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SNAKE VENOMS: THEIR PHYSIOLOGICAL ACTION AND ANTIDOTE.

By GEORGE LAMB, M.D. Glasg.,
Captain, Indian Medical Service.

(*Reprinted from the "Glasgow Medical Journal" for February, 1903.*)

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By GEORGE LAMB, M.D. Glasg.,
Captain, Indian Medical Service.

(*From the Research Laboratory, Bombay.*)

When your Honorary Secretary, Dr. Hunter, asked me if I would read a paper before this Society, I readily acceded to his request. I was, however, soon met with various difficulties. In the first place, on looking over the agenda of this meeting, I saw that Dr. Hunter had entitled the subject matter of my remarks as "Some Recent Work on the Action of Snake Venoms." Well, this recent work has been occupying my attention almost exclusively for the last two years and more. I have, therefore, to compress into the space of a short paper the results of this work. You will understand, then, that I cannot hope to give you more than a summary, and that a short one, of the observations which I have made during this period. For the details of these observations, I must refer those of you who are interested to the various papers which I have published from time to time. In the second place, I

[1] Read at a meeting of the Glasgow Medico-Chirurgical Society held on 7th November, 1902.

have to remember that I am dealing with a subject which is full of what I might call technicalities, a subject possessed of a language peculiar in a way to itself, known only to the workers on the subject, and of which the medical man in general has little or no cognisance. In the third place, investigators have by no means arrived at any absolutely definite conclusions as to the exact methods by which the various snake poisons cause their lethal actions; that they do differ in this respect there can, however, be no possible doubt. It is, therefore, you will readily imagine, a subject around which controversy still runs high. Every day new facts are being brought to light, new hypotheses are being expounded, and old theories exploded. Finally, I have also to remember that to some of you at least the subject is a new one, that it may be the extent of your knowledge is limited to appreciating that there are some snakes which secrete a poisonous saliva, while there are others which have not this function. I have, therefore, to crave your indulgence, especially so as, for the few weeks I have been in this country, my time has been so fully occupied as to prevent me from making any written preparations for this paper. It is not my intention to enter into the question of the differences by which naturalists know a poisonous from a non-poisonous snake. In fact, I am not competent to do so. I propose to confine my remarks to a short description of the physiological action of the different venoms with which I have worked, and also to say something about the antidotes to these poisons.

There are many poisonous snakes in India. Of these, however, only four or five varieties can be said to offer any danger to man. Naturalists divide these into two groups, viz., (1) colubrine and (2) viperine. In the colubrine group of poisonous snakes, we have (1) the cobra, (2) the king cobra, (3) the krait family, of which there are at least four varieties, the best known being the bungarus cœruleus and the bungarus fasciatus. In the viperine group of poisonous snakes dangerous to man, we have (1) daboia Russellii or chain viper, and (2) echis carinata or phorrsa.

At the outset, however, I should like you to understand that my remarks will be, for the most part, confined to a summary of the observations which I have made with the poisons of the two most deadly of these snakes, viz., the cobra and the daboia. I shall also have a few words to say about the venom of one of the krait family, viz., bungarus fasciatus; but my experiments with this poison are by no means complete. I have little or no experience of the poison of the king cobra,

or of that of the echis, nor do I know of any thoroughly trustworthy scientific observations which have been made with the poisons of these two species. And let it be clearly understood that, although the kraits and the king cobra are colubrine snakes, and echis a viper, it by no means follows, as I have good reason to know, that the poisons of the krait family and of the king cobra have the same physiological action as the venom of the cobra, or that of the echis the same as the venom of the daboia, nor even that the poison of one variety of bungarus is the same as that of another variety of the same family.

The poison of snakes is secreted by two glands, one on each side of the head. These glands are the homologue of the parotid salivary glands of other vertebrates. They are situated behind the orbit, quite superficially beneath the skin. They are, in the case of the cobra, about the size of, and somewhat resemble in shape, an almond. Each gland is enclosed in a dense fibrous capsule. This capsule serves as an attachment to the muscle, which, as we shall see, compresses the poison out of the gland. The muscle is the masseter muscle. It assists powerfully in closing the lower jaw. In a dissected specimen, you will see that it is divided into two portions. The upper portion, arising from the skull along a curved line behind and above the orbit, passes downwards and backwards to be inserted along the upper and posterior margin, as well as to the external surface of the capsule; it envelopes the gland above and behind. The lower portion arises from the internal surface of the gland capsule at the back part, and, widening out, passes down to be inserted into the lower jaw. When this muscle contracts, as it does powerfully when the snake closes its jaws on its prey, you will understand how the poison gland is, as it were, forcibly wrung between these two portions of the muscle, much in the same way as a housewife wrings a wet cloth between her hands. In this way, the poison is ejected into the duct at the right moment, viz., when the fangs are buried and ready to convey the death-dealing dose. From the front portion of the gland, the poison duct passes forward, runs along the lower margin of the orbit, and opens on the top of a small papilla which is situated at the base of the fang on the anterior wall of a sheath of mucous membrane, which embraces the fang. This duct, therefore, is not directly continuous with the canal of the poison fang. I regret that time does not permit of me explaining to you how it comes about that no leakage of the poison takes place at this junction.

The fang, as you no doubt know, is nothing more or less than a tooth, which has undergone a special development, so that it may act as a functional tube to convey the poison into the wound which it inflicts. Let us look for a moment at this development. The structure of a young poison fang is the same as that of a tooth, viz., a central cavity, the pulp cavity, containing vessels and nerves, and an outer hard shell covered over with enamel. During development, this becomes flattened out, and soon a groove appears on the anterior surface. This groove is limited on each side by a ridge. Then these ridges, by a process of folding over of the whole tooth, approach one another anteriorly, and ultimately are brought into contact and coalesce. There are therefore, now, two complete cavities in the poison fang, viz., (1) the original pulp cavity, and (2), the new poison canal, situated anteriorly to the pulp cavity. But at the base and near the point of the fang, this folding over is not completed. We have left there the opening by which the poison enters the fang from the duct, and the opening by which it leaves the fang. These openings, you will understand if you have followed my description of the development, are not at the two very extremities of the fang, but are situated anteriorly a little short of the base and of the point respectively. I pass round some fangs of the daboia, so that you may see this point more clearly.

The fangs which are functioning are completely ossified to the superior maxillary bone. While the mouth is shut and at rest, they lie along the roof of the mouth, pointing almost straight backwards. Again I regret that time does not permit of me making clear to you the somewhat complicated and interesting mechanism by means of which the so-called "erection of the fangs" takes place when the animal strikes.

All the older experiments with snake venom were made by allowing the snake to bite some animal or other. This method of experimentation is, as you can well understand, an exceedingly crude method, and affords us no information as to the amount of poison which a snake can inject, or as to the exact quantity which can prove lethal to a given animal. Nowadays, all investigators work with dried and carefully weighed quantities of venom. The poison is collected in the following manner, photographs of which I pass round, so that you may the more easily follow my description:—

The snake is first caught, and held firmly behind the neck. This is done by means of a guillotine arrangement, or a strong

pair of long forceps. If these are not available, a trained snakeman will serve the purpose equally well. This man uses nothing but a short, stout stick. First catching the snake by the tail, he pins the head to the ground with this stick. Then, holding the tail between his toes, with the hand thus made free he seizes the animal just behind the head. He then discards his stick. The lower jaw is forcibly opened by catching the skin covering it. The fangs become erected, and the duet continuous. In the case, however, of the daboia, which has exceptionally long fangs, it is well to pass a piece of string behind them, and pull them forward by means of this. The poison may then be extracted by one of two methods. With the finger and thumb of the free hand, firm steady pressure from behind forwards is made over the glands behind the orbits. The liquid poison escaping from the fangs is caught in a watch-glass held by an assistant in a pair of long forceps. The other method is to allow the animal to bite through a piece of rubber, tightly stretched over the mouth of a stout wine-glass. The fangs penetrate through the rubber, the jaws close on the side of the glass, and the poison, escaping from the fangs, collects in the bottom of the glass.

The liquid poison collected in either of these ways is then quickly and thoroughly dried over lime or sulphuric acid. I have carefully estimated the average amount of venom which can be got in this way. I find that a medium-sized cobra—that is, one from 500 to 1,000 grammes in weight—will give about 150 to 200 milligrammes of dried poison; the larger-sized cobras may give as much as 300 milligrammes. Let us say that a cobra gives 200 milligrammes of dried venom. This is sufficient to kill about 5,000 ordinary rats. It is, of course, without actual experiment, impossible to say how much cobra venom it takes to kill a man. Calmette has stated that the lethal dose, weight for weight, increases as the animals increase in size. I am afraid I cannot corroborate this statement; for from many experiments with mice, rats, guinea-pigs, rabbits, monkeys, donkeys, and horses, I have found that the horse is by far the most susceptible of these animals. It is quite unnecessary for me to-night to enter into the detailed figures of these observations.

Fresh liquid poison is of a yellowish or straw colour. Cobra venom is, as a rule, quite clear, while daboia venom has usually a small quantity of undissolved suspended matter. The amount of water contained in these two

venoms, as well as the speeific gravity, differs considerably. The figures are as follows:—

	Water.	Specific Gravity.
Cobra venom, . .	68·5 per cent.	1110
Daboia venom, . .	75·6 ,,	1077

The reaction of both these venoms is invariably aeid to litmus paper, unless there has been much admixture with the alkaline secretions of the mouth.

Cobra venom has a very bitter taste; chewing daboia poison is like chewing ordinary gum acacia—there is no taste at all.

Venom dried rapidly in a thin layer over calcium chloride eracks into small pieces. In the case of cobra poison, these partieles are of an irregular shape, as broad as they are long; they are yellowish and translucent. In the case of daboia venom the cracking is more or less in longitudinal striæ, and, in eonsequenee, fine needle-shaped particles are found. I show you here good specimens of both these venoms. Thoroughly dried venoms retain their toxic power for an indefinite period. They dissolve again readily and completely in water or in salt solution.

It is quite unnecessary for me to-night to enter into the complicated question of the chemical composition of these poisons. At one time, not very long ago, it was thought that the toxic constituents of snake venoms were alkaloids, similar to the poisonous vegetable alkaloids, such as strychnine. This, however, has been shown to be an entirely erroneous supposition. I think I am right in saying that all investigators are agreed that all snake venoms owe their poisonous properties to the proteid or albuminous substanees which they contain in solution. All snake venoms are, in fact, almost pure solutions of proteids, and contain little else, except a trace of inorganic salts, a small quantity of an organic acid, and colouring matter. Further, there is no doubt that eaeh venom contains two or more different proteids, and that the physiologieal aetion of a partieular venom depends on the nature of the proteids whieh it contains. Organic chemistry has, unfortunately, not advaneed far enough as to be able to separate in pure form these various proteids, or to arrive at any estimate of their ehemical composition. We have, therefore, to eontent ourselves at present with various erude methods of studying the physiological aetions of the different proteids in snake venoms.

When a solution of snake venom is heated, the poison is affected in two ways:—

1. Some of the proteids present become coagulated.

2. The toxic power of the proteids which are not coagulated is impaired, while their solubilities are not altered.

Whether the toxic power is completely destroyed by heating or not depends on the degree of heat used, the duration of time for which it is applied, and the strength of the solution which is heated. Different poisons are affected in different ways. Thus, while a 0·1 per cent solution of cobra venom can be heated for half an hour at 73° C., with the result of only slightly diminishing its original toxicity, heating a 0·1 per cent solution of daboia venom, at the same temperature for the same length of time, completely destroys its toxic power, so that large quantities can now be introduced into the blood-stream of an animal without causing any symptoms.

You will appreciate from this, then, that we have arrived at the stage when we can say that the poison secreted by a cobra is in all probability of quite a different nature from the venom manufactured by a daboia. In this connection I may say, without entering into tedious details or long explanations, that I feel to-day in a position to state, without fear of contradiction, that cobra venom contains no poisonous element which is contained in daboia venom, and, *vice versa*, that daboia venom is necessarily quite free from any of the toxic constituents of cobra venom. I know that this opinion is in contradiction to the working hypothesis put forward by Martin, of Melbourne, some years ago—an hypothesis which, however, was only provisional, and fitted to the facts then available. I have put forward in detail elsewhere the results of the observations which support this opinion.

We have now to pass on to a brief consideration of the manner in which each of these venoms brings about its fatal result when injected into an animal. Let us begin with cobra venom, the poison which has received more attention from investigators than any other.

If one injects a solution of cobra venom into a hot-blooded animal, no matter what the species of the animal may be, one observes a train of symptoms which, there is no doubt, points to the poison having acted directly on the central nervous system. The animal after a time becomes lethargic and disinclined to move—there is no preliminary stage of excitement; then one observes that the hind legs have become paralysed, the animal drawing them after it when endeavouring to progress. The paralysis of the hind legs gradually becomes more marked, while at the same time it spreads forwards and involves the forelegs. Ultimately the animal becomes completely paralysed,

and lies down unable to move. The breathing still continues. Thus one sees in all such experiments a most striking and typical picture, the animal, be it bird or mammal, mouse or horse, lying on the ground completely unable to stir, the breathing still going on, and the saliva trickling from its mouth.

This, however, does not last long. The paralysis soon involves the respiratory centres, gasping in the search for air becomes marked, and the scene is closed with the total cessation of respiration. Just before this, however, there may be slight general convulsive movements, due to the accumulation of carbonic acid gas in the system. Mark you, there has been no word of failure of the heart, there has been no diminution in the strength of the pulse. After the breathing has completely stopped, if one opens the chest, one sees the heart beating away as if nothing had happened. I have observed this beating go on for twenty minutes to half an hour after the thorax has been laid open, and gradually to become weaker and weaker, and ultimately to cease altogether.

As well as this action on the central nervous system, cobra venom has got an action on the blood, which, however, is of secondary importance to the action on the nervous system. In the first place, it has a marked destructive action on the red corpuscles. *In vivo* the effect of this is not very apparent, but *in vitro* a most beautiful demonstration of this hæmolytic effect can be obtained. If, however, a sample of blood be taken after death from an animal which has received a large dose of cobra venom, it is seen that the serum which exudes from the clot is darkly stained with hæmoglobin. In the second place, cobra venom has an action on the coagulability of the blood plasma, which action is also best demonstrated *in vitro*. It has the power of diminishing the coagulability of the blood, and even of entirely preventing clotting taking place. In animals dead of cobra venom intoxication, it is noticed that when a sample of blood is drawn, the clot which forms is not so firm or so compact as in normal blood, and the time which it takes to form may be much lengthened.

As far as my experiments have shown me, I can find no possible relation between the nervous symptoms which I have described, and this action which cobra venom has on the blood. A further proof that the action of this poison on the nervous system is a direct one is afforded by the recent observations which Dr. Hunter has made on the changes in the cells of the central nervous system and in the peripheral

nerve fibres resulting from an injection of cobra venom. I shall leave Dr. Hunter himself to demonstrate these changes. I shall only add that these important and interesting observations appear to me to entirely disprove Cunningham's opinion —viz., that the action of cobra venom on the blood is the primary one, and that the nervous symptoms are dependent on, and result from, the destruction of the blood cells.

If cobra venom be injected directly into the blood stream, the same train of symptoms as I have described above is observed, the only difference being that the symptoms come on more quickly and march to a fatal termination much more rapidly than when the injection is given under the skin.

When a man is bitten by a cobra, the same general symptoms, which I have sketched above as following the artificial injection of the poison into an animal, are observed. As well there is, as a rule, at the beginning, sickness and vomiting, and a feeling of lethargy and disinclination to work; paralysis soon sets in, and life ends, as we have seen, by cessation of respiration. In addition to these general symptoms, however, there are marked signs of poisoning locally at the site of the bite. There is very severe pain, which follows immediately on the infliction of the wound. The parts around become swollen and tender, and a bloody plasma oozes away from the punctures. If the bite has been inflicted on a dependent part, such as a finger, the swelling spreads up the digit, which soon becomes exceedingly tense and extremely painful. Should the patient ultimately recover from the general condition, the tissues for a short distance around the bite die, a black slough forms, and, on separating, leaves a deep hole. This hole heals up very slowly, and there is left an ugly depressed cicatrix. To complete the picture, I may state that in man the general symptoms do not, as a rule, set in for an hour or two after the bite, and that, on the average, death takes place about six hours later. The fatal result, however, may be accelerated, or, on the other hand, it may be delayed for some considerable time, even a day or two, according to the amount of poison injected. You will appreciate, nevertheless, that we have got in all cases a certain interval of time—as a rule, some hours—between the bite and the onset of symptoms and death, an interval of time precious indeed, as you will see, when I come to speak of the treatment of these cases.

Such, then, is a short sketch of cobra venom intoxication. We have now to pass on to the consideration of the effects of an injection of the poison of Russell's viper or daboia. Experiments with this poison, and clinical observations on

actual cases, show quite a different picture to what I have described in the case of cobra venom intoxication. I have had the privilege of studying the action of daboia venom on many varieties of animals—mice, rats, fowls, pigeons, guinea-pigs, rabbits, dogs, monkeys, donkeys, and horses. At the outset, then, it would be well to clear the ground by stating that, as far as my experience goes, it would appear that daboia venom does not produce the symptoms which, as is the case with cobra poison, point to its having a direct action on the central nervous system. I cannot definitely state that it has no degenerative action on the nerve cells and nerve fibres. This point will be shortly settled by our friend, Dr. Hunter, when he has examined the sections, the material for which I have already given to him. At present I can say that I have never seen paralysis of the legs, even in the prolonged cases, follow the injection of this venom. The respiration appears to be interfered with only as a result of the action on the blood and heart. Its action, in short, seems to be confined entirely to the circulatory system, viz., the blood plasma, the blood corpuscles, the capillary walls, and the heart.

In order to make the action of this poison clear to you it will be well to divide all cases of daboia intoxication into two groups, viz., (1) Those cases in which death follows very rapidly—say, within ten or fifteen minutes, or sometimes it is only a few seconds—after the injection; and (2) those cases in which death is prolonged for some hours or even some days after the injection. Let us take the first group.

When a small quantity of daboia venom is injected directly into the blood-stream of an animal—say, into the marginal vein of the ear of a rabbit—or when a comparatively large quantity is put under the skin, say, of a pigeon, death follows rapidly, sometimes in a few seconds. You will notice that the animal first becomes unsteady on its legs, its powers of equilibration are seriously affected; then it falls down, and almost immediately violent convulsions set in. Death follows in a few seconds after the onset of these convulsions. From the observation of these symptoms, Cunningham was led to believe that they resulted from the direct action which the poison had on the central nervous system. This, however, I have conclusively shown to be quite an erroneous hypothesis. What, then, has really taken place? On opening such an animal immediately after death, if the dose has been at all a large one, the whole of the blood is found to be clotted solid—the cavities of the heart, the veins of the lungs and the abdomen, and even the arteries are found full of solid clot.

The heart has, of course, ceased to beat. If the dose has been a smaller one, the clotting may be confined to the pulmonary arteries, the right heart, and the portal vein. The degree and the extent of the clotting depend on the amount of the venom injected, and the rapidity with which it has been injected. But in all cases of rapid death resulting from daboia intoxication, there can be no shadow of doubt but that the fatal result has been caused by this most extraordinary and remarkable intravascular thrombosis.

The symptoms, which Cunningham interpreted as resulting from a direct action of the poison on the central nervous system are due to carbonic acid poisoning, the result of the non-aëration of the blood in the lungs.

In the second group of cases, viz., those in which death is delayed for some time, we have several different phenomena presenting themselves. In the first place, death may follow in a few hours after the injection. In such a case the fatal result is, I am of opinion, due to the depressing action which the poison has on the heart. Thus, I have seen a horse, which had received into a vein a quantity of poison not sufficient to cause a fatal intravascular thrombosis, fall down quite collapsed; its pulse has become feeble, hardly to be felt; its body cold and covered with perspiration—a typical picture of cardiac syncope. There was no paralysis. After a rest the animal got up and walked about, only, however, after the slight exertion, to fall down again in another faint. This condition sometimes ends in death, while, on the other hand, it may be recovered from.

In the second place, should the period of syncope be survived, then a whole series of phenomena develops, which are dependent on the action of the poison on the blood corpuscles, the coagulability of the blood plasma, and the capillary walls.

I have told you that when large doses of this venom are given, either intravenously or subcutaneously, the coagulability of the blood is so increased as to lead to rapid intravascular clotting and death. Should, however, the quantity be not sufficient to cause this thrombosis, and especially will this be the case if the subcutaneous method of injection has been used, then the very opposite condition of blood coagulability is observed. In some cases the blood remains absolutely unclotted when drawn into a test-tube, while in others it clots only after a long interval of time, and the clot is very loose and soft.

As well as this action on the coagulability of the blood, daboia venom has a very marked destructive effect on the red

blood corpuseles. In contrast to what obtains in the case of eobra venom, this destructive aetion of daboia venom is much more easy to demonstrate *in viro* than *in vitro*. Further, other circumstances, which it is unnecessary for me to detail, go to show that the hæmolytic effects of these two venoms are of a somewhat different nature the one from the other. It is, however, difficult to say in what the essential difference really eonsists. Finally, daboia venom has a destructive action on the eapillary walls, making them more permeable to the blood they eontain—a blood more ready, owing to its deficiency in coagulability, to exude.

As a result of these various effects on the blood, heart, and capillary walls, it comes about that hæmorrhages and œdemas are very common in these ehronic eases of daboia poisoning. Thus, around the site of the actual punetures or injections in experimental eases there are a large bloody extravasation and mueh swelling. This swelling spreads rapidly up the limb, and the tissues all around the place of injection die. Thus, there is formed a suitable nidus for all sorts of baeteria. It happens, in consequence, that death in these cases usually results from some bacterial infection, such as tetanus, malignant œdema, or general septieæmia. As well as this local action, hæmorrhage may take plaee from every orifice of the body—from the nose, from the mouth, from the bowels, or from the kidneys and bladder. The blood is in a fluid eondition, and clots badly, while the destruction of the capillary walls allows of it to exude easily. The blood-stained fluid which exudes contains few red corpuscles; the eolouring matter of these has been dissolved out, and now stains the plasma.

Such, then, is the picture of a typical case, either actual or experimental, of chronie daboia venom intoxication. It is this state which is usually seen to follow the bite of a daboia in the human subjeet. This condition can be, and often is, recovered from, the great danger being, as I have indicated, a secondary baeterial infection. Thus, while I have said that a man bitten by a fresh, medium-sized eobra, will, if the snake succeeds in injecting even a modicum of its poison, invariably die if left untreated, it often happens that authentic cases of bites from daboia reeover even after serious hæmorrhages have occurred from many places. As I have said, I have never seen paralysis in all my experiments with daboia venom, nor can I find any authentic record of such having occurred in actual cases.

To sum up, then, it would appear that daboia poison acts mainly, if not entirely, on the circulatory apparatus.

1. It affects the coagulability of the blood. Injected directly

into the blood-stream, or in large does under the skin, it so increases the coagulability as to cause extensive intravascular thrombosis. In small doses it causes, no doubt after a short-lived phase of increased coagulability, a marked and prolonged phase of diminished coagulability, so that in some instances I have noticed the shed blood remain absolutely unclotted even after twenty-four hours.

2. It has a destructive action on the red blood-cells, breaking these up and setting free the hæmoglobin contained in them.

3. It has a destructive action on the capillary walls, rendering them more permeable to their fluid contents.

4. It has a marked depressing action on the heart, so marked, indeed, as to sometimes lead to a fatal termination from this action alone.

Such, then, as far as I know, is the physiological action of the venom of the daboia Russellii.

As regards the poisons of the various members of the bungarus or krait family of snakes I have had little experience. I have, however, made some preliminary observations with the venom of one of this family, viz., the banded krait or bungarus fasciatus. And as Dr. Hunter is going to say something about the degenerative action of this poison on the nerve cells and nerve fibres, I think it would be advantageous if I were to introduce his remarks by a short description of the observations I have made. Let it be clearly understood, however, that my observations are by no means complete, and, further, that they only apply to the poison of bungarus fasciatus, and not to that of any other member of this family.

In the first place, then, if a sufficient quantity of this venom be injected into the blood-stream of an animal, there is brought about a rapid and extensive intravascular thrombosis, similar to what is observed in the case of daboia venom. Death takes place rapidly, and is preceded by the same symptoms as I have already described. I have not up to the present made any observations as regards the condition of the blood coagulability in the more chronic cases of intoxication with this venom. Further, I have not been able to demonstrate any hæmolytic action of this venom either *in vivo* or *in vitro*.

In the second place, if the poison be injected subcutaneously, death may take place in an hour or two, or may be delayed for several days, according to the amount injected. I have seen an animal live as long as seven days. In the more rapid cases one sees paralytic symptoms, which are clinically indistinguishable from the symptoms which I have already described, result from an injection of cobra venom. In the chronic cases,

however, a very different picture is presented. For two or three days, perhaps, the animal appears to be perfectly well. Its eats well, and retains its weight. Then one notices that it refuses to eat, and soon a marked emaciation, affecting the whole body generally, is observed. The loss in weight is rapid and marked. At the same time, paralysis, beginning in the legs, becomes apparent. This paralysis soon extends, and ultimately involves the whole body. A purulent discharge from one or both eyes is a marked feature of the later stage. Ultimately the animal, after lying two or three days completely paralysed, dies from involvement of the respiratory centres.

This short description of the clinical symptoms resulting from an injection of the venom of the banded krait is, I think, sufficient to convince you that there is a marked difference between the action of this venom and the action of cobra venom. The histological appearances which Dr. Hunter will demonstrate to us may, perhaps, substantiate this statement.

In conclusion, I have a few words to say as regards the treatment of snake-bite. When we consider the terribly dramatic, even tragic, circumstances attending these cases, it is not to be wondered at that the treatment of cases of snake-bite has been surrounded by all kinds of quackery and roguery, especially in a country like India, where the people's emotional reflexes are easily stimulated to belief. What resident in India has not heard of the method still in vogue of applying the cloacæ of fowls to the bite? One after the other the fowls mysteriously die, almost as soon as the application is made, until there is arrived a time when the poison has all been "sucked out," and the fowls no longer die. Who has not heard of the magic stone, of the virtue of nim leaves, both when locally applied and when internally administered, of spells and incantations? What remedy has not been tried and vaunted as a specific for these cases? Strychnine, alcohol pushed to cause helpless drunkenness, &c., have at various periods been praised and put forward as absolutely infallible. All these methods and drugs, and many others besides, have had, however, to give way before the test of scientific research. While, however, scientists have so ruthlessly demolished all these so-called specifics, they have given us a remedy certain and trustworthy for at least cases of cobra-bite. I speak, gentlemen, of the anti-venomous serum prepared by Dr. Calmette, of Lille, which can be prepared and easily used by anyone. I have carefully guarded myself by saying that this serum is useful at least for cases of cobra-bite, for while Martin, of Melbourne, has shown that it has

little or no power to neutralise the poisons of the poisonous Australian snakes—viz., pseudechis and the dreaded hoplocephalus—I have demonstrated, in many experiments with different animals, that it is of no avail whatever in counteracting the poisonous effects of daboia venom. I have also recently made some series of experiments with Calmette's serum and the venom of bunganus fasciatus. These experiments, which are in process of publication, definitely show that this serum has no neutralising power for this venom.

It is not my intention to-night to enter into any polemical explanation as to the reasons why Calmette's serum is efficacious for cobra venom and not for the other two venoms I have mentioned, nor for the poisons of the two Australian species. I am quite aware that Calmette claims that his preparation is equally effective against every kind of snake venom. But Martin, Cunningham, Stephens, Hanna, and myself have shown beyond a doubt that this statement is an untrue one, and must be considerably modified.

But it is a great step in advance that we have at hand an antidote to the venom of the cobra. If such is possible to obtain, then we have hopes, amounting almost to certainty, that antitoxic sera will ultimately be obtained for the poisons of the other Indian snakes.

It would be a waste of time for me to go into the details of the method which Calmette uses to prepare his anti-venomous serum. Suffice it to say that the serum is obtained by immunising horses with a mixture of snake venoms, of which mixture cobra poison is the principal constituent. Calmette takes from eighteen months to two years to immunise his horses. The process is a tedious one, and much delay and trouble are caused by the formation of abscesses at the site of injection.

As regards, then, the method of administration of this antidote, it is well to make the injections directly into the blood-stream. Our aim is to get the serum as quickly as possible into contact with the venom, and this object is best achieved, as you can well understand, by intravenous injection. By this method less serum is required, and the results would undoubtedly be more satisfactory. But, unfortunately, in cases of cobra-bite trained medical assistance is not always at hand, and such cases admit of no delay in their treatment. We have then to fall back on injecting the serum subcutaneously, and allowing it to be absorbed into the blood from there, a process which Martin has shown occupies a considerable time. The best site for injection is, I think, the loose

tissues of the flank. A large quantity of serum can be injected there, if the needle is plunged deeply enough, without giving the patient the slightest inconvenience.

As to the dose to be injected, Calmette contends, on very slender, in fact, on empirical grounds, that from 10 to 20 c.c. of serum are sufficient for any case of cobra-bite. In my opinion—and I speak from a large experimental experience with this poison, as well as from some interesting observations which I was privileged to make a year or two ago on an actual case of cobra-bite at the laboratory in Bombay—this dose would in many cases fail to save the life of the patient. A short account of this case might perhaps interest you. An officer of the laboratory, while assisting in extracting the poison from a full-sized cobra, put his fingers where he had no business to—that is, in the neighbourhood of the snake's mouth. In a moment the animal had buried one of its fangs in the point of the right thumb. The thumb was at once withdrawn, but not before the total amount of poison in the gland had been injected. The symptoms, both subjective and objective, which followed, were carefully noted as they occurred.

Locally, there was much pain at the site of the injection. Swelling of the parts soon began, and gradually became well marked. A bloody serum oozed out from the puncture, and continued to do so for about twenty-four hours. Fortunately for the experiment, no fresh serum was available, and we had to inject two bottles (20 c.c.) of a serum which was at least four years old. Just the week previous to the accident, I had tested this serum with cobra venom on rats, and had found it had little or no neutralising power. The patient then went on with his work. About three hours after the bite he began to get lethargic and lazy—did not wish to work and preferred to lie down. This was soon followed by sickness and vomiting. Then it was noticed that his legs were weak; he was unable to move about, and had perforce to adopt the prone position. It appeared, then, that the serum had had little or no effect, and that the case was hopeless. Just at this time, however, some fresh serum arrived. Ten c.c. were at once injected, and the symptoms watched. In about half an hour the paresis of the legs showed signs of improvement. A short time later our patient was able to walk away. Locally, the pain and swelling continued for some time. A small slough formed; this, on separating, left a deep hole, which gradually healed up. A depressed scar is now the only sign of the accident remaining.

It is, of course, apparent to you that the dose of antitoxin necessary in the case of any cobra-bite must depend on two unknown quantities, viz., (1) on the amount of venom injected by the snake, and (2) on the smallest quantity of venom which can kill a man. It is also apparent that we must, however, always calculate on the assumptions that the snake has been a full-sized one, and that it has injected the maximum quantity which can be squeezed out from the gland, and, further, that man is as susceptible, weight for weight, as the most susceptible animal with which we are acquainted. Granted these assumptions, there is no doubt that at least 40 c.c. would be necessary in some cases of cobra-bite, in order even to save the life of the patient. It is, of course, evident that in many cases, such as when the snake has been a small one, when it has already exhausted its poison, when it has not got properly home with its bite, &c., a much smaller quantity would suffice. I should, however, recommend that this quantity of serum be injected right off in all cases of cobra-bite, and the result be watched. If no symptoms appear, nothing further need be done. Should symptoms come on after this injection, another injection of the same amount should be given.

The above dose applies only to those cases in which marked nervous symptoms have not developed before the patient comes under treatment. Should symptoms have set in, then intravenous injection of a large quantity of serum should be made. The symptoms show us that the venom has already joined on to the nerve centres, and to affect it now, "mass" action must be resorted to. The toxin must be separated from its connection with the nerve centres by means of an overwhelming amount of antitoxin.

Now, a word, in conclusion, as regards the local treatment of these cases. Nothing should be done, with the exception, perhaps, of applying a tight ligature above the bite. This delays the absorption of the poison and gives the serum time to be absorbed into the blood and to neutralise the poison circulating there. Cutting open the wound, sucking, cauterising with the actual cautery or with strong acids, and such like heroic measures, are of little avail. They may destroy a small quantity of the poison with which they come in contact, but in animal experiments it has been definitely shown that they do not—or only slightly—delay the march of the symptoms. In the cases where recovery has resulted after the use of these measures alone, the explanation undoubtedly is either that a fatal dose has not been injected, or that the snake has been a

non-poisonous one, or perhaps a lizard. The injection of chloride of lime, permanganate of potash, or chloride of gold at the site of the bite has been, I know, recommended by Calmette. Martin, however, has shown that this also has no effect in delaying the symptoms, if a ligature has not also been applied. When a ligature has been applied along with such an injection, it is the ligature, and not the injection, which has been beneficial.

As regards the treatment of daboia venom intoxication, I know of no specific. These cases have to be treated on general principles—stimulants of a diffusible nature to tide over the stage of cardiac depression might be given. Beyond this I can suggest nothing which would be at all likely to influence these cases for the better. I have already mentioned that Calmette's serum has no power to neutralise the venom of bungarus fasciatus. Cases, therefore, of bites from kraits must also be treated on general principles.

I should have liked to tell you more of this most interesting subject, especially should I have desired to say something of the "precipitin" story, but I find I have detained you long enough, and I have now only to thank you for giving me such patient attention.

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