Snakes

Summary

- Not all snakes are venomous
- Often dry bites by venomous snakes
- Vipers: primarily haemorrhages and necrosis
- Elapids: primarily paralysis and necrosis.
- No arterial tourniquet.
- Pressure-immobilisation technique during transport (neurotoxic snakes)
- Antivenom if symptoms of envenomation
- Neostigmine + Atropine if paralysis
- Potential side effects of antivenom (anaphylaxis, serum sickness)

Description

There are around 2700 snake species, including around 375 venomous snakes with medical relevance. Of the latter, around 200 are potentially lethal. The biotopes vary greatly: from the arctic circle to the equator, and from sea level to 5000 m in elevation. Venomous snakes are not found in Chile, Madagascar, New Zealand, Hawaii and New Caledonia. In Belgium there are a very small number of indigenous vipers (*Vipera berus* = common European adder), ringed snakes (*Natrix natrix* or grass snake) and smooth snakes (*Coronella austriaca*). The last two are not venomous.

It is estimated that at least 421,000 envenomings and 20,000 deaths (figures may be as high as 1,841,000 and 94,000 resp.) occur annually worldwide. The highest burden of snakebites is in South Asia, Southeast Asia and sub-Saharan Africa. People most at risk are agricultural workers and children. One of the most frequently bitten people are drunken young men harassing a snake.

The majority of snake-bite victims seek traditional treatment and may die at home unrecorded. The amount of disability (permanent sequelae due to snakebites) is unknown and underreported. Although it is more common in rural areas, snakes can be present in town

areas (e.g. in India). Snake bites have been recognized as a neglected disease by WHO.

Crotalus atrox, the Western diamondback rattle snake. Photo Protherics, used with permission

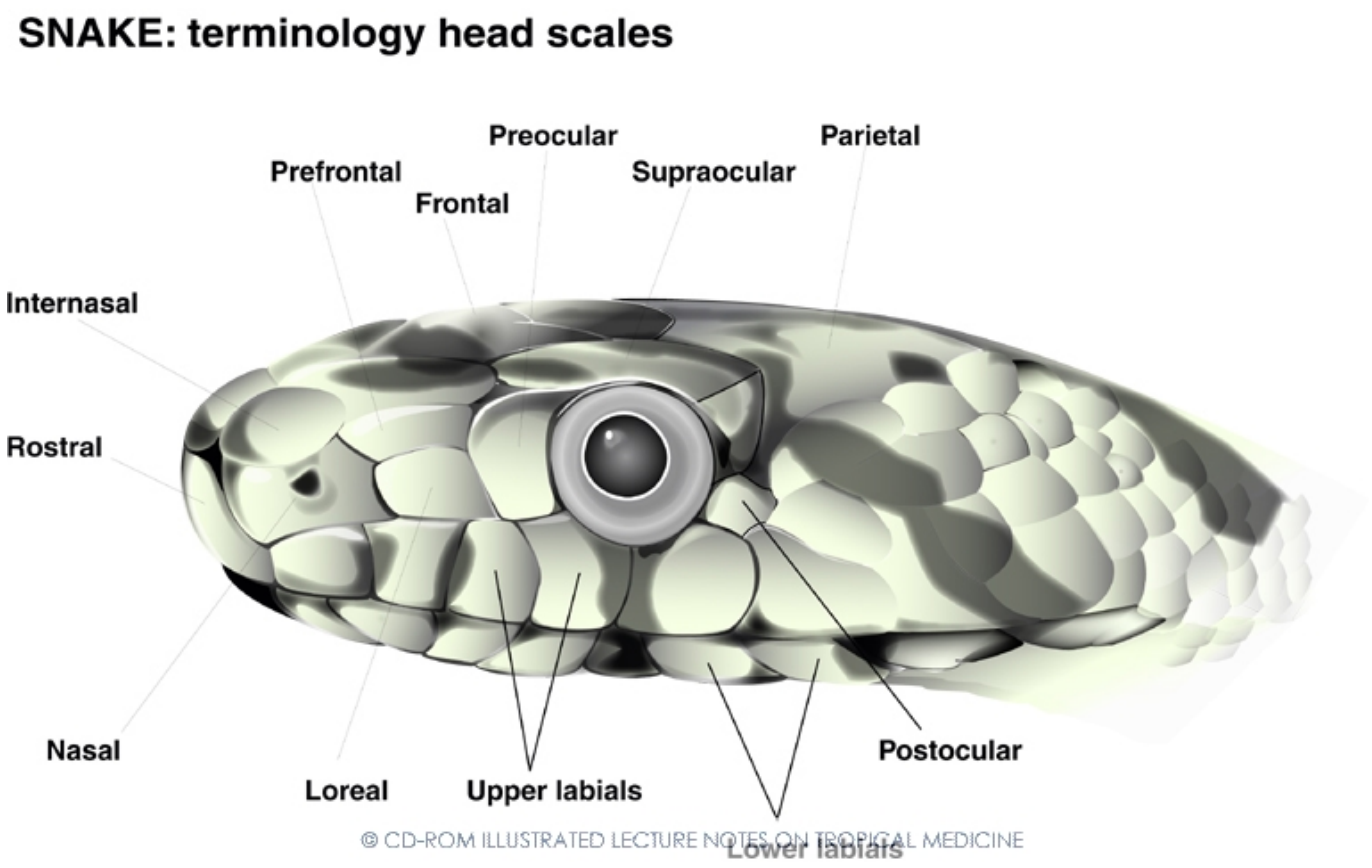
Juvenile Elaphe situla snake (Leopard snake), not venomous. This escaped (?) specimen was found in the middle of a main street in Antwerp, Belgium. Illegal breeding of protected species is common. Copyright ITM

Biology of snakes

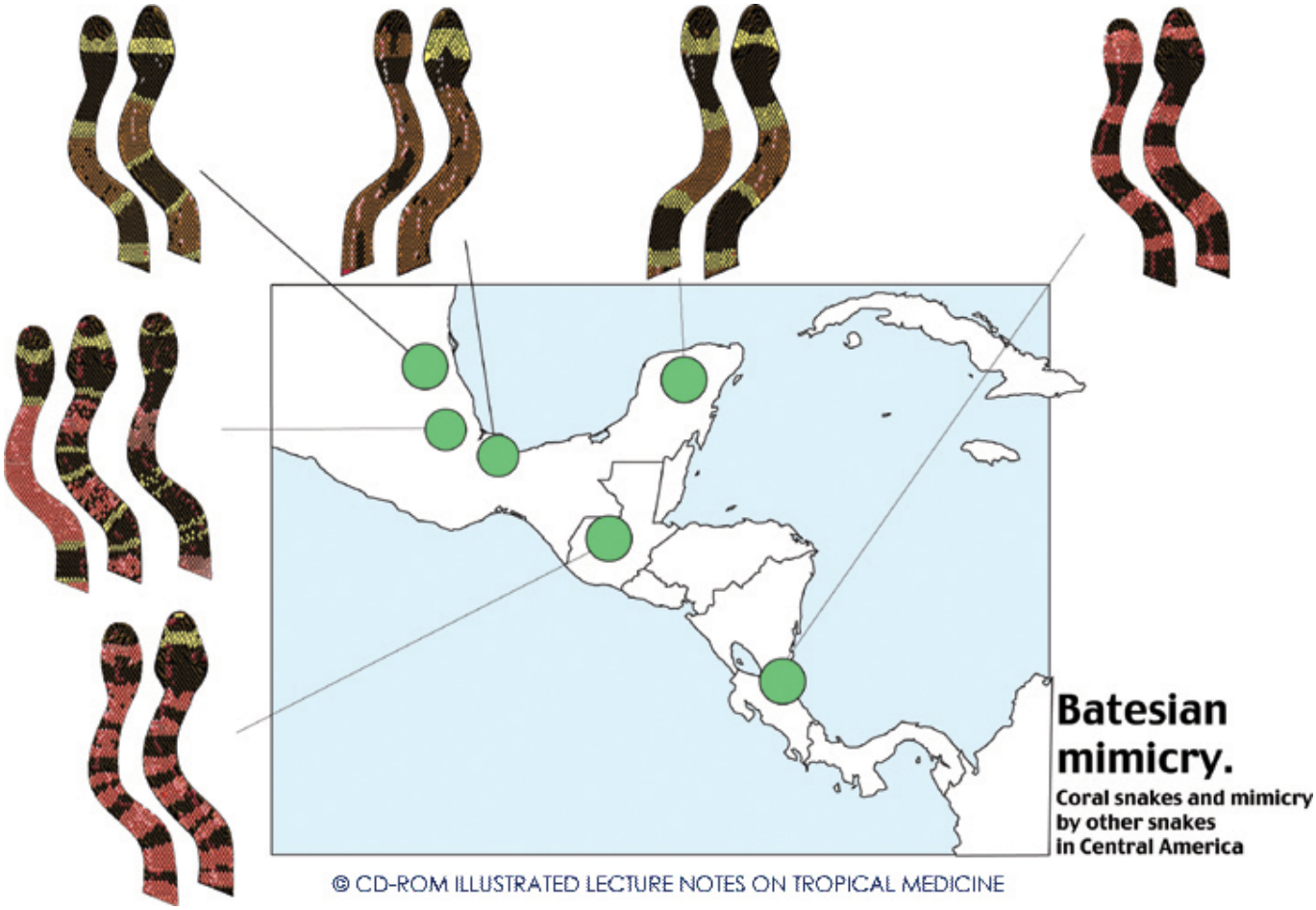
Snakes are quasi-cylindrical reptiles without limbs. They move using a concertina movement, rectilinear, curvilinear, via “sidewinding” or by a combination of these methods. There are even 5 species of “flying” (gliding is a better word) snakes. In snakes, the left lung is atrophic, except in boas. The right lung can have an extension in the throat, which is important for the animal because there is airway compression when it swallows large prey. In general, the length of the lung is about one-half of the total body length, although in seasnakes the lung is longer. In reptiles, the nostrils come out in the mouth cavity (there is no palate to separate the mouth cavity from a nasal cavity). They can

breathe through their mouth if it is empty. A full mouth blocks respiration. They can tolerate apnoea for a fairly long time, because as poikilothermic animals they have a rather low oxygen demand. By exhaling quickly some snakes can produce a hissing noise (cf. the puff adder).

Description, scales and colour



The scales on the head of a snake are rather constant within a species and are used for taxonomic identification. Adapted from ”The Encyclopedia of Snakes” by Chris Mattison



Examples of Batesian colour and shape mimicry in Central American snakes. The left snake in each pair and the outermost snakes of the triple cluster are dangerous Micrurus species. The snakes on the right side and the central of the 3 snakes are non-venomous Pliocerus sp. The similarity is striking. Drawing adapted by ITM, from original.

Stripes and/or spots can act as a camouflage, breaking up the visual outline against the surroundings. A harmless snake can imitate a venomous one when both live in the same environment, i.e. Batesian mimicry (1861, Henry Walter Bates, English naturalist). In this way predators avoid the snake, if they have learned earlier that an animal with such coloration is dangerous.

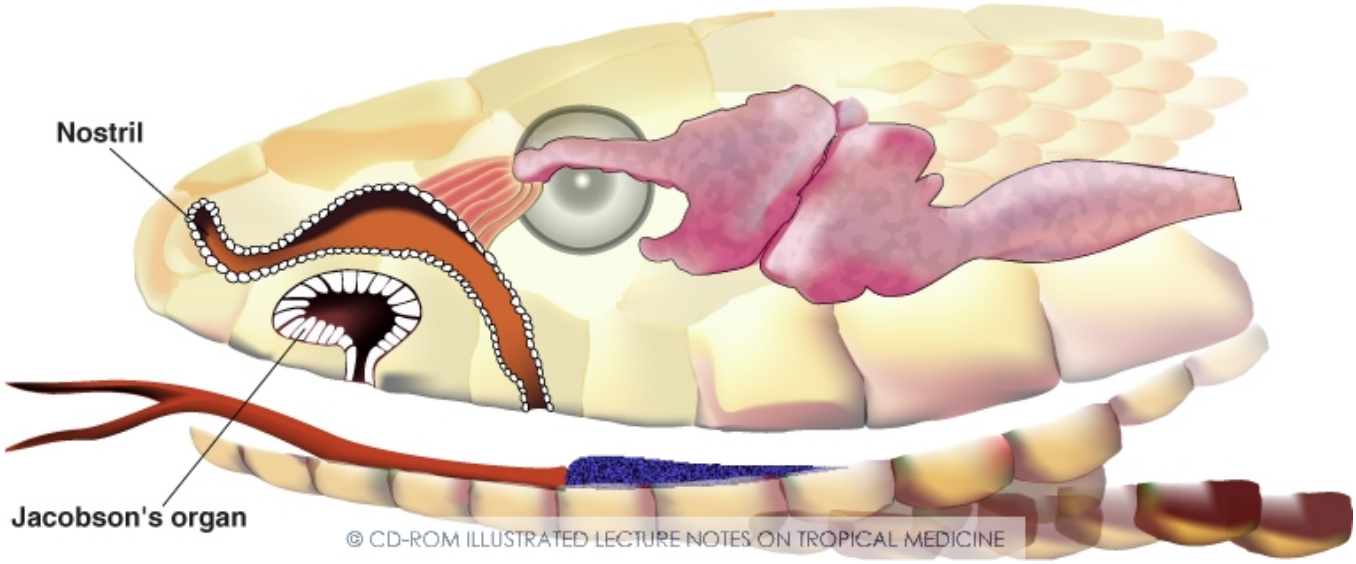
Description, heat sensors and Jacobson´s organ

Most snakes have poor hearing and limited visual acuity. By contrast, in the roof of their mouth they possess an extremely sensitive organ, known as a Jacobson´s organ. It consists of two openings lined with sensory cells. The animal flicks out its forked tongue and brings it back into the mouth, inserting the tips into the two openings of Jacobson´s organ. The tongue brings molecules from the environment into the organ. In this way the snake can sense its environment. Snakes are very good at perceiving vibrations, e.g. of the ground. Some people use this as a means of prevention, by regularly beating a stick on the ground in front of them when they walk in an area with venomous snakes.

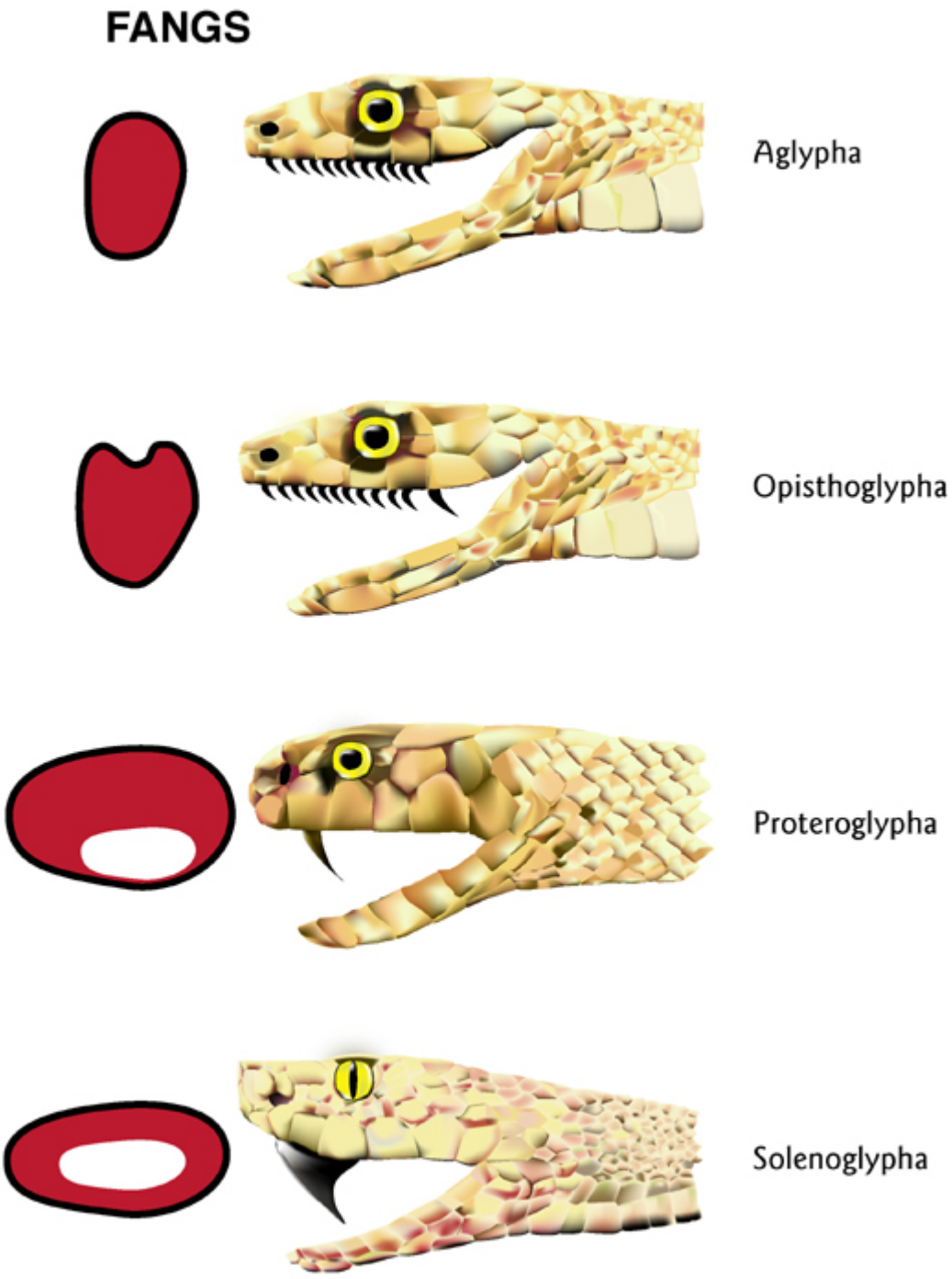
Description, food and body heat

All snakes are carnivorous. Because they do not have to continually maintain their body at a constant temperature, their food intake requirement is a good deal lower than that of warm-blooded animals. Because chronic “constipation” is most pronounced among sit-and-wait predators – animals for which body weight is of great importance – some people assume that these snakes make good use of the extra weight (3 to 22% of their body weight is faecal material). These animals lie still on the ground and use their heavy intestine as a counterweight in order to be able to strike more quickly with the mouth. Since the environment of the snake is so important for the animal, it is not unusual for a snake to lie at night on a path or road, where the temperature is somewhat higher than in nearby vegetation. Obviously this increases the chances of an accidental bite being suffered by a night time walker. In order to conserve heat, they can roll themselves up (small surface/weight ratio). This is also important to limit transcutaneous loss of water. In cold regions snakes can hibernate, individually or in a group. Many snakes have a limited territory. After having bitten somebody, a snake can generally be found within a rather small radius around the site of the incident, even after several hours.

Description, venom gland



Jacobson’s organ in the roof of the mouth of a snake is covered with chemosensory cells. The tongue will bring chemicals from the environment in contact with the epithelium. Nerves connect the organ to the olfactory lobes of the brain.



Snakes. The structure of the fangs differs between taxonomic groups. Copyright ITM

Colubrids have a modified salivary gland (Duvernoy´s gland), which discharges near the

fangs at the rear of the mouth. The venom is slowly introduced into the prey via capillary action. Therefore, in order to get sufficient venom into the tissues, a long contact period is necessary. However, this occurs only exceptionally in humans. This explains why most bites by colubrids are harmless. This also explains why occasionally envenomations are described by snakes that traditionally are regarded as non-venomous. In elapids and vipers, in contrast the venom glands consist of the uppermost labial salivary glands. They can be actively emptied by the musculus constrictor glandulae, so that the animals can actively and very quickly inject venom, or even spit venom (several meters).

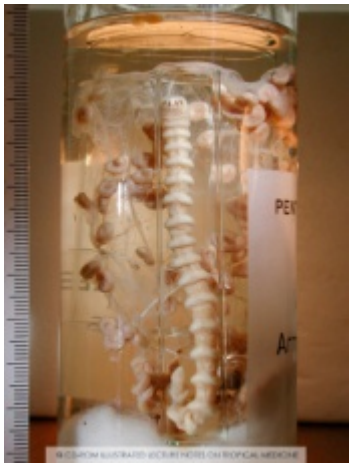
Description: jaws, fangs and teeth

The left and right sides of the jaws can move independently of one another. This makes it possible to swallow large prey, yet the animals cannot chew. Snakes have no sternum, so that a large ingested prey does not constitute a mechanical obstacle when it is being swallowed (some prey have a diameter which is greater than the resting diameter of the snake).

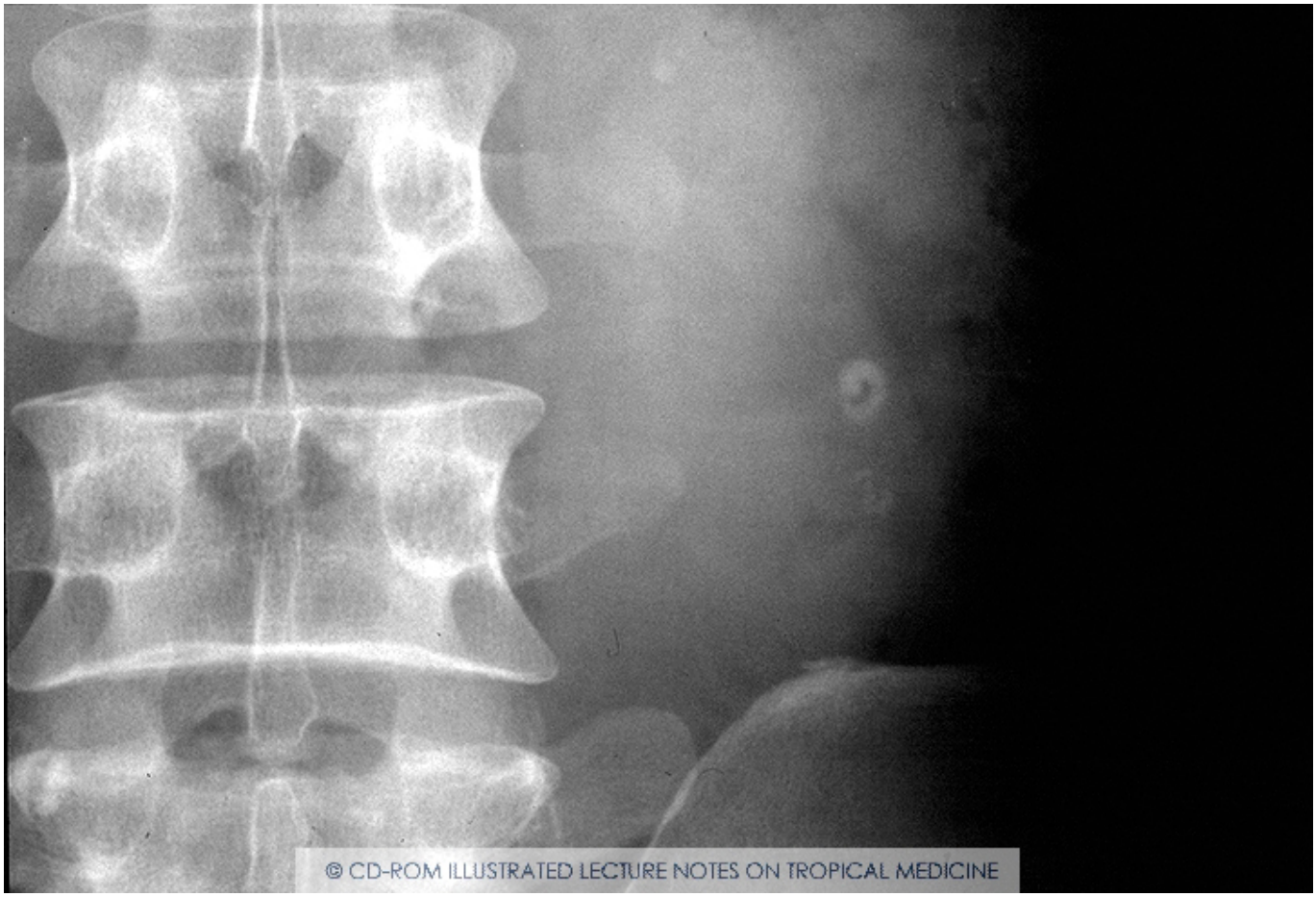
In snakes, the teeth are not so firmly attached to the top/inner side of the jawbones (so-called “pleurodont dentition”). This makes it possible for the teeth to be easily replaced throughout a snake´s lifetime. The teeth break off easily. This influences the biting behaviour. Thus vipers bite, inject venom and release again in rapid succession, because a struggling prey could cause injury or break the teeth.

A temporomandibular joint is a purely mammalian characteristic that is not found in snakes. In snakes, the joint between lower and upper jaw is formed by the os articulare at the bottom and the os quadratum (quadrate bone) at the top.

Infections transferred via snakes



Pentastomiasis. Armillifer armillatus causes porocephalosis in humans. This tongue worm normally infects snakes. Copyright ITM



C-shaped calcifications due to infection with Armillifer armillatus, a tongue worm.

Pentastomiasis is also known as porocephalosis. Photo ITM

Pythons can be infested by tongue worms (Pentastomida) such as *Armillifer armillatus* in Africa or *A. moniliformis* in Asia. These parasites live in the lungs of the reptiles. The eggs in the snake's sputum can infect humans, e.g. through contamination of drinking water or when a snake is prepared as food. Porocephalosis (syn. pentastomiasis) is the result. In general, infection leads to asymptomatic crescent-shaped calcifications in the abdomen. Living parasites are rarely found elsewhere (e.g. subconjunctival). Gnathostomiasis (infection with the nematode *Gnathostoma spinigerum*) can also follow consumption of undercooked snake meat. A larva migrans syndrome or a very serious eosinophilic meningo-encephalitis can then develop. *Spirometra* sp. can be transferred via snakes (also via frogs) and cause sparganosis, whereby the immature cestode can be found in the eye. These worms can survive for up to nine years in humans.

Taxonomy

Introduction

The classification is important because a certain correlation exists between snake family and pathology. This correlation is not absolute. Studying the fangs in the mouth of a dead snake which has been brought in can help determine the treatment. However, it is better to be cautious when doing this (the bite reflex can continue for over 1 hour after death even after decapitation). It can be useful to have on hand a number of photos or a poster illustrating most of the snakes in the surrounding area. On the basis of these pictures, a patient can sometimes indicate which animal has bitten him or her.

Table 1: Examples of venomous snakes

Snake family	Species – some examples

Elapidae A large and diverse Family of exclusively venomous snakes, covering all continents (except Antarctica) and several major oceans, these snakes have well developed fangs towards the front of the mouth, which can deliver often highly potent venom, produced in paired venom glands.	Cobra's, including spitting cobra's (*Naja*), coral snakes (*Micrurus, Micruroides*) Kraits (*Bungarus*) Mamba's (*Dendroaspis*) ? *D.polylepsis* Sea snakes
Viperidae A large and diverse Family of exclusively venomous snakes, covering most continents (except Australia and New Guinea, Antarctica), with a highly evolved fang structure. The fangs are at the front of the mouth, attached to a mobile maxilla, enabling the fang to fold away against the roof of the mouth, thus permitting longer fangs compared to head size.	Subfamily Viperinae "Old World" and Subfamily Crotalinae (Pit Vipers) Russel's Viper Puff viper, Gabon Viper, rhinoceros -horned viper (*Bitis*) Bush Viper (*Atheris*) Echis carinatus
Colubridae This is the largest Family of snakes, generally considered non-venomous and distributed globally. However, a few species have evolved fangs towards the back of the mouth, which deliver venom from venom glands.	Dispholidus typus (Boomslang) – sub-Saharan Africa Thelotornis (Twig Snake)
Atractaspididae A small Family of exclusively venomous snakes, found only in Africa and the Middle East, characterised by their side-striking fangs and unique venom components (sarafatoxins), only a few species of which appear able to significantly envenom humans.	Atractaspis microlepidota (Burrowing Asp)

Taxonomy, vipers (Viperidae)

Vipers and pit vipers have very long hollow fangs in the front of the mouth. When the mouth is closed the fangs lie folded up against the roof of the mouth. Vipers are slow, heavy snakes and are generally "sit-and-wait" predators. They move flat over the ground. One does not expect vipers to be present among tree branches for example. Venomous European vipers have vertical pupils. Non-venomous snakes in Europe have round pupils.

Daboia russelli

Russell´s viper (*Daboia russelli* = *Vipera russelli* = "tic-polonga") is one of the most dangerous Asian snakes. This nocturnal animal is often lethargic and will avoid dense jungle. It can hiss loudly through its large nostrils. There are 5 subspecies, which is important because antivenom from one country is often not effective on the local subspecies in another country. The symptomatology too will depend on the subspecies: pituitary haemorrhages and chemosis in Burma and southern India, anticholinesterase-resistant neurotoxicity in India and Sri Lanka; haemorrhages with all subspecies.

Bitis arietans

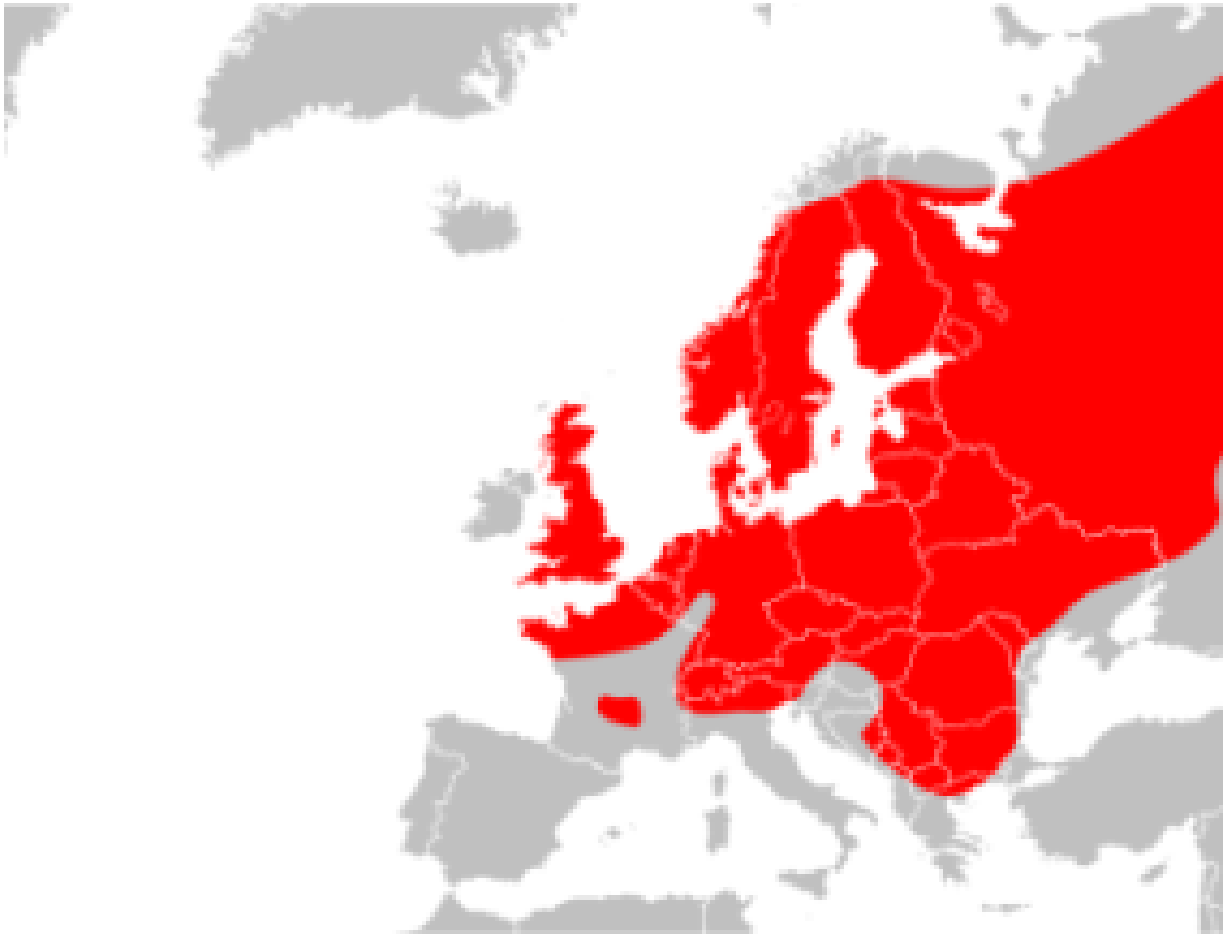
The puff adder (*Bitis arietans,* la vipère heurtante) gives rise to considerable problems in Africa. They can strike very quickly.

Bitis nasicornis

Bitis nasicornis belongs to the vipers. The exact function of the horns on the snout of this snake is not clear. Copyright ITM

Vipera berus (Common viper or adder)

Vipera berus, the common European adder or common European viper, is a venomous viper species that is extremely widespread and can be found throughout most of Western Europe and as far as East Asia. Known by a host of common names including common adder and common viper, adders have been the subject of much folklore in Britain and other European countries. They are not regarded as especially dangerous; the snake is not aggressive and usually bites only when alarmed or disturbed. Bites can be very painful, but are seldom fatal.



Vipera Berus distribution in Europe

Bitis gabonica

Bitis gabonica is also known as the Gabboon viper. Most animals have typical markings.

Bitis gabonica is also known as the Gabon viper. Most animals have typical markings. Copyright ITM

Echis carinatus complex

The saw-scaled vipers are among the most important venomous snakes in the world, it is estimated that they are responsible for 50% of the global mortality caused by snakes.

Taxonomy, pit vipers (Crotalidae)

The pit vipers or Crotalidae get their name from the presence of two pits at the front of the head, about halfway between the eyes and the nostrils. These contain infrared sensors with which the animal can better locate its prey.

Agkistrodon sp.

Pit viper: Agkistrodon piscivorus, also known as Mocassin. Courtesy of Protherics

Crotalus sp.

Pit viper: Agkistrodon piscivorus, also known as Mocassin. Courtesy of Protherics

Crotalus atrox, the Western diamondback rattle snake. Photo Protherics, used with permission

Rattlesnakes belong to the genus *Crotalus* and *Sistrurus*. When a rattlesnake administers a venomous bite to a human being, it injects 25-75% of its venom. It takes on average 3 weeks for the venom supply to be entirely replenished. Rattlesnakes have a typical tail structure. The rattle is used when the snake feels threatened. In this situation, the snake will raise its head and front part of the body, as well as the rattle and hold the body in an S-shape, ready to strike. The North American *Crotalus cerastes* is also called the “sidewinder”, referring to the way it moves. There are several desert snakes which demonstrate this behaviour.

Taxonomy, burrowing vipers or Atractaspididae

These animals (mole vipers or burrowing vipers) were earlier classified among the Viperidae, but currently form a separate family with over 50 species. They are primarily found in Africa. They are rather small animals, although some individuals can be as long as 1 meter. They live primarily underground. Bites are rare, but can have serious consequences. The hollow fangs can be moved sideways, even without opening the mouth. The venom of *Atractaspis engaddensis* contains an extremely powerful cardiotoxin, the so-called “sarafotoxin”, a word

deriving from the Hebrew “Saraf ´En Gedi” (saraf meaning ‘snake’, En Gedi refers to an oasis in the Judea desert in Israel).

Taxonomy, Elapidae

This family includes the cobras, mambas, kraits and coral snakes (Gr. Elaps: snake). The venom produces primarily local necrosis and paralysis. Elapids have moderately short, immobile fangs on the maxillae, at the front of the mouth. They cannot be folded backwards as in vipers. Often these snakes have small teeth behind the fangs and sometimes there is a small diastema.

Cobras

A cobra often raises its head and neck when it is threatened. The animals are characterised by the typical “hood”, the widening of the neck caused by spreading its cervical ribs when threatened. The king cobra (*Ophiophagus hannah*) is a very large Asian elapid, which eats other snakes. Some African and Asian cobras can spit venom.

Geographical distribution of asiatic cobras (*Naja* sp.). Copyright ITM

Coral snakes

Elapids also live in the New World: the coral snakes. They often have a beautiful colour pattern. A mnemonic device for the colour bands in North America: “red on yellow, kill a fellow; red on black, venom lack”. This phrase does not work in other geographical areas.

Bungarus sp.: Kraits

Often the animals are distinctly passive during the day. At night, however they are active and they sometimes enter houses and bite. People with krait bites generally experience

remarkably little local pain.

Dendroaspis sp. : Mambas

Mambas are only found in sub-Saharan Africa. These venomous snakes are notorious. They belong to the genus *Dendroaspis*: *D. polylepis* (black mamba), *D. viridis* (Western green mamba), *D. angusticeps* (Eastern green mamba) and *D. jamesoni* (Jameson´s mamba).

Australian elapids

The fauna of Australia is complex, and in differs in many ways from the fauna on other continents. The medical relevant Australian snakes belong to the elapids.

Taxonomy, sea snakes or Hydrophiidae

The taxonomical classification is controversial, but these animals can be classified among the Elapidae or be grouped in their own family. Taxonomically they are broken down into the Hydrophiinae (real sea snakes) and the Laticaudinae (sea kraits). In some taxonomic diagrams these groups get the status of family: Hydrophiidae and Laticaudae.

Taxonomy, Colubridae

The name derives from the Latin “coluber”, which means snake. Only a few are genuinely dangerous. They have short small fangs on the maxillae at the back of the mouth so that they have to open their mouth very wide (170 to 180°) to inject venom. They also require a long contact period to introduce enough venom into the bite wound. Colubrids are often kept as pets. , e.g. *Elaphe* sp. (rat snakes) or *Lampropeltis* sp. (king snakes, milk snakes). The boomslang (*Dispholidus typhus*) in southern Africa is another dangerous colubrid, yet bites by this animal are quite exceptional. Haemorrhages are the most obvious symptom after a bite by a boomslang.

Taxonomy, Boidae

The Boidae include boas and pythons. Constrictor snakes such as the anaconda, boas and pythons are not venomous. Boas are viviparous snakes from the New World and pythons are oviparous snakes from the Old World. Because they must be able to hold their body in small-diameter loops, they have short vertebrae. When they are wrapped around their prey, what makes them so deadly is not that they squeeze so hard, but rather that they can very effectively resist attempts to stretch. Every time the unfortunate prey exhales, the snake contracts a little bit more, and prevents the prey from inhaling. After this has been repeated a few times, the prey simply suffocates.

Distribution

As far as native venomous snakes are concerned, only vipers are found in Europe.

In Africa there are elapids, vipers and colubrids.

The most important snakes in America are the pit vipers and several coral snakes.

In Asia, all families are represented (but not all genera).

A number of elapids live in Australia.

Problems with venomous sea snakes are limited to coastal areas of Asia and Australia.

Imported exotic pet snakes can be responsible for bites, especially in affluent countries.

Viper populations in Belgium

There are three isolated wild viper populations in Belgium: the largest one in Brecht (Groot Schietveld), and much smaller populations in Kalmthoutse Heide and in the Visbeekvallei (Lille).

Distribution of the most important snakes

It is useful to have an idea of which major venomous snakes can be found where.

In **Southeast Asia** Russell´s viper (Daboia russelli), Echis carinatus, the habus and the Malayan pit viper (Calloselasma rhodostoma) are the most important.

In **Africa** the saw-scaled vipers (*Echis carinatus* complex), the puff viper (*Bitis arietans*) and to a lesser extent cobras and mambas are important.

In **South and Central America** the cascabel (*Crotalus durissus terrificus*), jararaca (*Bothrops jararaca*) and fer-de-lance (*Bothrops atrox*) are the most important venomous snakes. Bites by the notorious bushmaster (*Lachesis muta*) are actually quite rare.

In **North America** the various rattlesnakes (*Crotalus* sp. and *Sistrurus* sp.) are the most important, with *Crotalus atrox* (Western diamondback) heading the list. Mocassins (*Agkistrodon* sp.) and coral snakes (*Micrurus* and *Micruroides*) are statistically less important.

Coastal areas in Southeast Asia and Northern Australia: sea snakes such as *Pelamis*, *Laticauda* sp, *Enhydrina* sp.

Australia: Brown snake (*Pseudonaja* sp), black snake (*Pseudoechis*), death adder (*Acantophis*), Taipan (*Oxyuranus*), tiger snake (*Notechis*).

The five medically most important snakes in the world are:

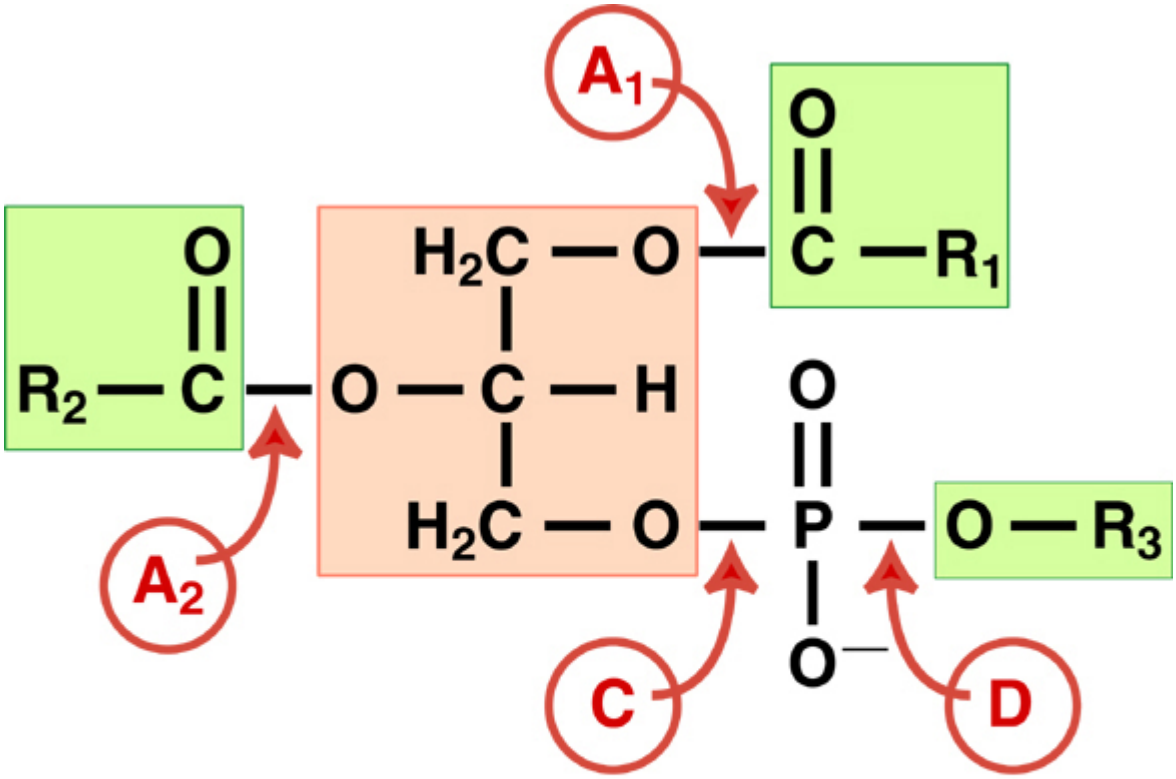
Echis carinatus complex
Bitis arietans
Daboia russelli
Calloselasma rhodostoma
Bothrops atrox

Snake venom

Snake venom, composition

Snake venom is a complex mixture of enzymes, toxins and all sorts of smaller molecules. The most important components are the substances with a cytotoxic effect, neurotoxins and the factors leading to bleeding tendency. Some toxins have multiple effects.

Snake venom, necrosis



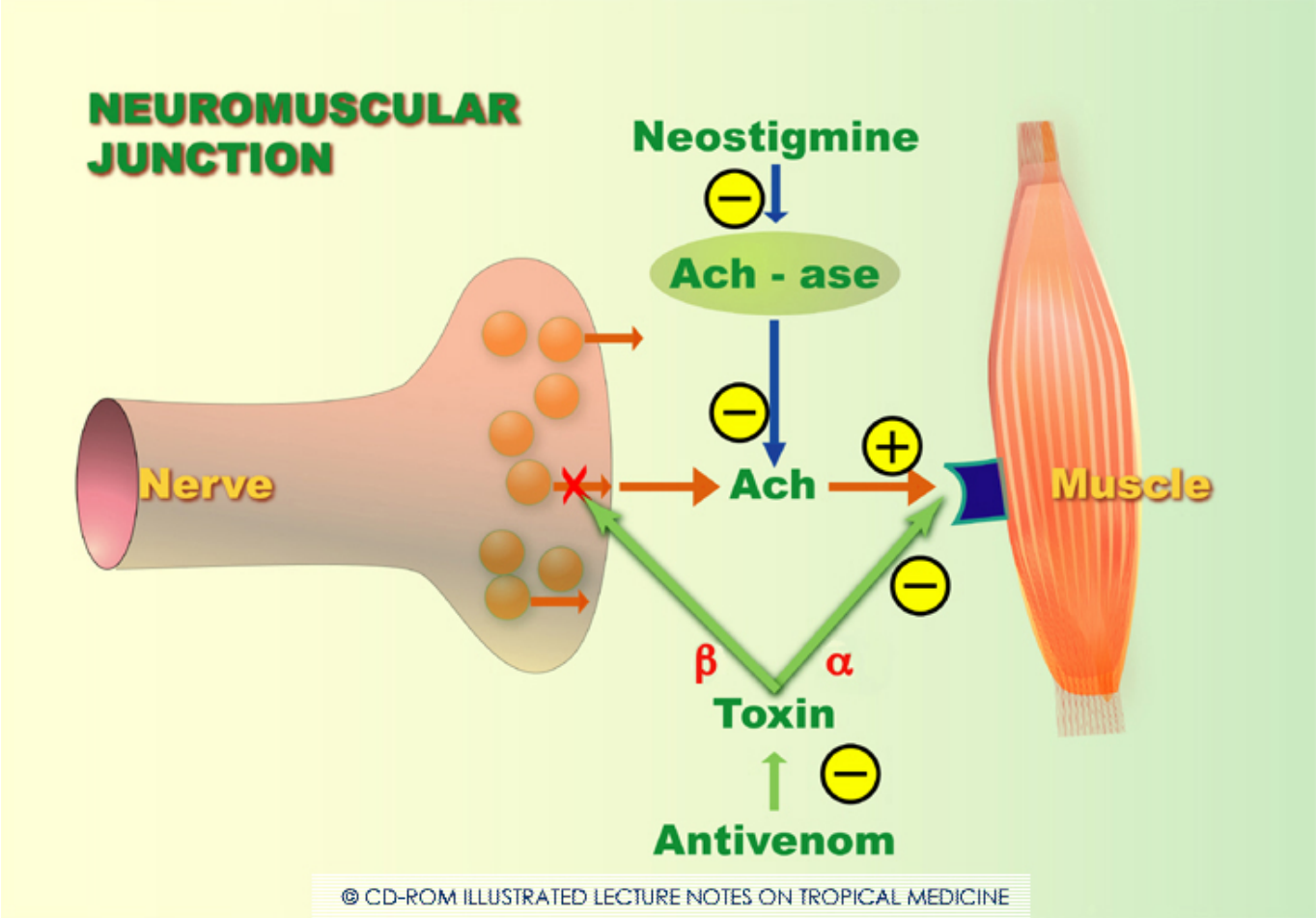
Mode of action of phospholipase A1, A2, C and D on cell membrane phospholipids. Several

snake venom components have phospholipase A2 activity. Copyright ITM

Enzymes which help the snake to digest its prey are often cytotoxic for man. Proteolytic enzymes have a trypsin-like activity. Hyaluronidase splits acidic mucopolysaccharides and promotes the distribution of venom in the extracellular matrix of connective tissue. Snake venom often contains various phospholipases A_2. These are esterolytic enzymes which break down membrane phospholipids. This causes cellular membrane damage ("lyso", lysis: destroy). Certain venom components have phospholipase C activity. In humans, all these enzymes cause oedema, blister formation and local tissue necrosis.Myotoxins are present in sea snakes and Australian elapids, as well as in *Bothrops, Crotalus, Naja* and certain colubrids (*Philodryas* sp). They bind to potassium or calcium channels on muscle membranes and provoke massive rhabdomyolysis.

Snake venom, paralysis

Neurotoxins are divided into several subgroups. The venom of all elapids contains alpha-neurotoxins. They act on the post-synaptic nicotinic acetylcholine receptors of the motoric end-plate. With regard to their activity on the neuromuscular junction, the alpha-neurotoxins can be compared with curare or with the autoantibodies in myasthenia gravis. They block the stimulus transmission from nerve cell to muscle and cause paralysis. The postsynaptic effects are reversible with antivenom and neostigmin.



Neurotoxic snake venom with presynaptic and postsynaptic components. Neuromuscular junction with acetylcholine and inhibition of acetylcholinesterase by neostigmine. Copyright ITM

A second subgroup are the presynaptic beta-neurotoxins. They inhibit recycling of acetylcholine and augment the action of the presynaptic alpha-neurotoxins. Presynaptic neurotoxins inhibit the fusion of the vesicles containing acetylcholine, with the nerve's membrane of the neuromuscular junction. Neostigmin will not be effective in these cases.

Snake venom, blood coagulation

Some components of certain snake venom interfere with blood coagulation. The diversity is staggering. It seems that nearly every step of the coagulation cascade, as well as the

fibrinolysis mechanism can be activated or inhibited by one or other component in snake venom.

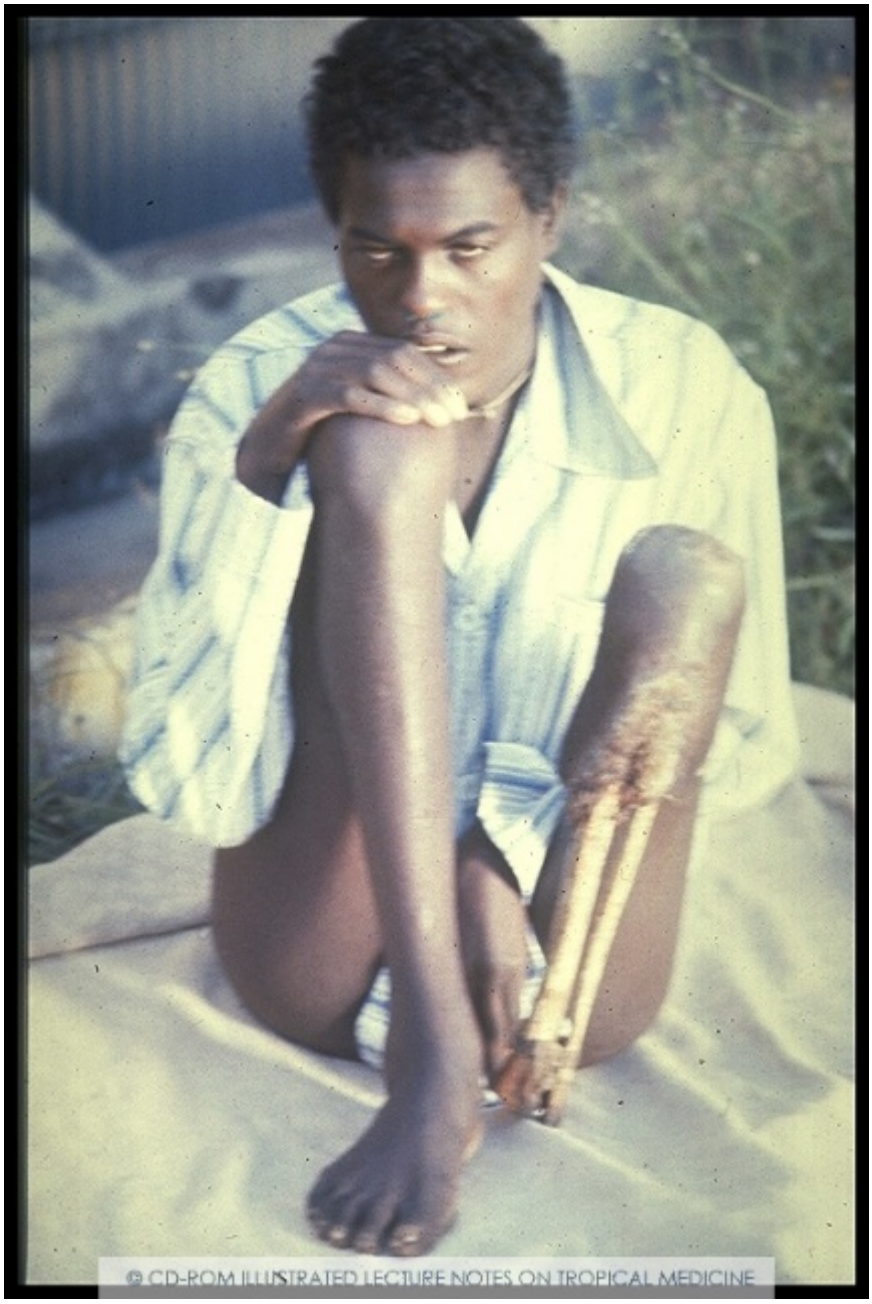
Clinical aspects

Bites by venomous snakes are not always accompanied by venom injection and symptoms of envenomation (so-called “dry bites”). Dry bites occur in 50 to 80% of bites. The interval between bite and possible death can vary greatly. In general it can be said that death comes most quickly after cobra bites and most slowly after viper bites. A 24-hours observation period after a snake bite without envenomation symptoms is recommended before a patient can be discharged with clear advice about alarm signs that require readmission.

Inappropriate pre-hospital treatment, such as prolonged arterial tourniquet, incisions at the bite site and sustained aspiration by suction pumps; can cause major complications. Clinical effects of venomous snake bites include vomiting, pain at the bite site and anxiety. This anxiety can lead to dizziness, sweating, shortness of breath or hyperventilation (not to be confused with neurotoxicity). Further, there are a number of specific problems:

Local cytotoxicity

The patient was bitten by Bothrops atrox, a venomous South American pit viper. Extensive skin necrosis for which skin grafts are needed. Copyright Alexander von Humboldt Institute, Peru.



Necrosis of the lower leg after a viper bite. Copyright ITM

Local cytotoxicity is characterised by local swelling and blister formation. Later necrosis can develop which can be promoted by arterial thrombosis, inappropriate tourniquet use and local excess pressure in the tissues. A compartment syndrome is probable if the tissue pressure amounts to >30 to 40 mm Hg. This is rare. Prophylactic fasciotomy is not

recommended. Local necrosis is primarily encountered with vipers, pit vipers and some elapids. Wound infections are not unusual and can aggravate local necrosis. Sometimes fangs or teeth break off and remain in the wound. Most tissue destruction develops in the first 3 days. Chronic ulceration, osteomyelitis or arthritis can follow a snakebite.

Cardiovascular toxicity

Cardiovascular toxicity can occur with viper bites. Hypotension can result from vasodilatation, extravasation, haemorrhages and direct myocardial toxicity. Venom-induced shock leads to a combination of hypotension, lactic acidosis, haemoconcentration and hypoproteinemia. The venom of mole vipers includes so-called “sarafotoxins”, peptides which strongly resemble mammalian endothelins and provoke profound vasoconstriction, including the coronary arteries. On the other hand, vasodilatation can occur due to ACE inhibition. Historically, the first angiotensin-converting enzyme inhibitor was discovered in the venom of a South American venomous snake, Bothrops jararaca. This formed the basis for developing captopril, the prototype of a very important class of drugs (Lasker Award 1999). The effect of some components of certain snake venom is comparable to an overdose of captopril, with serious hypotension as a consequence.

Haemostasis disturbances

Haemostasis disturbances are primarily seen with vipers, pit vipers, Australian elapids and colubrids.

The haemorrhagic tendency manifests itself as minor subcutaneous haemorrhages, bleeding gums, epistaxis, haematemesis, melena and/or bleeding from venipuncture sites. Haemorrhages in the adrenal gland and pituitary gland are found with bites by the Russell´s viper. This last symptom can be compared with Sheehan´s syndrome (post-partum pituitary necrosis). An acute Addison crisis can follow; which must be treated with steroids. Panhypopituitarism, secondary hypogonadism and diabetes insipidus can be late consequences.

Neurotoxic effects

Neurotoxic effects are a characteristic of elapids and sea snakes. The venom of the rare "berg adder" (*Bitis atropos* in South Africa and Zimbabwe) is also neurotoxic, which is highly exceptional for a viper.

Gradually ptosis develops, with vision impairment and eye muscle paralysis (ophthalmoplegia) and mydriasis. Afterwards hoarseness, dysphagia and pharyngeal paralysis develop producing drooling of saliva. The patient can sometimes have difficulty sticking out his or her tongue. Weakening of the neck muscles means the patient can appear to have a "broken-neck symptom". When the patient is drawn up by the hands from a supine position to 45°, the head hangs backwards if there is neck muscle paralysis. Ultimately the patient develops respiratory paralysis.

Neurotoxicity must be distinguished from the symptoms caused by anxiety. Some people who believe that they have been bitten by a snake (even if this is not the case), will hyperventilate, resulting in perioral or diffuse paresthesiae or rigidity and tetany of the hands (decrease of the free plasma Ca^{++}-concentration due to respiratory alkalosis). Others experience dizziness or syncopal tendencies including vasovagal syncope. A few people will become agitated, possibly with a series of bizarre complaints.

Muscle toxicity

Severe muscle pains and myoglobinuria develop. Cardiac arrhythmia can occur as a result of hyperkalaemia. Hyperkalaemia results as a result of rhabdomyolysis with the additional consequence of acute renal failure.

Renal toxicity

Kidney toxicity is often multifactorial. Hypotension/shock, diffuse intravascular coagulation with intrarenal micro-thrombi, myoglobinuria and haemoglobinuria are major causes of kidney damage.

Myoglobinuria as a result of rhabdomyolysis can cause acute tubular necrosis. Myoglobin is filtered through the glomeruli and causes renal vasoconstriction and tubular injury. The urine is dark and will test positive for blood. Massive haemolysis causes a similar picture. Another cause of renal failure is immune complex nephritis following administration of antiserum.

Eye lesions

Eye lesions can occur when a snake spits venom in the eyes (spitting cobras). The snake can spit its venom over distances of up to 3 meters. Burning pain, itching, oedema and eyelid spasms develop. In more than 50 % of cases there are corneal erosions, sometimes leading to blindness. After rinsing copiously with a non-irritating liquid, a local anaesthetic can be given to stop the pain and the blepharospasms. Afterwards an eye ointment containing antibiotics is applied. In case of bites by Burmese Russell´s vipers, chemosis can develop (conjunctival oedema), sometimes combined with subconjunctival haemorrhages. Chemosis reflects a generalised increase in vascular permeability and has a poor prognosis. Due to this increased capillary permeability, periorbital oedema, facial oedema and serous effusions can develop.

Clinic: rule of thumb

Local necrosis	vipers, pit vipers, elapids
Paralysis	elapids and sea snakes
Haemorrhages	vipers, pit vipers, colubrids, Australian elapids

However, there are exceptions to this rule of thumb:

e.g. *Naja nigricollis* (black-necked cobra): only haemotoxic

e.g. *Crotalus durissus terrificus*: primarily neurotoxic

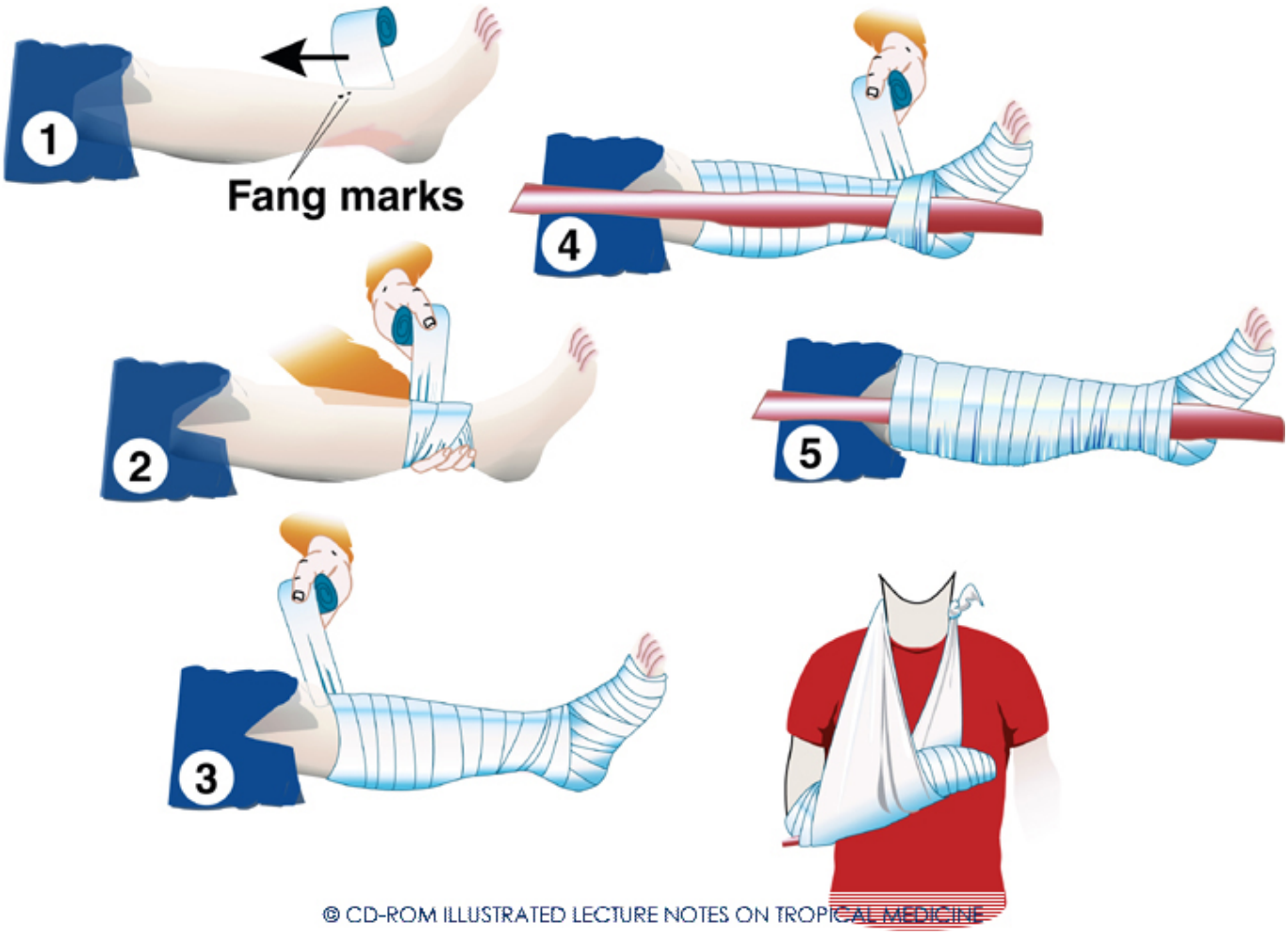
e.g. *Bitis atropos* (“berg adder”): primarily neurotoxic

Prognosis after snakebite – example

Chance of envenomation symptoms		
Rattlesnake bite	80%	
Sea snake bite	20%	
Russell´s viper bite	50%	
Malayan pit viper	50%	
Mortality		
Crotalus durissus terr.	75% if untreated; 12% with antiserum	
Echis carinatus	20% if untreated; 3% with antiserum	
Dendroaspis polylepis	almost 100% lethal if untreated	
Local necrosis		
Echis carinatus	9%	
Bitis arietans (puff viper)	36%	
Naja nigricollis (cobra)	71%	
Interval between snakebite and death		
Naja naja (cobra)	8h	(1/4-60h)
Crotalus species (rattlesnakes)	16h	(2h-26h)
Bungarus caerulus (Indian or common Krait)	18h	(3h-63h)
Vipera berus (European viper)	34h	(6h-60h)
Vipera (Daboia) russelli (Russell´s viper)	40h	(1/4h-9 d)
Calloselasma rhodostoma (Malayan pit viper)	60h	(5h-10 d)
Echis carinatus (saw-scaled viper)	5 d	(1-41 d)

Treatment

Initial



Australian compression and immobilization technique used in neurotoxic snake bites. A large (minimum 15 cm) elastic bandage is used. Peripheral arterial pulsations should remain present. The optimum pressure under the bandage lies probably between 55 and 70 mm Hg. Adapted from Wilderness Medicine 4rd edition, Mosby.

Device for the extraction of snake venom shortly after a bite, by applying underpressure over the bite site (inverted syringe). This technique is controversial. Copyright ITM, Dr Van den Enden

Victims are often afraid of dying. This anxiety must be reduced which is best done by showing a professional approach. The bitten body part should be immobilised, ideally with a splint as for a broken limb. Immobilisation reduces absorption of the venom, which delays systemic effects. A tight elastic bandage is wrapped around the bitten limb (slower lymph flow). It is important to use a large (15 cm) elastic bandage, tight enough to impair spread of

venom, but not too tight in order to avoid interfering with oxygenation. If a bite by a cytotoxic snake is involved, this might be contraindicated, as necrosis could increase locally. For immobilisation the elastic bandage and the **splint** are of equal importance.

They must be applied as soon as possible. A tourniquet is not useful and can aggravate the injuries through ischaemia. The sudden removal of a tourniquet in the case of cobra bites can cause an acute worsening of the symptoms (situation e.g. soon after arrival in the hospital). Dangerous procedures such as incision, sustained suction pumps on the skin, amputation of a finger, prolonged tourniquet, etc. should be avoided. The commercial "Extractor" device consists of a syringe and a vacuum cup. If used within three minutes after the bite, it can remove up to 2-30% of the venom (the device remains on the site for 30 minutes). However, the negative pressure of almost 1 atmosphere also causes massive oedema. Whether there is a clinical benefit is not established (it might be counterproductive).

Quickly sucking out (< 3 minutes after the bite) the bite wound can remove up to 50% of the venom, but the usefulness of this has not been demonstrated. With eye injuries, immediate and copious rinsing with any non-irritating liquid is indicated. If possible and if this can be done without danger, it is best to bring the dead snake along for identification (note carefully: the bite reflex continues long after death, even after decapitation!). Attempting to kill the snake is dangerous and could lead to further bites.

Correct species identification is often difficult, but it is of course important to have an idea of the family to which the animal belongs.

Treatment upon arrival in hospital

A **plasma expander** and **corticosteroids** such as methylprednisolone must be available. Antivenom is given as indicated (see below). In case of vomiting an anti-emetic can be administered. **Adrenaline** (adult 0.5 ml of 0.1 % SC or IM ; for a child 0.01 ml/kg) can be used against angioedema. Endotracheal intubation may be required. If shock and inadequate response to 1 to 2 litres of IV-Ringer or 0.9% saline solution (adult dose), IV albumin is administered. Albumin remains in the bloodstream longer. No salicylate derivatives (aspirin) should be used for painkilling, due to the risk of haemorrhage. **Tetanus vaccination** must

not be overlooked. Take blood for full blood count and cross matching (check for thrombocytopenia, spherocytosis, schistocytes, anaemia). Coagulation parameters must be determined if possible. In under-equipped labs it is often impossible to perform conventional coagulation tests. Yet it is essential to determine whether there are blood coagulation problems. For this 2 ml of blood is taken in a dry clean glass tube. Normally blood coagulates and forms a clot within 15 minutes. If the blood has still not clotted after 20 minutes, then there is a haemotoxin present. This simple test can be repeated. If there are coagulation problems, antivenom should be given, if needed followed by or simultaneously with cryoprecipitate or fresh frozen plasma. The thrombocytopenia which often develops is sometimes not corrected by antivenom.

Treatment if respiratory paralysis

In case of respiratory paralysis, the patient must be artificially ventilated. On average this lasts 1 to 4 days if no antiserum is given, but longer periods of paralysis do occur. Neostigmine -an acetylcholinesterase inhibitor – ensures that more neurotransmitter is present, so more stimulus transmission can take place. In this way, neostigmine reduces the effect of certain types of neurotoxins (cobra, mamba). For an adult 0,02 mg/kg and for a child 0,04 mg/kg is injected IM. Afterwards a neostigmine maintenance dose can be infused. Unpleasant side effects (diarrhoea, intestinal cramps, excessive salivation, sweating) are attributable to stimulation of the parasympathetic nervous system (muscarinic receptors). In order to prevent this, the anticholinergic atropine as antidote (0.6 mg IV every 4 hours) is also given. Atropine is a competitive inhibitor of the muscarinic receptors with constipation, dry mouth and mydriasis as side effects.

Treatment of hyperkalaemia

Hyperkalaemia occurs primarily in sea snake bites with severe rhabdomyolysis (see above). In case of cardiac arrhythmia, 10 ml 10% calcium gluconate IV can save a life. This does not reduce the kalaemia, but counters the effects of potassium on the heart. Treatment is coupled with 250-500 ml of a 10% glucose-infusion together with 10-20 units of fast-acting insulin. Sodium bicarbonate can also be given. Salbutamol or albuterol (b_2-agonists) can be administered via inhalation to lower the kalaemia, since they also cause a potassium shift to

intracellular. In case of persistent hyperkalaemia, peritoneal or haemodialysis is necessary.

Hyperkalaemia – treatment
Calcium gluconate
Insulin + glucose
$NaHCO_3$
$beta_2$-agonist, salbutamol
Kayexalate (no clear data on efficacy)
Dialysis

Treatment with antivenom

Stock of antisera in the Antwerp Zoo. Snake antivenom. In 2007, FAV-Afrique was available via this Zoo. Copyright ITM

Antivenom, to whom?

To whom should antivenom (antiserum) be administered? The presence of “fang marks” – wounds caused by the fangs – is not per se an indication since dry bites also leave “fang marks”. Many bites from nonvenomous or mildly venomous species result in discrete local tissue swelling. When the offending snake cannot be identified, giving antivenom for this situation will result in many patients receiving antivenom unnecessarily. Antivenom is administered to patients with local symptoms of envenomation, such as progressive important swelling, intense pain in and around the bite wound, haemorrhages which are difficult to stop, blister formation and/or when there are signs of systemic effects of the

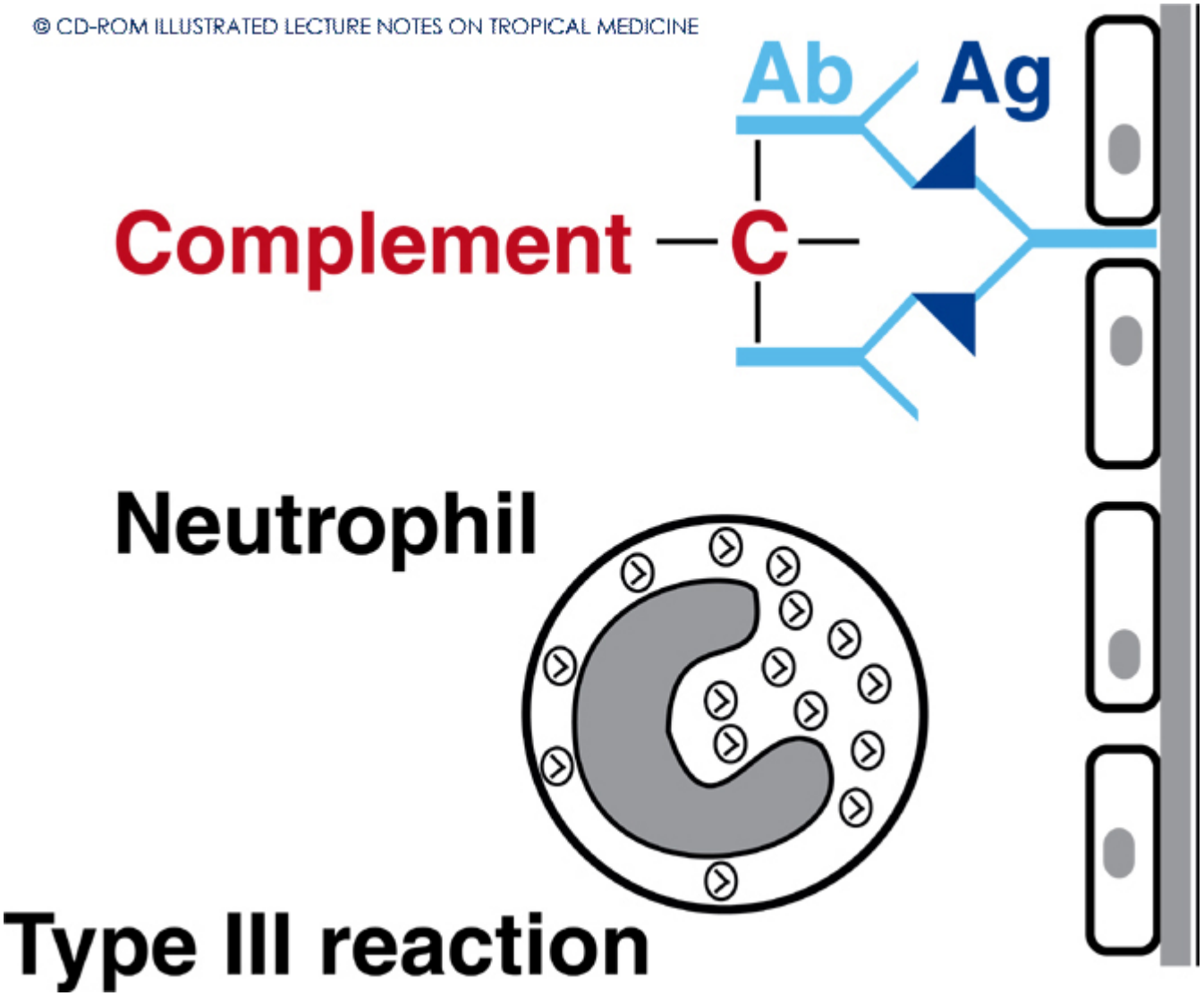
venom (muscle paralysis, blurred vision, difficulty in speaking, diffuse haemorrhages, respiratory problems, pulmonary oedema, shock, prolonged coagulation times). Antivenom is still useful up to more than one week after the bite. It is never too late to administer antivenom if there are symptoms of envenomation.

Antivenom, dose

The initial dose of antivenom to be administered to a victim is subject of debate. In clinical practice, the severity of the symptoms will determine the amount of antivenom given to a specific patient. For example: one vial of any Indian polyvalent antivenom represents only 4.5 or 6 mg of total neutralising capacity, depending upon the offending snake species. Each vial neutralises a minimum of 6 mg of *Naja naja* venom and *Daboia russelli* venom and 4.5 mg of *Bungarus caeruleus* venom and *Echis carinatus* venom. But a Russell viper injects an average of 63 mg of venom in a bite. If one would give 2 vials as loading dose, one can expect to neutralise about 20% of the venom. In this case, the loading dose should be around 10 vials. Even “low-dose” strategies recommend a minimum of 6 vials as a starting dose. The objective of additional antivenom is to neutralise any circulating unbound venom that was not neutralised by the initial dose. In hemotoxic bites, the dose is repeated if coagulation is not restored after 6 hours. The liver requires 6 hours to restore clotting factors. Additional antivenom before this period is potentially unnecessary. In case of neurotoxic bites, the antivenom can be repeated after 1 or 2 hours if the patient has not improved or if his condition is worsening. True reversibility of neurotoxic envenomation (detaching tissue-bound post-synaptic neurotoxins) is only possible within the first 1 or 2 hours. After that period, the role of antivenom is to neutralise unbound venom. Patients paralysed due to destruction of the presynaptic nerve terminals will respond much less to antivenom.

The treatment with antivenom is effective for problems of blood coagulation, shock and specific neurotoxicity. For other problems (nephrotoxicity, local necrosis and some paralyses) the effect is a great deal less spectacular. **Note: the same dose of antivenom is required in children, as the amount of venom injected is the same as in adults.**

Antivenom side effects



Immunological Type III reaction. Serum sickness. Copyright ITM

Antivenom which is prepared from horse serum, contains foreign proteins and frequently produces side effects. Anaphylaxis (IgE-mediated type I reaction), anaphylactoid reactions (not IgE-mediated, but via complement activation through protein aggregates in the antivenom) and serum sickness (immune complex or type III reaction) can develop. Anaphylaxis risk is higher in a patient who has previously been treated before with

antivenom (e.g. a snake hobbyist bitten on different occasions).

Soon after administration, ±20% of the patients develop itching, urticaria, fever, cough, tachycardia, nausea and/or vomiting. Sometimes there are quite serious bronchospasms. Antihistamines do not reduce the incidence or seriousness of these symptoms, in contrast to a low dose of adrenaline (0.25 ml SC of a 1/1000 solution). Most clinicians currently advocate no routine prophylaxis, but will have adrenaline, corticosteroids and antihistamines drawn up, so they are ready to treat an early reaction.

Serum sickness as a result of immune complexes develops in 30 to 90% of the patients. It manifests itself after 5 to 24 days (average 7 days). The frequency depends on the dose of antivenom administered. Fever, itching, joint pain and periarticular swelling, lymphadenopathy, mononeuritis multiplex and immune complex nephritis with albuminuria characterise this disorder. If serum sickness develops, steroids are given for 5 days.

Examples of antivenom:

CroFab® (= earlier CroTAb®, Protherics Inc.) was approved in October 2000 by the American FDA. The product includes Fab fragments against 4 North American venomous snakes: *Crotalus atrox* (Western Diamondback rattlesnake), *Crotalus adamanteus* (Eastern Diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake) and *Agkistrodon piscivorus* (Cottonmouth). This antiserum covers via cross-protection virtually all pit vipers in North America and several in Central America.

ViperaTAb® is a monovalent antiserum that is used for bites by *Vipera berus*.
ViperFav® (Aventis Pasteur Merieux) is a polyvalent, yet narrow-spectrum F(ab´)$_2$ antivenom against *Vipera berus, V. ammodytes* and *V. aspis*.

Venom detection kit

In Australia there has existed for many years a detection kit to identify venom and determine the snake species (Commonwealth Serum Laboratories). This is based on a two-step enzyme immunoassay in which the wells in the ELISA plate are coated with antibodies

against the various types of snake venom. Using a swab some venom is taken from the bite wound (in a person or a pet) and identified. This makes it possible to use specific antivenom. However, this method still has to be further developed for other parts of the world. A positive “venom detection kit” result per se is no indication for antivenom. The results must always be interpreted in the clinical setting.

Monitoring antivenom therapy

When an adequate quantity of antivenom has been given, the following response can be expected:

1. The patient rapidly feels better.
2. Gum bleeding stops within 15 to 30 minutes.
3. The coagulation test (20´ test) normalises within 3-9 hours, but the clinical haemorrhages stop much earlier.
4. The blood pressure normalises within an hour. Cardiac arrhythmias disappear.
5. Neurotoxic effects begin to disappear within 30 minutes; complete recovery takes much longer. Bites by kraits and sea snakes (presynaptic venom) improve slowly.
6. Active haemolysis and rhabdomyolysis stop within several hours. Urine afterwards returns to its normal colour.

Indications to repeat antivenom administration:

1. Persistence or recurrence of non-coagulability after 6 hours or new bleeding after 1-2 hours.
2. Worsening neurotoxic or cardiovascular signs after 1-2 hours.

Treatment of complications

Supportive therapy is necessary (fluid balance, analgesics, transfusion). Blood pressure, pulse, respiration, muscle functions, central venous pressure, urine production, blood coagulation and circumference of the bitten body part (leg, arm) must be monitored. Wound

infections including tetanus must be prevented and combated.

In case of compartment syndrome, fasciotomy should only be considered in extreme cases (tissue pressure >40 mmHg). It often does more harm than good. With local necrosis, operative intervention is necessary (wound debridement, skin grafts, amputation). Deep abscesses can develop and must be drained. After the acute episode scars are likely. Skin grafts might be needed. A Volkmann´s ischaemic contracture of the forearm can occur and requires intensive physiotherapy to regain some function.

Kidney failure can sometimes make (peritoneal) dialysis necessary. Strict fluid balance monitoring should be introduced in order to avoid any overload. With heavy myoglobinuria or haemoglobinuria an infusion of mannitol (200 ml of 20% over 20´) may be given and alkalinisation of the urine is advised. An adequate hydration of the patient must be maintained. Muscle rest is obligatory if rhabdomyolysis is suspected.

Shock

Shock can be the result of anaphylaxis, direct vasodilatation due to the venom, cardiotoxicity with or without arrhythmia, hypovolaemia (fluid shift to extravascular and/or internal/external bleeding), respiratory failure, acute Addison crisis or sepsis. Plasma expanders under continuous control of the central venous pressure (watch carefully for pulmonary oedema), dopamine and steroids may be necessary.

Errors in evaluation/treatment of snakebite

1. Not thinking of a venomous snake bite when confronted with a swollen ecchymotic limb
2. Cryotherapy and/or incision of the wound
3. Insufficient immobilisation of a bitten limb
4. Not looking for fang marks
5. Not keeping in mind that envenomation can change over the course of time, with clinical deterioration as a result
6. Only giving vasopressors to support the blood pressure, without giving IV fluid
7. Forgetting to check coagulation repeatedly

8. Delaying antivenom treatment if signs of envenomation are present, or thinking that it is too late to give antivenom
9. Administering a too low dose of antivenom
10. Not having adrenaline ready on stand-by
11. Applying an arterial tourniquet for a prolonged period
12. Performing a fasciotomy when not needed

Prevention

It is very rare for a snake to be spontaneously aggressive. Snakes tend to note the presence of a person through detection of vibrations. If given the chance they generally flee as a person approaches. Never attempt to corner a snake. Many bites occur when people are attempting to kill the animals. The risk of a snakebite increases if the victim is drunk, reckless or imprudent. However, people can accidentally tread on a snake on a path at night or in a field. More than 50% of venomous snake bites are on the feet or lower legs. Wearing sturdy, high-topped footwear in areas with increased risk is recommended. Some snakes follow their prey (generally small rodents) all the way into houses, and can bite a sleeping victim if they are surprised. Control of rats and mice around houses is not only beneficial in itself; but also reduces the number of snakes attracted to the area. The grass around the house must be kept short. There are specific high risk environments and professions. This encouraged the development of various experimental vaccines. Naturally they do not protect against the bite itself, but are designed to reduce mortality and morbidity. Sleeping under a bednet protects against snakebites, especially in these areas where snakes tend to enter houses when looking for their prey.

To the question whether people routinely need to carry preventive antivenom when travelling in remote areas, the answer is “no”. The chance of incurring a venomous snake bite with envenomation is low. Furthermore antivenom is not a harmless product, it is expensive and must be stored in specific conditions. Taking a couple of elastic bandages along is recommended. These can also be used for other purposes.

Antisera: useful information

- MAVIN (Münich Antivenom Index) available via: http://www.toxinfo.org/antivenoms/

- http://www.who.int/bloodproducts/snake_antivenoms/en/
- For Belgium: Antigif centre Brussels: tel 070.245.245. Usually antivenom against European vipers (Viperfav) should be available.

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