Venomous bites and stings

Snake bites

Introduction

- Fear of snakes is a powerful, primordial, and, possibly,innate human emotion that has fascinated experimental psychologists and evolutionists.
- But snakes are not yet taken sufficiently seriously as agents of human disease, and the scientific insights provided by the clinical phenotype of human envenoming have been ignored for a long time.
- More than a century of research has shown that snake venoms are rich sources of pharmacologically active peptides and proteins

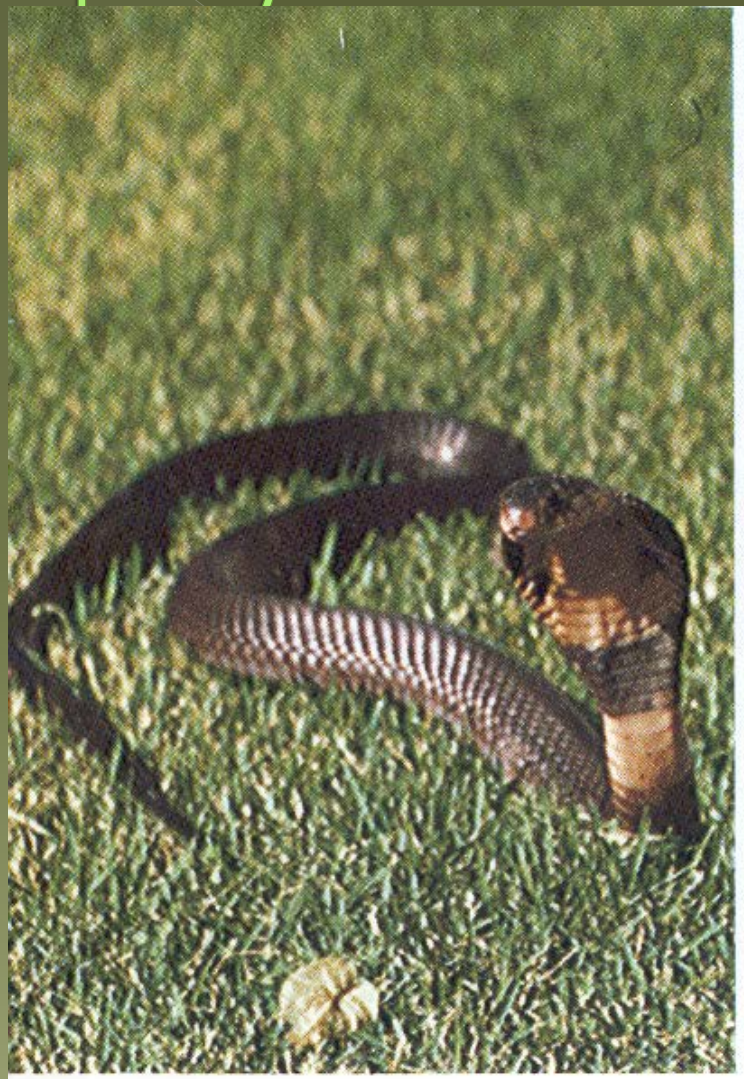
Introduction

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

Taxonomy, identification and distribution

- Of the 2500-3000 species of snakes, about 500 belong to the four families of venomous snakes (Atractaspididae, Elapidae, Hydrophiidae and Viperidae).
- Only about 200 species have caused death or permanent disability in biting humans.
- All medically important species of snakes have one or more pairs of enlarged teeth with venom channels, called fangs, in the upper jaw, by which venoms are introduced through the skin of a human victim.

Venomous snakes (cobra, viper)



Green mamba

Black mamba

Epidemiology

- The sequelae of envenoming can also be severe; disability from a severely damaged limb following snakebite is particularly problematic in the tropics.
- Furthermore, antivenom and the intensive treatment needed by victims increase health costs in tropical countries with limited health budgets.
- Envenoming can be caused by a large variety of terrestrial and marine animals.
- The most important are species of snake, scorpion, spider and jellyfish.
- Bee and wasp stings and marine animals also cause problems in some parts of the world.

EPIDEMIOLOGY

The problem is so underrated that it was only added to WHO's list of neglected tropical diseases in April, 2009.
Yet an estimated 5·4–5·5 million people are bitten by snakes each year, resulting in about 400 000 amputations, and between 20 000 and 125 000 deaths

	Incidence	Deaths
Chagas' disease[4]	217 000	14 000
Cholera[5]	178 000	4000
Dengue haemorrhagic fever[6]	73 000	19 000
Leishmaniasis[4]	1 691 000	51 000
Japanese encephalitis[4]	44 000	14 000
Schistosomiasis[4]	5 733 000	15 000
Snake bite envenoming[1–3]	420 000–2 682 000	20 000–125 000
Yellow fever[6,7]	100–2100	60–100

Table: Comparison of snake bite incidence and mortality rates with some other formally recognised WHO neglected tropical diseases

Venom biochemistry and pharmacology

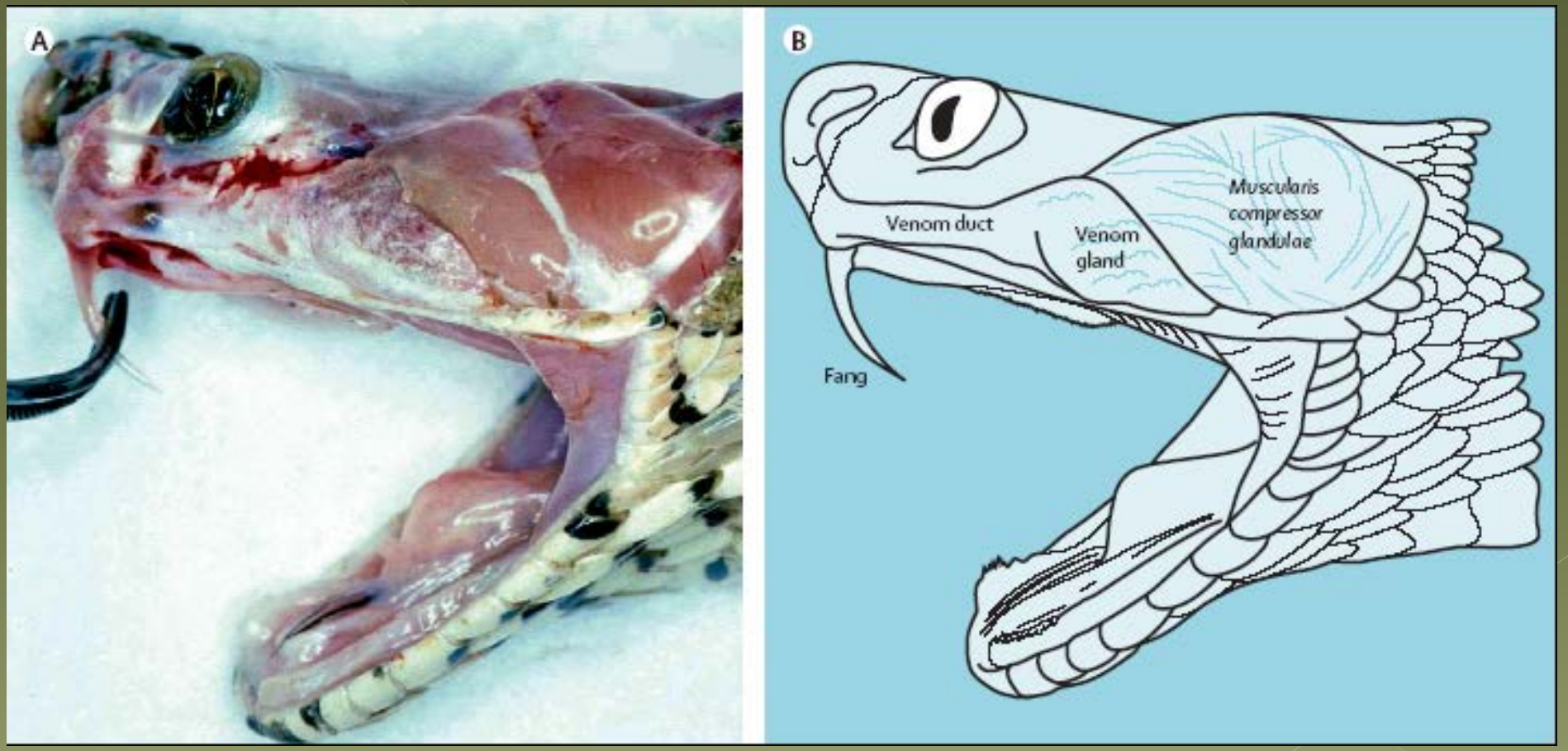
- Snake venoms are the most complex of all natural venoms and poisons.
- The venom of any species might contain more than 100 different toxic and non-toxic proteins and peptides, and also non-protein toxins, carbohydrates, lipids, amines, and other small molecules

Venom biochemistry and pharmacology

- Venomous animals and their venoms have evolved to take full advantage of many ecological niches and prey species that include a range of animals and their eggs—ie, annelids, onychophorans, molluscs, arthropods, amphibians, reptiles, fish, birds, and mammals.
- Evolutionary pressures have selected venom toxins that are specific for many targets in animal tissues

Venom apparatus of Russell's viper (*Daboia siamensis)*

(A) Dissected specimen. (B) Annotated diagram of dissected specimen.



Venom composition 1.

- Snake venoms may contain 20 or more components.
- More than 90% the dry weight is protein.
- Non-protein ingredients of venom include carbohydrate and metals, lipids, free amino acids, nucleotides and biogenic amines.
- Pathophysiological disturbances are related to the venom procoagulants (activating the coagulation cascade).

Venom composition 2.

- Hyaluronidase promotes the spread of the venom.
- Hydrolases may be responsible for local changes (oedema, blistering and bruising).
- The polypeptide toxins are neurotoxins found exclusively in elapid and hydrophiid venoms.

Effects of the toxins

- Snake venom neurotoxins block or excite peripheral neuromuscular junctions by acting at various sites
- Snake venom neurotoxins are thought to be virtually excluded from the CNS —eg, two low molecular-weight phospholipases A2 from the venom of Russell's viper were innocuous when given intravenously to rodents but were lethal or sedative when given intraventricularly.
- However, a common symptom of snake bite is drowsiness, suggesting the possibility of a central sedative action such as that associated with a small non-protein toxin that is found in king cobra (*Ophiophagus hannah) venom.*

Effects of the toxins

- Most venom neurotoxins bind to their receptors with high affi nity, making reversal of paralysis by antivenom implausible.
- However, rapid improvement in neurotoxicity has been noted when postsynaptic toxins were implicated—eg, after envenoming by Asian cobras and Australasian death adders (*Acanthophis spp).*

Effects of the toxins

- Binding of toxin α, α three-finger-fold polypeptide from the venom of the black-necked spitting cobra (*Naja nigricollis), to the* acetylcholine receptor was reversible by antibodies in vitro and in rodents, although this venom is not neurotoxic in man.
- By prolonging the effect of acetylcholine, anticholinesterases sometimes reverse postsynaptic neurotoxicity in envenomed patients.

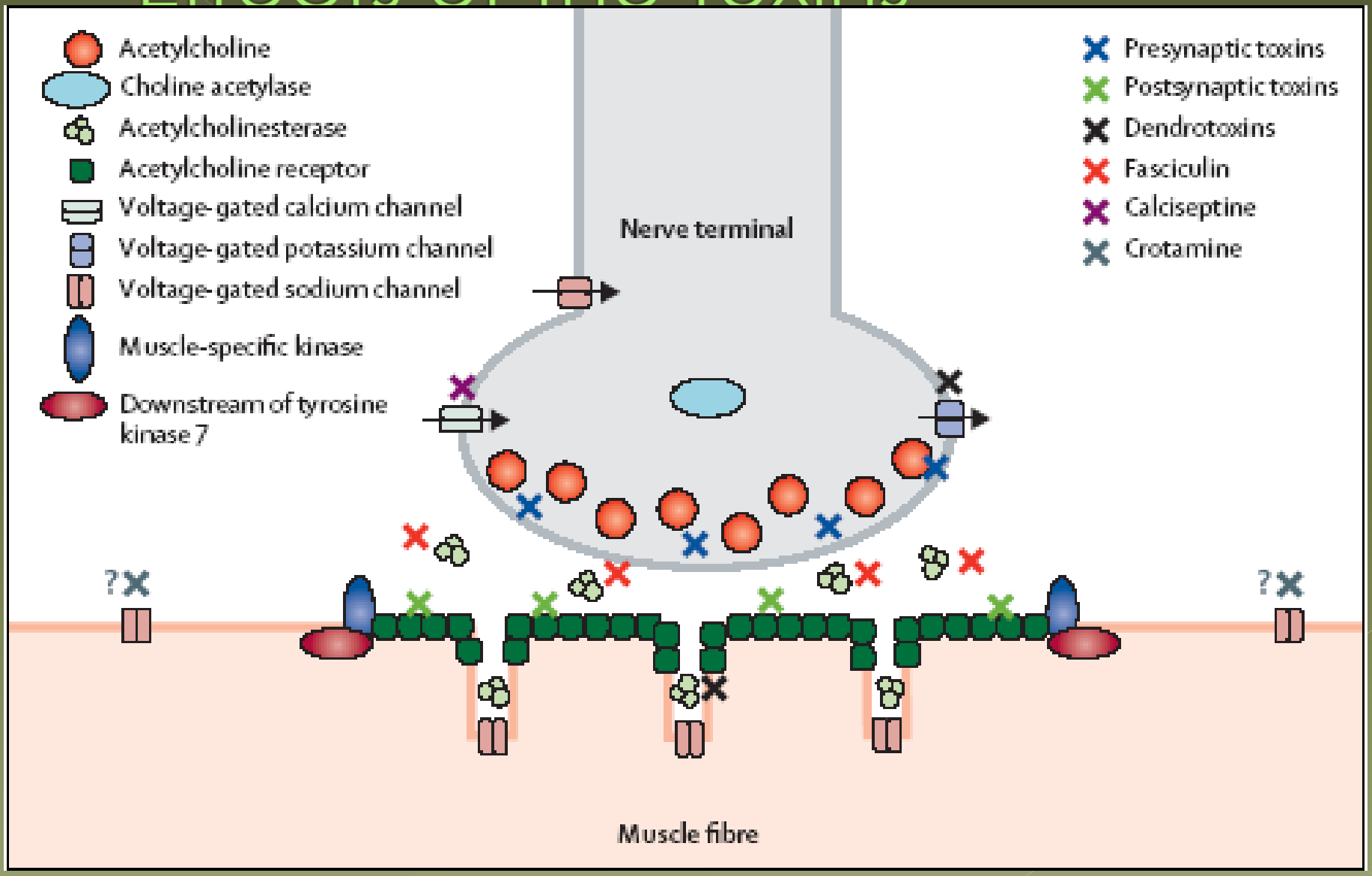
Effects of the toxins

- Paralysis in envenomed people starts with ptosis, external ophthalmoplegia, and mydriasis, descending to involve muscles innervated by the other cranial and spinal nerves and leading to bulbar and respiratory paralysis and, if ventilation is supported, eventually to total flaccid paralysis.

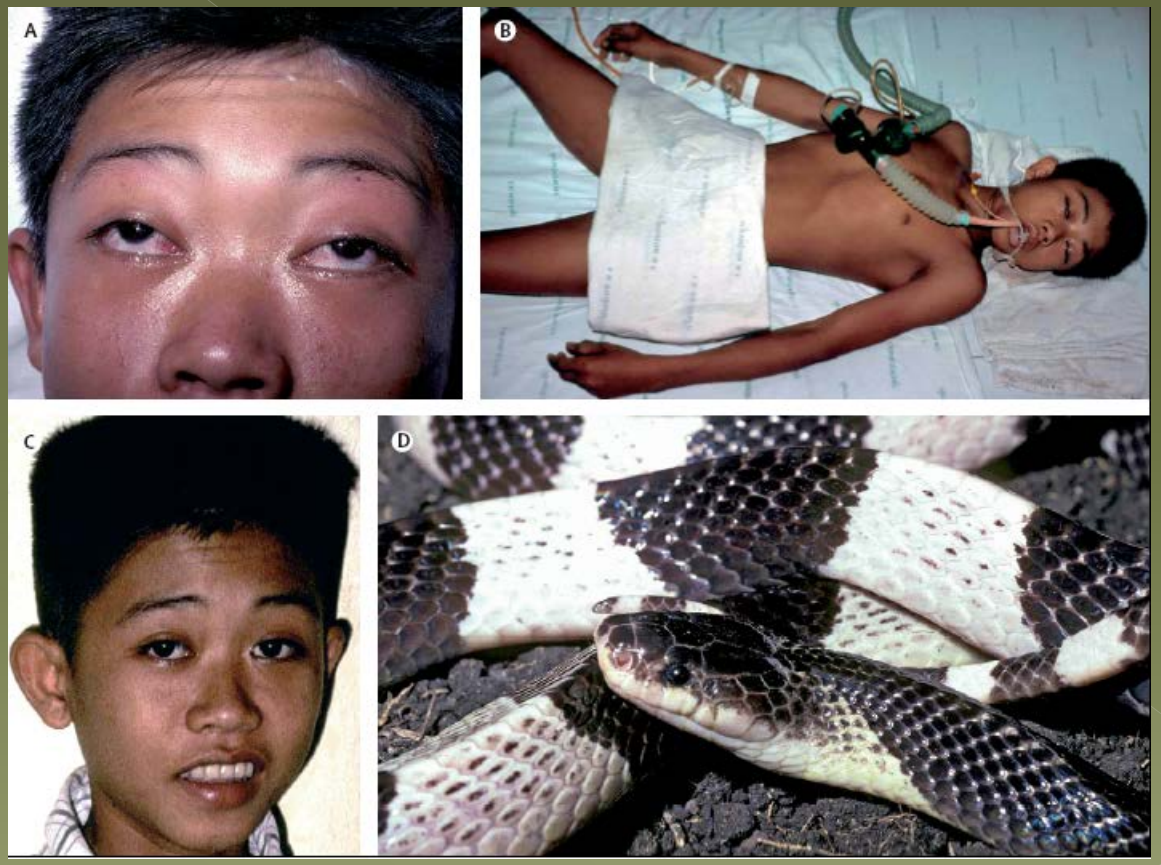
Effects of the toxins

- The initial involvement of levator palpebrae superioris, as in botulism, myasthenia gravis, and Graves' disease, might be attributable to the small size, unusual anatomy and physiology, and the low safety factor of the neuromuscular junctions of this muscle, features shared by all the extraocular muscles.
- The subsequent pattern of descending paralysis is difficult to explain neurophysiologically.

Effects of the toxins

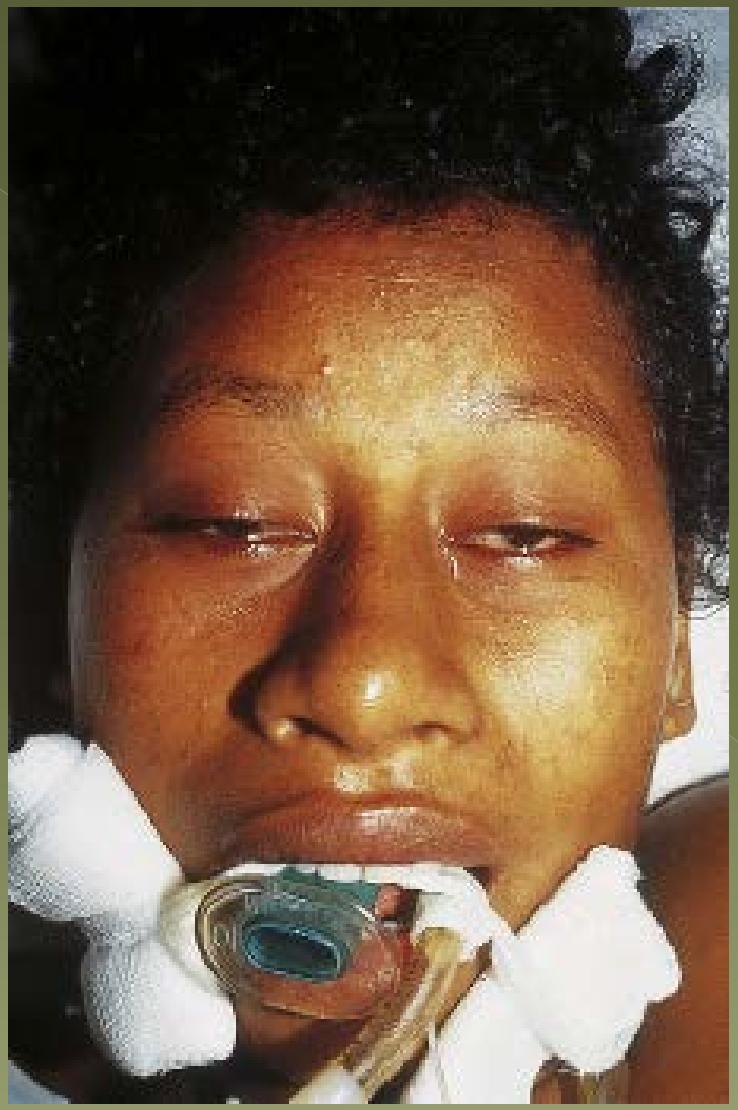


Descending paralysis of muscles innervated by cranial and spinal nerves in a boy envenomed by a Malayan krait (*Bungarus candidus*)

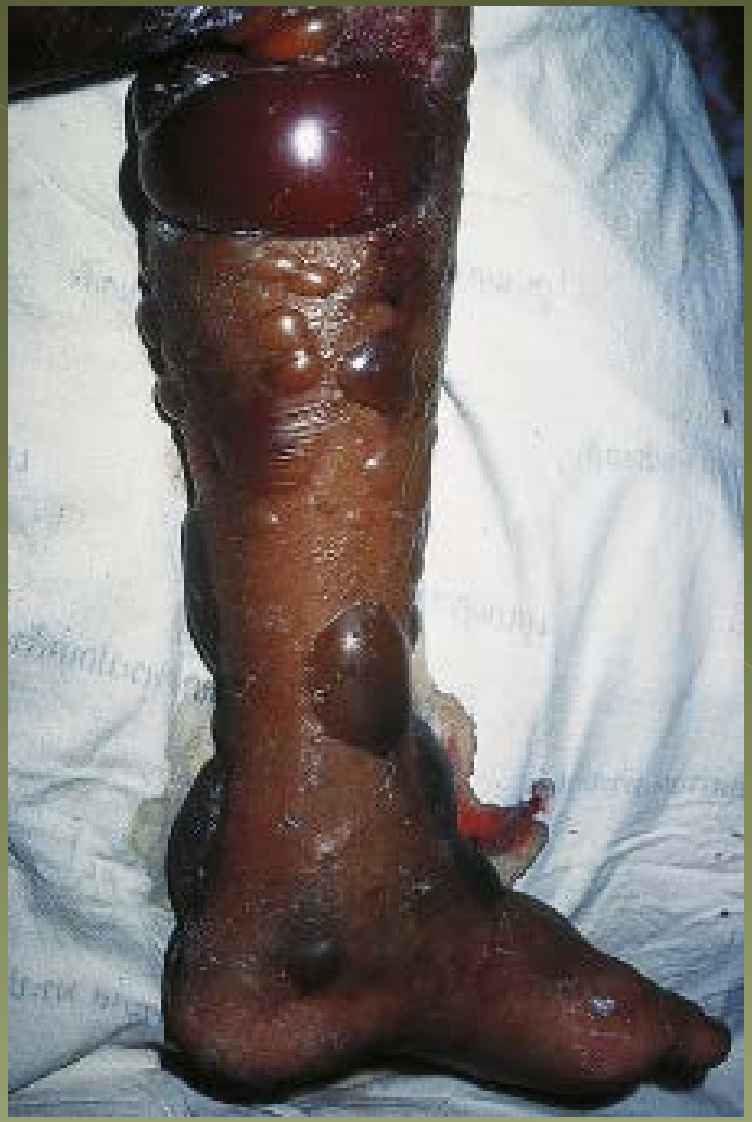


Neurotoxicity (bilateral ptosis and facial paralysis), myoglobinuria resulting from generalised
rhabdomyolysis, and acute renal failure in a girl bitten by Russell's viper (*Daboia russelii) near Anuradhapura,* Sri Lanka

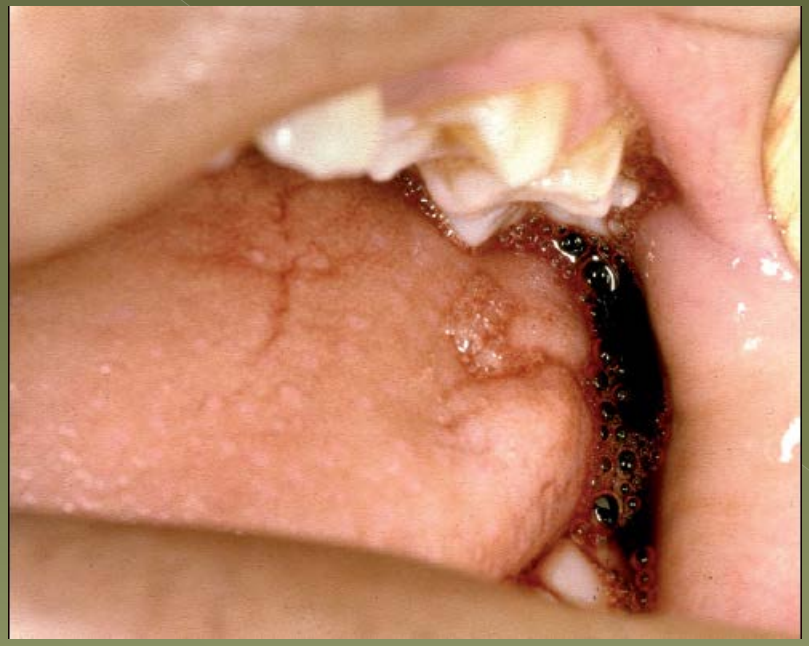
Snakebites



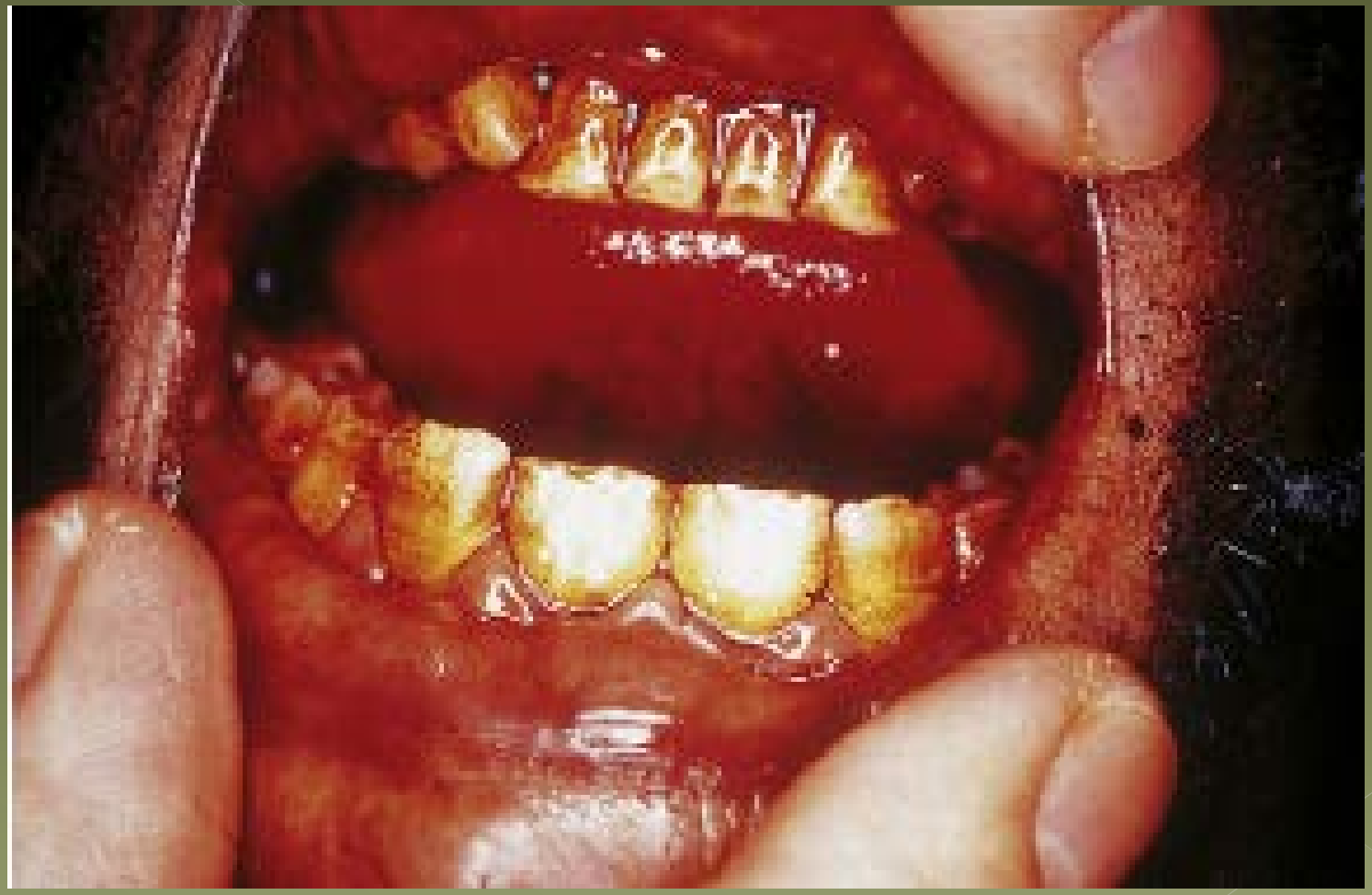
Snakebite blistering



Spontaneous bleeding from the gingival sulci of a boy bitten by a Papuan taipan (*Oxyuranus scutellatus canni) near Port Moresby, Papua New Guinea*



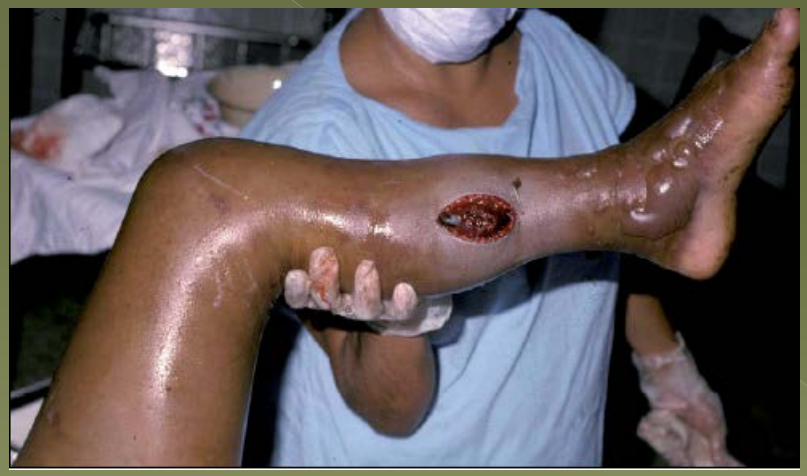
Snake bite, bleeding



Effects of the toxins

- Hypotension after snake bite is attributable to various venom activities, including permeability factors that cause hypovolaemia from extravasation of plasma, and toxins acting directly or indirectly on cardiac muscle, vascular smooth muscle, and on other tissues.
- An oligopeptide from the venom of the Brazilian jararaca (*Bothrops jararaca) activated bradykinin41 and, through a* bradykinin-potentiating peptide, prolonged bradykinin's hypotensive effect by inactivating the peptidyl dipeptidase that destroys bradykinin and converts angiotensin I to angiotensin II.

Massive swelling of a bitten limb with bruised muscle bulging out of a fasciotomy wound



Effects of the toxins

- This discovery led to the synthesis of captopril and other angiotensin-converting enzyme (ACE) inhibitors.
- Bradykinin-potentiating and ACE-inhibiting peptides have been found in several other crotaline and viperine venoms.
- Venom of the Israeli burrowing asp (*Atractaspis engaddensis: Atractaspididae) contains* sarafotoxins that have 60% sequence homology with endogenous mammalian endothelins.

Effects of the toxins

- Sarafotoxins and endothelins are 21-aminoacid polypeptides that potently vasoconstrict coronary and other arteries, and delay atrioventricular conduction.
- Natriuretic peptides in mammalian tissues and in many snake venoms reduce blood pressure by several mechanisms.
- The B-type natriuretic peptide in the venom of the green mamba (*Dendroaspis angusticeps) has therapeutic potential*

Effects of the toxins

- Some snake venoms contain serine proteases, metalloproteinases, C-type lectins, disintegrins, and phospholipases that disturb haemostasis by activating or inhibiting coagulant factors or platelets, and disrupting vascular endothelium.
- Viperid and Australasian elapid venoms contain procoagulant enzymes—eg, thrombinlike fibrinogenases and activators of prothrombin, factors V, X, and XIII, and endogenous plasminogen.

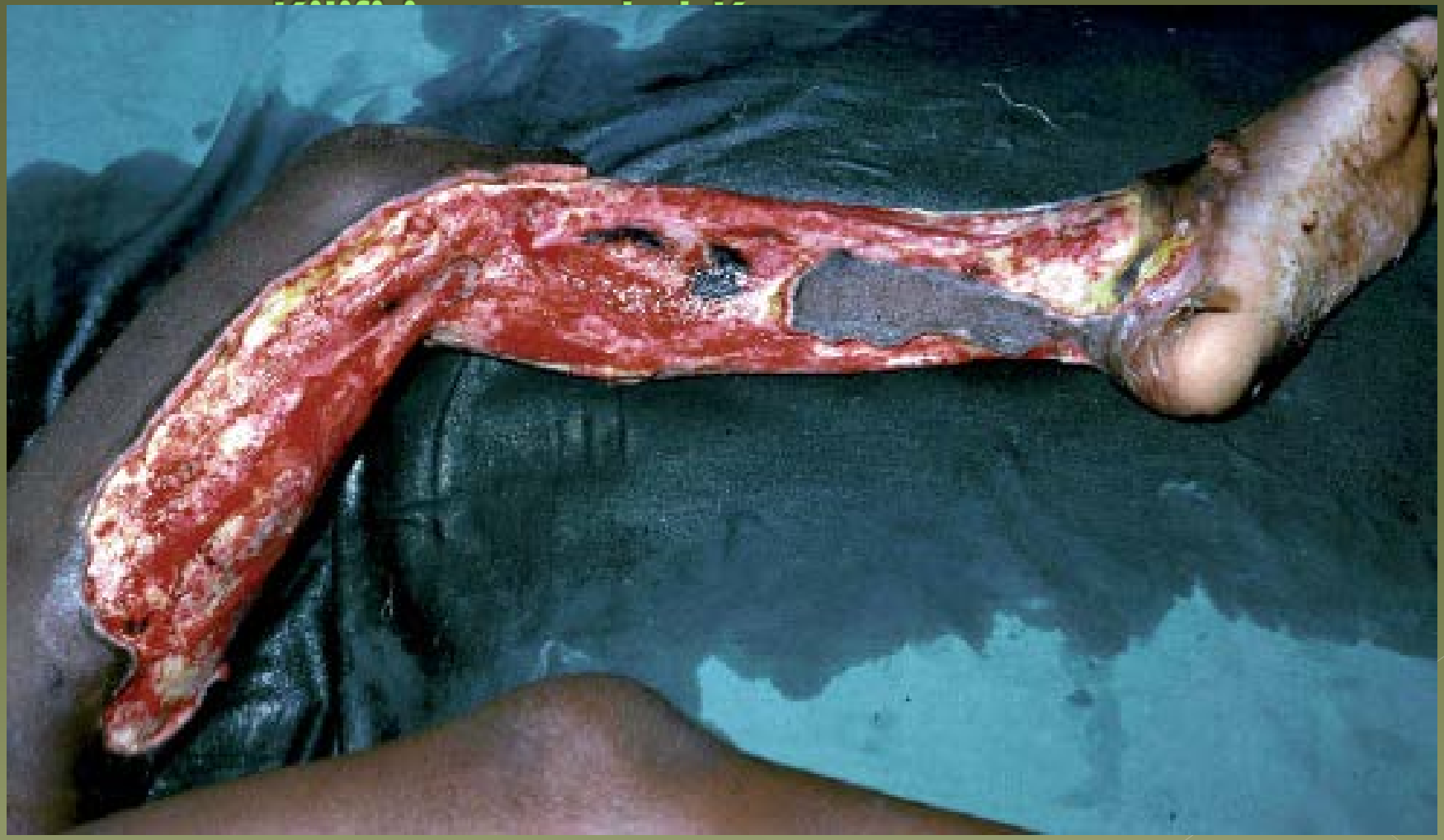
Effects of the toxins

- Toxins bind to a range of platelet receptors, inducing or inhibiting aggregation.
- Anticoagulant venom phospholipases A2 hydrolyse or bind to procoagulant phospholipids and inhibit the prothrombinase complex.
- Spontaneous systemic bleeding is caused by haemorrhagins (metalloproteinases, some with disintegrin-like and other domains), which damage vascular endothelium.
- The combination of consumption coagulopathy, anticoagulant activity, impaired and few platelets, and vessel wall damage can result in severe bleeding, a common cause of death after bites by *Viperidae, Australian Elapidae, and some Colubridae.*

Effect of toxins

- A range of venom myotoxic and cytolytic factors might contribute to local tissue necrosis at the site of the bite
- Studies of terciopelo (*B asper) venom-induced* necrosis implicate zinc-dependent metalloproteinases and myotoxic phospholipases A2.
- Other digestive hydrolases, hyaluronidase, polypeptide cytotoxins (*Elapidae), and* perhaps secondary eff ects of infl ammation are implicated in envenomings by diff erent snake species.
- In some cases, ischaemia, resulting from thrombosis, intracompartmental syndrome, or application of a tight tourniquet, contributes to tissue loss.
- Myotoxic phospholipases A2 in venoms of some species of *Viperidae and Elapidae, especially sea* snakes, cause generalised rhabdomyolysis that is often complicated by acute renal failure

Extensive dermonecrosis in a girl 3 weeks after being bitten by Ashe's spitting cobra (*Naja ashei*)



African girl with scars and contractures from her encounter with a black-necked spitting cobra

Cathegories

- Patients can be classified as follows:
  - those with a history of a bite but no physical evidence were termed ‘putative bites without envenoming’;
  - those with puncture marks and/or local swelling restricted to the bitten segment (e.g. foot) were termed ‘confirmed bites with neither extensive local nor systemic envenoming’; and
  - those with more extensive local swelling and/or systemic envenoming were termed ‘bites with envenoming’.

Clinical features of envenoming 1.

- Local swelling: increased vascular permeability leads to swelling and bruising. Local tissue necrosis results from the direct action of myotoxins and cytolytic factors.
- Hypotension and shock: profound hypotension is part of the „autopharmacological" syndrome which may occur within minutes after the bite (Viperidae). The mechanism is ACE inhibiting. Massive bleeding can also produce hypotension.

Clinical features of envenoming 2.

- Bleeding and clotting disturbances: the venoms producing consumption coagulopathy.
- Intravascular haemolysis: certain snakes can produce massive haemolysis.
- Complement activation: cobra venoms activate complement cascade via alternative pathway, which might interfere with the clotting system.

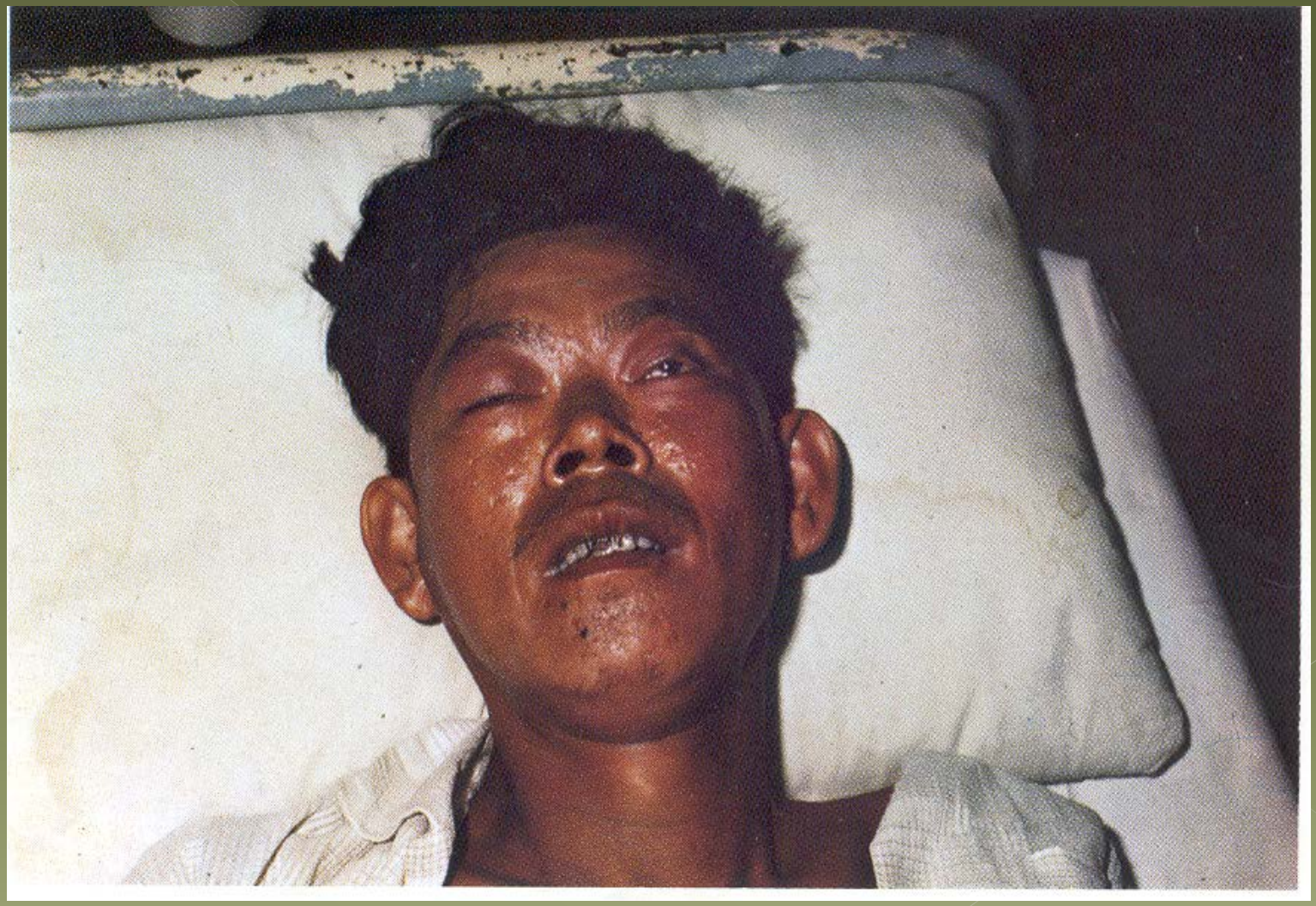
Clinical features of envenoming 3.

- Renal failures: is a rare complication, but most of the snakes can produce it through different mechanisms (hypotension, DIC, direct toxic events, rhabdomyolysis etc.)
- Neurotoxicity: the neurotoxic polypeptides cause paralysis by blocking transmission at the neuromuscular junction (coral snakes, kraits, mambas, kobras).

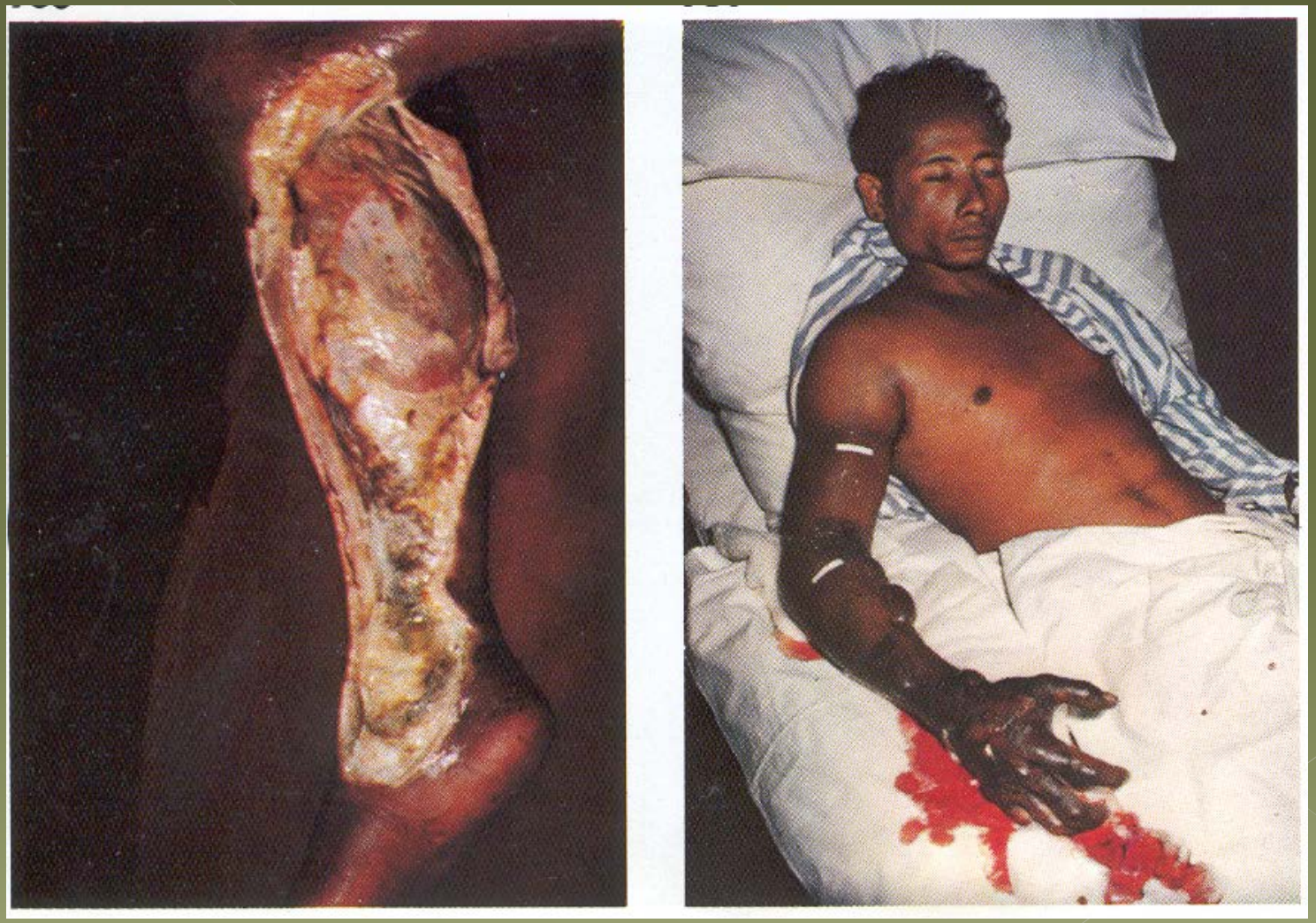
Clinical features of envenoming 4.

- Rhabdomyolysis: generalysed rhabdomyolysis with release of myoglobin, muscle enzymes and potassium is an effect in man of praesynaptic neurotoxins of sea snakes.
- Venom ophtalmia: the venom of spitting cobras are intensely irritant and even destructive on contact with mucous membranes such as conjunctivae and nasal cavity.

Ptosis after cobra bite



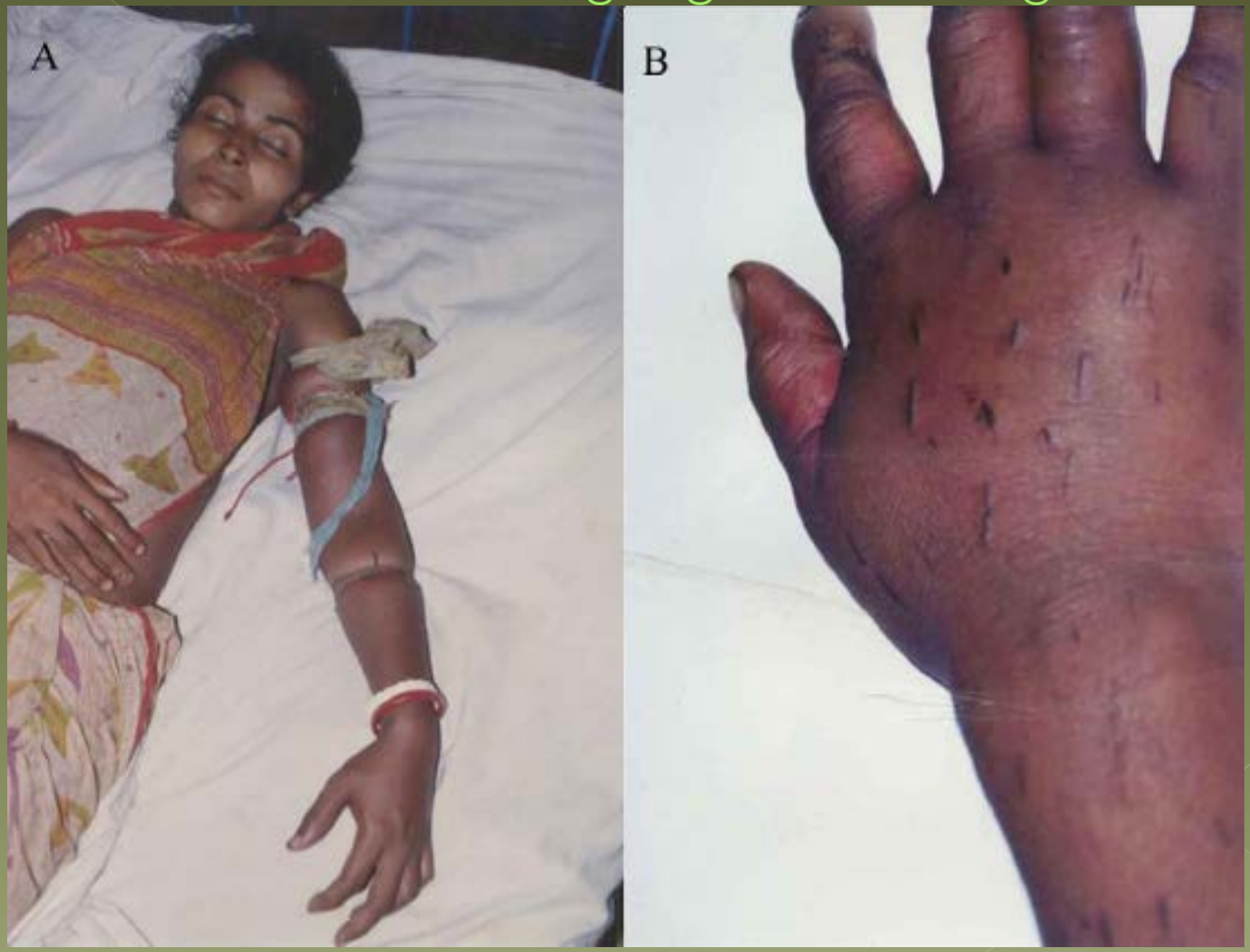
Extensive soft tissue necrosis following cobra bite, bleeding and haemorrhagic shock after viper bite



Management of snake bite 1.

- Reassure the victim, who will almost certainly be terrified.
- Do not temper with the bite wound, but immobilize the bitten limb.
- The patient should be immediately hospitalized.
- Avoid harmful and time -wasting treatments.
- Species diagnosis is important, when possible (but do not search for the snake if it is still at large).

(A) Ligatures and (B) incisions to the limbs of victims of snake bite in Chittagong District, Bangladesh



Management of snake bite 2.

- Treatment of early symptoms:
- *Local pain:* oral paracetamol (avoid aspirin!). In serious cases morphin-like drugs can be used.
- *Vomiting:* Patient should lie on their side with the head down to avoid aspiration.Persistent vomiting should be treated with chlorpromazine.
- *Syncopal attacks and anaphylactic shock:* antihistamines and/or adrenaline can be given (0,1% solution, 0,5ml for adults, 0,001ml/kg in children by subcutaneous injection.
- *Respiratory distress:* this may result from the paralysis of the jaw and the tongue or respiratory muscles. Manual ventillation is important.

Indications for antivenom

- Haemostatic abnormalities
- Cardiovascular abnormalities
- Neurotoxicity
- Generalized rhabdomyolysis
- Impaired consciousness.
- Signs of serious local envenoming.

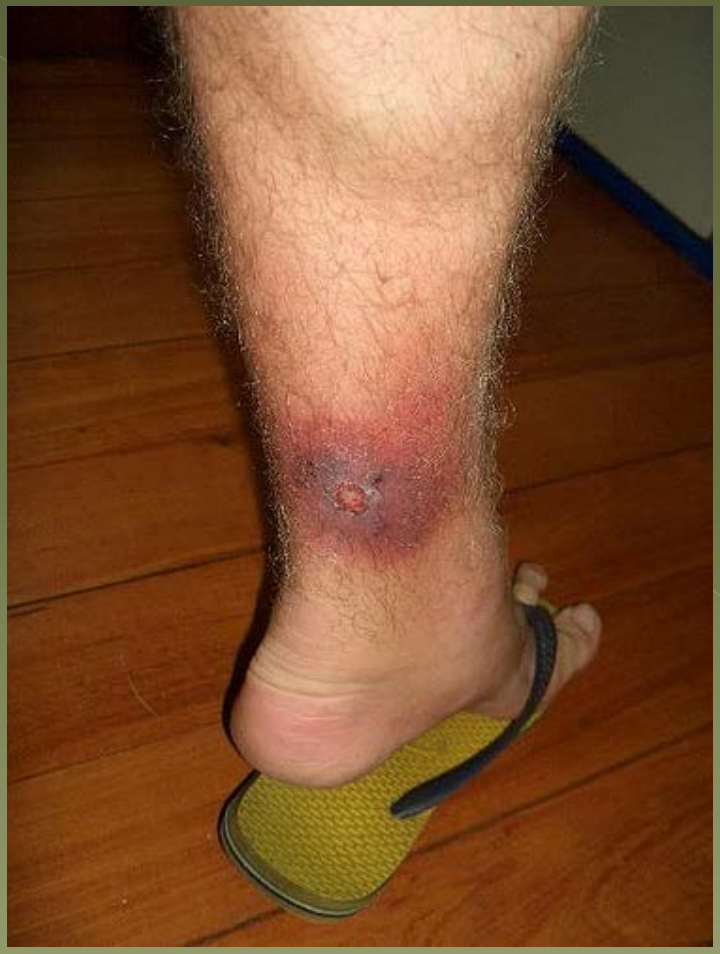
Administration of antivenoms

- Antivenom should be given as soon as possible, but it is never too late to give it as long as signs of systemic envenoming persist.
- The intravenous route is the most effective. 30/60 minutes infusions are preferred.

Spitting cobra

Scorpion stings

Scorpion stings



Scorpion stings

- Venomous scorpion stings are a major problem in the Americas, North Africa, the Middle East and South Asia.
- Scorpion venoms are usually less complex than snake venoms; most components are peptides that affect sodium and potassium channels.
- The severity of envenoming varies between species.

Scorpion stings

- Clinical features:
  - severe pain in the region of the sting is common.
  - A small proportion of patients, particularly children, develop signs and symptoms caused by the action of scorpion venom on the autonomic nervous system.
  - Hyperexcitability, sweating, lacrimation, excessive salivation and tachypnoea may occur.
  - In severe envenoming, catecholamine release causes hypertension, cardiac arrhythmias, myocardial failure and pulmonary oedema.
  - Skeletal muscle stimulation can lead to muscular spasms.

What to do

- Wash the area of the scorpion sting with soap and water.
- Apply a cool compress on the area of the scorpion sting.
- Ice (wrapped in a washcloth or other suitable covering) may be applied to the sting location for 10 minutes.
- Remove compress for 10 minutes and repeat as necessary.
- If stung on a limb (arm or leg) elevate the limb to heart level.

Scorpion stings

- Management :
  - antivenom therapy is the mainstay of therapy, with supportive medical treatment.
  - Atropine may be required in patients with severe bradyarrhythmia, but has no other proven value.
  - Vasodilator therapy (particularly prazosin) can be useful in the treatment of cardiovascular manifestations of envenoming.

Spider bites

- Species of venomous spiders are found throughout the world, in temperate and tropical regions.
- Clinical features e the most common venomous spiders are the widow spiders (Latrodectus spp.): their venom stimulates:
  - transmitter release from neurones throughout the nervous system,
  - causing severe local and generalized pain, muscle cramps and
  - spasms, sweating, and occasionally severe hypertension.

Spider bites

- The predominant feature of envenoming by recluse spiders (Loxosceles spp.) is severe, slowly-evolving local necrosis.
- The Australian funnel web spider (Atrax robustus) releases a presynaptic neurotoxin that can stimulate the autonomic and peripheral nervous system and can cause cardiovascular instability and severe pulmonary oedema.
- Management:
  - pressure immobilization is recommended for funnel web spider bites, but is not used for other species.
  - The availability of antivenom depends on the species and the geographical location.
  - Antivenom should be used for significant systemic envenoming.

Venomous fish

- Many different venomous fish sting if they are stood on or touched.
- Systemic envenoming is rare.
- Excruciating pain at the site of the sting is the major effect.
- Regional nerve blocks and local infiltration of lidocaine can be effective, but most marine venoms are heat labile.
- Immersing the stung part in hot water is extremely effective in relieving pain.
- Care should be taken to avoid scalding; the envenomed limb may have abnormal sensation.

Venomous fish

- Coelenterate stings:
  - Venomous jellyfish occur throughout the world, but are particularly common in the tropical waters of the Indo-Pacific region.
  - A mechanical stimulus causes nematocysts on the tentacles to discharge, injecting venom subcutaneously.

Venomous fish

- Clinical features depend on the species:
  - Most cause immediate pain at the site of contact and an acute local inflammatory response.
  - The box jellyfish, Chironex fleckeri, can cause full-thickness skin damage and systemic involvement; death can occur rapidly from myocardial toxicity.
  - Some tiny carybdeid jellyfish stings cause Irukandji syndrome, often in the absence of skin lesions.
  - Pain, hypertension and cardiopulmonary decompensation can occur 30-40 minutes after the sting.

Box jellyfish

Venomous fish

- Management:
  - undischarged nematocysts adherent to the skin should be prevented from firing; vinegar is effective on stings from the box jellyfish found in Pacific and Australasian regions. S
  - Stings from hydroids (e.g. Portuguese man-of-war), should be washed with fresh sea-water and adherent tentacles picked off.
  - In patients with box jellyfish stings, compression bandaging can reduce systemic absorption of venom. In severe envenoming, collapse may occur on the beach.
  - Cardiopulmonary resuscitation may be life-saving.

Venomous fish

- Antivenom is not available for hydroid stings or Irukandji syndrome.
- Pain relief can be achieved by the use of ice and opioids: immersion in hot water is also effective for some species.
- Supportive therapy is necessary for the management of cardiovascular manifestations.