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## A Contribution to the Study of the Action of Indian Cobra Venom

R. H. Elliot

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XIII. *A Contribution to The Study of the Action of Indian Cobra Venom.*

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*under the orders of the Rt. Hon. The Secretary of State for India.*

*Communicated by Sir THOMAS R. FRASER, M.D., LL.D., F.R.S.*

(From the Materia Medica Laboratory of the University of Edinburgh.)

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AT the suggestion of Sir THOMAS FRASER, H. M. Secretary of State for India very kindly placed me on special duty for Snake Venom research in the Pharmacological Laboratory of the University of Edinburgh. Professor FRASER, under whose superintendence I was directed to work, suggested that I should carefully study the pharmacology of Indian Cobra venom, and the work herein set forth is the outcome of that suggestion. Professor SCHÄFER also very kindly placed his laboratory at my disposal, and both to him and to Sir THOMAS FRASER I owe my most cordial acknowledgments for their unvarying kindness and for their very valuable and always ready assistance.

*Previous Work on the Subject.*

Some of the earliest work done on the pharmacological action of Cobra venom was that by LAUDER BRUNTON and FAYRER,\* published about thirty years ago. They considered that Cobra venom selected the cerebro-spinal nerve centres for its seat of action ; it paralysed these, and in large doses it acted also on the ganglia of the heart, causing arrest of cardiac action. They laid little stress on the rôle played by circulatory failure, and in support of their views they quoted a number of experiments in which cardiac pulsations continued after the apparent death of the animal. In volume 22 they go on to discuss the subject still further. With the facts at their disposal they were unable to come to any definite conclusion as to the exact influence of the venom on the heart, but they thought that the heart's arrest in systole, which they at times observed was due to "some action on the cardiac ganglia." They drew attention to the great difference observed in the effect of venom according as it was applied to the surface or to the interior of the heart. In this connection they quote an experiment in which they perfused the frog-heart with a solution of Cobra venom, and obtained arrest of it in a position midway between systole and diastole. The strength of solution used is not stated and details are wanting, but the experiment is of great interest, as it is the only record I can find in any writer's works of an attempt to perfuse an isolated part with Cobra venom. They thought the action was due to an influence on the cardiac ganglia. They found that in large doses Cobra venom destroyed the inhibitory power of the vagus, which it did not do in small doses. That the inhibitory branches of the vagus were sometimes affected they were confident, but they do not seem to have been able to differentiate clearly between a direct action of the venom on the vagal system, and the indirect effects brought about by means of interference with respiration. In dealing with the last-named subject, they clearly observed the paralysis of the phrenic nerve ends, and divided the responsibility for respiratory failure between this and a direct interference with the centre in the medulla oblongata.

It is difficult to do justice within one's limits of space to these papers, which will ever remain classics in Snake-venom literature, and only two more points can be touched upon. The first is the conclusion, founded on only two experiments, that the rise of blood pressure in cobraism was due to contraction of the arterioles opposing a barrier to the exit of blood.

The second point referred to is the influence of artificial respiration in restoring function to a cobraised animal. Lastly I would venture to offer, with the greatest respect, a few criticisms on this work, for it was those very criticisms which led me to go over again some of the ground BRUNTON and FAYRER had covered. Firstly they do not seem to have standardised the venoms they worked with ; secondly they omitted to accurately graduate their dose to the weight of animal used, and thirdly

\* 'Roy. Soc. Proc.,' vols. 21, 22, and 23.

they did this work about thirty years ago, when physiological and pharmacological knowledge had not reached the position it enjoys to-day, and when some of our present methods of experiment were unknown or nearly so. CUNNINGHAM, in "Scientific Memoirs by Medical Officers of the Army of India,"\* advanced the view that Cobra venom acted on the respiratory mechanism through the blood, and not through the nervous system. He has found few supporters.

The next important paper on the subject is that by WEIR MITCHELL and REICHERT, published in the 'Smithsonian Contributions to Knowledge,' of 1890. Like BRUNTON and FAYRER they appear to have omitted to standardise the specimens of venom they used, or to calculate the dose to the body-weight. Farther, the doses of venom used were far in excess of those a snake-bitten man would receive, for death ensued in less than 20 minutes in a large number of the experiments, and life seldom far exceeded this period of time after the injection. The same objection applies to a large number of the experiments which other observers have made whilst working at this subject; and yet it is obvious that the dosage in which a poison is usually received is a very important factor in the determination of the effects produced. It is unsafe to argue as to the action of any poison from a consideration of the symptoms, etc., produced by it in a concentrated form.

WEIR MITCHELL and REICHERT observed a temporary fall of blood pressure, followed by a decided rise thereof, which eventually yielded to a final fall. The first fall they attributed chiefly to "depression of the vaso-motor centres," but they thought it may be partly cardiac. The rise they considered "capillary," and the final fall cardiac.

They believed that two antagonistic factors are at work on the rate of the heart, viz., an increased activity of the accelerator centres tending to quicken the beat, and a direct action on the heart tending to slow it. The former influence is apparently called in to explain those cases in which they gave doses fatal in very short periods of time and found marked quickening of the beat.

They ascribed death in most cases to paralysis of the respiratory centres and seem to attach no weight to an affection of the phrenic nerve-ends. They laid stress on the influence of the venom on the vagal peripheries whereby respiratory effort is increased. It is only fair to add that their paper does not primarily concern itself with Cobra poison, and that it is a difficult, if not impossible, task to deal with many varieties of venom at one and the same time. Recent research has clearly shown that this is so.

The last important paper which calls for review is that by RAGOTZI.† RAGOTZI shows that in order to produce peripheral paralysis it is necessary to carefully graduate the amount of venom used, avoiding a rapidly fatal dose on the one hand and one which is too weak on the other.

\* 1895, Part IX., and 1898, Part XI.

† Virchow's 'Archiv,' vol. 122, p. 201.

He found that artificial respiration might keep warm-blooded animals temporarily alive, but that it would not lead to recovery. In such animals the endings of the phrenics and of the trunk-muscle nerves were paralysed, the paralysis being of such a nature that prolonged artificial respiration did not bring about recovery of the nerve-ends.

He does not think that the failure of respiration is due to an affection by the venom of the respiratory centre, but holds the motor nerve-ends alone responsible. In marked contrast to Curara, he finds that Cobra venom spares the vagal centres and nerve-ends.

In his blood pressure work he used very heavy doses of venom, if one may judge from the rapidity of cessation of respiration; the dose per kilo. is unfortunately not stated. He observed that artificial respiration affected the blood pressure, and he therefore concluded that the vaso-motor centre had remained active.

He observed that large doses of Cobra venom stopped the frog-heart in systole. In the mammal strong doses of venom lessened the amount of the heart's movements, whilst smaller doses increased it. To kill the heart in diastole small doses, subcutaneously given, were required. He surmised that systolic death must be due to a direct action of the poison on the heart-muscle, and that "diastolic death" is to be attributed to paralysis of the intracardiac ganglia. He did not find the vagal ends in the heart affected.

C. J. MARTIN's able article in ALLBUTT'S 'System of Medicine,' is also of considerable interest, although the writer concerns himself largely with other than Indian snakes. Working with an open thorax, he finds that after the injection of Viperine venom the heart beat is first increased and later diminished. If the heart is cut off from all centric influences, by cutting the cardiac nerves, no primary increase occurs. In Cobra poisoning alone he believes that the circulatory mechanism is not easily affected, the heart beating strongly even after respiratory death. All venoms produce a sudden fall of blood pressure if in large doses. In *Pseudechis* poisoning, the cause of the primary fall, as shown by simultaneous tracings of carotid blood pressure and of the volumes of the spleen and kidney, is mainly cardiac. If vascular dilatation of the abdominal area occurs at all, it is masked by cardiac depression. He states that an excised frog-heart fed with dilute solutions of venom stops in diastole, while if the venom solution is more concentrated, it at once stops the heart in partial systole. The kind of venom is not stated, but from the context I infer that it was Viperine.

MARTIN finds that vagus stimulation stops the heart in Cobra and *Pseudechis* poisoning up till near the end of life. In his views on the action of Cobra venom on the respiratory system, MARTIN closely follows WEIR MITCHELL and REICHERT.

I greatly regret that exigencies of space prevent me from discussing at much greater length the previous valuable work on this subject which has been done by others.



*Object of this Research.*

The main object of this research was to try to fill in some of the gaps still left in our knowledge of the pharmacology of Cobra venom. I particularly desired to ascertain the precise part played by the various important centres, nerves and organs, in the production of death from cobraism. To this end I made it my first object to study the action of the venom on the isolated frog-heart and on the vessels of frogs whose central nervous system had been destroyed. The same structures were then experimented on in frogs whose brains above the medulla oblongata had been removed. The isolated mammalian heart was next submitted to the action of the venom, and finally, the ground having been thus cleared, more complicated experiments were undertaken on various living mammals.

The minimum lethal dose per kilo. of body-weight of the specimens of venom used was carefully calculated at an early stage of the research, and to save repetition and explanation, the doses quoted throughout this paper are stated in fractions or multiples of the M.L.D. for the particular animal under discussion.

*Perfusion of the Vessels of the Frog.*

The animal was always carefully and thoroughly pithed at least half-an-hour before commencing the experiment. A continuous record was taken of the amount in cub. centims. of the escaping fluid. In the earlier experiments a solution of sodium chloride in Edinburgh tap water (.6 per cent.) was used for the normal, and also as a vehicle for the venom. It was found that with this solution slight but steady dilatation of the vessels took place after long perfusion, and RINGER'S fluid, as modified by RUSCH, was therefore substituted for it.\* The result was satisfactory.

A 1/50,000 solution of Cobra venom reduced the flow in a little over an hour from 1.3 cub. centims. per minute to .3 cub. centim. in the same time. The following solutions were then tried in turn:—1/100,000, 1/300,000, 1/1,000,000, 1/2,500,000, 1/5,000,000, and 1/10,000,000. A constriction of the vessels was distinctly observed even down to the last and weakest strength, in which indeed the flow was halved in less than an hour. Solutions of the venom at 1/15,000,000 and at 1/20,000,000 gave negative results.

The next step is the estimation of the concentration of Cobra venom in the blood of a bitten man. This can only be made approximately. CALMETTE has calculated that the larger venomous snakes, such as the Cobra, yield on an average about .050 gramme of venom (weighed in the dry) at each bite. He thinks this a liberal estimate, and he infers that the fatal dose for a man is about .010 gramme.†

\* *Vide* Pfüger's 'Archiv,' vol. 73, p. 546.

† *Vide* Calmette's note to the article on Venom in Allbutt's 'System of Medicine.'

Sir T. FRASER has calculated an average of ·255 gramme of Cobra venom for each bite, but thinks an average of ·195 gramme to be probably a truer estimate. Reckoning on the cat-basis, he places the M.L.D. for man at ·317 gramme, but again he thinks a lower estimate more correct, and gives ·0317 gramme as nearer the true mark. The duration of life after Cobra bite in most of the fatal cases leads one to think that but little over the minimum lethal dose is usually injected. The margin between CALMETTE'S average amount for a bite and FRASER'S minimum lethal dose is by no means large, when the difficulties of the investigation are considered. We shall probably err on the side of safety if we consider that a fatal dose for an average man is about 30 milligrammes, as this figure is covered by both the estimates given above. Assuming the weight of an average man to be about 70 kilos., and the weight of his blood to be about one-thirteenth of this figure or rather less than 5·5 kilos., and assuming also that the whole dose of venom injected is absorbed into the circulation, we find that the concentration of the poison solution in the body will be about 1 : 183,333.

Even if the above calculations are considered to be over-liberal, or if it is objected that the whole quantity of venom would not be in circulation at one time, we have still a very wide margin between 1/183,333, the figure we have just arrived at, and 1 : 10,000,000, which has been found to be a sufficiently strong solution to act on the isolated vessels within an hour. Two additional facts are to be borne in mind, viz., that the tissues of a victim of snake bite are exposed to the action of the venom for many hours, and that it is extremely difficult to dislodge Cobra poison from those tissues, once it has fastened on to them. In illustration of the last point, it may be mentioned that isolated vessels or isolated hearts, which have been submitted to long perfusion with the venom, cannot be recovered by perfusion with a normal fluid; farther, if the original venom perfusion has been short, and if recovery under normal fluid takes place, a second irrigation with the lethal fluid acts much more quickly and decisively than did the first one.

It is clear, therefore, that the sustained high pressure, which is so marked a feature of blood-pressure tracings in slow death from cobraism, is explainable without going any farther than the direct action of the poison on the walls of the vessels. The present state of physiological knowledge does not permit of a discussion of the exact method of this local action. To my volunteer assistant, Mr. JOLLY, my acknowledgments are due for his valuable help in the work of this section of my paper.

#### *Perfusion of the Frog-heart with Cobra Venom.*

In order to test the action of Cobra poison on cardiac tissue, SCHÄFER'S plethysmograph was used for frog-hearts. The instrument was modified by substituting a metal for a glass cylinder for the piston. Moreover, oil was done away with in the body of the instrument, and RINGER'S fluid used in its stead. The fluid used for

perfusion consisted of one part of defibrinated ox-blood and two parts of RINGER'S fluid (RUSCH'S formula already quoted). This was used for the normal and also for conveying the venom, both portions of the solution being taken from the same bottle each time.

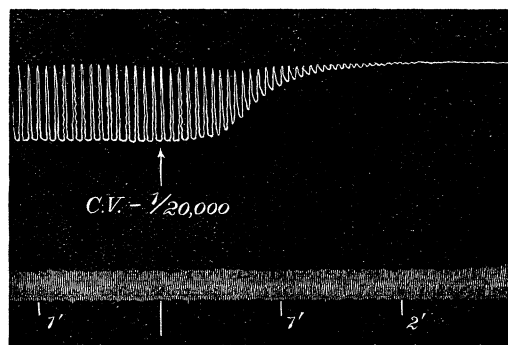
There is nothing of note to be said about the method of removing the heart from the body and fastening it into the plethysmograph, except that air was most carefully excluded from the interior of the organ.

In dealing with strong solutions of Cobra venom, and by this term must be understood anything stronger than  $1/100,000$ , the duration of a perfusion experiment is to be reckoned in seconds or, at the outside, in minutes. The beat of the heart is quickened, and the organ passes into a condition of systolic tone in which it speedily dies. The diastolic end of each excursus becomes progressively shortened, whilst the systolic end remains the same or may even be lengthened. It is not possible within the limits of this paper to attempt even a summary of the mass of tracings which have been taken, but a few typical experiments have been selected for analysis, the original records being preserved in the Archives of the Royal Society (Plate I).\*

On 29.10.03 a heart was perfused with blood mixture till a normal was obtained, and a  $1/10,000$  solution of Cobra venom in the same medium was then run through. The normal shows four beats in 20 secs. 1 min. after venom was turned on, the beats had risen to seven in 20 secs. ; 1 min. later the figure was 9.5 for the same period ; and after 3 mins. of venom perfusion the organ was dead in tight systolic position.

On 31.10.03 a heart was similarly perfused with a solution of  $1/50,000$  of the venom. Before venom was run in there were four beats in 20 secs. ; 2 mins. after poison was admitted there were 5 beats in 20 secs. ; 4 mins. after poison was

Extract 1.



Extract from a Tracing of a Perfusion of a Frog-heart with a solution of Cobra venom  $1/20,000$ . Systole is upwards. The arrow shows where the venom was run in. Time is marked in seconds and minutes.

admitted there were 6.5 beats in 20 secs. ; 5 mins. after poison was admitted the heart was in tight systolic position.

\* These references to plates are to the originals, from which only extracts are reproduced in this paper.



On 2.11.03 a solution of 1/100,000 was used for perfusion. Within 7 mins. of the admission of the poison, the rate of heart-beat had more than doubled, and in 20 mins. the organ was dead in tight systolic position.

In all of the above experiments an early contraction of the excursus took place, and in each case it will be observed that the shortening was at the expense of the diastolic portion of the curve, and never at that of the systolic portion. In the first experiment the contraction had begun in 30 secs., in the second in 100 secs., and in the third in less than 3 mins.

TABLE designed to show the Influence of comparatively weak Solutions of Cobra venom in increasing the Rate of Beat of the isolated Frog-ventricle, when perfused through its Cavity.

Time in minutes before venom-perfusion commenced.	10				5.75	9	10
	9				5.75	8.5	10
	8				6	8	8.5
	7				5.75	8.3	8
	6				6	8.5	7.5
	5	9	9.5		6.5	8	7.5
	4	9	9	7.5	6.5	—	7
	3	9	8	7.5	—	8	6.5
	2	9	8.5	7.5	7	8	6.5
	1	9	8.5	7.5	6.25	8.5	6.5
		1/500,000*	1/500,000*	1/1,000,000*	1/5,000,000*	1/10,000,000*	1/50,000,000*
Time in minutes after venom- perfusion had commenced.	1	9.25	8.5	8	6.25	8	6.75
	2	11	—	10	7.25	8.75	7.5
	3	13	10	10.25	8.75	9	7.75
	4	14	9.5	10.25	9	9	8.0
	5	14	10.5	10.25	9.25	10	8.5
	6	14	9.5	10.5	9	9.5	9
	7	14	8.5	10	9	9	9
	8	14	9		9	9	9
	9		9		9	9	9.5
	10		9		9	9.5	9.75
	11		9.5		8.5	10	10
	12		9.5			10	—
	13		9			10	—
	14		10			10	—
	15					10	11

\* Strengths of solutions of cobra venom used for perfusion.

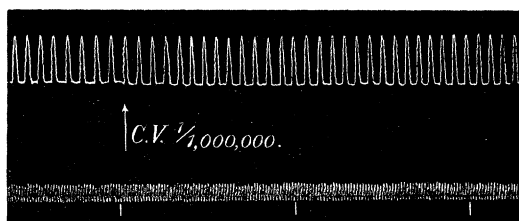
The figures in the first column give the number of minutes before and after the perfusion of venom solution. The remaining columns (one for each experiment) give the number of beats per minute of the isolated frog-ventricle in successive minutes. The strengths of the different solutions of venom used are also shown.

We pass next to the consideration of the effects of Cobra venom in more dilute solutions, and are now confronted with new difficulties. A heart which is perfused for 2, 3, 4, or more hours shows definite changes in its tracing, even to a superficial observer. When one comes to closely analyse such a record, and

to count the beats in successive minutes throughout, one finds that the rate of beat varies more than one had suspected. There is in fact a gradual tendency for the heart to beat faster at first and slower later on. At the same time its excursions slowly and steadily diminishes, and the organ drifts towards a position of diastole. Rarely one finds a heart pass very slowly towards the systolic position, but this is almost certainly due to some change in the blood used. Such a sample of nutrient fluid should, of course, be rejected, as it introduces fallacies into the research. Bearing the above facts in mind, one had to make a large number of tracings, both normal and otherwise, and to carefully exclude all those into which fallacies, due to the changes above described, had apparently crept.

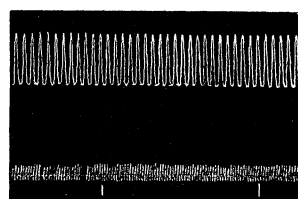
Some of these results are given in the subjoined table, and were selected from tracings in which the heart was either very steady, or actually slowing, at the time venom was introduced. (For tracings illustrating this section see Plate II.) Briefly, the case may be thus stated. Solutions of Cobra venom of a strength of  $1/250,000$ , of  $1/500,000$ , and even at times of  $1/1,000,000$  increase the rate of heart beat and kill the organ in a position of systole. With the last-named strength this result is, however, far from a certainty, but the influence of the venom in "toning up" and quickening a heart, especially if feeble before, is unmistakeable. Solutions of a

Extract 2.



Extract from a Frog-heart Perfusion Tracing, with a  $1/1,000,000$  solution of Cobra venom, at the time of running in the venom. Time marked in seconds and minutes.

Extract 3.



From the same experiment as Extract 2, but 25 minutes later.

strength of  $1/5,000,000$  and of  $1/10,000,000$  show no tendency towards producing systolic tone, but they quicken the rate of heart-beat, and make it very regular. Even a weaker solution ( $1/50,000,000$ ) has been shown to have the same action, but the experiment requires repetition.

For comparative purposes, experiments were next made with a very pure specimen of strophanthin, kindly given me by Sir T. FRASER. This was selected as being the most powerful known glucoside of the group to which it belongs. It has also the virtue of constancy in action. The tracings on Plate III. speak for themselves. They show that the action of the glucoside is much slower than that of the venom. (Compare plates I. and II. with III.). The tendency to diastolic phases alternating with periods of systolic tone are also noteworthy. The main features of similarity of

action of these two powerful poisons are, however, sufficiently striking, and closely ally them in their essential properties.

As an allied substance, acokantherin (one of the famous arrow-head poisons) was also tested. It taught but little of interest for the purposes of this paper, and its action appears to be linked up to that of Cobra poison through the intermediation of strophanthin. The specimen of acokantherin was kindly given me by Sir T. FRASER.

Lastly, I studied the action of sulphate of atropia on the isolated heart. This drug has been recommended for the treatment of cases of snake-bite in India.

At first sight one would expect atropine and its salts to be of value by virtue of its action on the vagus nerve-ends in the heart; for blood-pressure tracings show clearly that the heart is slowed in cobraism by means of stimuli which reach it through the vagi. Practically, it was found that, whilst sulphate of atropia had a slight beneficial action on the heart in the early stages of a Cobra poison blood-pressure tracing, the opposite was the case later on in the experiment. The heart, under the influence of the drug, would suddenly collapse, and pressure would fall to zero with a run. Indeed, Dr. PRENTICE (Vans Dunlop Scholar of Edinburgh University) and I found that even the careful administration of the drug at such a stage was most hazardous. I had previously tested atropine in various doses on rats, rabbits, and frogs, which had received very low lethal doses of Cobra poison. The results were entirely negative, so far as any remedial action was concerned. All this is readily explained in the light of my recent work; I find that, whereas the sulphate of atropia in strong solutions (1/1000) causes death of the heart in diastolic position (probably a nerve-end action), the opposite is the case with weaker strengths. Thus a 1/5000 or a 1/10,000 solution quickens the heart and causes it to pass into a condition of systolic tone, in which the excursus is greatly diminished at the expense of the diastolic portion of the curve. This systolic effect is lost with still weaker solutions, or at least cannot be demonstrated in frog-heart perfusions.

If we now combine Cobra venom and sulphate of atropia in the same solution, taking care that each substance taken separately is well below the strength which is capable of throwing the heart into systolic tone, we find that the joint action of the two is that of a powerful systolic poison. Indeed, the result appears out of proportion to what might have been expected from a knowledge of each substance's separate action. In order to illustrate this point, the three tracings shown on Plate IV. were taken on the same day from the same specimens of blood and under the same conditions in all respects. The heart on which the atropine test was made was not a very active one.

The absence of any tendency towards systolic tone in this tracing and in that of the venom alone is conspicuous, whilst in the case where the substances are combined, it is very marked indeed. One admits freely that such a strength of atropine as was used here would never be found *in corpore*, but on the other hand a much stronger

solution of venom might easily be present, and farther the action would be much more greatly prolonged. The main point is that the two substances may reinforce each other's action, and may thus possibly embarrass a heart. The sulphate of atropine would therefore appear to be a hazardous drug to use in cobra poisoned individuals.

I would take this opportunity of acknowledging the valuable help given me in my heart-perfusion work by my volunteer assistant, Mr. E. BURNETT, B.A. Lond.

*Comparison of Cobra Venom with certain other Powerful Poisons.*

Having carefully standardised the action of Cobra venom on frog-hearts and frog-vessels, in the manner already shown, one is in a position to compare this poison with other drugs which it resembles pharmacologically.

Professor T. R. FRASER\* found that strophanthin exerted an appreciable action on the frog-heart in solutions as dilute as 1/20,000,000. He computed that such an action was 8 times as powerful as that of adonidin, scillotoxin, or erythrophleine; 20 times as powerful as that of helleborein, 30 times as powerful as that of convallamarin; 300 times as powerful as that of digitalin; 6000 times as powerful as that of saponin; and 30,000 times as powerful as that of sparteine and caffeine. He concludes his comparison with the following words:—"The action of strophanthin upon the heart is, therefore, more powerful than that of any other substance, with regard to which data exist wherewith to institute a comparison."

Dealing with the action of strophanthin on the muscular tissue of the blood-vessels, he compares this drug with digitalin. In solutions of the latter as dilute as 1/100,000, he finds an early and powerful constrictive action manifested, whilst strophanthin does not give a distinct action in solutions weaker than 1/20,000. I cannot find that he carried the testing of digitalin down to weaker solutions.

It is pertinent to remember that in dealing with Cobra venom, we are in all probability not handling the isolated poison. This makes it still more astonishing to find its action carried down to such extreme dilutions as 1/10,000,000 or less. Even as it stands, the venom will rank superior in rapidity, and probably fully equal in strength, to strophanthin in its direct action on the heart; whilst in its action on the vessels it is probably not inferior to digitalin.

Reading through Professor FRASER'S paper, another point of considerable interest strikes one. It seems probable that the diastolic action he speaks of as found in strophanthin solutions may be due to the drug acting directly or indirectly on the vagal cardio-inhibitory mechanism, thus allying it still more closely with Cobra venom. This side of the action of Cobra venom will be dealt with later on in this paper.

\* 'Roy. Soc. Edin. Trans.,' vol. 36, pp. 403 *et seq.*



*The Action of Cobra Venom on the Frog-Heart in Situ.*

Having ascertained the action of the venom on the isolated frog-heart, the next stage in the investigation was the study of the organ *in situ*. *Rana esculenta* was used throughout.

After the destruction of the central nervous system, the body cavity was filled with strong venom solution (.001 gramme = 1 c.c.), and the heart movements were recorded by the suspension method. No change in rate was observed. When the same solution was dropped continuously on the suspended heart for 10 mins. at a time, the organ passed into a state of moderate systole, and its rate slightly increased. The action is interesting, as it is in opposition to the usual tendency of a suspension tracing, which is towards diastole and slowing (Plate V.).

The next step was to inject Cobra venom subcutaneously into frogs, and to closely observe the changes in rate of the heart-beat. Contrary to what holds in mammals, one found that the heart was not slowed by the venom. On the contrary, a distinct increase in rate was first observed at an intermediate stage, whilst late in cobraism the organ was beating with a frequency but little below that of the normal. It was thought possible that a slowing, due to the descent of vagal impulses, might be masked in these experiments by another factor, such as the influence of the poison on the heart muscle. In order to settle this point, a very careful count was kept of the exposed and undisturbed heart in various stages of cobraism, both before and after the application of atropine. No quickening of the heart was in any case observed, but, on the contrary, a distinct slowing was found in most cases. This latter phenomenon is very difficult to explain. At all events, it was clear that no increase of cardiac inhibition was actively present, and that the only observable action of the venom was to quicken the heart by directly acting on its muscular tissue.

Some farther series of experiments were undertaken, in order to ascertain whether Cobra venom had any direct influence on the centres, trunks, or nerve-endings of the vagi. Frogs were injected subcutaneously with doses of Cobra venom, which would be lethal, (1) in less than 12 hrs., and (2) in the course of several days. The animals were killed at various periods, by destruction of the brain in front of the medulla oblongata, and the activity of the vagal centres, and of the vagal nerves, was then carefully tested in each case by means of a secondary current. The centres were tested by laying bare the medulla oblongata, and directly applying the electrodes to its surface. The minimal stimulus required to definitely stop the heart was noted carefully, the current being applied for 10 secs. each time. The vagi were exposed in the usual way, and raised on the electrodes with a minimum of disturbance. They were not dissected free from the two nerves which accompany them, as this would have involved unnecessary handling. The results of these experiments went to prove most clearly that neither the vagal centres, the nerves, nor the nerve ends were at all affected by venom. This result was obtained whether the poison was in sufficient

dose to kill within a few hours, or in 2 or 3 days. Nor could it be found that the stage of Cobra intoxication the animal had reached had at all influenced the question. Normals were, of course, freely taken from uninjected frogs on the same days, and under precisely the same conditions.

Lastly, Cobra venom was directly applied to the exposed medulla oblongata of frogs, whose brains above this region had been previously destroyed. The earlier applications were made in solutions of various strengths. As no effect was thus produced, the poison was applied in as concentrated a form as possible, only enough RINGER'S fluid being added to dissolve the dry venom. This viscid fluid was then dropped on to the floor of the medulla oblongata. Muscular spasms at once occurred, but the suspension tracing showed that no slowing of the heart had taken place. It was evident that, under the conditions of the experiments, the vagal inhibitory mechanism of the frogs used (*Rana esculenta*) was unaffected by the venom.

One must bear in mind the frog's independence of its pulmonary respiration, especially in winter time. A cobraised frog will live on for hours, or even days, at any time of the year, after all perceptible signs of pulmonary respiration have ceased. Obviously, we have here a marked difference from the condition of affairs in the mammal, whose important medullary centres are speedily affected by any blood change brought about by deficient aëration. Moreover, these experiments were carried out during an Edinburgh winter, in a room whose temperature varied from a maximum of 56° F. to a minimum of some degrees below freezing point. For a large part of the 24 hours it was below 41° F.

In the summer I had performed a few experiments to study the action of Cobra venom subcutaneously injected into frogs, and I then found a distinct, though not very great, decrease in the rate of frog-heart beat under cobraism. In winter, as has been seen, I obtained no such decrease of rate. I am, therefore, prevented from drawing any definite conclusions from my winter work on the vago-inhibitory mechanism of the frog. Dr. PRENTICE, who was working last summer on similar lines, tells me that he, too, found some decrease of heart rate as the result of hypodermic injections of African Cobra venom.

#### *Perfusion of the Mammalian Heart.*

The number of experiments of this kind so far performed has been limited, but some very clear indications of the action of Cobra venom have been obtained. By the kindness of Professor SHERRINGTON and Miss SOWTON I was enabled to do a few experiments with their apparatus in Liverpool. This apparatus is fully described by them in the Report of the Chloroform Committee, which is printed as a supplement to the 'British Medical Journal' of July 18, 1903. The solution used for perfusion was as follows:—NaCl .9 per cent., CaCl<sub>2</sub> .24 per cent., KCl .42 per cent., NaHCO<sub>3</sub> .01 per cent., glucose, .1 per cent. The required quantity of Cobra

venom was dissolved in a portion of this fluid taken from the common stock. Care was taken to keep both the normal and the venom solutions at the same temperature, and under the same pressure. Cats and rabbits were used, and the isolated hearts were fed by tying the cut aorta on to the cannula, and perfusing through the coronary vessels; the aortic valves, of course, closed under the pressure.

The following notes give a brief summary of some of the results obtained, and the original tracings are also furnished.

(1) A cat's heart was perfused with a solution of Cobra venom, 1/10,000. In less than 5 secs. both auricle and ventricle passed into a stage of violent excitement, which was so marked that the levers could not be kept on the drum; they over-rode its edges. This lasted 175 secs. The heart then steadied down, and beat with great regularity for 140 secs. A second period of excitement then ensued, and lasted 105 secs. The excursus of the beats rapidly diminished after this, and the heart had ceased beating 125 secs. later. After 85 secs., perfusion with normal fluid was resumed, and at the end of another 200 secs., the ventricle recommenced to beat, the auricle having preceded it by nearly a minute. The singular phenomenon was then observed, of the occurrence of 2 ventricular beats for each beat of the auricles. This did not last long, but is of interest, as it is sometimes observed during the course of a blood-pressure tracing taken on a cobraised animal. The onward passage of a wave of contraction is apparently obstructed in its course from the auricle to the ventricle in such a way that it enters the ventricle at two spots, an interval occurring between the two invasions. The result is that two waves of contraction enter the ventricle at each auricular beat. After the heart had been beating for 7 mins., and had again settled down to fair regularity, the venom solution was re-introduced, with the result that the excursus of both auricle and ventricle rapidly diminished. The latter had ceased beating in  $1\frac{1}{2}$  mins., and the former in 4 mins., thus closing the experiment.

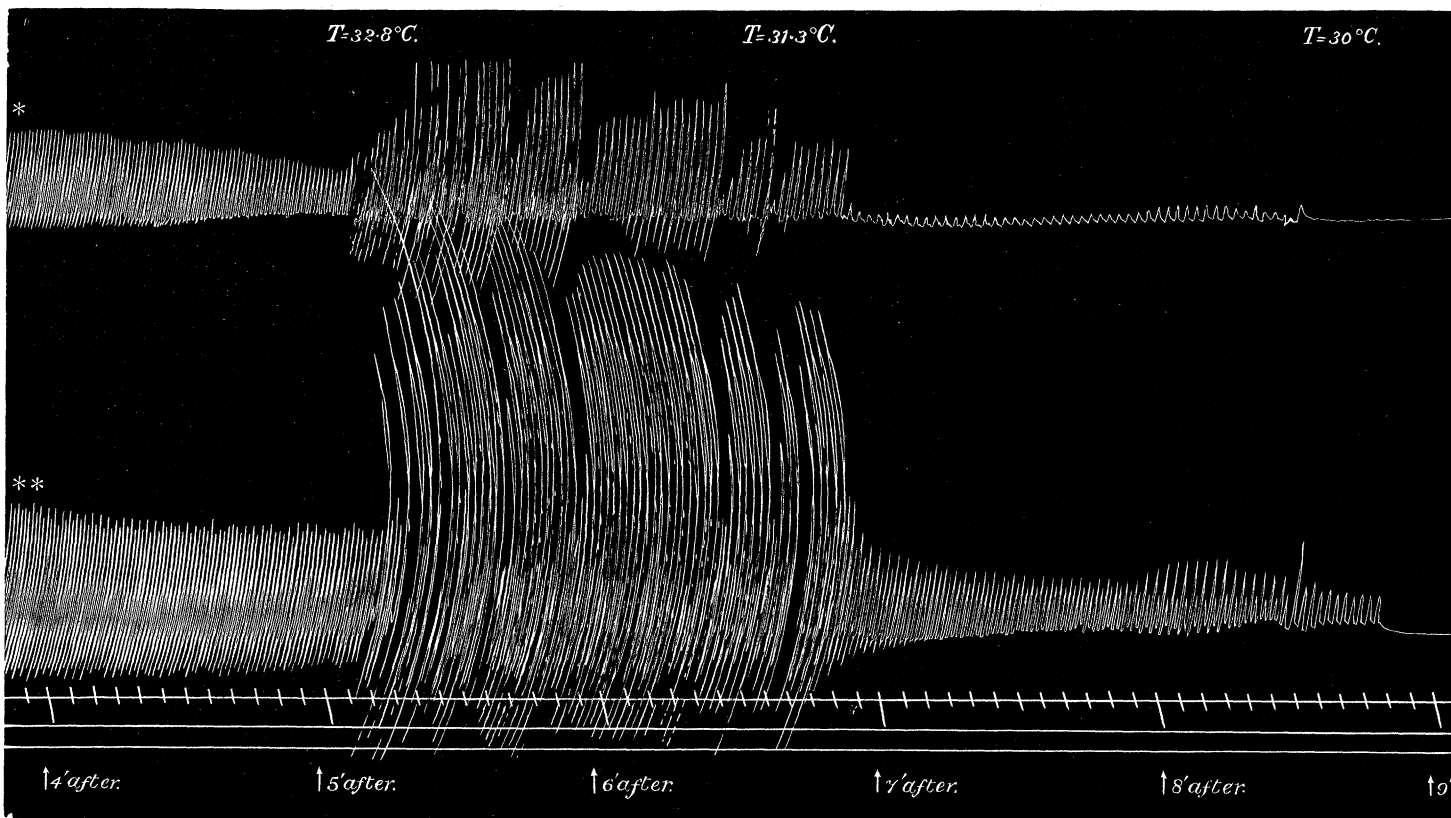
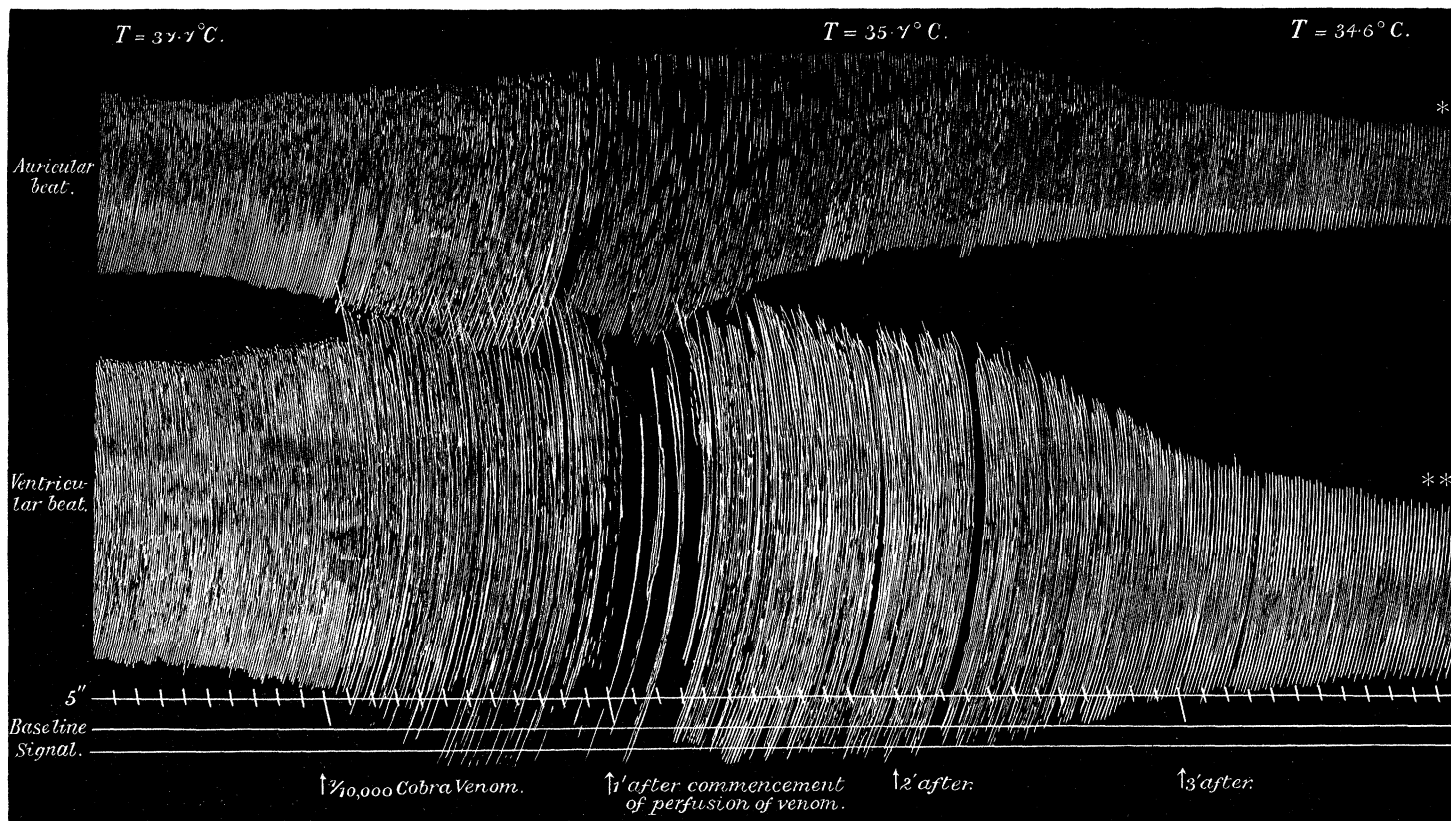
The tendency of both chambers to pass into a systolic phase was obvious, though masked, in both stages of the experiment. The flow through the coronary vessels decreased rapidly, and had almost ceased at the end of the experiment. This is, doubtless, to be attributed partly to the state of systolic tone into which the ventricle was thrown, and partly to a direct constrictive action of the venom on the coronary vessels. Any delay in perfusion will, obviously, lead to a cooling of the heart, and it has been abundantly proved that cooling at once slows the organ. The result is, that the tendency of the venom to increase the rate of the heart is in all these experiments largely masked. Careful analysis of a number of tracings shows, however, that the tendency to quickening of the beat is actually present. This brings the action of Cobra venom on the mammalian heart into line with what we have seen occurs in the frog-heart.

(2) A cat's heart was perfused with a solution of Cobra venom of a strength of 1/50,000. The amplitude of the ventricular excursus began to increase almost at once, reaching its maximum between the 11th and 20th mins. It then decreased



THE ACTION OF INDIAN COBRA VENOM.

Extract 4.



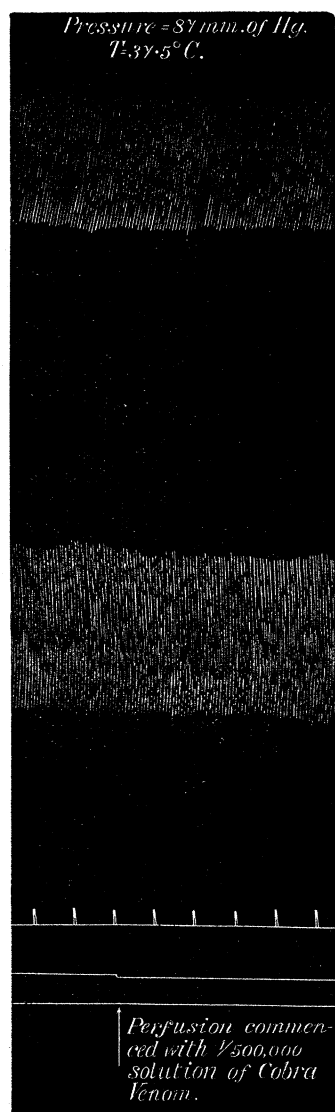
The tracing from the first half of Experiment (1). Cat-heart Perfusion with 1/10,000 Solution of Cobra Venom.



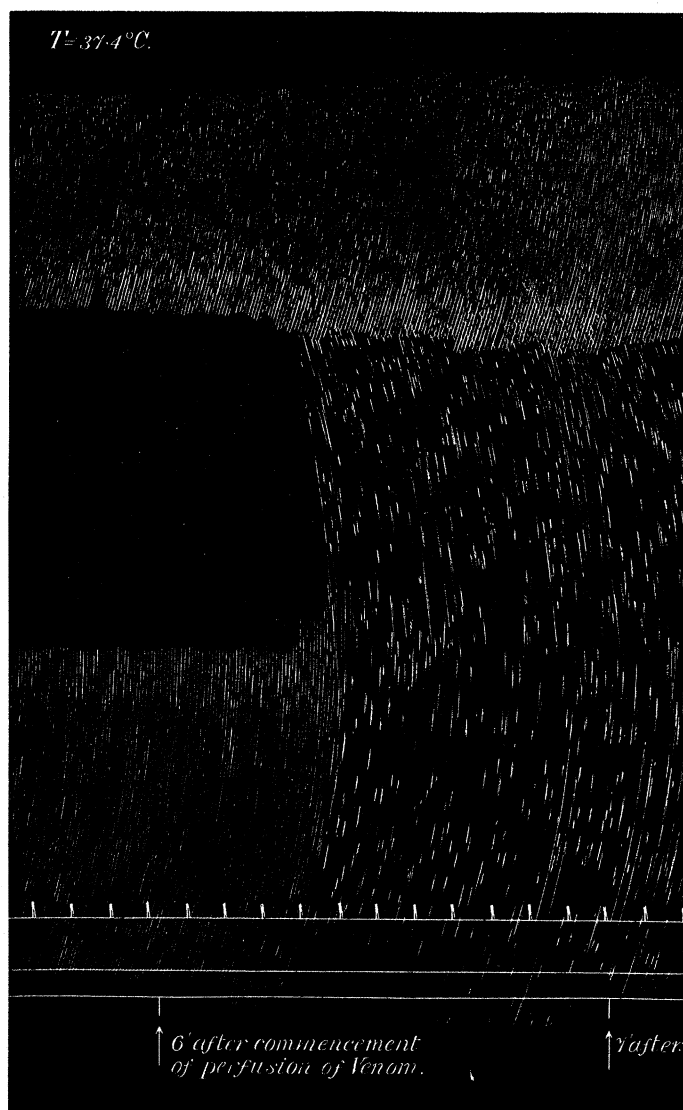
rapidly and the beat had practically ceased 7 mins. later. The auricle was much slower in first becoming affected, and also continued beating about 1 min. after the ventricle had ceased. Phases of excitement with intermissions are observable throughout both the auricular and ventricular tracings, but are much better marked in the latter than in the former. Both chambers showed a decided tendency towards systolic tone, as may be seen on the record. The same phenomena, dependent on constriction of the coronary circulation, again appear on this tracing.

(3) A cat's heart was perfused with a solution of Cobra venom of a strength of 1/100,000. The heart showed a tendency to beat in groups whilst being perfused

Extract 5.



Extract 6.

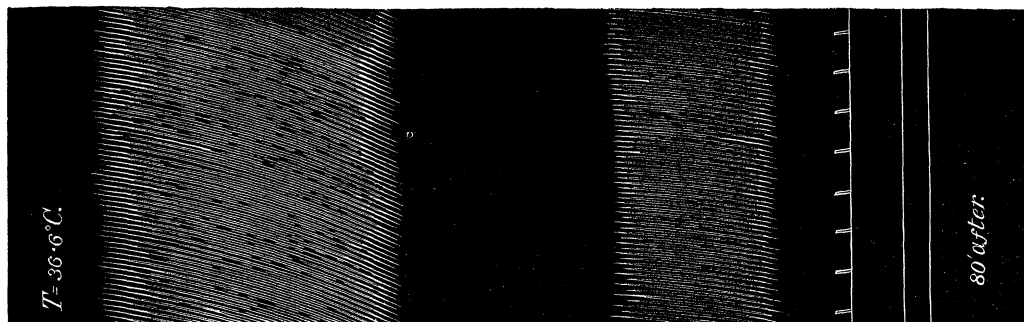


Extracts from Cat-heart Perfusion Tracing, with Solution of 1/500,000 Cobra Venom.  
(See also Extracts 7 and 8.)

Extract 7.



Extract 8.



with the normal fluid. One minute after venom solution was admitted, the auricular excursus (which alone was recorded), began to show signs of excited cardiac action. This stage lasted 7 mins., and was succeeded by an intermediate phase in which the heart became much more regular than it had hitherto been. This lasted another 7 mins. The heart then became more irregular than ever, and ceased to beat about 9 mins. later. The tendency of the organ to pass into systole was well marked.

(4) A cat's heart was perfused with a solution of Cobra venom of a strength of 1/500,000. Within 2 mins. of the venom reaching the heart, both beats (auricular and ventricular) commenced to increase in volume, and displayed a decided rhythm in so doing. Four and a half mins. later the ventricle became suddenly and violently excited. This stage lasted 11 mins. and an increase in the rhythmical variation of the strokes was observed. At the same time the auricle was passing through a similar but less pronounced phase of excitement. It is of interest to notice that the periods of rhythmical excitation and remission are not synchronous in the records of the two chambers. The heart at first showed quickening of its beat, but this was soon masked by the cooling consequent on systolic retraction. For over an hour a steady, even and regular beat was maintained, but the excursus gradually diminished. The experiment was stopped by the venom solution running out. When allowance is made for the interference with the coronary circulation, this tracing reminds one strongly of the results yielded by frog-hearts, for the organ after a preliminary period of excitement is first steadied and then slowly poisoned. It is important to remember that a strength of 1/500,000 of venom might possibly be present in the circulation of a Cobra-bitten man.

A number of other tracings are available to show the influence of Cobra venom on the heart of cats and rabbits in strong solutions (1/5000 to 1/50,000). In every one of them the inclination of the heart to pass into firm systolic tone is clearly shown, whilst most of them display a distinct tendency to quickening of the beat very soon after the heart is affected by the venom. The early phase of excitement and the rapidly following failure are also constantly in evidence. We may summarise the action of Cobra venom on the isolated mammalian heart, thus :—

(I.) Strong solutions kill the mammalian (cat or rabbit) heart very quickly in a position of systolic tone, both chambers being similarly affected.

(II.) The death of the organ is preceded by a phase of excitement, during which the heart movements are greatly exaggerated.

(III.) During the stage of excitation the rate of beat is sensibly increased, though this is obscured by a fall in the temperature of the perfused fluid, that fall being due to obvious instrumental defects, which are difficult to eliminate. The influence of the venom on the intra-cardiac terminals of the inhibitory mechanism may, and probably does, play an important part in these experiments.

(IV.) The condition of systolic tone, and almost certainly also, the constriction



of the coronary vessels, produced by the circulating venom, greatly interfere with the circulation through the heart-tissues.

(V.) Less strong solutions of Cobra venom appear to have a stimulating and steadying effect on the heart, but even so dilute a solution as 1/500,000 gives rise to a preliminary phase of excitation, and tends in the end to kill the organ.

(VI.) The greatly increased amplitude of cardiac excursus seen in the excitation phases of these tracings, would seem to indicate, as suggested in para. III. above, that two distinct influences are at work on the mammalian heart, when it is under perfusion with solutions of Cobra venom. These are (1) the direct action of the venom on the muscle or on the nerve terminals which convey impulses leading to contraction, and (2) its action on the terminals of the vago-inhibitory mechanism. The former tends to throw the heart into strong systole, whilst the latter draws it towards diastole.

#### *Blood-Pressure Experiments on Rabbits.*

Early in 1903, Dr. PRENTICE and I made a number of blood pressure experiments on cobraised rabbits under chloroform. Each tracing was subsequently analysed by me in the following manner. At short and regular intervals, the blood pressure was estimated in millims. of Hg, the heart beats and respirations were counted for the corresponding 10 secs., and the amplitude of the respiratory excursus was measured. The amplitude of the beat was not measured on the tracings, since it is no criterion of the force of the heart. The details thus obtained were then mapped out on charts, so that a comprehensive survey of the whole experiment could be easily and quickly obtained. It would be impossible within the limits of this communication to do more than give a summary of the results obtained.

The tendency of most of the past work on the subject has been to give doses of snake venom which proved fatal in very short periods of time (ranging usually from 10 mins. to 1 hr.). We desired to avoid this as far as possible, bearing in mind that such poisons take, as a rule, from 3 hrs. upwards to kill, and that it was therefore unsafe to draw deductions from what must obviously be extreme overdoses. We accordingly endeavoured to graduate our doses so as to kill in periods of from 5 hrs. downwards. Intravenous injections were made almost invariably.

It was observed that when a relatively large dose of Cobra venom was given (one that would prove fatal in an hour or less), the blood pressure fell rapidly and suddenly, whereas when the dose was graduated to kill in the course of several hours, little or no primary fall took place. Whether there was an initial fall or not, the blood pressure subsequently rose in most cases to or beyond its previous level, which it frequently greatly exceeded during the asphyxial stage which heralded death. Rarely there was no recovery to speak of after the first fall of blood pressure; this occurred when doses were given which proved fatal in 20 mins. or



less. When the dose was a low one and gradually given, the blood pressure rose steadily from the first, and sometimes attained very high levels. A point of great interest was that it was impossible to trace any sufficient relationship between the early falls of blood pressure and changes in the rate of the heart beat at the time. For instance, in one case a rabbit received half the subcutaneous M.L.D. intravenously, and the blood pressure fell from 108 to 55 millims. in the carotid, and again recovered till it stood at 98 millims. The whole took place in 4 mins. and the rate of heart beat only varied from 41 to 39 in the time. Obviously the force of the beat must have varied greatly, or some other powerful factor must have come in.

The general tendency in these tracings was for the rate of heart beat to decrease steadily till near the end of life, when the fall became suddenly rapid, and was accompanied by a corresponding rapid descent of blood pressure. Occasionally a slight rise in cardiac rate was observed for a short time after the injection of the venom; this only occurred when low lethal doses were given.

The sudden final fall of blood pressure was the more remarkable, since in most cases the pressure was very high just before it occurred, though the heart beat had been diminishing steadily in frequency for a long time previously. The final run down of these two curves (blood pressure and heart rate), strongly suggests cardiac failure as the cause of the ultimate collapse of blood pressure.

To what was one to ascribe such failure?

The following suggested themselves as its possible causes:—

- (1) Inhibition of the heart by the direct action of Cobra venom on its vagal inhibitory mechanism.
- (2) Inhibition due to asphyxiation of the same mechanism, as an outcome of respiratory failure.
- (3) Direct or indirect action of the venom on the cardiac muscle or on its vagal ganglia.
- (4) Direct or indirect interference with the vaso-motor centre, leading to vasodilatation of the splanchnic area, and possibly
- (5) A contributory reflex inhibition of the heart as the result of high arterial pressure.

In order to throw light on these obscure points, we adopted a number of devices.

(A) We tested the activity of the vaso-motor centre in the rabbit, by stimulating in turn the depressor and sciatic nerves in animals which were in various stages of cobraism. We found that a marked response was elicited in either case up to the very end of life. There was, therefore, a strong presumption that the vaso-motor centre was not markedly affected by Cobra venom, though the TRAUBE-HERING curves which we noticed as a common feature in our tracings, suggested that it was in a state of excitement, probably as a result of asphyxiation. It is just possible that the leakage of magnesium sulphate into the blood may be sufficient to account for the presence of these curves.

(B) We cut the two vagi at various stages of our experiments, and observed the effect. As is well known, the vagal inhibitory mechanism of rabbits is not very active. We found comparatively little change produced by section of these nerves before the injection of venom or even after the injection, provided that marked slowing had not yet occurred. Later, however, the section of the vagi caused a distinct rise, both in the rate of the beat and in the height of the blood pressure. When the section of the nerves was made during the final fall of pressure, it raised the rate of beat slightly, but the pressure not at all. It is noteworthy that preliminary section of the vagi did not prevent the ultimate cardiac slowing, though it appeared to distinctly delay its evolution. Stimulation of the vagi always caused active inhibition, thus negating any idea of paralysis of the vagal nerve-end mechanism in the heart.

(C) We injected small doses of atropine sulphate intravenously at various stages of our experiments, and observed the effects. Before marked cardiac slowing had set in, the result of these injections was inappreciable, but later, when the rate of beat had fallen considerably, each injection was followed by a distinct quickening of the heart, a quickening which seemed to hold some relation to the amount of slowing which the venom had previously produced. In no case, however, was the rise in rate associated with a corresponding rise in blood pressure; on the contrary there was always a fall in pressure, following each injection.

The apparent conclusions were as follows:—

(1) The vaso-motor centres were not responsible for any of the main features of change in a blood pressure tracing of an animal poisoned by Cobra venom.

(2) Inhibitory impulses descending the vagi played a part in the slowing of the heart; the vagal mechanism remained active throughout.

(3) The cardiac slowing observed was only partly due to central vagal inhibition and a farther explanation for it must be sought.

*Respiration.*—The respiratory movements were recorded, either by the double stethograph or by a modification of HEAD'S method.

These tracings taught but little that has not already been observed as to the changes in respiration during cobraism. The main tendency was for the rate of respiration to fall, and for the type to become at first irregular and then spasmodic. This irregularity influenced both the rate and also the amplitude of respiration. As death approached, the spasmodic gasps became more and more frequent, culminating in dyspnœal storms which were followed by periods of apparent respiratory exhaustion. Respiration always ceased before the final fall of blood pressure, and it was not uncommon to find the blood-pressure curve rise steeply just before death. This was presumably due to excitation of the vaso-motor centre by venous blood. The same cause will explain the cardiac inhibition which we have seen brought about the final fall of blood pressure.

I have dealt with these experiments apart from the rest of my blood-pressure work,

because I desire to acknowledge the assistance I received, both from Dr. SILLAR and from Dr. PRENTICE, in carrying them out. For the conclusions drawn, I must, however, take the whole responsibility.

*Blood-Pressure Experiments on Cats and Dogs.*

In order to follow up the subject, I undertook a further series of experiments on cats and dogs. Very few of the latter were used. Cats are preferable to rabbits, as they are more hardy, and have tougher vessels and tissues. These experiments were, by Professor SCHÄFER's kind permission, carried out in the Physiological Laboratory of the Edinburgh University.

A few tracings were first taken with the object of comparing the results obtained with those already dealt with above (on rabbits). The shortest experiment lasted 40 mins. and the longest 4 hrs. An added point of interest lay in the tracings of intestinal volume taken simultaneously with the general blood pressure, by means of a modification of SCHÄFER's plethysmograph. It may at once be said that all the evidence showed that the vascular pressure in the splanchnic area was affected by the venom in exactly the same way as was the general blood pressure. It in no sense reacted independently. In fact, it is possible to trace each change of general blood pressure on the plethysmographic tracings. With cardiac inhibition or with cardiac recovery they move down or up together, whilst the constriction of their respective vessels by the direct action of the venom on their walls is indicated by a downward movement of the plethysmographic lever and an upward movement of the manometer needle.

These results clearly support the conclusion arrived at by Dr. PRENTICE and myself, that the vaso-motor centre is not profoundly affected by Cobra poison, and that the final fall of blood pressure in cobraism is not due to a paresis of this centre.

This preliminary work on cats brought out a farther point of interest, namely, that in these animals the early fall of blood pressure which immediately follows the injection of a large dose of Cobra venom is due to cardiac inhibition. This is well shown by the extract (9) from a blood pressure tracing to be found on Plate VI.

The slowing of the beat is well marked. I presume that the absence of this feature dwelt on in rabbits is to be explained by their lessened activity of cardiac inhibition. This question of inhibition will be dealt with more fully in the next section.

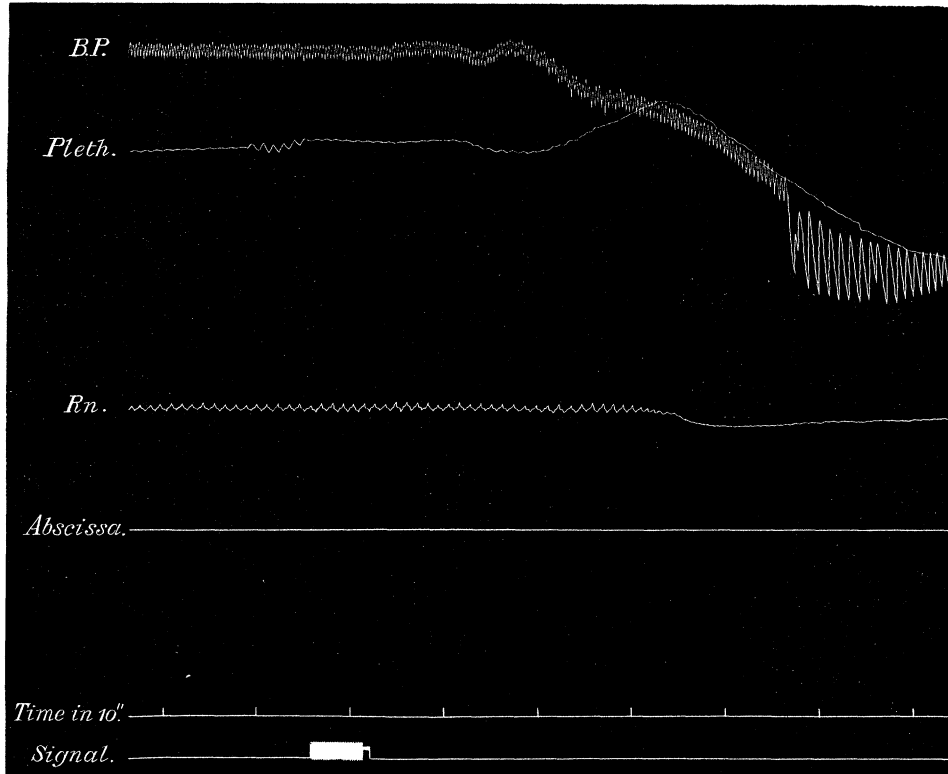
*Experiments on the Exposed Mammalian Heart (in situ).*

My next step was to study the effect of venom, with the chest opened. Artificial respiration was kept up from the first; a portion of the thoracic walls was removed to expose the heart, and the movements of the auricle and ventricle were conveyed to two levers by means of silk threads working over pulleys and attached by hooks to the auricular and ventricular walls. The blood pressure in a large artery (carotid or femoral) was at the same time recorded, and in a few cases the vascular changes of

volume in a loop of small gut was also taken by means of a plethysmograph. Care was taken to fix the heart steadily by means of a pair of forceps, clamped in place, and taking a good hold of the fat at the auriculo-ventricular junction. The animal was carefully kept warm throughout the operation.

In some of the experiments, large doses of venom were given in order to study the cause of the blood-pressure fall which has been already alluded to as occurring under

Extract 9.

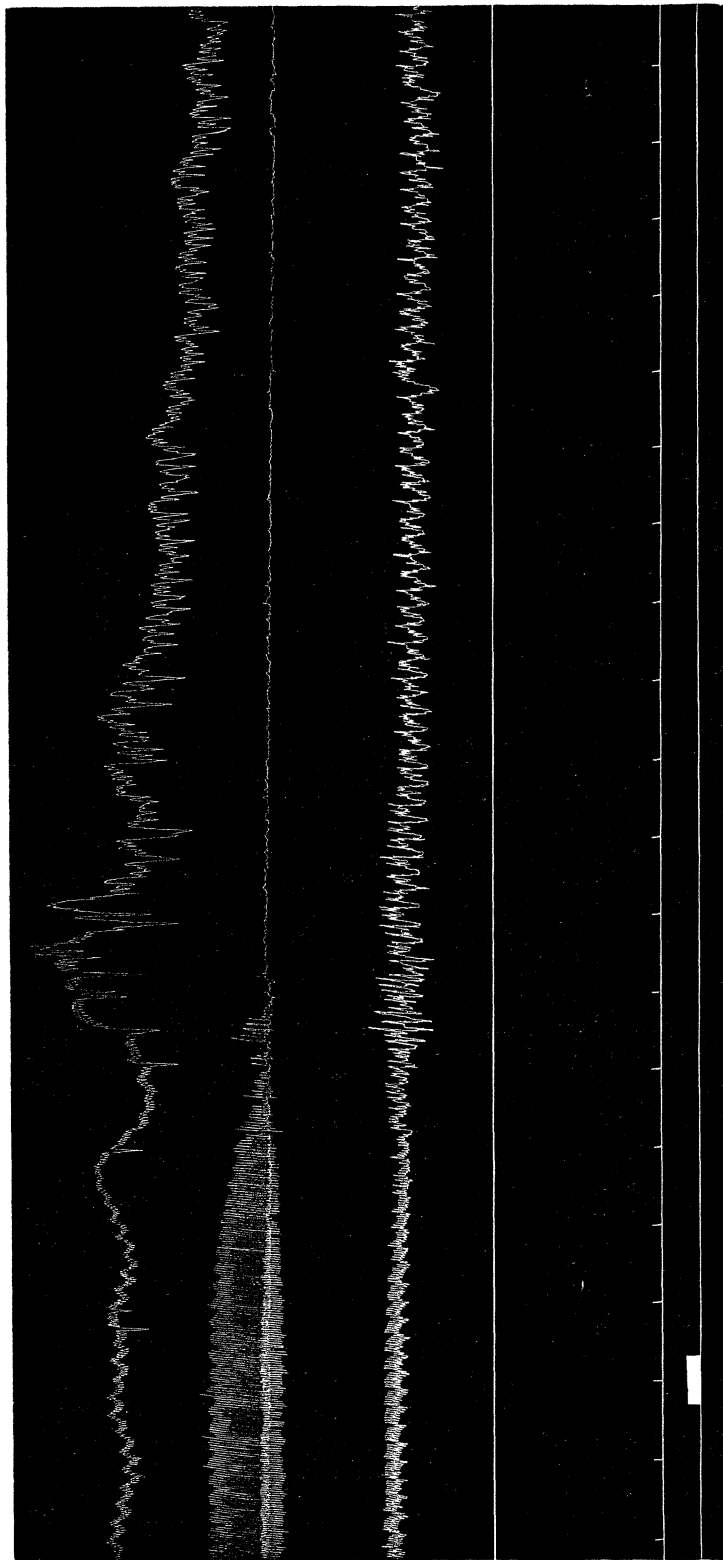


Extract from Plate VI. A male cat, weight 2 kilogrammes, received intravenously one-sixth of the subcutaneous M.L.D. at the point signalled. B.P. = blood-pressure trace; Pleth. = record of intestinal volume taken in Brodie's plethysmograph; Rn. = respiratory trace taken by a double stethograph. Note the evidence of cardiac inhibition and respiratory failure quickly following the injection of venom.

such circumstances. Plate 7 throws a good deal of light on this subject (Extract 10). In it extracts are given from two tracings, one of which was taken from a dog and one from a cat. The doses of venom given were speedily fatal, though the dog rallied temporarily, as shown in the plate. In both cases it will be observed that marked inhibition took place, the auricle stopping in complete diastole, and the ventricle beating very irregularly. On the same plate will be found analyses of the whole of the two experiments. (Full explanations accompany each chart, but it may be said that throughout this paper all tracings are to be read from left to right; systole is always upward; the charts analysing tracings are kept on the same plan throughout, the same colours being always used for the same purpose, blood pressure



Extract 10.



Extract from Experiment II., Plate VII. A dog, weight 10·7 kilogrammes, received intravenously one-fourth the subcutaneous M.L.D. at the point signalled. The traces in order from above are blood pressure, auricular beat, ventricular beat, abscissa, time in 10", and signal. Note the marked cardiac inhibition.

is always estimated in millims. of mercury ; heart-beat rate in beats per 10 secs. ; respirations in respirations per 10 secs. ; the auricular and ventricular excursus are charted by multiplying the actual by 10, and stating in millims.).

To what is this cardiac inhibition\* due? Clearly it is not brought about by asphyxiation of the vagal inhibitory mechanism, for the animal was under artificial respiration throughout in each case. Farther, if one refers again to Plate VI., extract 9, it is obvious that the failure of respiration cannot wholly account for the inhibition seen, though it may have contributed to produce it; for the cessation of breathing precedes the manifestation of cardiac failure by too short an interval.

Returning to Plate VII., it is observed that in extract 10 (the cat) the auricle was inhibited and the ventricle became feeble and irregular. The latter appeared to have taken on the independent rhythm characteristic of the ventricular beat, when removed from the control of the auricles. In extract 2 the auricular inhibition is early and complete, while the ventricle passes into an even more pronounced stage of irregularity than that of the cat. It is particularly noticeable that we have here to do with *distinct inhibition*, the auricle stopping in diastole, and the ventricles tending to do the same.

If now we turn back for a moment to the work on the isolated frog and mammalian hearts, several points of interest present themselves. An easy calculation shows that the concentration of venom in the two experiments of Plate VII. was below  $1/50,000$  ; in fact, it was about  $1/10,000$  in the dog, and  $1/18,000$  in the cat. These calculations omit to make allowance for the fact that at first, at any rate, the venom could not have been distributed throughout the entire volume of blood. The strength of solution must therefore have been greater than the calculation shows. Such a concentration of Cobra venom would, as we have seen, kill a frog-ventricle in a few minutes, acting on its muscular tissue, and throwing it into systolic spasm. On the mammalian heart we have observed that the same tendency to pass into systolic tone is manifested, but that it is largely masked in the early stages of the experiments by the violent excitation of the heart muscle, and possibly also by the action of the venom on the terminals of the vago-inhibitory mechanism in the heart. Of this, more later on. We noticed that the isolated mammalian heart took much longer to be killed than the frog-heart, when the same strengths of venom were used, and that the marked quickening of the beat, which was so obvious a feature in the latter, was masked in the former, partly, no doubt due to the cooling of the perfused fluid, when obstruction was offered to its outflow. The influence of the action of the venom on the terminals of the vagal inhibitory mechanism must not, however, be lost sight of.

The differences between the behaviour of the isolated heart and of the heart *in corpore*, which we have just been reviewing, show that two active and opposite

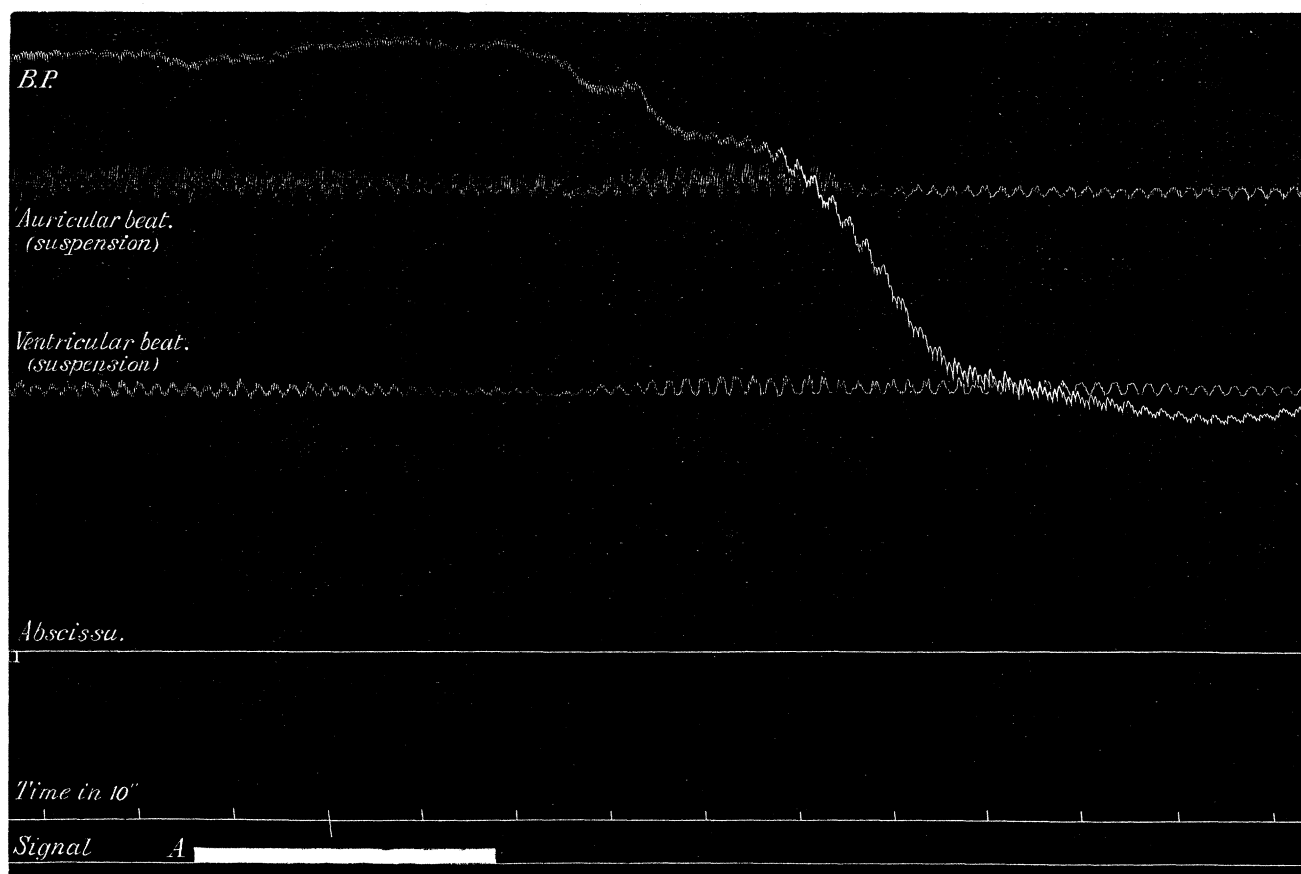
\* Throughout this paper I have ventured to include two elements under the term "cardiac inhibition," viz. : (1) A decrease in heart-rate, and (2) A diminution in heart-force.

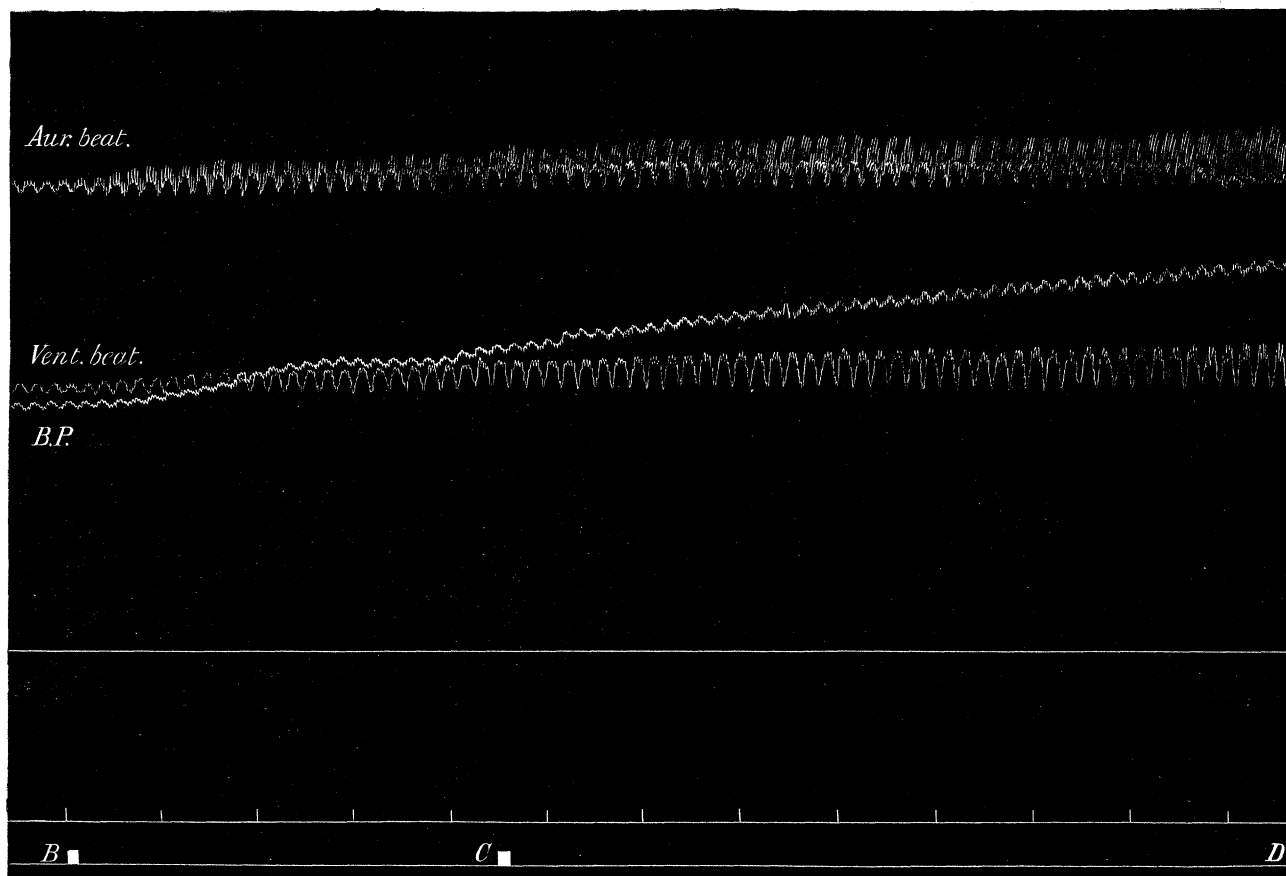
forces are called into play by the injection of Cobra venom. On the one hand we have the direct action of the venom on the heart muscle throwing it into systolic tone, and on the other we have evidence of inhibition powerful enough to mask and overcome this direct action. The rapidity of the inhibition was suggestive of central action, and in order to test this point the vagi were cut in animals whose hearts had been inhibited by the action of various doses of venom.

Plate VIII. contains extracts from three such experiments. Extract 1 is from a cat which had received intravenously one-seventh of the subcutaneous M.L.D.; inhibition of both auricle and ventricle was marked, but not complete; section of the nerves produced a striking effect, for not merely was the inhibition removed at once, but the beat became much stronger than before. The last circumstance I attribute to the action of the venom on the heart muscle, which has already been noticed in connection with the isolated heart.

Extract 3 is from a similar experiment in which the dose of venom was much lower, being only one-twelfth of the subcutaneous M.L.D. The fall in blood pressure was less marked and longer delayed, and inhibition was less complete; the auricles were very distinctly affected, the ventricles decidedly less so. Here, again, the influence of section of the vagi was immediate and unmistakeable; the inhibition, brought

Extract 11.



Extract 11—*continued*.

Extract from Experiment 1 of Plate VIII. The traces in order from above downwards are (1) blood pressure, (2) auricular beat, (3) ventricular beat, (4) abscissa, (5) time in 10", and (6) signal. (A) marks the injection of venom, (B) the section of the left vagus, and (C) that of the right vagus.

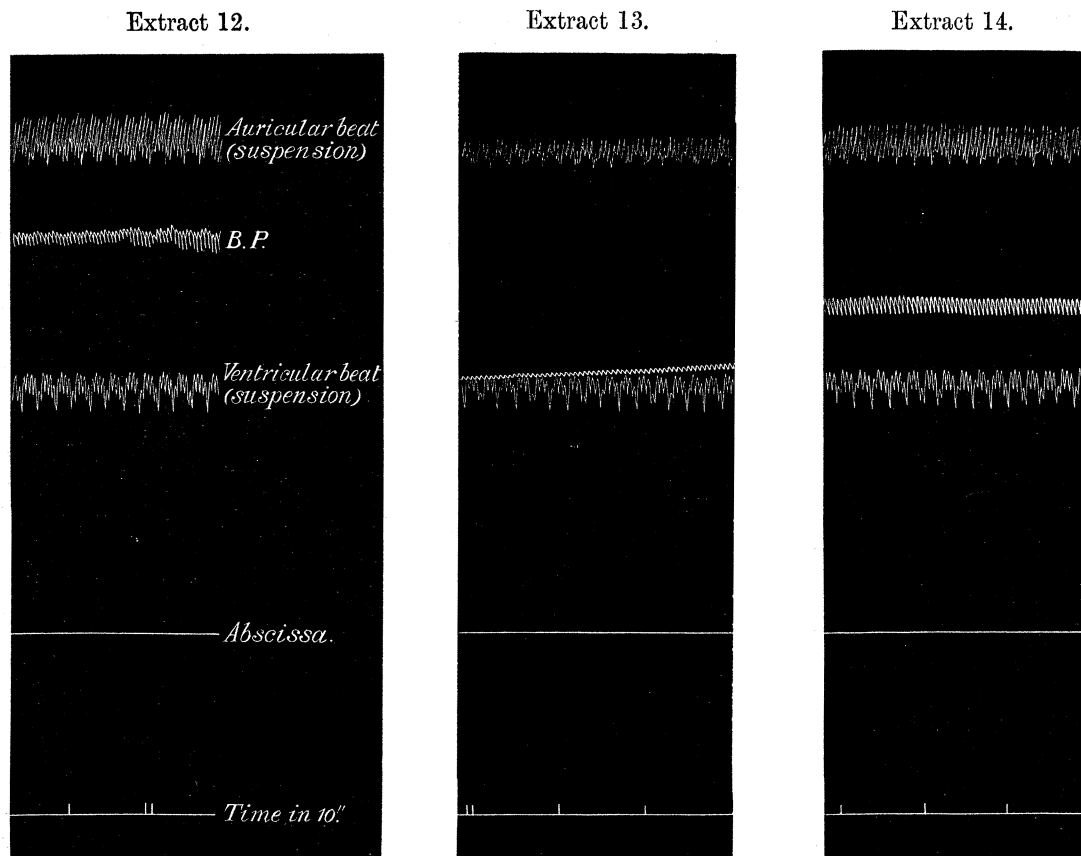
about by the injection, was at once removed for the time, at least. An analysis of the experiment is shown at length on Plate VIII. (see back thereof), and it will there be seen that inhibition reasserted itself, and was again checked late in the experiment by the division of an overlooked strand of the right vagus.

Extract 2 of Plate VIII. shows that in the cat, late section of the vagi produces a much less pronounced effect than an early section. This must not, however, be taken as in any sense contradictory of the results in rabbits, for we are not now dealing with the effect of Cobra venom on an animal which is being gradually killed by an ordinary lethal dose, but with the effects of a dose which would long before have proved lethal had not artificial respiration prolonged life far beyond its ordinary term. Here the question of nerve-end paralysis comes in.

A farther light on the subject is obtained by study of the extracts from the tracing on Plate IX. The complete analysis of the tracing is also given. A dose of venom corresponding to one-eighteenth of the subcutaneous M.L.D. was first given intravenously, and subsequently (the vagi remaining intact) small doses (half the first each



time) were injected in the same way. It is abundantly clear that there are two forces pulling against each other, viz., inhibition lowering the force of the beats, and a direct muscular action increasing their force.



Extracts 12, 13, and 14, from Plate IX. The traces in order from above down are (1) auricular beat (2) blood pressure, (3) ventricular beat, (4) abscissa, (5) time in 10''. The first extract is taken before the administration of the second small dose of venom, the second 8' after this injection, and the third 5' later still. Note that the blood pressure first falls and then rises, whilst the auricular and ventricular beats vary correspondingly in their amplitude.

Plate XI. affords an interesting contrast to the last. Here we have practically the same experiment, with this important exception, that the vagi were divided after the first dose of venom. A steady diminution of the beat-excursus is here observed, but the up and down character of the chart is lost. The only apparent explanation is that the vagal impulses of central origin, which are sent out under the influence of cobraism, have been cut off.

How, then, are we to explain the fall of blood pressure, beat-rate, and beat-force, which occur even after division of the vagi. Due allowance being made for the shock inseparable from so severe a procedure as opening the chest, I think there still remains a residue to be accounted for, and the only explanations that offer themselves are (1) exhaustion of the muscle (which is indicated as probable in the late stages of

experiments with isolated hearts), and (2) stimulation of the vagal terminal apparatus in the heart, as suggested by BRUNTON and FAYRER. If such a stimulation really takes place, it would be not unlikely that some evidence of nerve-end affection could be obtained by giving an animal large doses of Cobra venom, and keeping it alive for long periods by artificial respiration. I tried this on several occasions, and the result was always the same. The vagal nerve ends were not paralysed, but they were always greatly dulled. Plate X. illustrates this, and I think it will be admitted that after every allowance has been made for fallen blood pressure, for repeated stimulation, etc., the nerve-end mechanism shows decidedly the effect of the venom.

*Experiments to Test the Action of Artificial Respiration with the Chest-Walls Intact.*

I next turned my attention to the influence exerted on the heart, and on blood pressure, by artificial respiration used with the chest walls intact, after ordinary respiration had failed. The experiments were of great interest, and I, therefore, give them each in turn, but as shortly as possible.

*Plate XII.*

Dog, weight 5·7 kilos.; chloroform by tracheal tube; blood pressure taken in femoral; respiration recorded by a stethograph clamped in position on the chest wall; intestinal volume by the plethysmograph; all injections of venom solution made by a cannula tied into the external saphenous vein (the venom was dissolved in RINGER'S fluid, as usual in my experiments, '0005 gramme = 1 c.c.).

In all, a little over one-fourth of the subcutaneous M.L.D. of venom was injected in rather more than 70 mins., the injections being given at regular intervals. Eighty-four mins. after the first injection respiration had failed, having ceased 2 mins. earlier, the heart-beat had fallen from 21 to 22 in the 10 secs., and blood pressure was at danger point. Artificial respiration was at once commenced, and the recovery of heart-rate and blood pressure was immediate; the former went up to 28 per 10 secs., and the blood pressure shot up higher than it had yet been during the experiment. After 13 mins. the artificial respiration was stopped, and in less than 12 mins. the blood pressure was at zero, the heart had stopped, and the animal was dead. A complete analysis of this experiment is given on Plate XII., and extracts from the most interesting portions of the chart are also furnished there. A point to which I draw special attention is the partial recovery of respiratory function after a period of artificial respiration.

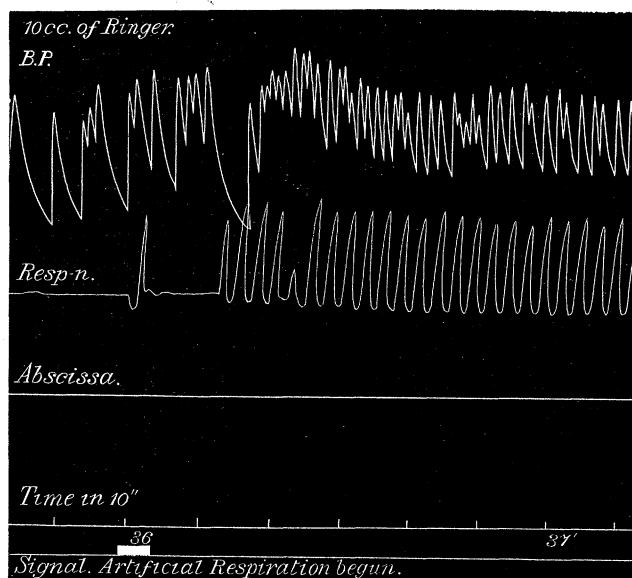
*Plate XIII.*

The next experiment closely resembled the last. The dog weighed 5·5 kilos.; no plethysmographic tracing was taken; the first injection was a very large one,

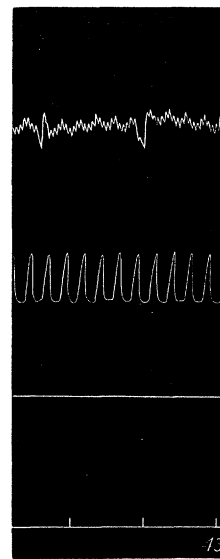
corresponding to five-sixths of a subcutaneous M.L.D. of Cobra venom. This was given by the external saphenous vein, as in the last case. The rate of heart-beat ran quickly up, and then as quickly went down again; blood pressure fell steeply; there was evident strong inhibition; respiration showed a short, sharp check, which will not, however, account for the inhibition, for it is too late, and too transient after a temporary recovery; a late fall of respiratory force and frequency set in, ending in complete failure, which necessitated the use of artificial respiration 36 mins. after the injection had been made. The heart-beat fell rapidly toward the end, reaching 3 in 10 secs., and there was an asphyxial rise of blood pressure. Artificial respiration steadied the blood pressure, and the heart-beat at once rose to more than its former level. A second injection of venom (half the previous one in strength) brought the heart-rate down from 23 to 24, and the blood pressure also began to fall. Section of the vagi quickly sent the beat up again to about its previous figure. From this time on, an interesting feature appeared on the tracing, for the beats occurred in phases which alternated with each other. In one phase the beats were exactly double those in the other. Evidently 1 beat out of 2 tended to be suppressed, or, rather, failed to be able to pass some obstructive barrier, probably at the auriculo-ventricular junction.

Three farther doses, each of the same strength as the last, were now given at intervals, the last two being injected, with only 2 mins. between them; yet there was no further evidence of inhibition beyond an increasing tendency for the phases of slow beat to lengthen to the exclusion of those of the faster beat. Blood pressure

Extract 15.

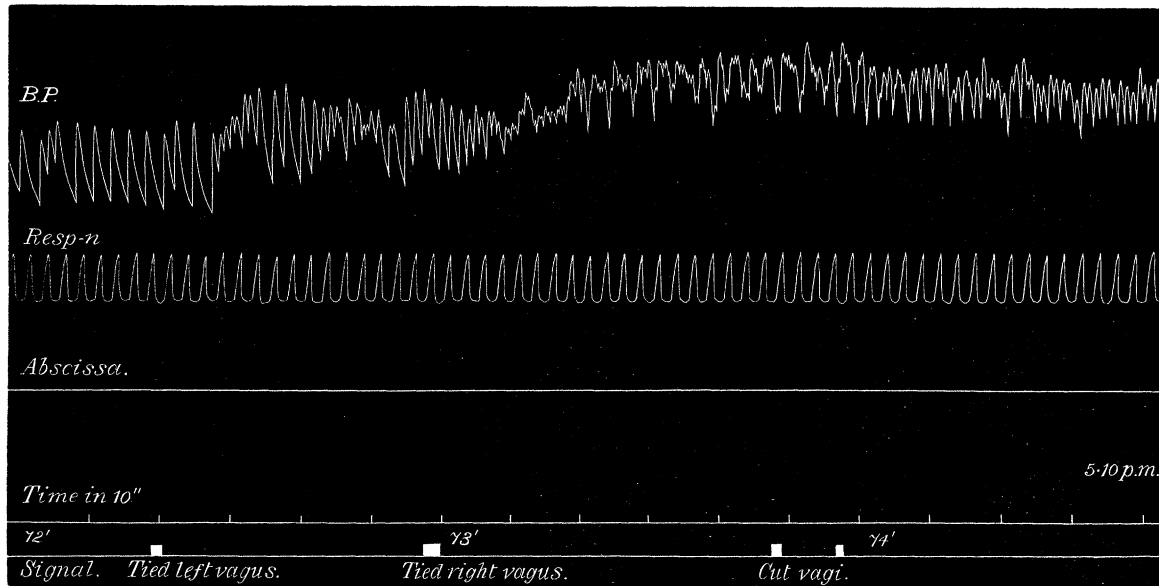


Extract 16.

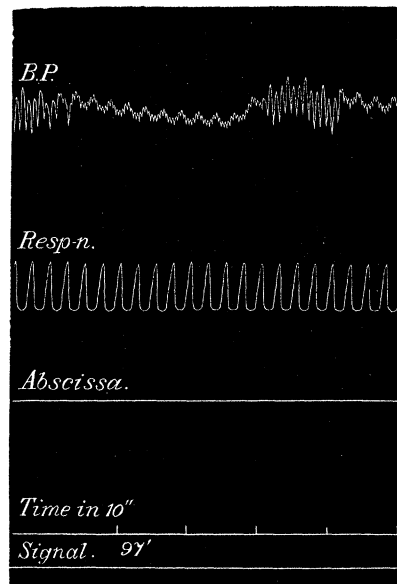


Extracts 15, 16, 17, and 18 from Plate XIII. The traces in order are (1) blood pressure, (2) respiratory movement, (3) base line, (4) time in 10". No. 15 is between the 35th and 38th minutes, No. 16 at the 45th minute, No. 17 between the 72nd and 75th minutes, and No. 18 between the 96th and 98th minute. A reference to the text explains these extracts. (See also Extracts 17 and 18.)

Extract 17.



Extract 18.



remained high. To end the experiment, a dose double the first one, was injected, and the animal was dead in a few minutes, with its heart tightly contracted, and very hard.

Plate XIII. gives all details of this experiment, which appears to prove (1) that the primary fall of blood pressure, which follows the injection of a large lethal dose of venom, is not due to respiratory failure alone; (2) that Cobra venom in large doses can, and does, act centrally on the heart through the vagal nerves; in other words, it has a direct action on the cardio-inhibitory centre; and (3), that, provided efficient artificial respiration is kept up with an intact chest, an animal is capable of resisting



for some time the action of enormous doses of the poison. At the same time, the frequent dropped beats seen on this tracing show that some measure of cardiac inhibition was present; the curious phases alluded to confirm one in this belief. Advantage was taken of this experiment to test the activity of the vagal nerve-ends from time to time. Extracts illustrating this point will be found on the back of Plate XIII., and the matter will be again returned to later on. For the present, it suffices to say that nerve-end paralysis was evidently beginning here.

The next experiment proved an instructive failure. A cat (weight 3 kilos.) received five-eighteenths of the subcutaneous M.L.D. intravenously in 65 mins., through the external jugular vein. The dose was given in ten slow injections. As seems to be the usual case, when the venom is thus administered, there was a steady fall of blood pressure following the first rise. Respiration became convulsive, and artificial assistance to breathing was delayed too long, and was, thus, of no avail. After several such failures, one learnt when to interpose with a good prospect of success, and yet without exercising undue haste.

*Plate XIV.*

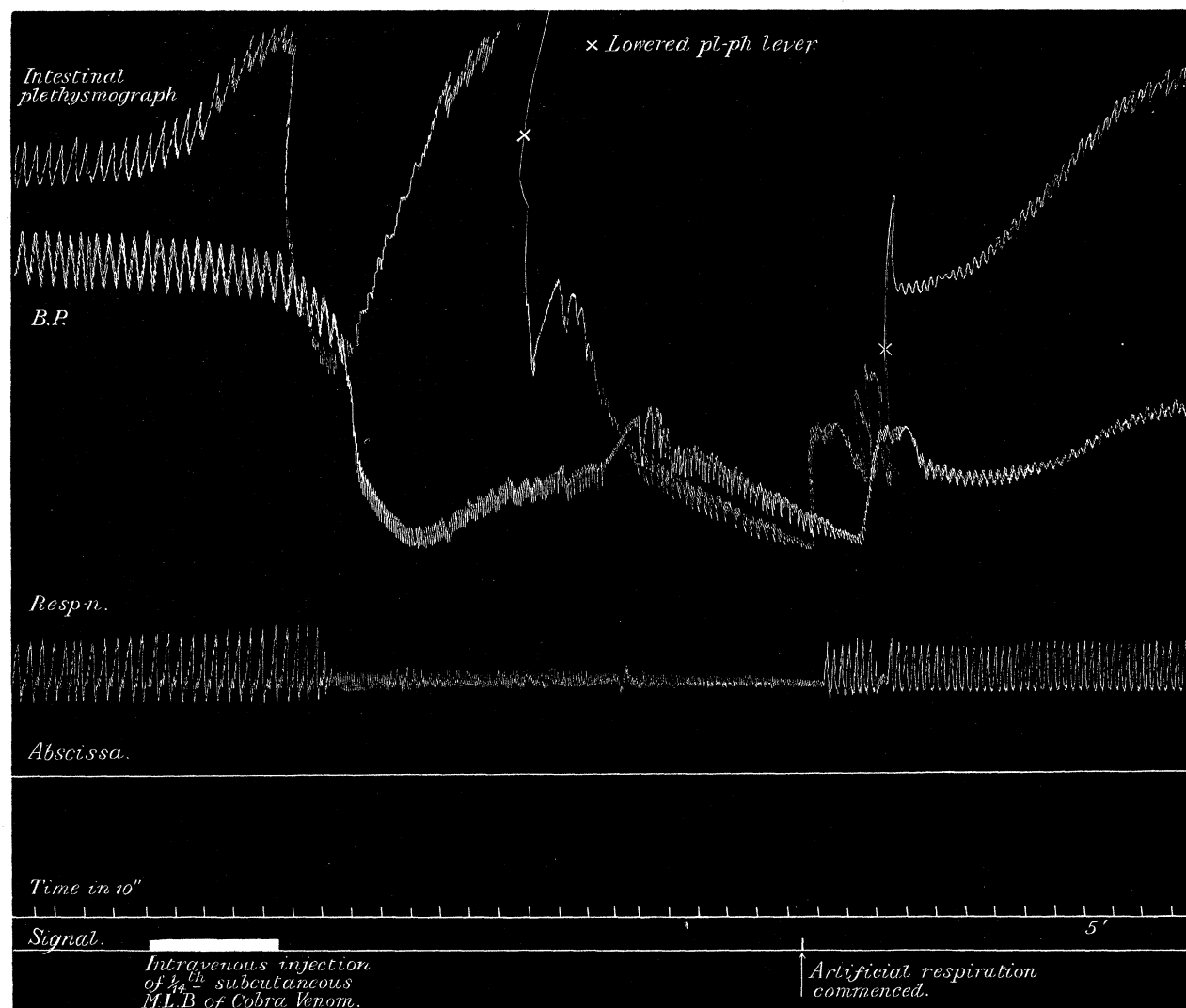
A cat (weight 3·4 kilos.), received three-fifths of the subcutaneous M.L.D. of Cobra venom intravenously, in 21 injections given at 3 mins. intervals. The blood pressure fell steadily, and artificial respiration had to be begun 69 mins. after the first injection. A control animal weighing 2·3 kilos. received the same proportionate dose similarly spread over an hour, and was dead 69 mins. after the first injection. As in the last experiment cardiac inhibition was evidently the cause of (threatened) death. Respiratory failure was in evidence, but had not become complete. The animal was unconscious. Artificial respiration raised the rate of heart-beat, partially restored the fallen blood pressure, and brought the cat back to consciousness. Moreover, instead of dying in about 70 mins., the animal lived on nearly 4 hrs. longer. Before artificial respiration was begun, occasional dropped beats were observed, later these became still more frequent, and the irregularity of the blood-pressure curve showed that the heart was acting very unevenly. At the same time respiration was failing in spite of the artificial aid it received. Towards the end of the experiment, there was almost no respiratory effort, and cardiac inhibition was very pronounced. For analysis of the tracing and for extracts therefrom, see the original Plate XIV. I will revert to discuss this, together with the next experiment, later on.

*Plate XV.*

A cat (weight 3·38 kilos.), received one-fourteenth of the subcutaneous M.L.D. of Cobra venom intravenously in one dose. There was a very rapid fall of blood pressure, with marked cardiac inhibition. Respiration failed whilst the blood pressure

was falling, and it appeared as if this failure was final. Artificial respiration was at once commenced (with the pump attached to the motor apparatus). The blood pressure and heart-beat at once began to recover, and reached nearly average levels. From time to time, artificial respiration was suspended. Each time this was done, there was a steep rise of blood pressure, and a fall in the number of beats; these were plainly asphyxial phenomena, occurring through the vaso-motor and vagal centres, and were speedily removed by a return to artificial respiration. During the earlier periods in which artificial aid was withdrawn, little or no respiratory effort was noticeable, but in time the oxygenation of the blood appeared to have restored the

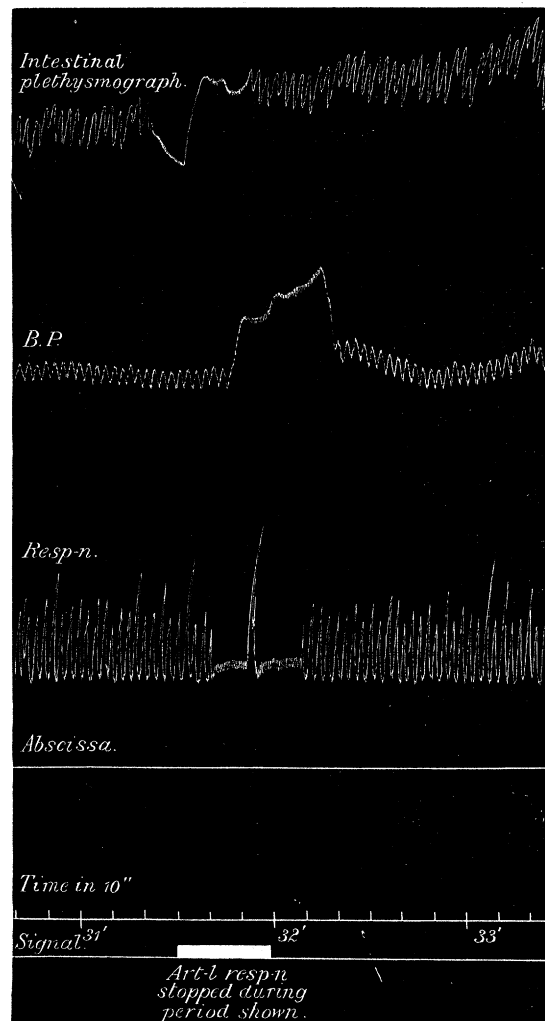
Extract 19.



Extracts 19, 20, 21 and 22 are from Plate XV. The traces in order from above down are (1) intestinal volume by plethysmograph, (2) blood pressure, (3) respiratory movements, (4) abscissa, (5) time in 10'', (6) signal. In Extracts 20, 21, and 22 the continuous signal shows the suspension of artificial respiration. The time in minutes after the injection is shown on the time trace. Extract 22 shows the last 5 minutes of the experiment. A reference to the text explains the extracts. (See also Extracts 20, 21, and 22.)

respiratory mechanism to activity. This restoration was a gradual one and may plainly be traced on Plate XV., both in the analysis and in the extracts from the tracing. The suddenness of the primary cessation of respiration, and the short period which elapsed before the commencement of the recovery of respiration, point unmistakably to the action having been a central one, for there would not have been time for nerve-end paralysis to have occurred. To this point I shall recur later. The experiment was brought to an end 3 hrs. after its commencement, by division of the

Extract 20.



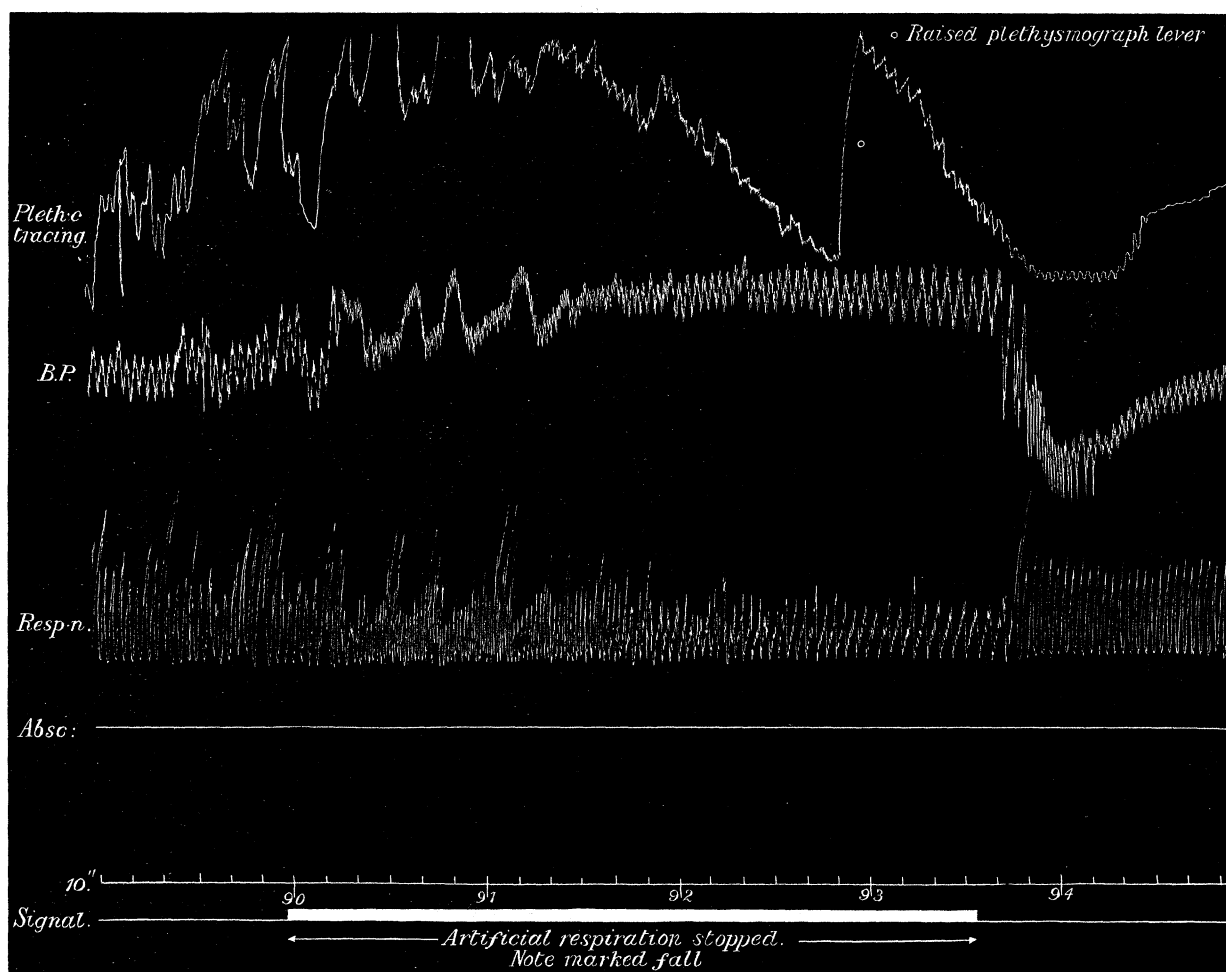
carotid, in order to allow the laboratory to be closed. During the last half hour of that period the animal was breathing freely and spontaneously, unaided; blood pressure and heart-rate were very steady, and the animal required constant anæsthetising to keep it unconscious. Whether or not nerve-end paralysis would have eventually closed life it is impossible to say, but it is clear that the artificial aid rescued the respiratory centre from death, and enabled the animal to be alive and functionally active nearly 3 hours after it would otherwise have been dead.

*The Effect of Cobra Venom on the Intra-Cardiac Vagal Nerve-Ends.*

The present seems to be a suitable opportunity to pause to examine the evidence in favour of a paresis of the vagal nerve-ends in cobraism.

(1) Dr. PRENTICE and I found, in one blood-pressure experiment on rabbits, that the cutting off of central vagal impulses from the heart, either by the severance of the vagi or by the use of atropine solutions, would check, but not stop, inhibition. The rate of beat declined, and the blood pressure fell in spite of these measures.

Extract 21.



(2) Again, in experiments on cats and dogs with the front of the chest removed and with artificial respiration maintained throughout, I observed that though section of the vagi played a much more pronounced part here than in the rabbit experiments, it was not sufficient to stop the onward progress of inhibition, though it undoubtedly greatly retarded it.

(3) The experiments with artificial respiration, used with intact chest-walls, threw a farther light on the subject. They showed that the free oxygenation of the blood

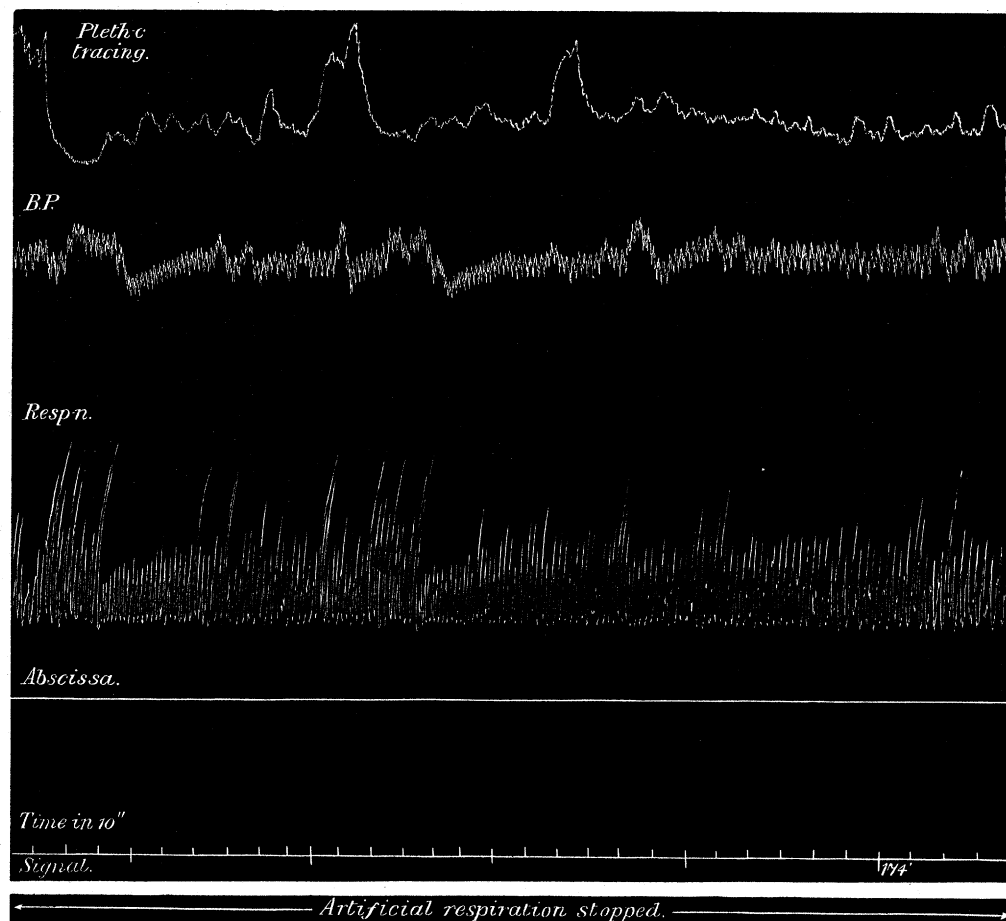


could retard the action of the venom on the centres, or at least could maintain those centres in activity, but they suggested that it had less power to stop the paralysis of the vagal and phrenic nerve-ends by the poison. Given sufficient time, the blunting of the vagal nerve-ends was seen to occur, whether the chest was opened or not.

Here, again, inhibition progressed though slowly after section of the vagi.

(4) The difference between the behaviour of the isolated hearts of the frog and mammal is suggestive. In the case of the former, we have the ventricle alone exposed to the venom, whilst in the latter the poisonous fluid traverses every portion

Extract 22.



of the organ, and acts unrestrainedly on the terminals of the cardio-inhibitory mechanism. In any case, we find in the cat and rabbit heart under perfusion a greater resistance to the venom, and a much lessened, though ever present, tendency for the organ to pass into systolic tone.

The whole evidence, therefore, points to the venom acting on the terminals of the cardio-inhibitory mechanism directly, and it is also probable that it has a farther indirect action on them by increasing the venosity of the blood, which it does by its interference with the respiratory mechanism.

*The Determining Factors in Respiratory Death from Cobra Venom.*

BRUNTON and FAYRER came to the conclusion that Cobra venom attacked the centres in the medulla oblongata, and especially the respiratory centre. RAGOTZI urged that they had brought no experimental proof to support their contention, and contrived an ingenious but complicated experiment to show that it was not the respiratory centre, but the phrenic and other motor nerve-ends which were at fault. He found that two factors were necessary to bring about such a nerve-end paralysis, viz., a sufficiently large dose of venom, and a sufficiently long period for that venom to act. If too large a dose of venom were given, he found that death occurred before the motor nerve-ends were paralysed, whilst if the dose were too small, it failed to produce the effect. His crucial test was made as follows :—A rabbit was fixed on its back, with its neck grasped by a fork-shaped iron, whilst an iron ring embraced its muzzle, pressing on the nasal bones and jaw in such a way, according to RAGOTZI, that the access of the poison to the nasal muscles was delayed, with consequent delay of their paralysis. The rabbit was then poisoned intravenously, and when complete motor paralysis had occurred, artificial respiration was commenced. So long as the animal was apnoeic, no movement of the nostrils was observed, but when artificial respiration was suspended, the nostrils began to move, at first gently and later in a more exaggerated fashion; convulsions of the posterior extremities also occurred. Under artificial respiration these nasal and other convulsions subsided. This experiment led RAGOTZI to conclude that the respiratory centre remained active after the motor nerve-ends of the muscles of respiration had been paralysed.

I have shown in the preceding pages that the injection of a large dose of Cobra venom intravenously causes an abrupt stoppage of respiration, side by side with an equally abrupt inhibition of the heart. In the experiment shown on Plate VI., the cessation of respiration lasted nearly 3 mins., then a number of inspiratory gasps occurred, heralding a rise in blood pressure, and after this respiration gradually re-established itself, and the animal lived over an hour in spite of a farther dose of the venom. Here there was clearly no time for the nerve-ends to have become affected, and the action was obviously a central one, for RAGOTZI found that rapidly lethal doses do *not* paralyse the phrenic nerve-ends, and it will be seen directly that my own work bears him out in this.

In the experiment given on p. 392 and on Plate XV., it will be remembered that there again respiration was abruptly stopped by a large intravenous dose of Cobra venom, and that apparently the animal would have speedily died but for the use of artificial respiration. Here we have a condition of affairs resembling that in RAGOTZI's experiment. The paralysed centre was restored to activity by artificial aid; consequently, the rises in blood pressure and the struggles of dyspnoea which RAGOTZI observed are likewise seen here. Moreover, in my experiment the evidence

of central activity became more and more obvious as the beneficial effects of artificial respiration had time to assert themselves.

RAGOTZI asserted that in his experiment the motor nerve-ends were paralysed, though he obviously can have had no absolute proof that this paralysis extended to the phrenic terminals. He called for experimental proof that the respiratory centre was affected by venom. To comply with this reasonable demand, I undertook a number of experiments, which I will arrange in series, giving a short outline of each such series.

*Series No. 1.*—To test the action of Cobra venom on the respiratory centre when it is directly applied to that centre.

Several experiments were performed, and always with the same result. In each case a rabbit, weighing a little over 2 kilos., was chosen for the experiment, and the venom used had a subcutaneous M.L.D. for the rabbit of '0006 gramme per kilo. The animal was etherised, and the anæsthetic was administered by a tracheal cannula, in order to secure evenness of administration. The medulla oblongata was exposed in the usual way, by removal of the posterior occipito-atlantoid ligament, after cutting through the superjacent structures. Respirations were recorded by means of a double stethograph, and in some of the experiments the blood pressure was also taken. Five milligrammes of dry Cobra venom were dropped on to the medulla oblongata, over the seat of the respiratory centre, and a few drops of RINGER'S fluid were added to hasten solution. The result in each case was speedy death by respiratory failure. A *post-mortem* examination was held at once, and the heart was always found to be beating actively and freely; there was no tendency for it to be killed in tight systole, as would have been the case had the large dose of venom produced death by its absorption into the system. The phrenic nerves responded readily to very weak stimuli, but no contraction of the diaphragm was produced by stimulating the medulla oblongata with even the strongest currents available.

Plate XVI. contains a tracing from one of these experiments, in which the blood pressure has been purposely omitted to save complication. It will be observed that death occurred 12 mins. after venom was applied. One must remember that Cobra venom when dried does not very quickly pass into solution, and looking at the curve it is probable that about half that time (6 mins.) was really occupied by the action of the venom.

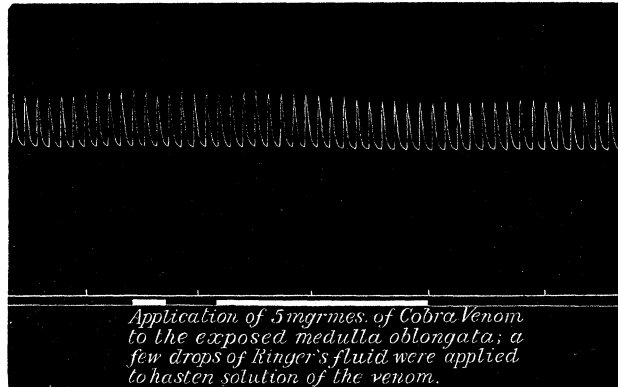
*Series No. 2.*—To ascertain whether diaphragmatic respiration ceased before the other respiratory movements. Two rabbits were used; each was etherised, and a tracheal cannula inserted. The chest movements were registered by means of a double stethograph and tambour, whilst the diaphragmatic movements were registered by a modification of HEAD'S method.

The first rabbit weighed 2·14 kilos., and received five-sixths of the subcutaneous M.L.D. intravenously in 34 mins. Respiration failed rapidly, and the animal was dead 56 mins. after the commencement of the injection. The diaphragm appeared

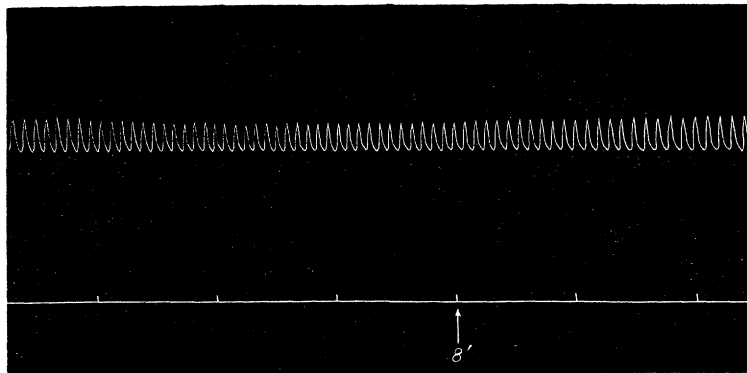
## THE ACTION OF INDIAN COBRA VENOM.

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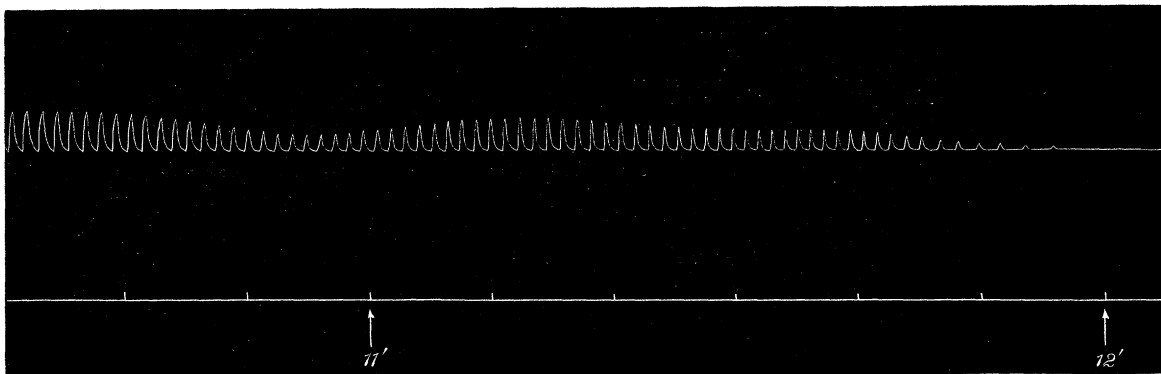
Extract 23.



Extract 24.



Extract 25.



Extracts 23, 24, and 25 from Plate XVI. Extracts from a stethographic tracing in a rabbit, whose medulla oblongata was exposed and Cobra venom applied thereto. No. 23 is at the time of application of venom, No. 24 is 8 minutes later, and No. 25 is just before and at death. The time in minutes is shown below.

to be active till the end, and the phrenic nerves retained full sensitivity; they were tested by make-and-break shocks; twitches of the diaphragm could be readily got with the secondary coil 330 millims. from the primary (the tongue could appreciate the current at 180 millims., but not beyond).



The second rabbit received half the subcutaneous M.L.D. in a little under  $\frac{1}{2}$  hr. and lived 2 hrs. after the first injection. The type of respiration seemed to change during the latter part of the experiment, and the action of the diaphragm appeared to have diminished. It was difficult to be certain of this, but, in any case, some diaphragmatic movement continued to the end, and the phrenic nerve-ends proved to have retained full activity, like those in the previous experiment.

*Series No. 3.*—To test the effect of large doses of venom on the phrenic nerve-ends.

Two cats were given rapidly fatal doses of Cobra venom intravenously, one being killed in 15 mins. and the other in 37 mins. In both the phrenic nerve-ends retained full activity. The hearts were found in tight systolic position.

A cat (weight 1.640 kilos.) received one-fifth of the subcutaneous M.L.D. of Cobra venom intravenously in 15 mins.; 13 mins. later artificial respiration was required to avert death. After 1 hr. 4 mins. of artificial respiration, the animal was killed and its phrenic nerves were tested. Make-and-break shocks were used, and a diaphragmatic twitch was obtained with the secondary coil at 70 millims., but not with a weaker current, and stimulations of the vagi stopped the heart at 140 millims. The apparatus used for these stimulations was the same throughout all these series, and could not have differed appreciably. Testing by the tongue showed that it did not change.

*Series No. 4.*—To test the effect of smaller doses of Cobra venom on the phrenic nerve-ends.

A cat weighing 1.720 kilos. received one and a-half M.L.D.'s of Cobra venom subcutaneously and died 4 hrs. 4 mins. later. Convulsions and cyanosis preceded death, and the heart was beating freely when the body was opened. It was, therefore, clear that death was due to respiratory failure. The phrenic nerves were tested with the secondary current, by make-and-break shocks, and contractions of the diaphragm were readily elicited up to 450 millims. distance of the secondary from the primary coil. The coil was, in fact, pulled out 100 millims. beyond its usual working distance. When the electrodes were directly applied to the diaphragm the muscle responded to make-and-break shocks up to a distance of 145 millims. of the secondary coil.

The heart was beating fairly well when it was stopped by a vagal nerve stimulus at 140 millims.

A rabbit, weighing 1.710 kilos., received one and one-third M.L.D.'s of Cobra venom subcutaneously, and was dead 4 hrs. 55 mins. later. Before death the heart slowed markedly, the animal became cyanosed, and there were pronounced convulsions. Obviously respiratory failure accounted for death. A *post-mortem* was made directly death occurred. The heart was still beating and was inhibited by a left vagus stimulation at 100 millims., having been slowed by a stimulus at 130 millims. The diaphragm responded readily to phrenic stimulation at 400 millims.

These experiments would seem to indicate clearly: (1) that the mammalian respiratory centre can be directly poisoned by Cobra venom; (2) that the phrenic

nerve-ends remain quite unaffected, or at least non-paralysed ( $\alpha$ ) in animals which have been poisoned by large intravenous doses of venom, and ( $b$ ) in those which have received doses of venom subcutaneously not greatly above the lethal, and which have taken 4 or 5 hrs. to die; (3) that the phrenic nerve-ends can be paralysed by the administration of large lethal doses of venom, provided that the animal be kept alive long enough by artificial respiration.

RAGOTZI observed that the diaphragm contracted more feebly as death approached, and argued from this that the phrenic nerve-ends were paralysed. But a central paralysis might equally explain this phenomenon if it be a fact. Then again, could RAGOTZI really cut off the blood supply of the snout for a long period (such as is demanded to produce nerve-end paresis, according to his own admission) without at the same time damaging the nutrition of the nerves and muscles he was studying? He used an iron ring for the compression of the parts. In proportion as his compression was efficient, so must his interference with the healthy action of the parts have increased; if his constriction was only partial the envenomated blood was still circulating, and was obviously acting at an advantage on tissues damaged by deficient nutrition. If the constriction was complete, or if on the other hand it was very incomplete, our conclusions are still more obvious.

I believe that the true interpretation of RAGOTZI's experiment is the one I have already given, namely, that by artificial respiration the partially paralysed respiratory centre was temporarily restored to activity, just as occurred in my experiment set forth on Plate XV.

In a recent paper in the 'Lancet' (2.1.04) LAMB and HUNTER have approached this subject purely from the histological point of view, and have found definite evidence that some of the centres in the medulla oblongata, and markedly the tenth (motor) and twelfth nuclei, were attacked by Cobra venom. I may add that my own work was finished and that my conclusions had been formulated before I saw their paper. Working on entirely different lines from LAMB and HUNTER, and without any communication with them, I have been simultaneously led to conclusions which strongly support those which they have arrived at.

Whilst insisting strongly that Cobra venom has a powerful and important central action, I have also admitted the motor nerve-end paralysis on which RAGOTZI and others have laid so much stress, and have indicated the conditions under which alone I found such paralyses to occur. The very fact that they progress whilst artificial respiration is actively maintaining life in the important medullary centres, is most significant in its bearing on treatment. In the experiment shown on Plate XIV. one can trace the partial recovery of an animal from the effects of a large dose of Cobra venom; but running through the whole tracing is evidence which can hardly be interpreted otherwise than as an indication of gradually increasing interference with the passage of respiratory impulses from the centre to the muscles.

RAGOTZI has shown that, in the case of Cobra poisoning of an isolated limb, it is

possible to obtain recovery from motor nerve-end paralysis, though the process was a very slow one. The recovery took 6 days. My own work on the subject is still very incomplete, but I have been led to think that the use of artificial respiration has been too much neglected in cases of cobraism. I am aware that a commission has pronounced on the subject, and that many have dealt with it, in past years, but I am not satisfied that any series of accurate experiments has carefully determined the limitations of a method which is at once simple and always available.

This much I can now say, if artificial respiration is to save life, it must be efficient and must not be too long delayed. As a therapeutic measure in the treatment of cases of Cobra bite, it ranks only second to the use of anti-venin. Needless to say local treatment of the bite should always be employed along with it.

#### *Summary of Conclusions.*

(1) Cobra venom acts directly on the muscular tissue of the blood vessels, or through their vaso-motor nerve-endings, constricting the arterioles, and thus raising the arterial blood pressure. It probably affects all organs alike. In the frog-vessels the action can be traced down to dilutions of 1/10,000,000. In a Cobra-bitten man, the concentration of venom in the blood is probably, at least, thirty times as great as this.

(2) Cobra venom also acts directly on the isolated frog-ventricle, killing it in a position of firm systole, if the solution be concentrated, and stimulating it if a weaker strength be employed. The limit of the speedy lethal action on the isolated heart is reached at a concentration of about 1/500,000. The stimulating action can be traced down to a dilution of 1/10,000,000. This action of Cobra venom brings it into line with the glucosides of the strophanthin group. Its action is more rapid than that of strophanthin, and is certainly not inferior to it in strength. Atropine sulphate and Cobra venom, when acting in the same solution, intensify each other's action, and produce more summation of effect than one would have anticipated. This detracts from the value of the atropine salt in the treatment of cobraism and makes it a dangerous remedy. The blood-pressure work has confirmed this view of the case.

(3) Cobra venom powerfully affects the isolated mammalian heart, when solutions of it are perfused through the coronary circulation. The action appears to be a dual one, viz., (1) a direct action on the muscular fibre or on the nerve-endings, closely resembling that which is produced on the isolated frog-ventricle; and (2) an action on the intra-cardiac vagal mechanism, which makes for inhibition. The result is that, in strong solutions, we find an irregular and extreme excitation of the heart, followed by early death in a position of systolic tone. If the concentration be less, the early stage of excitement yields to a prolonged phase, in which the tonic action of the poison on the heart is most pronounced; the beat is regular, steady, and

strong. Cobra venom interferes with the circulation through the heart in a marked manner; this is probably due (1) to a constriction of the coronary vessels, brought about by the direct action of the venom on the vessel walls; and (2) to the condition of tonus into which the heart is tending to pass.

(4) When given subcutaneously in low lethal doses, Cobra venom kills by paralysing the respiratory centre. Such a paralysis is, under these circumstances, gradually evolved, and in the early stages of the process there is often evidence of a phase of stimulation, preceding the paretic phase.

There is a gradually increasing venosity of the blood, and in consequence thereof, all the harmful results of slow asphyxiation are produced.

If life is prolonged beyond the usual term by artificial respiration, and possibly also if the dose of venom is a very low lethal one which takes many hours to kill, the phrenic and other motor nerve-ends may become paralysed, but this is certainly not an essential feature of death from lethal doses of Cobra venom, which kill within 5 hrs. I hope to make a farther communication on this subject later.

The convulsions which precede death are purely asphyxial, and can be at once stopped by artificial aëration of the blood. Each such convulsion is followed by a phase of exhaustion of the respiratory mechanism, which is almost certainly central.

If the dose of Cobra venom administered be a large one, and especially if it be given intravenously, the respiratory centre is quickly and severely affected, and respiration may cease almost at once. This cessation of breathing may be permanent, if artificial respiration be not quickly started, but if the dose be a less severe one, the rhythmic activity of the centre reasserts itself. At first there may be a number of deep spasmodic gasps, and then the movements of respiration re-begin, very gently at the commencement and gaining force as time goes on, till a normal rhythm is re-established, or even a stage of stimulation is manifested. Soon, however, the centre fails again, and all the phenomena of asphyxiation appear.

By applying Cobra venom directly to the exposed medulla oblongata of the rabbit, I have shown that the respiratory centre can be paralysed without the phrenic nerve-ends or the heart being appreciably affected.

If very large doses of venom are injected, death may take place by cardiac failure, before the respiratory mechanism has given way. We have here to do with the direct action of the venom on the heart muscle; the beats become rapid and shortened, and the heart passes into a systolic phase, in which it dies tightly contracted.

(5) Cobra venom, when given in low lethal doses subcutaneously, raises the general blood pressure. There may be a slight preliminary fall before the rise, but often this is wanting. In the absence of farther interference the blood pressure remains high till very near the end of life. In the asphyxial convulsions which herald death, a farther steep rise of blood pressure takes place; this is soon followed by a sudden and very rapid fall to death.



The high level of blood pressure is due to : (1) The direct action of the circulating venom on the muscular tissue of the arterioles, causing a constriction of these vessels, and thus opposing a barrier to the onward flow of the blood ; (2) the increased force of the heart-beat as the outcome of the direct stimulating action of the venom on its muscular tissue, and (3) the stimulation of the vaso-motor centre, as a result of the steadily increasing venosity of the blood.

The slight preliminary fall of blood pressure, which is sometimes seen, is due to cardiac inhibition, but this subject will be reserved for discussion when dealing in the next section with the action of large doses of the poison.

The late fall in the rate of the heart-beat is due to cardiac inhibition ; the latter is due to several factors :

(1) A gradually progressive asphyxiation is taking place throughout the experiment ; this affects the vagal centre in common with the rest of the nervous system ; the result is a stimulation of the inhibitory mechanism, and a consequent slowing and weakening of the heart.

(2) The direct stimulating action of the venom on the vagal inhibitory centre acts in the same direction as the asphyxiation of the centre.

(3) There is distinct evidence that even when the influence of the vagal centres is removed, inhibition of the heart continues to advance, though in a lessened degree. The obvious inference is that the vagal nerve-ends are stimulated by the circulating venom, and probably also as a result of deficient aëration of the blood.

(4) It is not improbable that a stage of exhaustion of the heart muscle follows the early stimulative action of the venom, and

(5) Exhaustion of the heart is probably predisposed to by the strain put upon the organ, in having to work for a long period against an abnormally high blood pressure.

We are now in a position to explain the sudden rapid fall of the curves of heart-beat-rate and of blood pressure, which usher in death at the close of one of these long experiments. An over-strained and weakened heart is suddenly and violently called upon to bear a farther burden, for respiration has ceased and the medullary centres are acutely asphyxiated. As a consequence there is a violent excitation of the cardio-inhibitory and vaso-motor mechanisms. The heart is slowed and at the same time has to work against a suddenly increased pressure, and it gives way. In fact, we have the phenomena of asphyxiation in their entirety.

The vessels of the splanchnic area are affected *pari passu* with those of the body generally, and they in no wise act independently. The vaso-motor mechanism remains active throughout, and is as we have seen profoundly affected by changes in the venosity of the blood.

(6) Cobra venom when injected in large doses, and especially when given intravenously, causes (1) a sudden fall of blood pressure ; (2) a subsequent rise, provided the dose has not been too large ; and (3) a final fall to zero.

The early fall is undoubtedly due to inhibition of the heart. It has been clearly

shown that this is mainly brought about by the direct action of the poison on the vagal centres in the medulla oblongata, as it occurs before the accompanying failure of respiration has had time to act. Moreover, it is seen whilst artificial respiration is being actively carried on, and can be checked under these circumstances by division of the vagi. On the other hand there can be no doubt that asphyxiation of the vago-inhibitory centre intensifies and maintains the inhibition which direct influence of the venom on the vagal centre produces.

The spontaneous recovery of respiration or the application of artificial respiration, has a powerful influence in mitigating the action of the venom on the vagal centre. In the same way artificial respiration, and to a less extent, the spontaneous recovery of respiration, appear to act beneficially on the poisoned respiratory centre.

Even if the heart is cut adrift from all central vagal impulses, whether direct or indirect, by the division of the vagi, there yet remains evidence of a continued inhibition which must be attributed to the direct action of Cobra venom on the terminals of the vago-inhibitory mechanism. This action would appear to be a direct one, but there is every probability that it is indirect as well, in other words, that it acts through asphyxiation of the vagal terminals, as well as by the poisoning of these parts by the circulating poison.

(2) When the secondary rise of blood pressure, which follows the primary fall, occurs, it is due to the same factors which determine its occurrence when small doses have been injected. It remains to explain why it is sometimes absent, brief or ill marked. The explanation is simple; it is merely a question of cardiac failure. We have seen that the direct inhibitory action of the venom through the vagal centre is capable of overcoming the tendency which the blood circulating through the heart muscle has to throw that muscle into death in systolic tone. Were it not for these two rival forces, to some extent balancing each other, Cobra poison would kill by its direct action on the heart muscle. When the doses are comparatively small or when the vagi are cut or thrown out of gear by atropine, we find the tonic cardio-muscular influence of the venom in evidence, but when the dose of venom is a large one, and especially when it is intravenously given (the vagi remaining intact), the inhibitory action overpowers the muscular excitation and failure of the heart occurs. If the inhibition is sufficiently well marked no amount of arteriolar spasm that occurs will compensate it, consequently the blood pressure falls.

When the dose of venom is a very heavy one, the direct muscular stimulation may be so intense as to overcome the maximum inhibitory impulse, and then the heart dies in systole with a quickened beat, and is found after death as hard as a contracted *post-partum* uterus. Under such circumstances, any increase in the force of the heart is temporary, for the beat is probably a very partial one; the heart passes through a stage of excitement into one of increasing systolic tonus, in which the beats are very limited in extent.

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