., (1952). Release of histamine from rat diaphragm by cobra venom. *Nature* **169**, 1064 – 1065.

Dwivedi, S., Sheshadri, S., D'Souza, C., (1989). Time limit for anti-snake venom administration (correspondence). *Lancet,* 622.

Edington, D.A., (1973). Snake-bite (correspondence). *S Afr Med* J **17**, 364.

Editorial., (1956). Snake bite. *Cent Afr J Med* **2** (9), 345 – 346.

Editorial., (1962). The treatment of snake-bite. *Cent Afr J Med* **8** (12), 473.

Editorial., (1976). IgE, parasites, and allergy. *Lancet* **2**, 894 – 895.

Edwards, I.R., Flemming, J.B.M., James, M.F.M., (1979). Management of a Gaboon viper bite: a case report. *Cent Afr J Med* **25** (10), 217 – 221.

Ellis, E.F., Smith, R.T., (1965). Systemic anaphylaxis after rattlesnake bite. *J Am Med Assoc* **193** (5), 151 - 152.

Els, R.A., (1988). *Naja haje annulifera.* Egyptian cobra envenomation. *J. Herp Assoc Afr* **34**, 52-53.

Entman, S.S., Moise, K.J., (1984). Anaphylaxis in pregnancy. *Southern Med J* **77** (3), 402.

Escalante, T., Franceschi, A., Rucavado. A., Gutiérrez, J.M., (2000). Effectiveness of batimastat, a synthetic inhibitor of matrix metalloproteinases, in neutralising local tissue damage induced by BaP1, a haemorrhagic metalloproteinase from the venom of the snake *Bothrops Asper*. *Biochem Pharmacol* **60**, 269 – 274.

Esperson, G.T., Larsen, K., (1987). NSAID (non steroid anti-inflammatory drug) of fasciitis necroticans. *Ugeskr Laeger* **149** (51), 3475 – 3477.

Evans, J., Ownby, C.L., (1999). Neutralisation of edema, hemorrhage and myonecrosis induced by North American *Crotalid* venoms in simulated first-aid treatments. *Toxicon* **37** (4), 633 – 650.

Fan, H.W., Marcopito, L.F., Cardoso, J.L, França, F.O.S., Malaque, C.M.S., Ferrari, R.A., Theakston, R.D.G., Warrell, D.A., (1999). Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for *Bothrops* snake bites. *Br Med J* **318**, 1451 – 1452.

Feldberg, W., Kellaway, C.H., (1938). Liberation of histamine and formation of lysocithin-like substances by cobra venom. *J Physiol* **94**, 187 – 226.

Fitzsimons, F.W., (1912). In: Fitzsimons F.W. (Ed). *The Snakes of South Africa, their Venom and the Treatment of Snake Bite.* Maskew Miller, Cape Town.

Fitzsimons, F.W., (1929). In: Fitzsimons, F.W., Fitzsimons V.F.M. (Eds.). *Snakes and the Treatment of Snake Bite.* Speciality Press, Cape Town.

Fleming, J.B.M., (1977). Anti-snakebite sera - their relevance in Rhodesia. *Cent Afr J Med* **23** (5), 93 – 96.

French, M.R., (1959). Case history of a puff adder bite in Salisbury. *J Herp Assoc Rhod* **8**, 9.

Gabriel-Robez, O., Clavert J.,(1969). Action d'une injection de venin de vipere *(Vipera aspis)* à la souris gestante sur la formation des emryons *C r. Séanc Soc Biol* **163**, 1576.

Gans, C., (1978). Reptilian venoms: some evolutionary considerations, In: Gans, S. C., Gans, K.A. (Eds.), *Biology of the Reptilia. 8B. Physiology*. New York, Academic Press, pp 1 - 42.

Garfin, S.R., Mubarak, S.J., Davidson, T.M., (1979a). Rattlesnake bites: current concepts. *Clin Orthop Rel Res* **140**, 50 – 57.

Garfin, S.R., Castilonia, R.R., Mubarak, S.J., Hargens, A.R., Akeson, W.H., Russell, F.E., (1979b). Role of surgical decompression in treatment of rattlesnake bites. *Am College Surg* **30** (30), 502 – 504.

Geddes, J., Thomas J.E.P., (1985). Boomslang bite - a case report. *Cent Afr J Med* **31** (6), 109 – 112.

Gerber, J.D.W., Adendorff, H.P.F., (1980). Boomslang *(Dispholidus typus)*– byt: 'n Gevalbespreking. *S Afr Med J* **57**, 710 – 711.

Glaser, H.S.R., (1948). Bactericidal activity of *Crotolus* venom in vitro. *Copeia* **4**, 245-247.

Glass, T.G., (1976). Early debridement in pit viper bites. *J Am Med Assoc* **235** (23), 2513 – 2516.

Goddard, M.G., (1962). Case history of a puffadder *(Bitis arietans)* bite. *J Herp Assoc Rhod* **17/18**, 15 –16.

Goldstein, E.J.C., Citron, D.M., Gonzalez, H., Russell, F.E., Finegold, S.M., (1979). Bacteriology of rattlesnake venom and implications for therapy. *J Inf Dis* **140** (5), 818-821.

Gomperts, E.D., Demetriou, D., (1977). Laboratory studies and clinical features in a case of boomslang envenomation. *S Afr Med J* **51**, 173 – 175.

Goodman & Gillman's *The pharmacological basis of therapeutics.* 10th edition, 2001. Eds Hardman, J.G., Limbird, L.E., Gilman, A.G. McGraw-Hill.

Gowdy, J.M., (1954). Treatment of snakebite with cortisone: report of four cases. *Am Practit Digest Treat* **5**, 569 – 572.

Grace, T.G., Omer, G.E., (1980). The management of upper extremity pit viper wounds. *J Hand Surg* **5** (2), 168 – 177.

Grasset, E., (1933). Concentrated African antivenom serum: its preparation, standardisation and use in the treatment of snake-bite. *S Afr Med J,* 35 – 39.

Guderian, R.H., Mackenzie, C.D., Williams, J.F., (1986). High voltage shock treatment for snake bite (correspondence). *Lancet* **2**, 229.

Gutiérrez, J.M., León, G., Estrada, R., Chaves, F., Rojas, G., Ovadia, M., (1998). Inhibition by Ca Na₂ EDTA of local tissue damage induced by *Bothrops* asper venom: application in horse immunization for antivenom production (abstract). *Toxicon* **36** (9), 1289.

Gutiérrez, J.M., Rucavado, A., Ovadia, M., (1999). Metalloproteinase inhibitors in snakebite envenomations. *Drug Discov Today* **4** (11), 532 – 533.

Gutiérrez, J.M., Rucavado, A., (2000). Snake venom metalloproteinases: their role in the pathogenesis of local tissue damage. *Biochimie* **82**, 841 – 850.

Haagner, G.V., (1987). *Dendroaspis angusticeps* (green mamba) envenomation. *J Herp Assoc Afr* **33**, 32.

Haagner, G.V., (1990). *Dendroaspis polylepis* black mamba envenomation. *J Herp Assoc Afr* **37**, 59.

Haagner, G.V., Morgan, R., (1991). *Dendroaspis polylepis* black mamba envenomation. *J Herp Assoc Afr* **39**, 28 – 29.

Harris, J.B., (1991). Phopholipases in snake venoms and their effects on nerve and muscle. In: Harvey, A.L. (Ed). *Snake Toxins*, Pergamon Press, New York pp 91 - 129.

Harvey, W.R., (1985). Black mamba envenomation. *S Afr Med J* **67**, 960.

Harvey, A.L., Anderson, A.J., (1991). Dendrotoxins: snake toxins that block potassium channels and facilitate neurotransmitter release. In: Harvey, A.L. (Ed.), *Snake Toxins*, Pergamon Press, New York, pp 131 – 164.

Hilligan, R., (1987). Black mamba bites. A report of two cases. *S Afr Med J* **72**, 220 – 221.

Ho, M., Warrell, M.J., Warrell, D.A., Bidwell, D., Voller, A., (1986). A critical reappraisal of the use of enzyme-linked immunosorbent assays in the study of snake bite. *Toxicon* **24** (3), 211 – 221.

Hoback, W.W., Green, T.W., (1953). Treatment of snake venom poisoning with cortisone and corticotrophin. *J Am Med Assoc* **152** (3), 236 – 237.

Hogan, D.E., Dire, D.J., (1990). Anaphylactic shock secondary to rattlesnake bite. *Ann Emerg Med* **19**, 814 – 816.

Howarth, D.M., Southee, A.E., Whyte, I.M., (1994). Lymphatic flow rates and first-aid in simulated peripheral snake or spider envenomation. *Med J Aust* **161**, 695 – 700.

Howe, N.R., Meisenheimer, J.L., (1988). Electric shock does not save snakebitten rats. *Ann Emerg Med* **17**, 254 – 256.

Huang, T.T., Blackwell, S.J., Lewis, S.R., (1978). Hand deformities in patients with snakebite. *Plast Recon Surg* **62** (1), 32 – 36.

Huang, T-F., Peng, H-C., Peng, I-S., Teng, C-M., Ouyang, C., (1992). An antiplatelet peptide, Gabonin, from *Bitis gabonica* snake venom. *Arch Bioch Biophy* **298** (1), 13 – 20.

Hutton, M., Rhodes, R.S., Chapman, G., (1982). The lowering of post ischaemic compartment pressures with mannitol. *J Surg Res* **32**, 239 – 242.

Hyslop, S., Marsh, N.A., (1991). Comparison of the physiological effects in rabbits of Gaboon viper *(Bitis gabonica)* venoms from different sources. *Toxicon* **29** (10), 1235 – 1250.

Iddon, D., Theakston, R.D.G., Ownby, C.L., (1987). A study of the pathogenesis of local skin necrosis induced by *Naja nigricollis* (spitting cobra) venom using simple histological staining techniques. *Toxicon* **25** (6), 665 – 672.

James, R.F., (1985). Snake bite in pregnancy (correspondence). *Lancet* **2**, 731.

Jansen, D.W., (1983). A possible function of the secretion of Duvernoy's gland. *Copeia* **1**, 262 – 264.

Johnson, E.K., Kardong, K.V., Mackessy, S. P., (1987). Electric shocks are ineffective in treatment of lethal effects of rattlesnake envenomation in mice. *Toxicon* **25** (12), 1347 – 1349.

Jorge, M.T., De Mendonça, J.S., Ribeiro, L.A., Da Silva, M.L.R., Kusano, E.J.U., Cordeiro, C.L., (1990). Flora bacteriana da cavidade oral, presas e veneno de *Bothrops jararaca:* possível fonte de infecçáo no local da picada. *Rev Inst Med Trop São Paulo,* **32**(1), 6 - 10.

Jorge, M.T., Ribeiro, L.A., (1997). Infections in the bite site after envenoming by snakes of the *Bothrops* genus. *J Ven Anim Toxins* **3** (2), 264 – 272.

Jurkovich, G.J., Luterman, A., McCullar, K., Ramenofsky, M.L., Curreri, P.W., (1988). Complications of *Crotolidae* antivenin therapy. *J Trauma* **28** (7), 1032 – 1037.

Kasilo, O.M.J., Nhachi, C.F.B., (1993). A retrospective study of poisoning due to snake venom in Zimbabwe. *Hum Exp Tox* **12**, 15 - 18.

Kerrigan, K.R., (1992). Bacteriology of snakebite abscess. *Trop Doc* **22**, 158 – 160.

Kerrigan, K.R., Mertz, B.L., Nelson, S.J., Dye, J.D., (1997). Antibiotic prophylaxis for pit viper envenomation: prospective, controlled trial. *World J Surg* **21**, 369 – 373.

Kirkland, G., (1990). Snake venom allergy (correspondence). *Med J Aust* **153**, 570 – 571.

Kloeck, W.G.J., (1999). A guide to the management of common medical emergencies in adults. Fifth edition, University of the Witwatersrand, Johannesburg, pp 65 – 67.

Kopp, P., Dahinden, C.A., Müllner, G., (1993). Allergic reaction to snake venom after repeated bites of *Vipera aspis*, (correspondence). *Clin Exp All* **23**, 231 – 233.

Krengel, B., (1967). A case of mamba bite. *S Afr Med J* 1150 – 1151.

Krige, J.E.J., Spence, R.A.J., Potter, P.C., Terblanche, J., (1985). Necrotising fasciitis after diflunisal for minor injury (correspondence). *Lancet* **2**, 1432 – 1433.

Lakier, J.B., Fritz, V.U., (1969). Consumption coagulopathy caused by a boomslang bite. *S Afr Med J*, 1052 – 1055.

Lath, N.K., Patel, M.M., (1984). Treatment of snake venom opthalmia. *Cen Afr J Med* **30** (9), 175 – 176.

Lee, C.Y., Lee, S-Y., Chen, Y.M., (1986). A study of the cause of death produced by *Angusticeps*-type toxin F7 isolated from eastern green mamba venom. *Toxicon* **24** (1), 33 – 40.

Lekagul, K., Nuchprayoon, I., (2001). Role of prophylactic antibiotics and steroid in the management of green pit viper bites in children (abstract). *Toxicon* **39** (2-3), 143.

León, G., Monge, M., Rojas, E., Lomonte, B., Gutiérrez, J.M., (2001). Comparison between IgG and F(ab)2 polyvalent antivenoms: neutralisation of systemic effects induced by *Bothrops asper* venom in mice, extravasation to muscle tissue, and potential for induction of adverse reactions. *Toxicon* **39** (6), 793 – 801.

Lomonte, B., (2001). Myotoxic phospholipases A2 from venoms of Crotolid snakes: properties, actions, and neutralisation. *J Venom Anim Toxins* **7**, 326.

Lomonte, B., Gutiérrez, J.M., Borkow, G., Ovadia, M., Tarkowski, A., Hansen, L.A., (1994). Activity of haemorrhagic metalloproteinase BaH-1 and myotoxin 11 from *Bothrops asper* snake venom on capillary endothelial cells in vitro. *Toxicon* **32** (4), 505 – 510.

Lomonte, B., Tarkowski, A., Hanson, L.A., (1993). Host response to *Bothrops asper* snake venom: analysis of oedema formation, inflammatory cells and cytokine release in a mouse model. *Inflammation* **17** (2), 93 – 105.

Louw, J.X., (1967). Specific mamba antivenom - report of survival of two patients with black mamba bites treated with this serum. *S Afr J Med* **41**, 1175.

MacIntyre, U.E., de Villiers, F.P.R., Owange-Iraka, J.W., (2001). Increase in childhood asthma admissions in an urbanising population. *S Afr J Med* **91**, 667 – 672.

Mackay, N., Ferguson, J.C., Bagshawe, A., Forrester, A.T.T., McNicol, G.P., (1969). The venom of the boomslang *(Dispholidus typus)*: in vivo and in vitro studies. *Throm Haem* **21**, 234 – 244.

Malasit, P., Warrell, D.A., Chanthavanich, P., Viravan, C., Mongkolsapaya, J., Singhthong, B., Supich, C., (1986). Prediction, prevention, and mechanism of early (anaphylactic) antivenom reactions in victims of snake bites. *Br Med J* **292**, 17 – 20.

Malz, S., (1967). Snake-bite in pregnancy. *J Obstet Gynaec Brit Cwlth* **74**, 935 – 937.

Manjra, A., (1994). Anaphylaxis. *Spec Med* 17 – 24.

Mars, M., Hadley, G.P., (1998). Raised intracompartmental pressure and compartment syndromes. *Injury* **29** (6), 403 – 411.

Marsh, N.A., Whaler, B.C., (1984). The Gaboon viper *(Bitis gabonica)*: its biology, venom components and toxicology. *Toxicon* **22** (5), 669 – 694.

Mason, J.H., (1963). Snakebite and its treatment. *Cent Afr J Med* **9** (6), 219 – 225.

Mason, J.H., Anderson, C.J., Spence, R.G., (1961). In: Annual Report of the South African Institute for Medical Research, Johannesburg, pp 132 – 133.

Matsen, F.A., Mayo, K.A., Sheridan, G.W., (1976). Monitoring of intramusclular pressure. *Surgery* **79**, 702 – 709.

McCollough, N.C., Gennaro, J.F., (1963). Evaluation of venomous snake bite in the Southern United States from parallel clinical and laboratory investigations. Development of treatment. *J Fl Med Assoc* **XLIX** (12), 959 – 967.

McGarity, B.H., Marshall, G.P., Loadsman, J.A., Carr, S.J., Harper, C.G., (1991). Fatal cerebral haemorrhage after tiger snake bite (correspondence). *Med J Aust* **155**, 61 – 62.

McNally, T., Conway, G.S., Jackson, L., Theakston, R.D.G., Marsh, N.A., Warrell, D.A., Young, L., Mackie, I.J., Machin, S.J., (1993). Accidental envenoming by a Gaboon viper *(Bitis gabonica)*: the haemostatic disturbances observed and investigation of in vitro haemostatic properties of whole venom. *Trans Roy Soc Trop Med Hyg* **87**, 66 – 70.

McNally, S.L., Reitz, C.J., (1987). Victims of snakebite. A five-year study at Shongwe Hospital, Kangwane, 1978 - 1982. *S Afr Med J* **72**, 855 – 860.

Mebs, D., (2000). Notes on the traditional use of plants to treat snake bite in northern Papua New Guinea. *Toxicon* **38**, 299 – 302.

Mebs, D., Claus, I., (1991). Amino acid sequences and toxicities of snake venom components. In: Harvey, A.L. (Ed.), *Snake Toxins*. Pergamon Press, New York, pp 425 – 439.

Meyer, W.P., Habib, A.G., Onayade, A.A., Yakubu, A., Smith, D.C., Nasidi, A., Daudu, I.J., Warrell, D.A., Theakston, R.D.G., (1997). First clinical experiences with a new ovine Fab *Echis ocellatus* snake bite antivenom in Nigeria: randomised comparative trial with Institute Pasteur Serum (Ipser) Africa Antivenom. *Am J Trop Med Hyg* **56** (3), 291 – 300.

Minton, S.A., (1990). Neurotoxic snake envenoming. *Sem Neurol* **10** (1), 52 – 61.

Mizuno, H., Liang, R-F., Kawarata, A., (1990). Effects of oral administration of various non-steroidal anti-inflammatory drugs on bone growth and bone wound healing in mice. *J Meikai Univ Sch Dent* **19** (2), 234 – 248.

Mohamed, A.H., Nawar, N.N.Y., Hanna, M.M., (1974). Some effects of *Naja nigricollis* envenomation on developing fetal tissue. *Toxicon* **12**, 477 – 480.

Mohamed, A.H., Nawar, N.N.Y., (1975). Dysmelia in mice after maternal *Naja nigricollis* envenomation: a case report. *Toxicon* 1975; **13**, 475 – 477.

Moran, N.F., Newman, W.J., Theakston, R.D.G., Warrell, D.A., Wilkinson, D., (1998). High incidence of early anaphylactoid reaction to SAIMR polyvalent snake antivenom. *Trans Roy Soc Trop Med Hyg* **92**, 69 – 70.

Moscati, R.M., Moore, G.P., (1990). Comparison of cimetidine and diphenhydramine in the treatment of acute urticaria. *Ann Emerg Med* **19**, 12 – 15.

Moss, S.T., Bogdan G., Dart, R.C., Nordt, S.P., Williams, S.R., Clark, R.F., (1997). Association of rattlesnake bite location with severity of clinical manifestations. *Ann Emerg Med* **30** (1), 58 – 61.

Mubarak, S.J., Hargens, A.R., (1983). Acute compartment syndromes. *Surg Clinic N Am* **63** (3), 539 – 565.

Munro Ford, R., (1992). Premedication before antivenom therapy (correspondence). *Med J Aust* **156**, 223.

Myint-Lwin., Tin-Nu-Swe., Myint-Aye-Mu., Than-Than., Thein-Than., Tun-Pe., (1989). Heparin therapy in Russell's viper bite victims with impending DIC (a controlled trial). *SE Asian J Trop Med Public Health* **20** (2), 271 – 277.

Naidoo, D.P., Lockhart, H.S., Naiker, I.P., (1987). Myocardial infarction after probable black mamba envenomation. A case report. *S Afr Med J* **71**, 388 – 389.

Nawar, N.N.Y, (1980). The effect of maternal envenomation by *Naja haje* (Egyptian cobra) snake on the developing central nervous system. *Sing Med J* **21** (2), 528 – 530.

Nicolson, I.C., Ashby, P.A., Johnson, N.D., Versey, J., Slater, L., (1974). Boomslang bite with haemorrhage and activation of complement by the alternative pathway. *Clin Exp Immunol* **16**, 295 – 300.

Nontprasert, A., Pukrittayakamee, S., Clemens, R., Charoenlarp, P., White, N.J., (1993). Synergy of antithrombin III concentrate and antivenom in preventing coagulopathy in a rat model of Thai Russell's viper envenoming (Abstract). *Toxicon* **31**, 937.

Oberholzer, W., Oberholzer, G., Dando, R.V., Reitz, C.J., (1991). Emergency treatment of neurotoxic snakebite with a self-inflating manual bag (correspondence). *S Afr Med J* **80**, 254.

Oredsson, S., Plate, G., Qvarfordt, P., (1994). The effect of mannitol on reperfusion injury and post ischaemic compartment pressure in skeletal muscle. *Eur J Vasc Surg* **8**, 326 – 331.

Osman, O.H., Gumaa, K.A., (1974). Pharmacological studies of snake *(Bitis arietans)* venom. *Toxicon* **12**, 569 – 575.

Otero, R., (2001). Epidemiological and clinical aspects of snakebites in Colombia. Severe *Bothropic* envenomation (Abstract). *J Venom Anim Toxins* **7**, 322.

Otero, R., Gutiérrez, J.M., Rojas, G., Núñez, V., Diaz, A., Garcia, M.E., (2001). A randomised blind clinical trial of two antivenoms, prepared by caprylic acid or ammonium sulfate fractionation of IgG, in *Bothrops* snake bites in Colombia. Correlation between safety and biochemical characteristics of antivenoms (abstract). *Toxicon* **39** (4), 453.

Pantanowitz. L., Guidozzi, F., (1996). Management of snake and spider bite in pregnancy. *Obstet Gynecol Survey* **51** (10), 615 - 620.

Pantanowitz, L., Scott, L., Southern, J., Schrire, L., (1998). Development of antivenoms in South Africa. *S Afr J Sci* **94**, 464 – 470.

Páramo, L., Lomonte, B., Pizarro-Cerdá, J., Bengoechea, J-A., Gorvel, J-P., Moreno, E., (1998). Bactericidal activity of Lys 49 and Asp 49 myotoxic phospholipases A_2 from *Bothrops asper* snake venom: synthetic Lys 49 myotoxin 11- (115 – 129) – peptide identifies its bactericidal region. *Eur J Biochem* **253**, 452 – 461.

Parrish, H.M., Hayes, R.H., (1971). Hospital management of pit viper venenations. *Clin Toxicol* **3**, 155 – 165.

Parrish, H.M., Khan, M.S., (1966). Snakebite during pregnancy: Report of four cases. *Obstet Gynecol* **27** (4), 468 – 471.

Pérez, J.C., Sánchez, E.E., (1999). Natural protease inhibitors to haemorrhagins in snake venoms and their potential use in medicine. *Toxicon* **37** (5), 703 – 728.

Petricevich, V.L., Teixeira, C.F.P., Tambourgi, D.V., Gutiérrez, J.M., (2000). Increments in serum cytokine and nitric oxide levels in mice injected with *Bothrops asper* and *Bothrops jararaca* snake venoms. *Toxicon* **38** (9), 1253 – 1266.

Phillips, L.L., Weis, H.J., Pessar, L., Christy, N.P., (1973). Effects of puff adder venom on the coagulation mechanism - 1. In vivo. *Toxicon* **11**, 423 – 431.

Pirkle, H., Theodor, I., Miyada, D., Simmons, G., (1986). Thrombin-like enzyme from the venom of *Bitis gabonica*. *J Biol Chem* **261** (19), 8830 – 8835.

Podgorny, G., (1982). Pressure and immobilisation for snakebite remains speculative (correspondence). *Ann Emerg Med* **2**, 702.

Pongprasit, P., Mitrakul, C., Noppakun, N., (1988). Histopathology and microbiological study of cobra bite wounds. *J Med Assoc Thai* **71** (9), 475 – 480.

Premawardhena, A.P., de Silva, C.E., Fonseka, M.M.D., Gunatilake, S.B., de Silva, H.J., (1999). Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes ; randomized, placebo controlled trial. *Br Med J* **318**, 1041 – 1043.

Pugh, R.N.H., Theakston, R.D.G., (1980). Incidence and mortality of snake bite in Savanna Nigeria. *Lancet* **2**, 1181 – 1183.

Pugh, R.N.H., Theakston, R.D.G., (1987a). Fatality following use of a tourniquet after viper bite envenoming. *Ann Trop Med Parasit* **81** (1), 77 – 78.

Pugh, R.N.H., Theakston, R.D.G., (1987b). Antivenom reactions and complement depletion in snake bite. *Ann Trop Med Parasit* **81** (1), 73 – 75.

Puterman, A.S., Nurse, B., (2001). Cytokine levels in urbanised Xhosa asthmatic children - a review. *Curr Allerg Clin Immunology* **14** (2), 4 – 8.

Qvarfordt, P., Eklöf, B.O., Ohlin, P., (1983). Intramuscular pressure in the lower leg in deep vein thrombosis and phegmasia cerulea dolens. *Ann Surg* **197** (4), 450 – 453.

Read, P.H., Foster, D.I., (1959). Case history of a brown mamba bite in Northern Rhodesia. *J Herp Assoc Rhod* **8**, 6 - 7.

Reid, H.A., (1976). Adder bites in Britain. *Br Med J* **2**, 153 – 156.

Reid, H.A., Chan, K.E., Thean, P.C., (1963a). Prolonged coagulation defect (defibrination syndrome) in Malayan viper bite. *Lancet* **1**, 621 – 626.

Reid, H.A., Thean, P.C., Chan, K.E., Baharom, A.R., (1963b). Clinical effects of bites by Malayan viper *(Ancistrodon rhodostoma)*. *Lancet* **1**, 617 – 621.

Reid, H.A., Thean, P.C., Martin, W.J., (1963c). Specific antivenene and prednisone in viper-bite poisoning: controlled trial. *Br Med J* 1378 – 1380.

Reid, H.A., Theakston, R.D.G., (1978). Changes in coagulation effects by venoms of *Crotolus atrox* as snakes age. *Am J Trop Med Hyg* **27** (5), 1053 - 1057.

Reitz, C.J., (1978). In: Reitz, C.J., (Ed.). *Poisonous South African Snakes and Snakebite*. Perskor Printers, Pretoria.

Reitz, C.J., (1986). Die noodhulpbehandeling van Egiptiese kobrabyt: 'n proefdierstudie. *Geneeskunde* **28**, 279.

Reitz, C.J., Goosen, D.J., Odendaal, M.W., Visser, L., Marais, T.J., (1984). Evaluation of the venom ex apparatus in the treatment of Egyptian cobra envenomation. A study in rabbits. *S. Afr Med J* **66**, 135 - 138.

Reitz, C.J., Olkers, P., van Gelder, L.W., Nel. J.D., (1989). Elektriese skokbehandeling vir slangbyt: 'n proefdierstudie. *Geneeskunde* **31** (1), 3 – 6.

Reitz, C.J., Willemse, G.T., Odendaal, M.W., Visser, J.J., (1986). Evaluation of the venom ex apparatus in the initial treatment of puff adder envenomation: a study in rabbits. *S Afr Med J* **69**, 684 – 686.

Reynolds, J.F., Noakes, T.D., Schwelinus, M.P., Windt, A., Bowerbank, P., (1995). Non-steroidal anti-inflammatory drugs fail to enhance healing of acute hamstring injuries treated with physiotherapy. *S Afr Med J* **85** (6), 517 – 522.

Rimailho, A., Riou, B., Richard, C., Auzepy, P., (1987). Fulminant necrotizing fasciitis and nonsteroidal anti-inflammatory drugs. *J Infec Dis* **155** (1), 143 – 146.

Rippey, J.J., Rippey, E., Branch, W.R., (1976). A survey of snakebite in the Johannesburg area. *S Afr Med J* **50**, 1872 – 1876.

Ro, J., Sudman, E., Marton, P.F., (1976). Effect of indomethacin on fracture healing in rats. *Acta Orthop Scand* **47**, 588 – 599.

Roberts, R.S., Csencsitz, T.A., Heard, C.W., (1985). Upper extremity compartment syndromes following pit viper envenomation. *Clin Orthop Rel Res* **193**, 184 – 188.

Rojas G., Jiménez J.M., Gutiérrez J.M., (1994). Caprylic acid fractionation of hyperimmune horse plasma: description of a simple procedure for antivenom production. *Toxicon* **32** (3), 351 – 363.

Rorabeck, C.H., Castle, P., Hargens, A., (1981). The slit catheter: a new technique for measuring intracompartmental pressures. *Orthop Trans* **5**, 324 – 325.

Rossouw, D.S., Bos, P., (1989). Snakebite. *Cont Med Educ* **7** (7), 847 – 851.

Russell, F.E., (1966). Shock following snakebite (correspondence). *J Am Med Assoc* **198** (9), 171.

Russell, F.E., (1980). In: Russel, F.E. (Ed.). *Snake Venom Poisoning.* J.P. Lippincott Co, Philadelphia.

Russell, F.E., (1982). Pressure and immobilisation for snakebite remains speculative. *Ann Emerg Med* **2**, 701 – 702.

Russell, F.E., (1987). Another warning about electric shock for snakebite (correspondence). *Postgrad Med* **82** (5), 32.

Russell, F.E., Carlson, R.W., Wainschel, J., Osborne, A.H., (1975). Snake venom poisoning in the United States: experience with 550 cases. *J Am Med Assoc* **233** (4), 341 – 344.

Russell, F.E., Emery, J.A., (1961). Effects of corticosteroids on lethality of *Ancistrodon contortrix* venom. *Am J Med Sci* 507 – 511.

Russell, F.E., Sullivan, J.B., Egen, N.B., Jeter, W.S., Markland, F.S., Wingert, W.A., Bar-or, D., (1985). Preparation of a new antivenom by affinity chromatography. *Am J Trop Med Hyg* **14** (1), 141 – 150.

Russell, F.E., Walter, F.G., Bey, T.A., Fernandez, M.C., (1997). Snakes and Snakebite in Central America. *Toxicon* **35** (10), 1469 – 1522.

Ryan, A.J., (1987). Don't use electric shock for snakebite (correspondence). *Postgrad Med* **82**, (2), 42.

Saunders, C.R., (1980). Report on a black mamba bite of a medical colleague. *Cent Afr J Med* **26** (6), 121 – 122.

Scharf, G.M., du Plessis, H.J.C., (1993). Guidelines for the management of puff adder bites. *Traum Emerg Med* 948 – 952.

Scheinberg, M.A., Rueda, H.O., Matheus, P.C., (1983). The effect of piroxicam on neutrophil and monocyte – macrophage function. *Eur J Rheum Inflam* **6**, 36 – 40.

Schmid, E.U., (1966). Slangbyt. *S Afr Med J* **40**, 766 – 770.

Schmutz, J., Stahel, E., (1985). Anaphylactoid reactions to snakebite (correspondence). *Lancet* **ii**, 1306.

Schmutzhard, E., (1986). Electric shocks for snakebite (correspondence). *Lancet* 578.

Schöttler, W.H.A., (1954). Antihistamine, ACTH, cortisone, hydrocortisone and anesthetics in snake bite. *Am J Trop Med* **3**, 1083 – 1091.

Schrire, L., Müller, G.J., Pantanowitz, L., (1996). In: *The Diagnosis and Treatment of Envenomation in South Africa.* S Afr Inst Med Res. Mission Print, Johannesburg.

Scott, L.E., Southern, J.A., Schrire, L., (1995). The immunological analysis of spitting cobra venom (poster). Fourth Herp Assoc Afr Symposium, St Lucia.

Seifert, S.A., Boyer, L.V., Dart, R.C., Porter, R.S., Sjostrom, L., (1997). Relationship of venom effects to venom antigen and antivenom serum concentrations in a patient with *Crotolus atrox* envenomation treated with a Fab antivenom. *Ann Emerg Med* **30** (1), 49 – 53.

Sheikh, A., Alves, B., (2000). Hospital admissions for acute anaphylaxis: time trend study. *Br Med J* **320**, 1441.

Shokuhi, S., Slavin, J., (2001). Sepsis/SIRS and multiple organ dysfunction syndrome. *Surgery* **19**, 1 – 5.

Siemers, A.H., (1958). Case history of an *Atractaspis bibronii* bite. *J Herp Assoc Rhod* **4**, 5 – 6.

Simon, T.L., Grace, T.G., (1981). Envenomation coagulopathy in wounds from pit vipers. *N Eng J Med* **305** (8), 443 – 447

Singh, S.A.S.C., (1925). A fatal case of snake-bite *(? Echis carinatus)* during pregnancy. *Ind Med Gazette* **60**, 471 – 472.

Skarnes, R.C., (1970). L-amino acid oxidase, a bactericidal system. *Nature* **225**, 1072 – 1073.

Smith, R.J., Berk, S.L., (1991). Necrotizing fasciitis and nonsteroidal anti-inflammatory drugs. *S Med J* **84** (6), 785 – 787.

Snyder, C.C., Murdock, R.T., White, G.L., Kuitu, J.R., (1989). Electric shock treatment for snake bite. *Lancet* **1**, 1022.

Solberg, C.O., Alfred, C.D., Hill, H.R., (1978). Influence of phenylbutazone on leucocytes chemilumescence and function. *Acta Pathol Microbiol Immunol Scand* **86**, 165 – 171.

Solomon, L., (1966). Activation of latent infection by indomethacin: a report of three cases. *Br Med J* 1, 961 – 962.

South African Medicines Formulary. (2000). Gibbon C.J. (Ed.). Fifth Edition, South African Medical Association, Woodstock, South Africa, pp 227 – 232.

Soveri, T., Seuna, E-R., (1986). Aerobic oral bacteria in healthy captive snakes. *Acta Vet Scand* 27, 172 - 181.

Spawls, S., Branch, W., (1995). In: Spawls, S., Branch, W. (Eds.). *The Dangerous Snakes of Africa.* Oriental Press, Dubai.

Stewart, M.M., (1965). A bite by a burrowing adder, *Atractaspis bibronii. J Herp Assoc Rhod* 23/24, 47 – 50.

Stiles, B.G., Sexton, F.W., Weinstein, S.A., (1991). Antibacterial effects of different snake venoms: purification and characterisation of antibacterial proteins from *Pseudechis australis* (Australian king brown or mulga snake) venom. *Toxicon* 29 (9), 1129-1141.

Stocker, J.F., Traynor, J.R., (1986). The action of various venoms on *Escherichia coli. J Appl Bacteriol* 61, 383 – 388.

Stoud, C., Amon, H., Wagner, T., Falk, J.L., (1989). Effect of electric shock therapy on local tissue reaction to poisonous snake venom injection in rabbits (abstract). *Ann Emerg Med* 18, 447.

Strauch, G.O., (1986). The uterus. In: Trunkey, D.D., Lewis, F.R. (Eds.), *Current Therapy of Trauma – 2.* B.C. Decker, Toronto, pp 298 – 301.

Strover, A.E., (1964). Some principles of the clinical recognition, assessment and treatment of snakebites. *Cent Afr J Med* 10 (8), 283 – 288.

Strover, H.M., (1961). Snakebite and its treatment. *Cent Afr J Med* 7 (3), 84 – 87.

Strover, H.M., (1967). Report on a death from black mamba bite *(Dendroaspis polylepis). Cent Afr J Med* 13 (8), 185 – 186.

Strover. H.M., (1973). Observations on two cases of snake-bite by *Naja nigricollis ss mossambica. Cent Afr J Med* **19** (1), 12 – 13.

Suchard, J.F., Lovecchio, F., (1999). Envenomations by rattlesnakes thought to be dead. *New Eng J Med* 1930.

Sutherland, S.K., (1977). Serum reactions: an analysis of commercial antivenoms and the possible role of anticomplementary activity in de-novo reactions to antivenom and antitoxins. *Med J Aust* **1**, 613 – 615.

Sutherland, S.K., (1991). Premedication before antivenom therapy (correspondence). *Med J Aust* **155**, 722.

Sutherland, S.K., (1992). Antivenom use in Australia premedication, adverse reactions and the use of venom detection kits. *Med J Aust* **157**, 734 – 739.

Sutherland, S.K., (1995). Pressure immobilisation for snakebite in southern Africa remains speculative (correspondence). *S Afr Med J* **85** (10), 1039 – 1040.

Sutherland, S.K., Coulter, A.R., Harris, R.D., (1979). Rationalisation of first-aid measures for elapid snakebite. *Lancet* **1**, 183 – 186.

Sutherland, S.K., Coulter, A.R., (1981a). Early management of bites by the eastern diamondback rattlesnake (*Crotalus admamanteus*): studies in monkeys (*Macaca fascicularis)*. Am J Trop Med Hyg 30 (2), 497 – 500.

Sutherland, S.K., Coulter, A.R., Harris, R.D., Lovering, K.E., Roberts, I.D., (1981b). A study of the major Australian snake venoms in the monkey (*Macaca fascicularis*). 1. The movement of injected venom, methods which retard this movement, and the response to antivenom. *Path* 13, 13 – 27.

Sutherland, S.K., Harris, R.D., Coulter, A.R., Lovering, K.E., (1981c). First aid for cobra *(Naja naja)* bites. *Ind J Med Res* **73**, 266 – 268.

Sutherland, S.K., Duncan, A.W., Tiballs, J., (1982). Death from a snakebite associated with the supine hypotensive syndrome in pregnancy. *Med J Aust* 2, 238 – 239.

Talan, D.A., Citron, D.M., Overturf, G.D., Singer, B., Froman, P., Goldstein, E.J.C., (1991). Antibacterial activity of Crotalid venoms against oral snake flora and other clinical bacteria. *J Inf Dis* **164**, 195 - 198.

Texeira, C.F.P., Cury, Y., Oga, S., Jancar, S., (1994). Hyperalgesia induced by *Bothrops jararaca* venom in rats: role of eicosanoids and platelet activating factor (PAF). *Toxicon* **32** (4), 419 – 426.

Theakston, R.D.G., (1986). Characterization of venoms and standardization of antivenoms In: Harris, J.B. (Ed.), *Natural Toxins: Animal, Plant and Microbial.* Oxford Science Publications, Clarendon Press, Oxford, pp 287 – 303.

Theakston, R.D.G., (1989). New techniques in antivenom production and active immunization against snake venoms. *Trans Roy Soc Trop Med Hyg* **83**, 433 – 435.

Theakston, R.D.G., (1997). An objective approach to antivenom therapy and assessment of first-aid measures in snake bite. *Ann Trop Med Parasit* **91** (7), 857 – 865.

Theakston, R.D.G., Fan, H.W., Warrell, D.A., Dias Da Silva, W.D., Ward, S.A., Higashi, H.G., (1992). Use of enzyme immunoassays to compare the effect and assess the dosage regimens of three Brazilian *Bothrops* antivenoms. *Am J Trop Med Hyg* **47** (5), 593 – 604.

Theakston, R.D.G., Kamiguti, A.S., (2002). A list of animal toxins and some other natural products with biological activity. *Toxicon* **40** (5), 579 – 651.

Theakston, R.G.D., Phillips, R.E., Looareesuwan, S., Echeverria, P., Makin, T., Warrell, D.A., (1990). Bacteriological studies of the venom and mouth cavities of wild Malayan pit vipers. *(Calloselasma rhodostoma)* in Southern Thailand. *Trans Roy Soc Trop Med Hyg* **84**, 875 - 879.

Theakston, R.D.G., Smith, D.C., (1997). Antivenoms: a review of current status and future developments. *Biodrugs* **7** (5), 366 – 375.

Thomas, L., Tyburn, B., Bucher, B., Pecout, F., Ketterle, J., Rieux, D., Smadia, D., Garnier, D., Plumelle, Y., (1995). Prevention of thrombosis in human patients with *Bothrops lanceolatus* envenoming in Martinique: failure of anticoagulants and efficacy of a monospecific antivenom. *Am J Trop Med Hyg* **52** (5), 419 – 426.

Thomas, R.G., Pough, F.H., (1979). The effect of rattlesnake venom on digestion of prey. *Toxicon* **17**, 221 - 228.

Tibballs, J., (1994). Premedication for snake antivenom. *Med J Aust* **160**, 4 – 7.

Tibballs, J., Henning, R.D., Sutherland, S.K., Kerr, A.R., (1991). Fatal cerebral haemorrhage after tiger snake (*Notechis scutatus*) envenomation. *Med J Aust* **154**, 275 – 276.

Tilbury, C.R., (1982). Observations on the bite of the Mozambique spitting cobra (*Naja mossambica mossambica*). *S Afr Med J* **61** (9), 308 – 313.

Tilbury, C.R., Branch, W.R., (1989). Observations on the bite of the southern burrowing asp (*Atractaspis bibronii*) in Natal. *S Afr Med J* **75**, 327 – 331.

Trevett, A.J., Nwokolo, N.C., Kevau, I.H., Seaton, R.A.,(1994). Cerebrovascular accident after Taipan bite (correspondence). *Med J Aust* **160**, 94.

Tun-Pe., Aye-Aye-Myint., Khin-Ei-Han., Thi-Ha., Tin-Nu-Swe., (1995). Local compression pads as a first-aid measure for victims of bites by Russell's viper (*Daboia russelii siamensis*) in Myanmar. *Trans Roy Soc Trop Med Hyg* **89**, 293 – 295.

Tun-Pe., Ba-Aye., Aye-Aye-Myint, Tin-Nu-Swe., Warrell, D.A., (1991). Bite by Russell's vipers (*Daboia russelli siamensis*) in Myanmar: effect of the snake's length and recent feeding on venom antigenaemia and severity of envenoming. *Trans Roy Soc Trop Med Hyg* **85**, 804 – 808.

Tun-Pe., Muang-Muang-Thwin., Myint-Myint-Than., Aye-Aye Myint., Kyaw-Myint., Thein-Than., (1994). The efficacy of compression immobilisation technique in retarding spread of radio-labelled Russell's viper venom in rhesus monkeys and "mock venom" NaI[131] in humans volunteers. *SE Asian J Trop Med Pub Health* **25** (2), 349 – 353.

Tun-Pe., Tin-Nu-Swe., Myint-Lwin., Warrell, D.A., Than-Win., (1987). The efficacy of tourniquets as a first-aid measure for Russell's viper bites in Burma. *Trans Roy Soc Trop Med Hyg* **81**, 403 – 405.

Van Ammers, P.M., Moore, P.J., Sacho, H., (1991). Necrotising fasciitis after caesarean section – association with non-steroidal anti-inflammatory drugs. *S Afr Med J* **80**, 203 – 204.

Van der Merwe, C., (1992). Snakebite In: Van der Merwe, C. (Ed.). *The Management of Emergencies*. Kirstenburg Printers, Pretoria, pp 743 – 764.

Van Mierop, L.H.S., (1976). Poisonous snakebite: a review. 2. Symptomatology and treatment. *J Florida Med Assoc* **63** (3), 201 – 210.

Vaughan-Scott, T., Lobetti, R.G., (1995). Boomslang envenomation in a dog. *J S Afr Vet Ass* **66** (4), 265 – 267.

Viravan, C., Veeravat, U., Warrell, M.J., Theakston, R.D.G., Warrell, D.A., (1986). ELISA confirmation of acute and past envenoming by the monocellate Thai cobra *(Naja kaouthia)*. *Am J Trop Med Hyg* **35** (1), 173 – 181.

Visser, J., Carpenter, G., (1977). Notes on a Gaboon adder bite. *J Herp Assoc Afr* **15**, 21 – 22.

Visser, J., Chapman, D.S., (1978). In: Visser, J., Chapman, D.S. (Eds.). *Snakes and Snakebite*. Purnell, Cape Town.

Wapnick, S., Levin, L. Broadley, D.G., (1972). A study of snake bites admitted to a hospital in Rhodesia. *Cent Afr J Med* **18**, 137 – 141.

Ward, A.N., (1976). Treatment of snakebite (correspondence). *J Am Med Assoc* **236** (16), 1843.

Warrell, D.A., (1986). Tropical snakebite: clinical studies in South-east Asia. In: Harris, J.B. Ed. *Natural toxins. Animal, plant and microbial*. Oxford Clarendon Press, pp25 – 45.

Warrell, D.A., (1987). Injuries, envenoming, poisoning and allergic reactions caused by animals. In: Weatherall, D.J., Ledingham, J.G.G., Warrell, D.A. (Eds.), *Oxford Textbook of Medicine*, Second Edition. Oxford University Press, Oxford, pp 6.66 – 6.77.

Warrell, D.A., (1996). Injuries, envenoming, poisoning and allergic reactions caused by animals. In: Weatherall D.J., Ledingham J.G.G., Warrell, D.A. (Eds.) *Oxford Textbook of Medicine*, Vol 2, Third Edition, Oxford Medical Publications, Oxford, pp 2944 – 2947.

Warrell, D.A., (1999). WHO/SEARO guidelines for the clinical management of snake bites in the southeast Asian region. *SE Asian J Trop Med Pub Health* **30**, Suppl 1, 1 – 85.

Warrell, D.A., Davidson, N. McD., Ormerod, L.D., Pope, H.M., Watkins, B.J., Greenwood, B.M., Reid, H.A., (1974). Bites by the saw-scaled or carpet viper *(Echis carinatus)*: trial of two specific antivenoms. *Br Med J* **4**, 437 – 440.

Warrell, .DA., Davidson, N. McD., Greenwood, B.M., Ormerod, L.D., Pope, H.M., Watkins, B.J., Prentice, C.R.M., (1977). Poisoning by bites of the saw-scaled or carpet viper *(Echis carinatus)* in Nigeria. *Quart J Med New Series XLVI* **181**, 33 – 62.

Warrell, D.A., *et al.*,(1985). Early (anaphylactoid) antivenom reactions: absence of complement activation and immune complex formation in human patients (abstract). *Toxicon* **23** (4), 628.

Warrell, D.A., Fenner, P.J., (1993). Venomous bites and stings. *Br Med Bull* **49** (2), 423 – 439.

Warrell, D.A., Greenwood, B.M., Davidson, N. McD., Ormerod, L.D., Prentice, C.R.M., (1976). Necrosis, haemorrhage and complement depletion following bites by the spitting cobra *(Naja nigricollis)*. *Quart J Med New Series XLV* **177**, 1 – 22.

Warrell, D.A., Looareesuwan, S., White, N.J., Theakston, R.D.G., Warrell, M.J., Kosakarn, W., Reid, H.A., (1983). Severe neurotoxic envenoming by the Malayan krait *Bungarus candidus* (Linnaeus): response to antivenom and anticholinesterase. *Br Med J* **286**, 678 – 680.

Warrell, D.A., Ormerod, L.D., Davidson, N. McD., (1975). Bites by the puff-adder *(Bitis arietans)* in Nigeria, and value of antivenom. *Br Med J* **4**, 697 – 700.

Warrell, D.A., Ormerod, L.D., (1976). Snake venom ophthalmia and blindness caused by the spitting cobra *(Naja nigricollis)* in Nigeria. *Am J Trop Med Hyg* **25** (3), 525 – 529.

Warrell, D.A., Pope, H.M., Prentice, C.R.M., (1976b). Disseminated intravascular coagulation caused by the carpet viper *(Echis carinatus)*: trial of heparin. *Br J Haem* **33**, 335 – 342.

Watt, G., Padre, L., Tuazon, L., Theakston, R.D.G., Laughlin, L.W., (1988). Tourniquet application after cobra bite: delay in the onset of neurotoxicity and the dangers of sudden release. *Am J Trop Med Hyg* **38** (3), 618 – 622.

Watt, G., Theakston, R.D.G., Hayes, C.G., Yambao, M.L., Sangalang, R., Ranoa, C.P., Alquizalas, E., Warrell, D.A., (1986). Positive response to edrophonium in patients with neurotoxic envenoming by cobras *(Naja naja philippinensis)*: a placebo-controlled study. *N Engl J Med* **315**, 1444 – 1448.

Weed, H.G., (1993). Nonvenomous snakebite in Massachusetts: prophylactic antibiotics are unnecessary. *Ann Emerg Med* **22**, 220 – 224.

White, J.A.M., (1984). Bites by highly venomous snakes. *Acc Emerg Med* 25 – 34.

White, J.A.M., (1985). Snakebite in Southern Africa. *Cont Med Ed* **3**, 37 – 45.

White, J.A.M., Goodwin, N.M., (1982). Snakebite in Southern Africa. In: White, J.A.M., Goodwin, N.M. (Eds.), *Resuscitation Manual*. Durban Natal Blood Transfusion Services, pp 2 – 23.

Whitesides, T.E., Haney, T.C., Hirada, H., Morimoto, K., (1975). A simple method for tissue pressure determination. *Arch Surg* **110**, 1311 – 1313.

WHO., (1981). Progress in the characterisation of venom and standardization of antivenoms. Offset Publication No 58, World Health Organization, Geneva.

Wilkinson, D., (1994). Retrospective analysis of snakebite at a rural hospital in Zululand. *S Afr Med J* **84** (12), 844 - 847.

Williams, V., White J., (1992). Variation in the composition of the venom from a single specimen of *Pseudonaja textilis* (common brown snake) over one year. *Toxicon* **30** (2), 202 – 206.

Xiong, Y.L., Wang, W.Y., Zhang, Y., Lee, W.H., Xu, T.R., Meng, Q.X., Lu, Q.M., Zhu, S.W., Li, D.S., (1998). Treatment of snakebite with trypsin and chymotrypsin (abstract). *Toxicon* **36** (9), 1287.

Yaksh, T.L., Dirig, D.M., Malmberg, A.B., (1998). Mechanism of action of nonsteroidal anti-inflammatory drugs. *Cancer Invest* **16** (7), 509 – 527.

Yerzingatsian, K.L., (1997). Snakebite - rest and elevation in the management of a selected group of patients in an urban setting. *S Afr J Surg* **35** (4), 188 – 189.

Zugaib, M., de Barros, A.C.S.D., Bittar, R.E., Burdmann, E. de A., Neme, B., (1985). Abruptio placentae following snake bite. *Am J Obstet Gynecol* **151** (6), 754 – 755.