COBRA VENOM—A CONSIDERATION OF ITS THERAPEUTIC POSSIBILITIES

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In the effort being made by man to conquer diseases, scientists all over the world are feverishly concentrating on producing more certain and speedier remedies. The sincere Homœopathic is as keen to have better weapons; and in seeking this he has the alternative of either discovering new ones or sharpening the weapons already with him.

Hahnemann's extremely original method of proving and potentization have made available to the world ways of discovering the inherent scope and field of activity of every drug and have made it possible to identify, release, develop and utilize for medicinal purposes the energy in every substance. It has been possible by these methods to expose the enormous possibilities present even in substances such as Silica and Carbon which are completely inert in their natural forms. He also destroyed once and for all the belief that there are in nature medicinal and non-medicinal substances.

Though it has thus been possible to absorb any substance into medicine, people have always been fascinated by those substances which have shown activity even in their crude form, e.g. Phosphorus. It is commonly believed that substances which show their powerful effects even in their crude form must make very valuable additions to medicine. So the attention of medical men has often turned towards substances which are very active or poisonous in their natural form.

Among the substances which are available to us from the various kingdoms, the degree of readily releasable energy seems to be greatest in the animal, less in the vegetable and least in the mineral. The plants which grow from the soil have already absorbed and assimilated the crude minerals available in the soil and have converted them into their organic or biological form. Similarly the animal has ingested and assimilated the plant and as such the elements present in

the animal seems to be on a still higher biological level. A Homœopath might say the elements have undergone a process of biological potentization. Such is the nature of the remedies derived from the animal kingdom ; and among these, poisons of the animals, particularly the snake and among the snake venoms, specially the venom of the Cobra which shows its terrible effects so surely and so quickly, calls our attention most.

*The Cobra or Naja tripudians** is characterized in its living condition by the presence of an expanded hood and is identified by the preocular shield touching the internasal and the presence of a small wedge-shaped scale between the fourth and fifth infralabial shield. This species of snake is found distributed throughout the whole of Southern Asia, India, Burma and Malaya. It is an inhabitant of the plains but has been observed at altitudes up to 7,000 feet. The snake may measure up to 6 feet in length and has variable colours from buff or wheat colour or brown or black or green ; the hood may be without marks or adorned with a spectacle-like device or an oval spot surrounded by an ellipse.

The King Cobra or Naja bungarus is a variety of the Cobra which is much bigger, more ferocious and venomous, measuring sometimes up to 15 feet, and is coloured jet black with conspicuous white or yellow cross bars.

The Cobra is undoubtedly fatal to man, but by no means every case of cobra bite proves fatal. It is estimated that 30 per cent. of all cases escaped with moderate or severe symptoms, the dose injected being sub-lethal.

SNAKE BITE

Very often snake bite and snake poisoning are mistakenly considered to be synonymous. It must be remembered that the majority of snakes are harmless, and quite often the symptoms persons exhibit after snake bite arise from fright rather than from the poisoning. It must be remembered that it is quite possible to be bitten by a poisonous snake.

(*i*) without being poisoned ;

* The word Naja having come out of the Hindi word Naga, meaning snake.

(*ii*) in the case of even so fatal a snake as the Cobra, it is quite possible to be poisoned but to receive a sub-lethal dose ;

(*iii*) it is possible for a person to die from the bite of a harmless snake merely out of fear and anxiety.

SNAKE POISONS

In the present system of classification of snakes, the snakes of the world are divided into nine families. All the poisonous species belong to one or other of two families, viz., the Colubridae and Viperidae. Many Colubrines are harmless, but all Vipers are poisonous, and among Indian poisonous snakes there are several representatives of both families.

Snake venoms of the Colubrine class differ but slightly among themselves in their composition and main effects upon animals, and the same applies to the Viperine class. The symptoms evoked by the Colubrine class, take collectively, differ considerably from those produced by the Viperine.

Colubrine poisons act chiefly on the central nervous system (cord and brain) and cause death by paralysing the respiratory centre in the brain. Their effects upon the blood are slight compared with the Viperine class, so that hæmorrhages are not usual, and when present are not severe.

Viperine poisons have no paralysing effect upon the nervous system, except on the vasomotor centre, but have a very marked effect on the heart and blood, death usually being brought about by paralysis of the vasomotor centre, exhaustion from profuse and persistent bleeding, or from septicæmia.

Compared with the venom of other snakes, Cobra venom ranks third in virulence among Indian snakes. The sea snake, Enhydrina valakadyn, stands first, and the krait, Bungarus coeruleus, a good second. The Cobra venom is estimated to be one-seventh as toxic as the former and one-fourth as the latter. The capacity of the glands has been computed at ten lethal doses for man, but under exceptional circumstances it may go up to twenty.

SYMPTOMS OF COBRA POISONING

In a subject poisoned by a Cobra, which we may take as the type of Colubrine toxæmia, the earliest constitutional symp-

tom is a feeling of intoxication, but this frequently passes unnoticed in an unobservant subject. Later the patient feels his weakness (paralysis) insidiously creeping upon him, till, uncertain of maintaining the upright posture, he voluntarily reclines. His paralysis begins in his legs, mounts to the trunk, and finally affects the head, which droops. Synchronizing with this drooping of the head, a drooping of the eyelids may be noticed, and simulaneously the muscles of the lips, the tongue and throat become gradually paralysed. As a result the lower lip falls away from the teeth, allowing the saliva to dribble from the mouth, speech becomes increasingly difficult, till the subject, unable any longer to control his lingual and labial muscles, attempts by signs to communicate to those around him, often striving with his fingers to remove the viscid saliva that clings to his ofen striving with his fingers to remove the viscid saliva that clings to his mouth. Breathing soon becomes embarrassed, later laboured, and finally impossible. Distress is written on the countenance, which becomes increasingly livid from defective aeration of the blood. Swallowing similarly becomes difficult, and later impossible, so that fluids taken into the mouth are apt to regurgitate through the nose. Nausea and vomiting are frequent symptoms. A convulsion often heralds the cessation of respiration, but the heart goes on beating for a minute or two longer. Consciousness is retained till the end. There appears to be no special sequence in the development of these paralyses. Those affecting the muscles of the lips, tongue, voice, throat, develop synchronously, and evoke a train of symptoms exactly comparable to the organic nerve disease "bulbar palsy". Such are the effects produced by the paralysing influence of the poison on the cord and brain, which may cause death in from 1½ to 6 hours usually.

Symptoms arising from the action of another toxin, viz. hæmorrhagin, on the blood, may be present, but a discussion of these will come more appropriately when dealing with Viperine poisoning.

Local effects are always more or less in evidence, but these again, being much more pronounced in Viperine poisoning, are better considered under that heading.

PHYSICAL AND CHEMICAL CHARACTERISTICS OF COBRA VENOM

Of Cobra poison, Dr. H. C. Sen says, "When fresh it is a clear, transparent fluid, varying in colour from a yellow to a straw tint to complete colourlessness. It has a faintly acid reaction; its consistency varies from that of water to that of the white of an egg. Its specific gravity has a wide margin of variation. Specimens taken from several cobras and mixed gave a specific gravity of 1.058. It has a very bitter taste, which is chiefly perceived along the margin of the tongue, and a faint sickly odour. When cobra poison is evaporated, it loses from 50 to 75 per cent. of water, and a yellowish substance, easily pulverizable, resembling gum arabic or dried egg albumen, is left behind. This dried substance possesses all the physiological and toxicological properties of cobra poison, and it can be kept in this stage for years. Chemically analysed, it is found to contain Carbon 45.76 per cent., Nitrogen 14.3 per cent., Hydrogen 6.87 per cent., Sulphur 2.5 per cent. When kept in the liquid state, cobra poison quickly becomes first neutral and then alkaline, and a few feathery and cubic crystals will form. When kept in hermetically sealed ampoules in a cool dark place, it retains its potency for a long period. If preserved in a loosely corked test-tube, it will become cloudy, smell offensively and will swarm with bacteria in active movement; but it will still remain poisonous."

The venoms are composed of variable amounts of proteins, albumoses, pigments, mucus, epithelial debris, fatty matters, salts like chlorides and phosphates of calcium, ammonia and magnesium, analogous to the constituents of normal saliva.

They are complex mixtures of pharmacologically very active components, many of which have been shown to be proteins having enzymic activities. They are powerful toxins to man and animals and as such have aroused the interest of investigators in various fields from early times.

Many chemical substances like 1 per cent. solution of potassium permanganate, gold chloride, chloride of lime and even hypochloride of calcium (1 in 12), chromic acid, bromine water, 1 per cent. trichloride of iodine, modify or delay the action of

venom. Cobra venom can stand a temperature of 100°C. for a short time without losing all its activity.

The enormous toxic power of venoms is illustrated by the fact that the minimum lethal dose for mice of a purified preparation of neurotoxin from cobra venom is 90 µg. to 0.03 µg. per gram weight of animal.

The complex nature of venoms gives rise to a variety of symptoms in the organisms. In early literature, the classification of venoms was based on the most dominant features of the clinical symptoms they produced in the animal organism. The three main classes of venoms on the basis of this criteria were neurotoxic, hæmotoxic and depressant.

PHARMACOLOGICAL ACTION OF COBRA VENOM

It was believed that the action of the cobra and viper venoms was the same and that the divergence of symptoms noticed in the two cases was only due to the difference in the degree of toxicity. Later it was suggested that these two venoms have entirely different seats of action.

Epstein (1930) studied the action of the South African Cobra, Naia flava (Naiva vivea) and found that it produced death by respiratory failure. The venom also has a direct action on the involuntary muscles, contraction being followed by relaxation. Chopra and Iswariah (1931) have made a pharmacological study of the action of the venom of the Indian Cobra, Naia naia vel tripudians. The M.L.D. of the venom varies with the species of the animals; cats and rats are less susceptible; dogs, rabbits and man are more easily affected. When given intravenously the venom produces an immediate effect, the animal dying within a few minutes of respiratory failure provided a large enough dose is given. The absorption is slower when the venom is given by the subcutaneous and intramuscular routes, death taking place in 4 to 24 hours. The venom is not absorbed at all from the gastro-intestinal tract or other mucous membranes. The venom has no effect on the activity of salivary, gastric and pancreatic secretions of man *in vitro*. It slightly increases the tone of the musculature of the gastro-intestinal tract in cats and rabbits.

Injections of sub-lethal doses of the venom produce a small but persistent rise of blood pressure in experimental animals. This rise is not due to any stimulant action on the accelerator mechanism of the heart or on the myocardium. None of the concentrations of the venom, however high or low, produce definite stimulation of the heart especially when it is failing. Very large doses appear to act directly on the heart, producing a marked depression and stoppage. The rise of blood pressure appears to be associated with the stimulation of the vasomotor centre in the medulla as it is absent in decerebrated animals. The fall of blood pressure produced by the large doses has been shown to be due to paralysis of the vasomotor centre. The main action of the venom in lethal and sub-lethal doses on the animals is on the respiratory centre, the effect being one of initial stimulation and final paralysis. The venom appears to have no effect on the motor end plates in the diaphragm or other respiratory muscles.

Observations on animals show that the venom produces initial stimulation on the higher parts of the brain, followed by paralysis.

The venom is also said to possess the power of destroying the bactericidal properties of the normal blood sera. Welch and Ewing (1894) explained that the rapid putrefaction which sets in in the animals after poisoning with cobra venom is due to this property.

Considering that the Colubrine snake venoms act mainly on the central nervous system, it is worth while studying their neurochemical effects.

NEUROCHEMICAL EFFECTS OF COBRA VENOM

Kellaway *et al.*, employing refined techniques, have studied the curare-like action of a variety of Australian snake venoms and many of the Indian colubrid venoms. They conclude that nearly all snake venoms possess to some extent the curare-like action, the colubrids being very much more potent than the vipers. Indian cobra (Naja naja) venom is the most potent, being active in concentrations of 1:200,000.

In another series of experiments, Kellaway, Cherry and Williams have been able to show that the central respiratory mechanism is still intact when failure of respiration has occurred in rabbits injected with a number of venoms from colubrid snakes. The curarization of the diaphragm was found to be complete at this stage. Results such as these have led to the conclusion that the colubrid venoms cause paralysis of the respiratory muscles by their curare-like action and not by an impairment of the central nervous system.

Although the paralysing action of venoms bears a strong resemblance to the effect of curare, important differences have been noted. The most striking difference is the irreversible nature of the action of venom.

Arthus demonstrated that in rabbits curarized by cobra venom the effect could be neutralized by the injection of specific antiserum only when administered within two hours. Kellaway was unable to reverse the paralysing action of Australian tiger snake and copperhead venoms even by giving massive doses of the specific antivenenes. Cushny and Yogi found that eserine which antagonizes the action of curare was ineffective with venom. Gautrelet *et al.* were able to show that the effect of cobra venom on the neuromuscular preparation of a frog could not be reversed by sparteine or strychnine, which neutralizes the effects of curare. They concluded from their results that the venom exerted a direct action on the nervous tissue, causing an irreversible change.

Extensive pharmacological studies on the central effects of venom have been made by Macht and his associates. It was concluded that in minute doses cobra venom affects specific areas in the brain, particularly those relating to the sensation of pain, and gives rise to the analgesic effect. This action of the cobra venom has led to its therapeutic application in various painful disorders. On comparing the analgesic effect of venom with that of morphine it was found that the analgesic action of venom supervenes more slowly but is more sustained and lasts for longer periods.

The presence of zinc in venoms had first been noted by Delezenne, who showed that it was combined with proteins and

could not be removed by dialysis. Furthermore, a certain parallelism between the zinc content and the phosphatidase activity was pointed out. It is noteworthy that one of the neurotoxins (neurotoxin C) crystallized by Michael *et al.* was found to be rich in zinc.

Wellers had demonstrated that potassium cyanide inactivated cobra venom and that the rate of inactivation parallels the liberation of thiol groups.

THERAPEUTICS OF COBRA VENOM

ANCIENT INDIAN MEDICINE

Though ancient Indian medicine is several thousand years old and had adopted the use of different drugs with a high degree of clinical benefit, the use of cobra venom was introduced comparatively recently, about two thousand years back. It has been used with success in a variety of conditions, usually very serious and often fatal. Unfortunately, it has usually been combined with a number of drugs to form medicines, but yet there is no doubt that in most of these medicinal combinations, cobra venom has been the most active ingredient. It has been used in the stage of collapse in fever, cholera, cirrhosis of the liver, etc. Dr. Sen considers that it is a powerful stimulant if administered by mouth, and has demonstrated its successful use in many cases of plague.* He suggests that the injection of snake venoms in plague cases should be done very cautiously, for the treatment itself is capable of adding fuel to the fire.

One has known cases where Indian physicians, when faced by desperate cases of illness where death appeared almost certain, had procured fresh cobra venom, mixed it with some other drugs and had administered this mixture, as a result of which the patients had often rallied. One also comes across reports of cases of carcinoma having been cured by cobra venom, but authentic evidence is found lacking.

* It is interesting to note that many of these cases of plague who have recovered after the administration of snake venom pills continued to feel burning sensation in their head for many years and to apply cold water to relieve this sensation.

MODERN MEDICINE

Kellaway and Holden (*Aust. J. Exp. Biol.*, **10**, 167, 1932) investigated the action of cobra venom and found that it has got a paralysing action on the nerve endings. Macht (*Compt. Rend. Soc. Biol.*, **120**, 286, 1935) demonstrated that sensitivity to pain, produced by the passage of electric current, was markedly reduced on injection of cobra venom and that the effect was the same order of magnitude as was produced by a similar dose of morphine and that it lasted many hours. In 1938, he published a further report on the use of cobra venom as an analgesic in the treatment of conditions where pain is present over a long period. He observed that its action was slow and not noticeable for two or three days, but persistent when once elicited. It has an action like morphia with important differences. It acts on the higher centres to abolish pain, but is non-habit forming. It does not depress cerebral function, in fact may stimulate it a little; it widens instead of contracting the fields of vision; it is excreted so slowly that there is a cumulative action; it does depress the respiratory centre, but the margin between therapeutic and toxic dosage is very wide.

Macht (*Tr. Amer. Therap. So.*, **40**, 62, 1940) listed thirty conditions in treatment of which cobra venom has been used. It has been chiefly used for the relief of intractable pain in a variety of conditions such as cancer, neuritis, arthritis, anthralgia, neuralgia, sciatica, migraine, herpes zoster, lumbago, etc. It is also being used in neuromatous leprosy, tabes dorsalis, epilepsy, thrombocytopenic purpura, angina pectoris and other cardiac conditions, besides malarial hæmoglobinuria and hæmophilia.

The Council of Pharmacy and Chemistry of the American Medical Association (1940, *J.A.M.A.*, **115**, p. 1196), in their preliminary report, expressed that cobra venom was of some value for the relief of pain especially that of inoperable cancer, but it did not displace morphine completely in more than a relatively few cases, that it appeared to be of limited value in the treatment of tic doulourex and conditions grouped loosely under the name of rheumatism and arthritis, and that its therapeutic effects were variable and uncertain in all painful con-

ditions. Disagreeable side-actions including nausea and vomiting, diarrhœa and pain of injection, were also mentioned. The Council stated that cobra venom must not be recommended to those who are severely ill except those suffering from operable malignant tumours or from incurable diseases.

The use of cobra venom, however, has not gained popularity, due to its slower pace of action, cumulative effects and uncertainty in results.

HOMŒOPATHIC USES

Since the indication of drugs in Homœopathy is based on symptom similarity, it is difficult to define clearly where and when *Naja* will be indicated. Yet, basing our views on provings and on our experience, it has been found useful in angina, diphtheria, cardiac conditions (toxic and myopathic), valvular affections various paralytic conditions, dysmenorrhœa, hay fever, etc., etc.

Many Homœopaths have expressed their disappointment over the provings of *Naja*. John Henry Clarke writes:

"The poison of the deadly cobra has been used from ancient times, says P. C. Majumdar (*Ind. Hom. Rev.*, vi, 6), by Indian practitioners in many nervous and blood diseases. It was introduced into Homœopathy by Russell and Stokes, who made the first provings along with some forty other provers, including Gillow, Pope and Drysdale. It is rather remarkable that with so many able provers *Naja* should not have attained anything approaching the place of importance occupied by *Lachesis*."

E. B. Nash, M.D., also has some comments to make. He writes:

"Here is a blood relative of *Lachesis*, if serpent poisons may be called relatives, and according to the symptoms arising from the bite of the serpent it ought to be equally valuable as a curative, but it has not yet been found so. Why not? On referring to Allen's *Encyclopædia* we find twenty-nine provers, poisonings and all, for *Lachesis*, and forty-five for *Naja*. Of course, *Lachesis* has been longest in use ; but has the difference in time been sufficient to account for the very great difference

in utility? Another thing is noticeable: the provings of *Lachesis* were made mostly with potencies as high as the 30th, while those of *Naja* are almost all with the lowest preparation or the crude poison from the bite of the serpent. Does this account for it?

"We also notice on referring to the same authority that all the most marked verifications are of symptoms produced by provings of the 30th of *Lachesis.* Does this indicate that *Naja* must be proven in the potencies to develop its most efficient powers?"

It is rather unfortunate that in the provings *Naja* did not bring out even a fraction of the fine symptoms brought out by *Lachesis,* resulting in a great restriction of its field of indication. Considering that cobra venom is even more poisonous that *Lachesis* and also that it has such a specific action on the C.N.S. and the heart, one would have supposed that it should prove to be a most useful medicine in modern times when neurological and cardiac conditions preponderate. Possibly with better provings one might find it quite useful in conditions preponderate. Possibly with better provings one might find it quite useful in conditions like disseminated sclerosis, poliomyelitis, etc.

Particularly it would appear that the therapeutic value of cobra venom in cancer has not been fully explored, exposed and exploited in any system of medicine. That it has some specific effect on cancerous-tissue apart from the mere analgesic action, there appears little doubt. Monaelesser and Aaguet (1933) have investigated efficacy of cobra venom in the destruction of neoplastic growth and as an analgesic for the intolerable pain of cancer. In all, 115 cases of different types of new growth were treated by them. Their results indicate that in a proportion of the patients the venom had an inhibiting action on the development of the neoplasms and had a definite value in relieving pain which otherwise required for its relief the administration of morphine. Levastien and Korossios (1933) have also explored the value of cobra venom in the treatment of cancer. Starting with the relatively high dose of 0.001 mg., they observe that most of their patients ceased to complain of pain after the

first injection of the venom, although before resorting to this treatment they required daily injections of heavy doses of morphine for relief of pain.

Calmette, Sanez and Costil (1933) have tried the effect of this venom on experimental and spontaneous neoplasms in animals and have noticed retardation of growth and even diminution in a number of cases. Macht treated 105 patients with cancer in various parts of their body. Beginning with two to four mouse units he raised the dose of venom to five mouse units and continued the injections daily until relief of pain was obtained. According to him 28.6 per cent. of the cases showed a definite amelioration of the symptoms, 38 per cent. of the cases obtained marked relief of pain, 21.9 per cent. of the cases recorded only slight relief and the rest did not seem to have been benefited by the treatment.

On the basis of such experiments carried out by Calmette and his disciples fresh poison of the Cobra is recommended in inoperable cancer, 1/100 mouse unit is injected at first and the dose gradually increased to 1/10th, 1 and 5 mouse units at intervals of 3-6 days, gradually advancing to the proximity of the tumour. The growth of the tumour is arrested. In several cases complete cures are said to have been effected (Dr. Madaus).

Cobra venom also seems to have a specific biological relationship to cancer. It has been used in the formachidis test for cancer. The test depends upon the activation by cobra venom of the hæmolytic action of serum in the deviation of complement test and the assertion is that the test occurs only with the serum of persons suffering from malignant disease (Chopra).

CONCLUSION

A careful analysis of the nature of and symptomatology by cobra venom seems to justify the belief that cobra venom ought to prove to be a drug with a much wider range of application than the limited area within which it is being utilized at present. It is quite possible that a re-proving with the higher potencies of fresh venom might reveal new possibilities.

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And thus it is that *Arsenicum iodatum,* when properly potentized by the homœopathic method of dynamization becomes a very important and effective remedy in acute and chronic diseases.

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