

Update Le point

Articles in the *Update* series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.

Les articles de la rubrique *Le point* fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.

The management of snake bite*

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The present article reviews current knowledge on the epidemiology, pathophysiology, and treatment of snake bite, with particular reference to the situation in developing countries. There is little reliable information on the incidence of snake bite in many parts of the world, and epidemiological studies are needed, using enzyme-linked immunosorbent assay to identify and quantify serum levels of venom antigen and antibody. The pathophysiology and clinical features of envenoming by medically important snakes are discussed. Antivenom, if used correctly, can reverse systemic poisoning even if given days after the bite. It is therefore wise to wait for the appearance of signs of systemic poisoning before administering antivenom, rather than using it routinely. WHO has designated the Liverpool School of Tropical Medicine as a Collaborating Centre for the Control of Antivenoms, and this Centre now holds a collection of reference venoms from several important snake species. Characterization of these and of standard antivenoms should significantly improve the management of snake bite throughout the world.

Most snake species are nonvenomous, have no fangs, and belong to the colubrid family; a few colubrids are technically venomous, having a venom gland connected to a solid fang at the back of the mouth. Bites from back-fanged colubrids are usually harmless to man, but with some species, such as the African boomslang, *Dispholidus typus*, serious and even fatal poisoning has occurred in snake handlers. The three families of venomous front-fanged snakes are the elapids, vipers, and sea snakes. Elapids are land snakes with short non-mobile fangs 3-5 mm long in adults; they include cobras, mambas, kraits, coral snakes, and the Australasian venomous land snakes. Vipers have mobile fangs 10-30 mm long which are easy to see when erected but difficult to recognize when folded back against the upper gum. Vipers are subdivided into crotalids or pit vipers, which have heat-sensing pits between eye and nose, and viperids which do not have these pits. Viper bites in man are much more common than elapid bites, except in Australasia, where vipers do not occur naturally. Sea snakes have very short immobile fangs and flat, rudder-like tails. Sea-snake bites occur among fishing folk of Asian and Western Pacific coastal areas.

There are over 400 different species of front-fanged snakes but only a few are known to be of medical importance. The foremost medically important vipers in developing

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countries are *Bothrops atrox* (Central and South America), *Bitis arietans* (Africa), *Echis carinatus* (Africa and Asia), *Vipera russelli* (Asia), and *Agkistrodon rhodostoma* (south-east Asia). In a few restricted areas of Africa and Asia, cobra bites are common; bites by mambas (Africa) and kraits (Asia) are rare. The carpet or saw-scaled viper *E. carinatus* can justifiably be labelled the most dangerous snake in the world to man; because of its wide distribution, abundance in farming areas, good camouflage, irritability, and toxic venom, it causes more deaths and serious poisoning than any other snake.

EPIDEMIOLOGY OF SNAKE BITE

Snake bite statistics based on hospital records in developing countries are often fallacious because most victims prefer to be treated by a traditional healer and do not go to hospital. A high incidence of snake bite is often related to the prevalence of one particular snake species, for example, *E. carinatus* in West Africa, Pakistan, and north-west India, *A. rhodostoma* in south-east Asia, and *V. russelli* in Burma and other areas of Asia. Adjacent to these regions of high snake prevalence, there may be similar terrain where the snake species is rare or absent and snake bite is correspondingly uncommon. A prospective 3-year study based on hospital cases in Malaysia confirmed that snake bite is mainly a rural and occupational hazard, most bites occurring in males during daylight, when more people are exposed to risk. The severity of poisoning showed no significant variation with the time of the bite (during the day or after dark), the part of the body bitten, the age of the victim, or the breeding habits of the snakes.

Enzyme-linked immunosorbent assay (ELISA) now permits reliable identification and sensitive quantification of venom antigen and antibody.^a The latter is an important adjunct to epidemiological studies since it provides objective evidence of the relative frequency of envenoming by various species. Natural venom antibody has been detected in the sera of patients within one week of envenoming. The antibody titre rises to a maximum in about a year and then falls to low levels by 3 years, although it may still be detectable 40 years after the bite. Administration of therapeutic antivenom reduces but does not necessarily abolish the development of natural humoral venom antibody. In Nigeria, rural surveys complemented by ELISA confirmed the medical importance of *E. carinatus*, but also demonstrated envenoming by other species. From these studies, a yearly total of almost 10 000 deaths were estimated.

A survey of the Waorani tribe, a jungle group totalling 612 people in Ecuador, revealed that 4.9% of all deaths were attributable to snake bite. Serum samples from over one-third of this tribe showed that 78% had venom antibody, chiefly against *Bothrops* species. Mouse protection tests indicated that these natural antibodies could neutralize venom and this finding was clinically confirmed in Nigeria when two patients recovered unusually rapidly from a second bite with initially severe poisoning. These applications of ELISA encourage further study of active immunization for small communities at high risk of snake bite.

An important finding from these and other epidemiological studies is that over half the human victims bitten by potentially lethal venomous snakes escape with only slight or even no poisoning. This is reassuring for the clinician, but it should be borne in mind that snake bite in its early stages can be unpredictable and all victims should be observed closely to assess the severity of envenoming and to ensure rational and effective treatment.^b

^a THEAKSTON, R. D. G. The application of immunoassay techniques, including enzyme-linked immunosorbent assay (ELISA), to snake venom research. *Toxicon*, 21: 341-352 (1983).

^b REID, H. A. Animal poisons. In: *Manson's tropical diseases*, 18th ed., London, Balliere Tindall, 1982, pp. 544-566.

PATHOPHYSIOLOGY

Snake venoms contain a complex mixture of enzymes, peptides, and proteins of low relative molecular mass with specific chemical and biological activities; caution should be exercised when extrapolating experimental work in this field to the clinical management of snake-bite patients.

Local swelling

Most viper venoms in man act predominantly on the haemostatic system, particularly on capillary endothelium. Locally, this causes swelling, which starts within minutes of the bite. Massive swelling of the whole limb may develop in the ensuing 48–72 hours and is often misinterpreted as resulting from venous thrombosis or bacterial infection from the mouth of the snake. The latter is discounted by the rapidity of swelling; necropsy in such cases has revealed patent veins and no evidence of bacterial involvement. Experimentally, haemorrhage may be the result of rhexis at endothelial gaps or diapedesis through intercellular junctions. The exudation may consist of plasma or whole blood, and in the latter case there is subsequent discoloration of the skin. Some haemorrhagic venom toxins have mainly local effects in man, while others are chiefly systemic. In bites by the European adder *V. berus*, spontaneous systemic bleeding is rare whereas discoloration of the bitten limb is typical; the reverse is the case with *E. carinatus* envenoming.

Local necrosis

Local necrosis with viper bites often appears to be mainly ischaemic, developing slowly over weeks and presenting like dry gangrene. Local effects with cobra bites are different; swelling does not usually appear until 2–3 hours after the bite, but necrosis develops rapidly, presenting like wet gangrene within a few days, with a putrid smell. Presumably, it is caused mainly by a direct cytolytic venom effect. As with burns, the dead tissue provides ideal culture for secondary growth of anaerobes, hence the importance of early excision.

Systemic absorption

Viper venoms are usually absorbed via the lymphatics, more slowly than are elapid venoms with their lower relative molecular masses. Preliminary studies using ELISA in patients bitten by *E. carinatus* indicated that serum concentrations of venom antigen rose to a maximum 6–24 hours after the bite, and at this time the urine contained significant amounts of venom. In contrast, when a patient was envenomed by the Australian elapid *Pseudonaja textilis*, ELISA showed peak serum levels within 30 minutes of the release of a compressive bandage (2 hours after the bite).^c This study gave convincing clinical validation of the use of a compressive bandage to delay venom absorption.

Nonspecific early systemic symptoms

With bites of some vipers, such as *V. berus*, *V. xanthina* (south-west Asia), some rattlesnakes, and Australian elapids, very early systemic symptoms are common. Within a few minutes of the bite, vomiting, headache, abdominal pain, explosive diarrhoea, and

^c PEARN, J. ET AL. First aid for snake bite. Efficacy of a constrictive bandage with limb immobilization in the management of human envenomation. *Medical journal of Australia*, 2: 293–295 (1981).

collapse with unrecordable blood pressure can occur. These features usually resolve spontaneously within 30–60 minutes, suggesting activation of the kinin system followed by inhibition of bradykinin, rather than a direct venom effect.

Shock

Shock starting later is the main cause of death in viper bites. Hypovolaemia from loss of blood and plasma into the swollen limb is one causal factor. However, shock may develop before the limb becomes grossly swollen, and intravenous antivenom can be dramatically beneficial in these patients without any significant change in the size of the bitten limb. Further important causal factors in the shock may be pulmonary intravascular clotting (which can be rapidly relieved by powerful natural fibrinolysis), pulmonary oedema, and cardiac effects as evidenced by abnormal electrocardiogram (ECG) and serum enzyme levels.

Spontaneous haemorrhage

Spontaneous oozing into a vital organ, especially the brain, is often lethal and may be delayed up to several days after the bite. Clinical research in *E. carinatus* victims has confirmed that antivenom can temporarily stop abnormal bleeding and restore clotting to normal; although ELISA no longer detected venom antigen in the sera of these patients, high venom concentrations were still found in blister aspirate at the bite site. It is likely that local swelling and blebs constitute a venom depot to which antivenom has poor access and from which further venom may be released to cause delayed effects. Breach of the blood-brain barrier by venom antigen was demonstrated by ELISA 48 hours after an *E. carinatus* bite causing subarachnoid haemorrhage; 20 ng/ml *Echis* venom was found in the cerebrospinal fluid. The patient subsequently recovered completely.^d

Effects on coagulation

Spontaneous oozing is caused mainly by direct endothelial damage by a venom component (haemorrhagin) which does not affect coagulation. The coagulation defect, defibrinogenation, caused by certain viper venoms, is not the primary cause of bleeding. This is shown by the following observations:

1. Abnormal bleeding occurs with viper venoms that do not affect coagulation.
2. With coagulant venoms, bleeding can precede change in coagulation.
3. Complete defibrinogenation can persist for days without spontaneous bleeding.

Procoagulant crotalid venoms act directly on fibrinogen, usually splitting off only fibrinopeptide A, and this activity is not affected by heparin. Viperine venoms and some Australian elapid venoms act indirectly by activating prothrombin or factor X; heparin inhibits this activity. These venom effects constitute *in vitro* procoagulant activity. *In vivo*, if the venom dose is large, as, for example, when attacking prey, massive intravascular clotting stops the circulation and causes very rapid death. With smaller doses of venom, such as those injected subcutaneously into human victims, there is a continual action on fibrinogen, producing a fibrin more susceptible to lysis than natural fibrin and resulting in non-clotting or poorly clotting blood because of absent or very low levels of fibrinogen.

^d REID, H. A. Enzyme-linked immunosorbent assay (ELISA) of snake venom antigen and antibody. *Postgraduate doctor (Middle East)*, 6: 274–280 (1983).

Non-clotting blood is a simple, very sensitive bedside test of systemic envenoming, giving warning that abnormal bleeding may follow. Non-clotting blood can indicate the species causing the envenoming; for example, *E. carinatus* envenoming in Africa causes non-clotting blood whereas the puff adder, *B. arietans*, does not. This can facilitate the choice of appropriate antivenom and can be used to monitor antivenom response.

Other haematological effects

Increased fibrinolytic activity usually follows procoagulant envenoming. There is increased lysis of unheated plates by patients' plasma euglobulin, probably as a result of release of plasminogen activator secondary to venom effect. Inhibitors such as aminocaproic acid have been observed not to benefit the patient. Although venoms may have anticoagulant effects *in vitro*, these are of no clinical importance in man. Associated with viper bite haemorrhage, the platelet count may be depressed although it is often normal. The low platelet count is probably caused by consumption of platelets in the repair of endothelial damage from haemorrhagin activity.

A polymorph leukocytosis is common in all types of envenoming and a white blood cell count or even an inspection of the margins of a stained thin blood film can give an early clinical indication of severe poisoning. Both viper and elapid venoms may have haemolytic activity *in vitro*, but abnormal haemolysis is rarely of clinical importance except perhaps as a factor in renal failure.

Neurotoxic effects

The systemic effects of elapid venoms are predominantly neurotoxic, causing a selective neuromuscular block affecting mainly the muscles of eyes, tongue, throat, and chest, leading to respiratory failure in severe poisoning. Experimentally, the myoneural block by some venom fractions can be partly or completely reversed by neostigmine. Observations in patients have been conflicting,^e and further evaluation of the use of edrophonium followed, if indicated, by neostigmine is being carried out.

Myotoxic effects

Although sea-snake venoms appear to be neurotoxic in animal experiments, the effects in man are primarily myotoxic. This is a diffuse, generalized effect on skeletal muscles; local effects on muscle at the site of the bite are minimal. Many venom fractions obtained in experiments have been labelled as myotoxins because they cause local muscle damage when injected into animals. In human subjects envenomed by sea snakes (and by some Australian elapids) the clinical and pathological findings are typical of generalized myopathic lesions in skeletal muscle.^f

Cardiac effects

Cardiovascular depression with sweating, cold extremities, tachycardia, hypotension, and ECG changes (usually in the ST segment or T-wave) may be prominent in severe cobra bites (*Naja* sp.) and some viper bites — *V. berus*, for example. Raised serum creatine phos-

^e WARRELL, D. A. ET AL. Severe neurotoxic envenoming by the Malayan krait, *Bungarus candidus* (Linnaeus): response to antivenom and anticholinesterase. *British medical journal*, 286: 678-680 (1983).

^f See footnote b, page 886.

Table 1. Main clinical features of snake bite

Snake	Percentage capable of poisoning	Effects of poisoning		Approximate natural mortality (%)	Average time to death (h)
		Local	Systemic		
Elapids	50	Slow swelling, then necrosis with Asian cobras, African spitting cobras. Usually no local effects with other elapids.	Neurotoxic effects: ptosis, glosso-pharyngeal palsy. Respiratory paresis. Cardiac effects.	10	5–20
Sea snakes	80	None	Myotoxic effects: myalgia on moving, paresis, myoglobinuria, hyperkalaemia.	10	15
Vipers	30	Rapid swelling. Necrosis in 5–10% (some vipers only).	Vasculotoxic effects: abnormal bleeding, non-clotting blood (some vipers only), shock.	1–15	48

phokinasase in such cases suggests a direct cardiotoxic effect. As might be expected, in severe poisoning from bites of sea snakes and some Australian elapids, potassium released from damaged skeletal muscle can cause death by hyperkalaemic cardiac arrest.

Renal failure

Acute renal failure may follow serious poisoning by all three types of venomous snake—viper, elapid, and sea snake—and appears to be unusually common after *V. russelli* bites. It usually becomes clinically evident towards the end of the first week after the bite. As with shock, the pathogenesis is probably multifactorial and includes ischaemia, haemoglobinuria, myoglobinuria, and direct nephrotoxic venom effects.

Exceptions

There are notable exceptions to the arbitrary classification of vipers as vasculotoxic, elapids as neurotoxic, and sea snakes as myotoxic. Some vipers, such as the rattlesnake, *Crotalus durissus*, have mainly neurotoxic effects. Many viper venoms, such as *B. arietans*, *B. gabonica* and *Causus* spp. in Africa, do not affect clotting in human victims. The African spitting cobra *Naja nigricollis* causes local necrosis and neurotoxic signs have not been observed. Some Australasian elapids are myotoxic; others can cause significant haemorrhage and non-clotting of blood in addition to neurotoxic effects.

CLINICAL FEATURES

The clinical features of snake bite are summarized in Table 1 and have been detailed elsewhere.⁸ A large number of snake-bite victims have little or no poisoning despite bites by potentially lethal snakes. However, envenoming can be unpredictable in the early stages,

⁸ See footnote b, page 886.

and fright can be an important factor in rural areas. In bites by most viper species, local swelling is an invaluable early index of envenoming. Systemic signs of viper envenoming are sometimes evident within 20 minutes, but may not appear until several hours after the bite. Systemic signs start 15 minutes to 5 hours after bites from Asian cobras, but up to 10 hours has been recorded with Australian elapid bites. If there are no myalgic features within 2 hours of a sea-snake bite, serious poisoning can be excluded.

Swelling with viper bites usually resolves completely in 2–3 weeks, occasionally it can take 2–3 months, and in exceptional cases the limb may remain permanently swollen. Healing of local necrotic lesions requires at least a month and may take over 6 months, even with expert surgical attention. Viperine shock and abnormal bleeding generally resolve within a week in patients surviving without antivenom, but coagulation changes can persist for over 3 weeks. In the absence of antivenom, elapid neurotoxic features usually resolve in a few days, but exceptionally may persist for 2–3 weeks. In contrast, full recovery from the myotoxic effects of sea-snake envenoming may take several months if effective antivenom is not given.

FIRST-AID AND PREHOSPITAL TREATMENT

Reassurance of the patient is important; if available, aspirin or alcohol in moderation are helpful for their calming effects. The site of the bite should be wiped but not incised because incisions can aggravate bleeding, especially in bites causing non-clotting blood, damage nerves and tendons, introduce infection, and delay healing. If evacuation to a hospital or clinic with antivenom facilities will take over 30 minutes, an absorption-delaying compressive bandage, preferably crepe, should be applied firmly, as for a sprain, over the bite site and up the whole limb. The bandage should not be released during transit. If the snake has been killed it should be taken, without handling, to hospital. During transit the body generally and the bitten limb in particular should be moved as little as possible, to minimize the spread of venom.

DEFINITIVE TREATMENT

In many tropical countries with poor transport facilities, paramedical staff in rural clinics can be trained to undertake definitive treatment, including successful antivenom therapy, of most snake-bite patients. An adequate supply of effective antivenom is essential, or the local community will quickly lose confidence in orthodox medical treatment. Except for cases in which there is no possibility of significant poisoning the patient should be carefully observed until at least the next day. The following items should be monitored and charted:

1. Hourly blood pressure, pulse rate, respiration rate;
2. Swelling (circumference at bite site compared with the unbiten limb);
3. Abnormal bleeding (at injection sites, gums, old wounds, etc.);
4. Blood clotting, haemoglobin, leukocyte count;
5. Local necrosis, if relevant (extent of blisters and skin darkening, putrid smell);
6. *In severe poisoning*, urine output and specific gravity, blood urea;
7. *In elapid bites*, neurotoxic features such as ptosis;
8. *In sea-snake bites*, myalgic pains, myoglobinuria, neurotoxic features;
9. Daily electrocardiogram and aspartate aminotransferase or creatine phosphokinase, if possible (more often if hypotension persists).

General measures

If a tourniquet or compressive bandage has been applied, it should be released. After cleansing, the site of the bite should be left uncovered; local dressings increase secondary infection and oozing soon stops after effective antivenom therapy. If a lower limb has been bitten it should be elevated on a pillow; if an upper limb has been bitten it should be rested in a sling.

Necrosis

Blisters should be left undisturbed to break spontaneously; they will then heal quickly providing there is no underlying necrosis. Cryotherapy aggravates necrosis. Antibiotics are not helpful unless and until local necrosis is clinically evident. In this case, sloughs should be excised. Necrosis is usually confined to the subcutaneous tissues; tendons and muscles are rarely involved, even though muscles may appear necrotic, and excision should be avoided. At this stage, antimicrobial drugs (such as metronidazole) given systemically may be helpful and skin grafting should be carried out early rather than late.

Fasciotomy

Fasciotomy rarely benefits and may permanently harm snake-bite patients. It should be obvious that it is contraindicated in patients with non-clotting blood. Massive local swelling usually resolves very satisfactorily after adequate antivenom treatment. Muscle necrosis of the anterior tibial compartment syndrome type is exceedingly rare in snake bite. The decision to use fasciotomy should be based on objective assessment of impaired blood flow using, e.g., ultrasound; clinical signs can be misleading in intensely swollen limbs.

Pain

Pain is rarely a problem once the patient has received an injection (placebo or antivenom, if indicated). For the first night, mild analgesics may be needed but morphine is virtually never required.

Heparin

Heparin does not help patients with coagulation defects and, indeed, may aggravate bleeding. Fibrinogen infusions do not help because the fibrinogen is rapidly "consumed" by unneutralized venom and the resultant degradation products can aggravate bleeding. In contrast, coagulation returns permanently to normal within a few hours of adequate antivenom treatment. Depressed platelet counts may take several days to reach normal levels, but this appears to be of no clinical importance.

Blood transfusion

Blood transfusion can help in the treatment of viperine shock, especially if the victim was anaemic before the bite, or if effective antivenom is not available. A controlled trial showed that prednisone helped neither local nor systemic viperine poisoning; in local necrosis following Malayan cobra bite (*Naja naja sputatrix*), steroids could delay the

appearance of necrosis but did not lessen the final severity. However, steroids are useful for treatment of delayed (but *not* immediate) serum reactions.

Spitting cobra venom

When African (*N. nigricollis*) or Asian spitting cobra (*N. n. sputatrix*) venom enters the eyes, a very painful reaction results; (the venom is not absorbed sufficiently to cause systemic symptoms). The patient's head should be rapidly immersed in water, and the patient told to blink; the venom will thus be quickly diluted and no further ill effects should ensue.

Respiratory insufficiency

Patients with glossopharyngeal palsy in elapid or sea-snake bite poisoning should be nursed in the prone position to minimize the risk of inhaling vomit or secretions. Endotracheal intubation and artificial respiration may be required briefly. There is a need for further evaluation of adjuvant treatment of certain elapid bites with edrophonium followed, if indicated by a dramatic improvement, by neostigmine.^h

Renal failure

In severe poisoning, low urine output coupled with "fixed" specific gravity indicates renal failure; this usually resolves with conservative treatment, although peritoneal dialysis may occasionally be needed.

Antivenom

Indications for use

In systemic snake-bite poisoning, specific antivenom is the most effective therapeutic agent available. If used correctly, it can reverse systemic poisoning even when given hours or even days after the bite. It is therefore not only safe but highly desirable to wait for clear clinical evidence of systemic poisoning before giving antivenom. It should not be given routinely in all cases of snake bite because it is expensive and can cause reactions, and its misuse (e.g., if given by the wrong route or in an inadequate dose) can quickly discredit antivenom therapy. A secondary and less certain application of antivenom therapy is in preventing or lessening local effects, especially local necrosis. Further research is urgently needed on this problem, but antivenom treatment should be considered in patients presenting within 4 hours of a bite by a known or suspected necrotizing snake such as *N. nigricollis* or *B. arietans* in Africa, and having swelling already spreading beyond the wrist or ankle.

Choice of antivenom

Monospecific antivenoms are more effective and less likely to cause reactions than poly-specific antivenoms. In Africa, non-clotting blood is a very useful indicator of *Echis* envenoming, for which an effective monospecific antivenom is sometimes available. In Australia, five different monospecific antivenoms are available for land snake bite and a capillary-tube ELISA kit has recently become available for determining the snake species involved and thus the appropriate antivenom to use. In most developing countries, only a

^h See footnote e, page 889.

single polyspecific antivenom is available as a rule and therefore the rapidity of immunodiagnostic tests is irrelevant to clinicians. Even if more potent monospecific antivenoms become available, the immunodiagnostic kits are unlikely to be of practical help unless their present high cost is substantially reduced. Nevertheless, there is great potential for the use of ELISA to obtain accurate retrospective diagnosis of snake species in the compilation of data on clinical patterns in bites by different types of snake.

Serum sensitivity tests

Serum sensitivity tests are unreliable and are not advisable prior to antivenom administration. Indeed, all patients given antivenom treatment should be regarded as likely to have a reaction. A known allergic history contraindicates antivenom unless the risk of death from envenoming is high. In that rare event, small amounts of epinephrine (0.5 ml of 1:1000 epinephrine solution) should be given subcutaneously before the antivenom administration and should be repeated if a reaction occurs. In routine antivenom therapy, epinephrine should be available in a syringe before the infusion is started. Initially, the intravenous drip should be slow (15 drops per minute), and at the first sign of an anaphylactoid reaction, should be temporarily stopped, and 0.5 ml of 1:1000 epinephrine solution should be injected intramuscularly. This is almost always quickly effective and the antivenom infusion can then be cautiously restarted.

Dose of antivenom

Depending on the potency of the antivenom being used, between 20 and 50 ml should be diluted in 3 volumes of isotonic saline. In severe poisoning (especially neurotoxic envenoming), 100–150 ml of antivenom would be a suitable initial dose. The dose for children is the same as that for adults. The speed of infusion should be progressively increased so that it is completed within 1–2 hours. If, by then, there has been little significant improvement, further antivenom should be considered. Monitoring, as detailed above, should continue at increasing intervals until the symptoms of envenoming have resolved.

FUTURE DEVELOPMENTS

Reflecting growing concern in tropical countries about the importance of bites by snakes and other venomous animals, a WHO coordination meeting was held in Zurich, Switzerland, in September 1979.¹ The meeting reviewed the epidemiology of snake bite, medically important snake species, clinical features and problems, characterization of venoms, and aspects of antivenoms such as standardization, distribution, clinical use, and reactions. It was decided to establish a collection of international reference venoms (IRVs), covering the following important snake species:

Echis carinatus (Iran)

Naja naja kaouthia (Thailand)

Notechis scutatus (Australia)

Trimeresurus flavoviridis (Japan)

Vipera russelli (Thailand)

Crotalus adamanteus (USA) (This has been replaced by *C. atrox*)

Bothrops atrox asper (Atlantic variant, Costa Rica)

Echis carinatus (Nigeria)

¹ *Progress in the characterization of venoms and standardization of antivenoms*. Geneva, World Health Organization, 1981 (Offset Publication No. 58).

The IRVs are to be characterized by collaborative studies, used for preparing international standard antivenoms, and will remain available for future standardization and research purposes.

The first six of these IRVs are now held at the WHO Collaborating Centre for the Control of Antivenoms, Liverpool School of Tropical Medicine, England, where characterization tests in accordance with the report have been carried out on these and other snake venom samples.^j *C. adamanteus* venom was included in the characterization tests, but the supply collected was insufficient to constitute an IRV and therefore *C. atrox* (USA) was substituted.

International standard antivenoms are currently being prepared, in accordance with the WHO report, against venoms of *E. carinatus* (Iran) and *V. russelli* (Thailand). Collaborative research is also proceeding on new methods of preparing antivenoms and of assessing their effectiveness by both laboratory and clinical tests. It is anticipated that these and other similar studies will significantly improve the understanding and management of snake bite throughout the world.

ACKNOWLEDGEMENTS

We thank Dr D. R. W. Haddock for examining the manuscript and Miss J. Taylor for typing the manuscript.

^j THEAKSTON, R. D. G. & REID, H. A. Development of simple standard assay procedures for the characterization of snake venoms. *Bulletin of the World Health Organization*, 61: 949-956 (1983).
