THE TREATMENT OF SNAKEBITE*

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No strict rules can be laid down for the treatment of snakebite, but frequent inquiries from colleagues and laymen indicate that some suggestions may be acceptable, even if they are over-simplified and open to criticism.

All patients suffering snakebite should be referred to a hospital or doctor for observation and treatment if necessary. The patient can be dismissed in cases of known viper bite if no signs of poisoning have appeared after a few hours. Patients bitten by an elapid snake (cobra, ringhals, mamba) or an unidentified snake should be observed for 24 hours. A patient suffering a suspected or known boomslang bite should be kept under observation for 3 or 4 days.

Serum treatment should take place under medical supervision whenever this is possible, but the suggestions presented in Table I were formulated with the assumption that the treatment before hospitalization would be carried out by a lay person. In the rare cases when the patient himself, or one of his companions, is medically qualified the scheme should be modified; e.g. intravenous rather than intramuscular injections would be recommended.

RECOGNITION OF A SNAKEBITE

Signs and Symptoms of Snakebite Poisoning

The boomslang injects a haemotoxic poison causing local pain, headache, nausea, vomiting, abdominal discomfort, bleeding from the mucosa and into the skin and a coagulation defect.

Viper bite, which is cytotoxic, causes severe local pain, swelling and induration, cellulitis, haemorrhages (ecchymoses) and necrosis. There is gross extravasation resulting in oligaemic shock, the cause of death in serious viper (puffadder) bite.[1]

Elapid bites are neurotoxic with little or no local pain or swelling. Dizziness, vomiting, restlessness, increased salivation, sweating, difficult swallowing and speech, ptosis, impaired eye movement, congested conjunctivae, respiratory distress and terminal failure are the usual signs and symptoms.

Identification of the Snake

It is always desirable to establish the identity of the offending snake, and it should be brought for identification if it has already been captured or killed. Identification may be of vital importance in countries and areas where only monospecific sera are available, but is less important in South Africa where the boomslang and the mambas are usually recognized and the other dangerous snakes are covered by a single polyvalent serum. Special attempts to capture or kill the snake should therefore not be made, since they would only result in more casualties.

Fang Marks

A person may claim to have been bitten when a snake has struck at him ineffectively, in which case there will be no puncture marks and he should receive no treatment but be calmed and kept under observation; the fang marks could be obscured by dirt or be invisible in the hard callus of a foot.[1]

An effective snakebite may result in a pair of clearly defined puncture wounds but there may be additional marks, in elapid bites sometimes caused by other teeth in the snake's jaws. There will be only a single puncture mark if only one fang has penetrated and in some cases the site of the bite shows only a scratch. Though highly variable, the appearance of the fang marks may help in establishing the type of offending snake and in estimating the likely severity of the bite, but it should be remembered that despite obvious puncture the snake may not have injected any venom, and that no venom may have entered a superficial wound, in which case no poisoning will result; on the other hand a mere scratch caused by a boomslang can have serious consequences.

A patient may present for urgent serum treatment with a wound on a bare foot which could have been caused by a snake; but no snake was seen and there was no immediate pain. If, on arrival for consultation (usually after some delay), there is no local change or systemic involvement indicating poisoning, such a patient should not be given serum but should be kept under observation for a while; he was probably injured by some object lying in the grass.

TREATMENT

Incision

Incisions are still occasionally recommended as a first-aid measure in certain types of snakebite, but most authorities, including Reid[2] and Chapman,[1] consider it a risky or useless procedure which therefore should be omitted. Furthermore, it may delay other and more important forms of treatment and add needlessly to the suffering of the patient.

Suction

Experimental studies with rattlesnake venom have demonstrated that substantial amounts of venom can be removed by suction in combination with incisions if applied early enough.[3,4] Similar experiments have not been carried out with African venoms but there is reason to believe that some venom may be removed in this way.[5] Applied to the fang marks without incision, suction can do no harm and gives the patient the reassuring feeling that something is being done. The use of the unguarded mouth may carry a slight risk for the person sucking and be the cause of infection in the patient, and suction is therefore best carried out with the mechanical device included in snakebite kits. Suction should not, however, supersede or take priority over other forms of treatment.

Tourniquet

The lethal toxins in elapid venoms are polypeptides with little or no local action, but, being rapidly absorbed directly into the blood stream,[6] they may exert their neurotoxic action soon after a bite. Consequently, the subcutaneous median lethal dose (LD_{50}) of elapid venoms for mice is only from 10% to 20% larger than the intravenous LD_{50}. The

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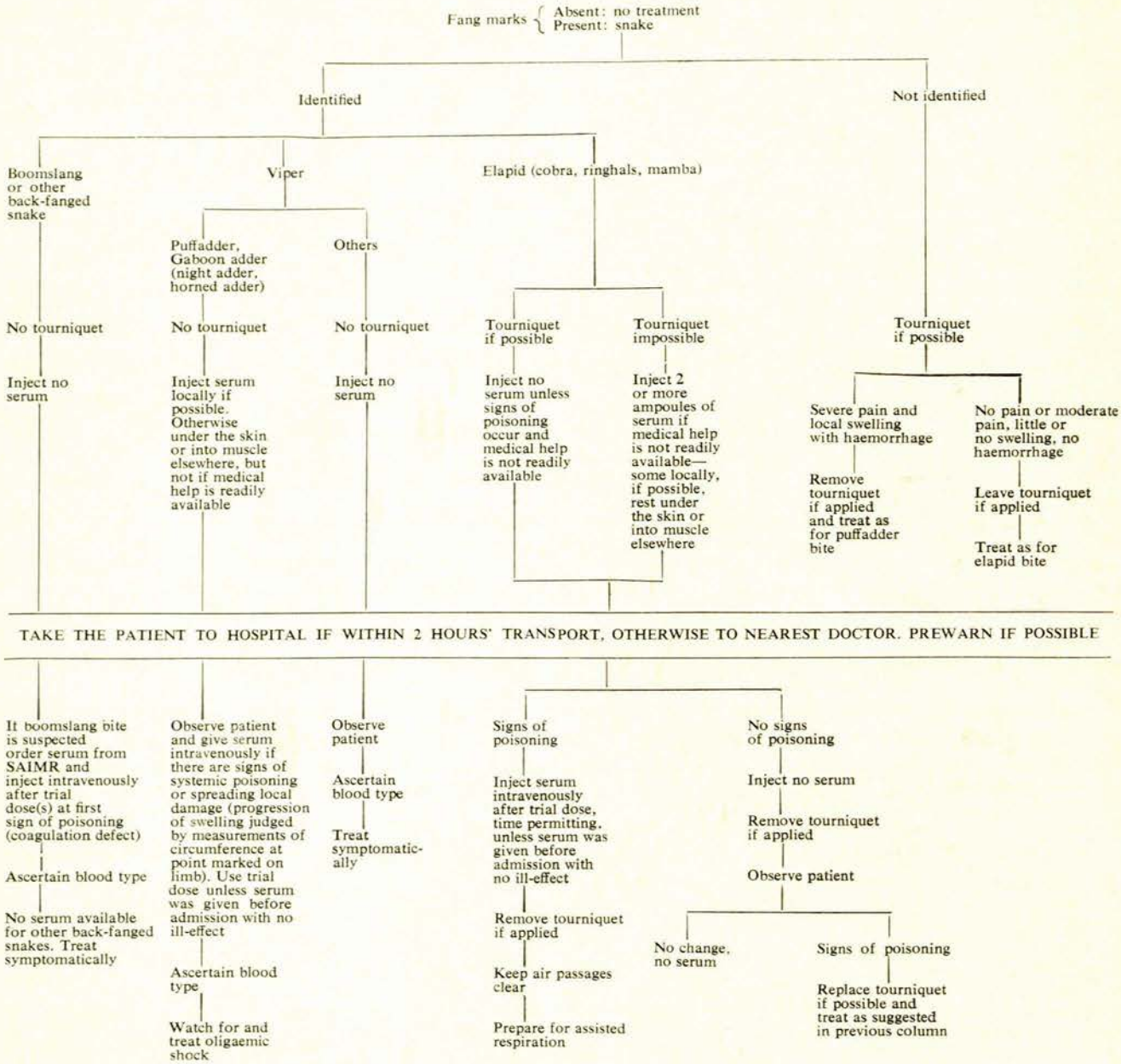
TABLE I. THE TREATMENT OF SNAKEBITE



lethal potency of viper venoms is about 8 times less when injected under the skin rather than into a vein, which is not surprising because the large molecular viper toxins are slowly absorbed via the lymphatics.[6] They cause devastating local tissue destruction, and according to Chapman[1] death due to viper bite is usually due to oligaemic shock.

A tourniquet is therefore of problematic value and not generally recommended in viper bite, whereas its value in delaying systemic poisoning with elapid venoms was demonstrated by the late Dr E. Grasset[7] and has been confirmed in mouse experiments (see Appendix 1).

The tourniquet should be arterial and placed on the upper arm or high on the thigh, depending on which limb is bitten. It should not be applied for more than 1½ hours and may be released for a few seconds every 30 minutes.[1] It should be discarded altogether as soon as an adequate dose of antivenom has been injected intravenously, but should be retained as long as possible without undue risk of permanent damage to the function of a limb when the serum has been given by any other route, thus allowing as much serum as possible to be absorbed before the venom enters the circulation.

Serum Treatment

The following sera are available for use in South Africa:

1. *Polyvalent antivenom* (Bitis, Naja, Hemachatus). This serum is specific against the venoms of the puffadder (*Bitis arietans*), the Gaboon viper (*Bitis gabonica*), the Cape cobra (*Naja nivea*) and the ringhals (*Hemachatus haemachatus*). It also neutralizes the venoms of the Egyptian cobra (*N. haje*), the spitting black-necked cobra (*N. nigricollis*), commonly called the *m'fesi*, the venom of the rare black-lipped forest cobra *N. melanoleuca*), and those of various non-African cobras. It has measurable paraspecific action on the venoms of our night adders (*Causus* species) and horned adders (genus Bitis), but it is disputable if serum should be used in case of bite by these lesser vipers and their names have therefore been placed in brackets in Table I. Neither this nor any other serum has any effect on the venom of the berg adder (*B. atropos*) and serum treatment in cases of berg adder bite is therefore pointless. Persons bitten by this snake have shown signs of neurotoxic poisoning (ophthalmoplegia) but have recovered without sequelae. Though experimental evidence is lacking, there is no reason to believe that any available serum will neutralize the venom of the burrowing adder (*Atractaspis bibroni*) and serum treatment is not justifiable.

Due to the adoption, some time ago, of additional immunization of the horses with mamba venoms, recent issues of this polyvalent serum have marked potency against the venoms of these snakes, and may be used as an emergency measure in cases of mamba bite although their mamba antivenom titre is not as high as that of the recommended specific mamba serum listed below.

2. *Polyvalent antivenom* (Dendroaspis). This serum is specific against the venoms of the green mamba (*Dendroaspis angusticeps*), the black mamba (*D. polylepis*) and Jameson's mamba (*D. jamesoni*), and has marked paraspecific action against the venom of the fourth African mamba, *D. viridis;* only the first two mentioned mambas are found in South Africa.

This serum may have some action on the venom of certain other snakes but should be reserved for use in cases of mamba bite.

3. *Boomslang* (*Dispholidus typus*) *antivenom.* This serum is not for general issue. A small freeze-dried stock is held at this Institute for issue to hospitals and doctors treating patients bitten by this particular snake. It cannot be expected to have any effect on the venoms of other snakes, back- or front-fanged. The slow onset of serious boomslang envenoming and the efficacy of the serum even after a considerable delay in treatment makes it possible for supplies to reach any part of the country in time if this Institute is notified at once.

The Route of Injection and Efficacy of Serum

The effect of serum in viper bite may not appear impressive when the results in hospitalized patients are surveyed[1]—possibly partly because most patients are admitted late and any serum administered before admission is not always given soon enough, by the best route, or in adequate dosage.

Laboratory observations and limited clinical experience leave one with no doubt that swift infiltration with serum of the site of venom introduction will either abolish or reduce the effect of viper venom. Local serum infiltration may, of course, not only be very painful but also inadvisable when certain parts of the body such as a digit are bitten.

Whether or not some serum is injected into or near the site of the bite, the bulk is usually injected elsewhere under the skin or into a muscle and not by the route through which it will reach its target with a minimum of delay, i.e. intravenously.

Working with rattlesnakes, Gennaro and McCollough[4] have recorded that about 86% of labelled antivenom administered intravenously may accumulate at the site of the bite within 2 hours after administration. Experiments in this laboratory have shown that small amounts of antivenom injected into the blood stream of guinea-pigs within 10 - 15 minutes after the venom injection will clearly reduce the size and severity of the local lesions caused by the injection of puffadder (*Bitis arietans*) venom into their shaven skin.

There is no particular reason to infiltrate the bitten site with antivenom in cases of bite by elapid snakes which have no local effect, but a local injection might possibly be more effective than injection into other parts, and the patient may feel comforted because to him it is the obvious site to choose.

The efficacy of specific serum given intravenously to patients with already established systemic elapid poisoning, often mentioned in the earlier literature, has recently been confirmed not only here,[3,8,9] but also in Asia[7] and Australia,[10] and is supported by the results of laboratory experiments (Appendix 2).

However, antivenoms are commonly injected under the skin or into a muscle, not only by the layman who cannot do otherwise, but also by doctors. What is the value of this?

For a given amount of serum the value will depend on the potency of the serum, on the rate of serum absorption, and on the amount of venom injected by the snake.

The potency of the sera mentioned above is high, and fairly constant from one batch to another. As far as the serum absorption rate is concerned, it is possible to determine the rate of increase in the blood-antibody concentration in human beings after a single large subcutaneous or intramuscular dose of diphtheria or tetanus antitoxin, which in their properties are akin to antivenom. Such experiments have shown that only about one-third of the injected antitoxin will have entered the circulation after 12 hours and that the maximum concentration in the blood will not be reached until 36 - 48 hours after the injection.[11]

Similar investigations cannot be carried out with antivenoms in human beings, but experiments in mice (Appendix 3) have shown that only about 16% of the injected antivenom had entered the circulation after 30 minutes, about twice as much in an hour, and the maximum concentration of circulating antibody was not reached until about 15 hours after the serum had been injected subcutaneously or intramuscularly.

The amount of venom injected by a snake in a bite is uncertain, but even if it is assumed that the average yield on milking a full-grown Cape cobra, about 120 mg.,[5] indicates the amount likely to be delivered in a naturally occurring bite, and if one may reason from mouse to man, one would expect (Appendix 2) that from 30 to 40 ml. of antivenom (the contents of 3 - 4 ampoules) given intravenously would be life-saving for human beings even after a considerable delay. But if, as in the mouse, about 30 times as much serum would have to be injected under the skin or into muscle to have the same effect (Appendix 3) then one might as well not inject any serum at all.

This attitude is probably too cynical. Some serum would be absorbed and could reduce the local damage caused by viper venom or delay death from elapid venom poisoning long enough for effective treatment to be instituted, as may have been the case in the mamba bite reported by Krengel and Walton.[8]

The Intravenous Dose

It is impossible to suggest a 'standard' dose, but, considering clinical data, the amount of a venom likely to be injected and its mode of action, and the potency of currently available antivenoms, the following doses are suggested:

The contents of 2 - 4 ampoules (20 - 40 ml.) should be given when bites by either the puffadder or the Gaboon adder necessitate intravenous therapy, which probably is superfluous in cases of bites by other vipers.

The contents of 3 or 4 ampoules (30 or 40 ml.) of the appropriate serum are needed in elapid bites treated before or soon after signs of systemic poisoning are apparent, followed by more serum if the response is unsatisfactory. The dose in advanced systemic poisoning should be 2 or 3 times as large.

The few patients so far treated with specific boomslang antivenom received the contents of 1 - 4 ampoules when poisoning was well advanced, and all survived.

The Dangers of Antivenom Treatment

Although the antivenoms discussed here are pepsin-refined globulins, delayed serum reaction (serum sickness) must be expected in some of the patients. It will occur in about 8% of treated Whites, whereas the expectation of serum sickness in pigmented patients is lower, which is fortunate because they are the main sufferers of snakebite. The patients should be warned about the possibility of serum sickness when they are dismissed, so that they can call for prompt treatment (antihistaminics, steroids) if necessary. Serious acute serum reactions are rare, and fatal reactions rarer still. In fact, the risk of fatal anaphylaxis must be considered minute compared with the risk to life or limb when a full bite has been inflicted by one of our dangerous snakes. Even so, antivenom should not be injected lightly and the usual rules for serum treatment should be followed as far as possible.

Except in cases of emergency, antivenoms should not be given in therapeutic dosage without a prior trial dose. Lay persons may have to omit it, but in the case of a fatal reaction a doctor might find himself in difficulties if, in the opinion of others, the circumstances would have permitted a cautious approach.

The trial dose is particularly important in patients with known hypersensitivity to horse serum or with a history of serious allergic manifestations (e.g. asthma or infantile eczema). Such patients should not be given antivenom if this is at all avoidable; if not, they should be tested subcutaneously with 0·1 or 0·2 ml. of serum diluted 1 : 10 or even 1 : 100 in sterile saline or water. Other patients may be tested with a similar volume of serum diluted 1 : 10, or even undiluted serum if a suitable diluent is not available. The patient should be under constant observation for at least 30 minutes and, needless to say, adrenaline should be at hand, already drawn into a syringe. Antihistaminics and steroids, and possibly coramine, may also be of value in the treatment of anaphylaxis. In the absence of signs of hypersensitivity, the full therapeutic dose can be given, but the patient must remain under constant observation.

The attending physician is left with a very difficult decision if the trial dose triggers off an anaphylactic shock. If in his opinion serum treatment is essential in order to save the patient's life, he can but wait for the patient to recover—in particular, for his blood pressure to return to a normal or reasonable value—then give another trial dose, observe again, and proceed as carefully as possible.

Luckily for the doctors, most patients have already received some serum without ill-effect before they arrive, which makes it possible to proceed without trial doses; this is not always realized.

It should be mentioned that a patient seen in a state of collapse after a snakebite may not be suffering from venom poisoning but may have reacted to injected serum, and he should be treated accordingly. Attention should also be called to the observation made by Reid,[2] that a state of semiconsciousness with cold clammy skin and rapid shallow breathing may be the result of fright, and is most effectively treated with a placebo injection.

General Management

The usual recommendation is to keep the patient warm, but if one can judge from the results of mouse experiments (Appendix 4) it might be better to keep him comfortably cool.

If possible, the patient, or at least the affected limb, should be immobilized. A pressure dressing applied with care in a known puffadder bite and before the swelling has progressed is recommended by Chapman,[1] who also suggests that a neutral position, rather than elevation or lowering of the affected limb, is preferable.

Antihistaminics and steroids have a place in the treatment of serum reactions but have no proved effect on local or systemic snakebite poisoning. They are sometimes contraindicated, and steroids particularly should be used with caution if they are used at all. It is too early to form any opinion on the possible clinical value of proteinase inhibitors and chelating agents.

For fear of respiratory depression the use of morphine to overcome pain is not considered desirable in snakebite. This seems reasonable in elapid poisoning, which in any case is not particularly painful, but less so in cases of viper bite. It may, however, be safer to rely on aspirin

and give the patient a little alcohol, if he requests it and it helps him to relax. At one time held to be an antidote, alcohol is today usually prohibited in snakebite—though not by all authorities[2]—and the results of mouse experiments (Appendix 5) do not indicate any dangerous effect.

Suitable antibiotics may be used to prevent or treat infection, and the patient's immune state with regard to tetanus should be ascertained.

There is no reason to think that the uncomplicated bite by a snake is a particularly 'tetanus prone' wound, and tetanus antitoxin should therefore be used with discretion, but non-immune patients who have already received anti-snakebite serum and shown no reaction may safely be given a prophylactic dose (1,500 or 3,000 units) of tetanus antitoxin. They should at the same time be given their first dose of tetanus formol-toxoid in its adsorbed form (tetanus PTAP) and be told to attend for subsequent doses at appropriate intervals. Those fully immunized in the past should probably never receive antitoxin, certainly not unless more than about 10 years have passed since the last injection, but receive boosting with either plain tetanus formol-toxoid (FT) or tetanus PTAP; the second preparation is preferable because antivenoms invariably contain some tetanus antitoxin, derived as they are from horses actively immunized against this disease.

APPENDIX

1. The Tourniquet

An occlusive tourniquet in the form of a 3-mm. wide elastic band was placed above the left knee of 10 mice and a dose containing 100 μg. of *N. nivea* venom in 0·1 ml. saline solution was injected into the muscle below the tourniquet. Ten other mice served as controls and received the same venom dose but no tourniquet was applied. The controls died in from 43 to 77 min., the mean log. death time being 1·749, corresponding to 56 min. One mouse in the tourniquet group died after 74 min. and another showed serious poisoning after 80 min. (the tourniquets presumably being faultily applied) when the other 8 mice appeared normal. There was clearly no need to prolong the animals' discomfort. The tourniquets were removed and the surviving 9 mice were given 30 μl. of serum intravenously, which protected all but the seriously envenomed mouse which died after 6 hours.

The serum-saving value of a tourniquet was demonstrated by determining the subcutaneous ED_{50} of serum injected immediately after an intramuscular challenge with 50 μg. of *N. nivea* venom in mice without a tourniquet and in mice with a tourniquet left in place for 30 minutes. The ED_{50} and 5% probability limits were 349 μl. (633 - 191) and 129 μl. (177 - 92) for the two groups respectively.

The tourniquet caused marked oedema and paresis of the leg, but normal appearance and function were completely restored in 1 - 2 weeks.

2. The Efficacy of Intravenous Injection

To demonstrate the efficacy of intravenous serum treatment in poisoning with elapid venom, a dose of 50 μg. (about 5 median lethal doses) of *N. nivea* venom contained in a volume of 0·25 ml. was injected under the dorsal skin of mice weighing from 16 to 18 G and the intravenous ED_{50} of a specific serum was determined by the injection of graded doses immediately afterwards, and after 10, 20, 30, 35 and 40 min. The results, evaluated by the probit method, are shown in Table II, which also shows the ED_{50} of the serum injected subcutaneously mixed with the venom.

Injected at once intravenously, the amount of serum required to neutralize the venom is only slightly larger than the amount required if the serum and venom are injected as a mixture under the skin, and a very moderately increased dose will save the mice even when 30 min. are allowed to lapse. The necessary dose increased steeply with further delay and, though some mice could still be saved, there was no significant regression of survival rate on serum dose after 40 min. and therefore seemingly no point in giving particularly large doses; some mice were obviously beyond saving even if the serum delayed death. Artificial respiration, not easily applied to mice, would probably save some human beings in the same situation. Mice challenged with 50 μg. of venom, the dose used in the experiment, but given no serum survived for 69 min. on the average: the probability of survival for less than 40 min. or more than 115 min. was less than 0·01.

TABLE II. THE ED_{50} (μl.) AND ITS 5% FIDUCIAL LIMITS FOR A SERUM TESTED WITH 50 μg. OF *N. nivea* VENOM*

Serum administration	ED_{50}	*5% limits*
Serum mixed with venom	11·1	11·7 - 10·5
Serum intravenously immediately	12·3	13·1 - 11·7
Serum intravenously after 10 minutes	13·0	13·9 - 12·5
Serum intravenously after 20 minutes	15·0	15·9 - 14·1
Serum intravenously after 30 minutes	14·5	16·1 - 6·6
Serum intravenously after 35 minutes	21·3	33·4 - 15·9
Serum intravenously after 40 minutes	41	?

*The venom was injected subcutaneously, the serum as indicated, in mice.

3. The Rate of Antivenom Absorption after a Subcutaneous or Intramuscular Injection

The relationship between the intravenous dose of *N. nivea* venom and the time to death of mice is known,[12] and 50 μg. of the venom preparation used here would kill mice in a mean log. time corresponding to just under 9 min. The potency of the serum used in these experiments was such that 16 μl. would just render 50 μg. of venom harmless when these amounts of the two reagents were mixed and injected under the skin (the calculated ED_{99} of the serum). All the mice in a large group were given this amount (16 μl.) of serum under the dorsal skin and challenged in groups of 10 with 50 μg. of venom intravenously after ½, 1, 2, 4, 8, 16, 32, 64 and 128 hours. The time to death was recorded for each mouse and from the known relationship between death-time and dose an estimate was obtained of the amount of venom left unneutralized at the different challenge times and therefore free to exert its lethal effect. The difference between this estimate and 50 μg., the dose injected, indicated the proportion of serum absorbed from the subcutis.

The resulting absorption curve conformed closely with the theoretically determined blood concentration-time relationship discussed in general by Heintz[13] for substances injected in this way. Increasing at a steady rate relative to the logarithm of time, the concentration of circulating antivenom reached a maximum after about 15 hours and only about one-third of the injected serum had entered the circulation after one hour.

The results obtained when the intramuscular route was used were essentially the same and did not, as one might have expected, indicate that this route of injection was superior.

The absorption curve indicated that about 16% of the serum injected subcutaneously (or intramuscularly) reached the circulation in about 30 min. Reference to Table II will show that this amount would have to represent about 15 μl. if half the mice were to be saved. One might thus expect that about 90 μl. of serum injected subcutaneously without delay would have this effect, but direct experiments showed that considerably more serum was required. The ED_{50} of the same serum injected subcutaneously on one side of mice which immediately before had received 50 μg. of venom under the skin of the other side was found to be about 500 μl. with wide 5% fiducial limits (790 - 258).

The reason for this is not clear, but very large doses are obviously required when the serum is injected subcutaneously or intramuscularly even at once, and any delay would make it almost or completely ineffective.

4. The Effect of Environmental Temperature

Sixty mice received 60 μg. of *N. nivea* venom subcutaneously and were immediately thereafter placed in groups of 20 at 4°C, 20°C and 37°C. The time of injection and the time of death were accurately recorded in minutes for each mouse and the mean log. death times for the 3 groups were 1·809 ± 0·0301, 1·828 ± 0·0212 and 1·608 ± 0·0199; thus there was no difference between the two 'cool' groups, but the mice kept at 37°C, just below their normal body temperature, fared worse than the others.

5. The Effect of Alcohol

A volume of 0·2 ml. of 20% ethanol (corresponding to 2 G ethanol/kg. or more than half a bottle of brandy for an adult man) was given slowly intravenously to mice, and 0·2 ml. of physiological saline to others which served as controls. Tested in a parallel line assay, there was no difference in the toxicity of *N. nivea* venom for the mice of the two groups, nor was there any difference between the mean log. death-time for mice of the two groups challenged with a larger dose of this venom.

A similar experiment with puffadder venom showed a slight but significant increase in the toxicity for the alcohol-treated mice, but this effect could not be demonstrated when the dose of alcohol was halved.

SUMMARY

Three different anti-snakebite sera are available in South Africa, effective against venom of the boomslang, the mamba, and vipers, cobras and the ringhals.

These sera should not be used lightly or indiscriminately. The absorption of elapid neurotoxins and the local effect of viper venom are rapid, whereas the absorption of anti-venom injected subcutaneously or intramuscularly is slow. Whenever possible, the serum should be injected intravenously, the only truly effective route in systemic poisoning.

The serum dose cannot be standardized, but it is suggested that the contents of 2 - 4 ampoules be given when a viper bite necessitates intravenous therapy. A suggested scheme for when and how the tourniquet and serum should be used in the treatment of snakebite is presented in tabular form.

The general management is briefly discussed. Antihistaminics, steroids, proteinase inhibitors and chelating agents have no proven effect clinically on local or systemic snakebite poisoning, and there is no obvious reason to condemn the use of morphine if the pain is severe, or to forbid the patient a little alcohol if he feels it would help him to relax.

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