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The Physiological Action and Antidotes of Colubrine and Viperine Snake Venoms

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VI. *The Physiological Action and Antidotes of Colubrine and Viperine Snake Venoms.*

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Part I.—Colubrine Venoms.

Although the poison of the Cobra has long been the subject of careful investigation, those of the other Indian poisonous Colubrine snakes have received comparatively little attention, in spite of their well-known deadliness. Now that Calmette's antivenin has been proved to be effective against Cobra venom it is a matter of considerable importance to ascertain if the physiological action of the remaining Colubrine snake-venoms is similar to that of the Cobra or not, and whether Calmette's serum is effective against them also, or if it is necessary to prepare others which will act in their case on similar lines. The fact, which I have recently demonstrated (1), that the poison of the Sea-snakes is identical in its physiological action with Cobra venom, although of greater potency, suggests the hope that it may prove possible to obtain a single antidote which will be effective against both these large classes of venomous snakes. I have, therefore, obtained the dried poisons from India, and in Part I. of this paper propose to describe their actions and to discuss the bearing of the facts recorded on the above problem.

I. Naia Bungarus, *or Hamadriad.*

This deadly reptile is found, according to Fayrer (2), most frequently in Bengal, Assam, Burma and Southern India, and is by far the largest of the Indian poisonous snakes, and probably the largest in the world, the specimen from which my venom was obtained having measured 13 feet in length. The dried poison has an orange colour. I am not aware that its physiological action has been closely investigated

before, although a few experiments were made with it by FAYRER (2) many years ago, and also I believe by D. D. CUNNINGHAM, who, I am informed, found it to closely resemble Cobra venom.

The symptoms produced by this venom in birds, in a few experiments performed at the Calcutta Zoological Gardens with the kind help of the Superintendent, BABU RAI SANYAL BAHADUR, were found to be precisely similar to those caused by Cobra poison, and the toxicity was also very similar in degree to that of the Cobra, the two being quite indistinguishable from each other by the symptoms produced, as the following example will show.

A pigeon, 225 grammes in weight, was injected with 2 mg. per kilogramme of dried Hamadriad venom, dissolved in 0·5 cub. centim. of normal salt solution, into the breast muscles.

After 30 minutes slight sleepiness and gaping were noted.
,, 40 ,, the bird was nodding slightly.
,, 60 ,, sleepy, nodding and gaping; respirations very deep and only 20 per minute.
,, 80 ,, the same, but cannot stand; respirations 18 per minute.
,, 110 ,, the same ,, ,, ,, 16 ,,
,, 140 ,, the same, but cannot raise head off the table, being nearly completely paralysed.

Death took place at the end of $2\frac{1}{2}$ hours. There was no intravascular clotting, and the blood was dark and clotted well on being removed from the vessels. Cobra venom in the same dose produces precisely the same symptoms and proves fatal in about the same time.

Hæmolytic Action.—This has been tested by adding a small drop of blood (5 cub. centims.) to solutions of different strengths of venom in isotonic salt solutions, and counting the number of red corpuscles remaining after varying periods, as well as noting the laking of the fluid and amount of undissolved sediment of corpuscles. It was found that the venom must be used in a solution of the strength of 1 in 1000 to produce marked hæmolysis, and that even with this strength 24 hours at least were necessary at room temperature (14° C.) to produce complete solution of human blood in the proportion of 1 part to 200 of the venom solution. Slight dissolution, however, was observed at the end of 3 hours, and marked after 7 hours. These effects are about the same as those produced by a 1-in-100,000 solution of Cobra venom under similar conditions. It is evident, then, that the hæmolytic action of Hamadriad venom is very small as compared with that of Cobra venom, being in fact about equal to that which I found in the case of the Sea-snake venoms (1), and it can have no direct part in producing the fatal effects of Hamadriad poison.

Blood Pressure and Respiratory Curves.

In order to ascertain how death is produced by Hamadriad venom, tracings of the blood pressure with a Gad manometer and of the respirations with a Sandström recorder connected with a tube in the trachea, have been taken, the poison being injected intravenously. The following table summarises the general results of three experiments :—

TABLE I.

Number.	Animal.	Dose per kilogramme.	Respiration failing.	Blood pressure rising.	Respiration stopped.	Final fall of blood pressure.
		mg.	mins.	mins.	mins.	mins.
1	Rabbit .	5	1	1½	1½	2
2	,, .	1	6	9½	9¼	10
3	Cat . .	2	11	21	20	44*

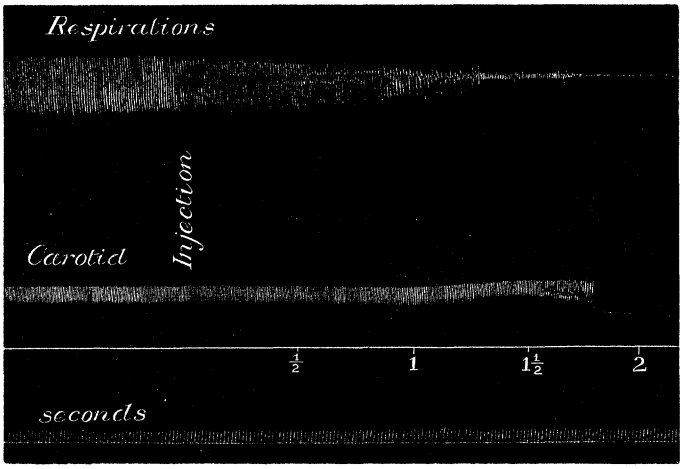
* Artificial respiration performed.

The sequence of events in the first two experiments is the same, the rapidity of the action of the poison being in proportion to the amount injected. The data of these experiments will serve to illustrate the results and bring out some other points of interest.

EXPERIMENT I.—Rabbit, weight 2¼ kg., under chloroform followed by ether. Cannula in carotid artery connected with manometer. Tracheal tube inserted and connected with a Sandström recorder. Phrenic nerve exposed on the right side of the neck, and stimulated with induction shocks at intervals, and the contraction of the diaphragm noted. A dose of 11·25 mg. (5 mg. per kilogramme) dissolved in 0·5 cub. centim. normal salt solution was injected into the external jugular vein.

Time.	Blood pressure.	Respirations.		Phrenic nerve.	
		Per ½ min.	Amplitude.	Coil at	Contraction.
	millims.		millims.	millims.	
Before injection .	85	45	7	17	Good.
After ½ min. . .	85	46	7	—	—
,, 1 ,, . .	85	40	4	—	—
,, 1½ mins. . .	100	18	0	18	Nil.
				15	Slight.
,, 2½ ,, . .	40	—	—	12	Nil.
				5	Good.
,, 4½ ,, . .	40	—	—	0	Nil.
,, 7 ,, . .	25	—	—	—	—

Five minutes later the sciatic nerve responded to stimulation with the secondary coil at 9 millims., and the leg muscles to the same degree, showing that the motor end-plates of these muscles were not completely paralysed at a time those of the phrenics were completely curarised. The blood after death was dark and fluid, but clotted quickly on being placed in a test-tube. No intravascular clotting could be found. (See Tracing I.)



Tracing I. (Hamadriad, Experiment I.).—Rabbit. Hamadriad venom. 5 mg. per kilogramme, intravenously.

Experiment II.—Rabbit, weight 1·7 kg., under chloroform followed by ether. Conditions as in Experiment I., except that the phrenic was not exposed. A dose of 1·7 mg. (1 mg. per kilogramme) in 0·5 cub. centim. salt solution was injected into the external jugular vein.

Time.	Blood pressure.	Respirations.		Remarks.
		Per minute.	Amplitude.	
	millims.		millims.	
Before injection	110	78	8	
After 1 min.	110	79	9	
„ 2 mins.	105	81	9	Respiration increased.
„ 3 „	103	78	9½	
„ 4 „	100	73	9	
„ 5 „	100	69	8½	
„ 6 „	97	62	7½	Respiration decreased.
„ 7 „	97	57	6	
„ 8 „	95	51	4	
„ 9 „	80	46	2	
„ 9½ „	100	6	1	Blood pressure rising.
„ 10 „	30	0	—	
„ 11 „	10	—	—	
„ 12 „	0	—	—	

Post-mortem.—On opening the chest immediately after the final fall of the blood pressure the heart was found to be still beating, confirming the opinion derived from the character of the tracing that the circulatory failure was quite secondary to the cessation of the respiration. There was no clotting in the portal veins, heart or large thoracic vessels, as sometimes occurs in Daboia poisoning. On at once testing the effect of stimulating the nerves with the induced current the results were as follows:—

	Secondary coil at	Contraction of muscle.
Phrenic nerve . . .	0 millims.	Nil.
Diaphragm	10 „	Good.
Sciatic nerve	10 „	Good.
Leg muscles	11 „	Good.

Here, again, we find the motor end-plates of the phrenic nerves completely paralysed immediately after the death of the animal, while those of the leg (and also the arm muscles) were still functionally active. Nevertheless, the data given in the last two columns of the record of Experiment I. show that the phrenic end-plates did not become paralysed until after the respiratory centre had ceased to work, so that (as I also found in the case of the *Enhydrina Bengalensis*), the primary effect of the venom is to paralyse the respiratory centre, the end-plates of the phrenic nerves being affected very shortly afterwards.

Another point of interest is the evidence in the record of Experiment II. of a preliminary stimulus of the respiratory centre by the smaller dose used in this instance, both the number and amplitude of the respirations having been increased during the second and third minutes after the injection of the venom (the effect being clearly observable in the tracing) followed by a slow, but steady, reduction of the breathing until it finally ceased after $9\frac{1}{2}$ minutes, the blood pressure then rising for a brief period before its final fall. These experiments clearly show that the poison of the Hamadriad is identical in its physiological action with that of the Cobra, and, consequently, also with that of the Hydrophidæ. It remained to be ascertained if the failure of the circulation could be averted by the use of artificial respiration as soon as the breathing stopped, as can be done in the case of the last two mentioned venoms, for which purpose Experiment III. was undertaken.

The following experiment shows very well the repeated effect of artificial respiration in lowering the excessive blood pressure due to approaching asphyxia owing to paralysis of the respiratory centre by the Hamadriad venom, just as in the case of Enhydrina poison. Further, even after what would naturally have been the final fall of blood pressure had commenced, artificial respiration repeatedly raised it once more, while twice feeble natural respiratory efforts recommenced. Yet within 3 minutes of its being finally left off a fatal fall of pressure occurred. It is evident,

Experiment III.—A Cat, weighing 3 kgs., was chloroformed and 6 mgs. of Hamadriad venom (2 mgs. per kilogramme) was injected intravenously.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection . . .	125	67	
After 2 mins.	125	71	Respirations quickened.
„ 5 „	125	68	
„ 8 „	125	63	
„ 11 „	125	41	Respirations slowed.
„ 14 „	125	31	
„ 17 „	115	36	
„ 19 „	100	31	
„ 20 „	90	6	Respirations ceased.
„ 21 „	120	0	Artificial respiration started.
„ 22 „	100	0	Artificial respiration left off.
„ 23 „	125	0	Artificial respiration re-started.
„ 24 „	95	0	Artificial respiration left off.
„ 25 „	135	0	
„ 27 „	100	28	Feeble natural respiration recommenced.
„ 28 „	75	23	Blood pressure falling.
„ 29 „	60	5	Respiration ceased.
„ 32 „	40	0	Artificial respiration recommenced.
„ 35 „	130	—	Blood pressure risen again.
„ 36 „	125	—	Artificial respiration left off.
„ 38 „	135	17	Feeble natural respiration recommenced.
„ 40 „	60	4	Respiration ceased. Blood pressure falling. Artificial respiration resumed.
„ 41 „	100	—	Blood pressure risen. Artificial respiration left off.
„ 44 „	40	0	Final fall of blood pressure.

then, that by means of artificial respiration cases of poisoning by this venom could be kept alive for long periods, which might conceivably, under certain circumstances, allow of antivenin or other remedies being obtained from some little distance, or of medical aid being brought to the patient, a remark which also applies to Cobra and Sea-snake poisoning.

II.—Bungarus fasciatus, *or Banded Krait.*

This snake, according to Fayrer (2) and Wall (3), is very common in Bengal and Eastern and Southern India generally, and grows to a considerable size, but has always been considered less deadly than its smaller cogener, *Bungarus cæruleus*, the Krait. Both Fayrer and Wall record a few experiments with it, the former finding that their bites were fatal to dogs in from $4\frac{1}{2}$ hours to 10 days, being much less rapidly fatal than the bites of Cobras, while Wall describes an acute form of poisoning with typical Colubrine symptoms, and also a chronic form, quite different to anything he had met with in the case of other Colubrine snakes, his description

resembling the symptoms of blood poisoning or of the chronic form of Viperine poisoning.

The injection of pigeons throws some light on this peculiarity, for although fairly rapidly fatal subcutaneous doses of the venom cause death with all the usual symptoms of Colubrine poisoning, yet if large doses be given another important change is found *post-mortem*, namely, intravascular clotting, most marked in the portal system, but extending to the pulmonary and systemic circulations. In short, we have to deal with a mixed Colubrine and Viperine poison, just as C. J. MARTIN (4) found in the Australian Colubrine Snake, *Pseudechis porphyracus*. This is further borne out by the antivenin experiments, for it was found that CALMETTE's antivenin neutralised the Colubrine symptoms, if given in a sufficient dose, but the animals, who had received ten times a fatal dose of *Bungarus fasciatus* venom, all died after 2–4 days of the chronic form of poisoning.

Hæmolytic Action.—This was found to be very feeble in the case of human blood, for when 5 cub. centims. were added to 1 cub. centim. of a 1-in-1000 solution of the venom, hæmolysis was not quite, although very nearly, complete after 24 hours. It is thus as feeble as Hamadriad and Enhydrina venoms in this respect.

Blood Pressure and Respiratory Curves.

The following table summarises four experiments in which blood pressure and respiratory tracings were taken after intravenous injection of this poison :—

TABLE II.

Number.	Animal.	Dose per kilogramme.	Respiration failing.	Blood pressure rising.	Respiration ceased.	Final fall of blood pressure.
		mg.	mins.	mins.	mins.	mins.
1	Rabbit . .	5	7	12	9	15
2	,, . .	10	3	3	4	$4\frac{1}{2}$
3	,, . .	20	2	$2\frac{1}{2}$	4	5
4	Cat . . .	10	8	Nil	19	21*

* Artificial respiration carried on.

Here, again, we see the same sequence of events as in the case of the Hamadriad, but a different degree of toxicity. Thus, 5 mg. per kilogramme of the latter killed more quickly than 10 mg. of the *Bungarus fasciatus* poison did, while 5 mg. of the latter was about as deadly as 1 mg. of the Hamadriad venom. Nevertheless, the following data of the experiments prove that the physiological action of the two is identical in its principal lethal action and similar to that of Cobra venom, but with the addition of another factor :—

EXPERIMENT I.—Rabbit, 1·8 kg., under chloroform followed by ether. Conditions the same as in the Hamadriad experiments above. A dose of 9 mg. (5 mg. per kilogramme) in 9 cub. centim. normal salt solution injected intravenously

Time.	Blood pressure.	Respirations.		Remarks.
		Per minute.	Amplitude.	
	millims.		millims.	
Before injection .	100	70	7	
After 1 min. . .	85	68	7½	Fall of blood pressure.
„ 2 mins. . .	65	72	8	
„ 3 „ . .	60	75	8	Respirations quickened.
„ 4 „ . .	75	76	8	
„ 5 „ . .	80	75	7	
„ 6 „ . .	85	69	6	
„ 7 „ . .	80	62	4½	Respirations slowed.
„ 8 „ . .	80	58	3	
„ 9 „ . .	80	53	1½	
„ 10 „ . .	80	34	1	
„ 11 „ . .	80	24	½	Respirations stopped.
„ 12 „ . .	100	0	—	
„ 13 „ . .	110	—	—	Respiratory convulsions.
„ 14 „ . .	110	—	—	
„ 15 „ . .	55	—	—	
„ 17 „ . .	25	—	—	

Post-mortem, the portal vein was found to be distended with fluid blood together with a soft clot, which is of interest in connection with the marked primary fall of blood pressure during the second and third minutes. The heart, pulmonary, arterial, and other large thoracic vessels were free from clot. The result of testing the nerves and muscles with the induced current was as follows :—

	Secondary coil at	Contraction of muscle.
Phrenic nerve	0 millims.	Nil.
Diaphragm	10 „	Good.
Sciatic nerve and brachial plexus . .	11 „	Good.
Leg and arm muscles	11 „	Good.

Here, once more, we find the motor end-plates of the phrenic nerves completely paralysed, while the limb nerve trunks are still physiologically active.

EXPERIMENT III.—Rabbit, weight 1·15 kg., under chloroform followed by ether. Conditions the same as in the above experiment, but a dose of 23 mg. (20 mg. per kilogramme) in 1 cub. centim. salt solution was given intravenously.

Time.	Blood pressure.	Respirations.		Remarks.
		Per ½ min.	Amplitude.	
	millims.		millims.	
Before injection .	100	52	7	
After ½ min. . .	75	54	7½	Primary blood pressure fall.
„ 1 „ . .	65	56	7½	
„ 1½ mins. . .	60	52	6	
„ 2 „ . .	65	45	3	Respiration failing.
„ 2½ „ . .	115	35	2	Blood pressure rising.
„ 3 „ . .	120	24	1	
„ 3½ „ . .	115	19	1	
„ 4 „ . .	120	8	½	
„ 5 „ . .	75	—	—	Respiration ceased.
„ 7 „ . .	50	—	—	Blood pressure falling.
„ 9 „ . .	20	—	—	

Post-mortem, the heart was found to be beating, and continued to do so for 15 minutes. There was no clotting of the blood in the portal vein, the heart, or the large thoracic vessels. The reactions of the nerves and muscles to the induced current were as follows :—

	Secondary coil at	Contraction of muscle.
Phrenic nerve	0 millim.	Nil.
Diaphragm	5 „	Good.
Sciatic and brachial nerves . .	0 „	Nil.
Leg and arm muscles	9 „	Good.

It is interesting to observe that, with the large and rapidly fatal dose of poison given in this case, the motor end-plates of the limb muscles, as well as of the diaphragm, were paralysed completely at the time of death, just as I had previously found to be the case when large doses of Enhydrina poison were injected. The absence of any clotting in the portal vein with this large dose, as well as in Experiment II. in which 10 mg. per kilogramme was injected, shows that its occurrence in the first experiment was of an exceptional nature. On the other hand, all three tracings show a marked primary fall of pressure occurring within 1 or 2 minutes of injection. This feature I have also found in a much smaller degree and somewhat inconstantly in my experiments with Enhydrina and Cobra poisons (although not with Hamadriad venom), but it is much more marked and constant in the case of the *Bungarus fasciatus* venom, which is a less powerful poison, weight for weight, to

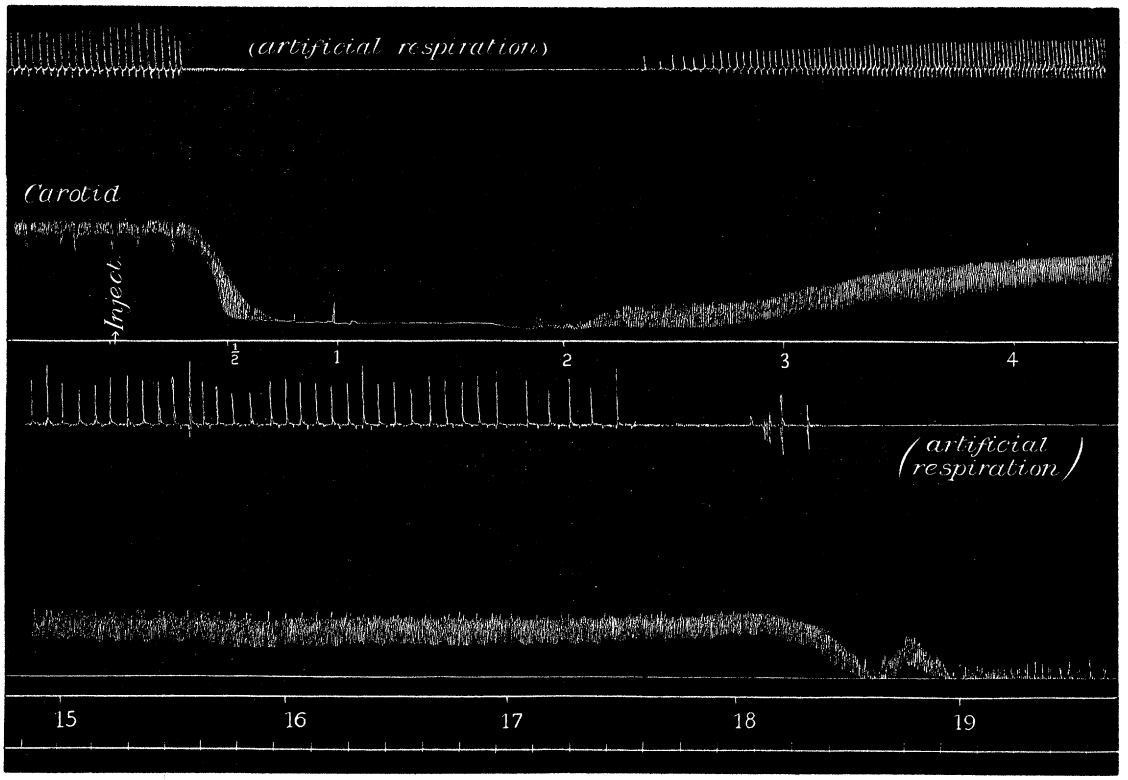
the respiratory centre than the other two. This blood-pressure fall appeared to be similar in nature to that which I have found to be so marked and essential a feature of poisoning by the Vipers and Pit Vipers (as shown in Part II. of this communication), and is, doubtless, due to the presence of a small quantity of the principal constituent of the Viperine poisons. In order to examine the effect of this venom on the blood pressure further, the following experiments were done on cats, and at the same time the effect of artificial respiration in keeping the circulation going after natural respiration had ceased was tested.

EXPERIMENT IV.—A Cat, weighing 3½ kg., was given chloroform followed by ether, and 3·5 in 1 cub. centim. salt solution (1 cg. per kilogramme) injected intravenously.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	140	31	
After ½ min. . .	70	9	Blood pressure fallen. Respirations stopped.
„ 1 „ . .	50	0	Artificial respiration started.
„ 2 mins. . .	50	0	
„ 3 „ . .	65	19	Respirations recommenced.
„ 4 „ . .	80	49	Blood pressure rising.
„ 6 „ . .	90	55	
„ 7 „ . .	90	49	
„ 8 „ . .	95	37	Respirations slowing.
„ 10 „ . .	95	27	
„ 13 „ . .	85	20	
„ 16 „ . .	70	14	
„ 19 „ . .	20	1	Respirations ceased. Artificial respiration.
„ 21 „ . .	0	0	Respirations ceased. Artificial respiration.

(See Tracing II., 1–4 and 15–19 minutes.)

In this case we have a very marked primary fall of blood pressure, which was rapidly recovered from to a very large extent, followed by the typical steady failure of respiration of Colubrine poisons, while artificial respiration after the cessation of natural breathing failed to keep the circulation going as in the case of the other Colubrine poisons. The circulatory conditions were very similar to those which I have found to occur constantly in the case of Viperine poisons, so this experiment confirms my conclusion that the poison of the Banded Krait is a mixture of both Colubrine and Viperine poisons, just as C. J. MARTIN showed the Colubrine Pseudechis of Australia to be. As the Viperine poisons are more readily destroyed by heat than is the Colubrine element, and in the case of the Pseudechis, C. J. MARTIN (4) has shown that the Viperine action can be eliminated by heating the venom to 90° C. for a very short time, leaving the Colubrine action intact; the following experiment



Tracing II. (*Bungarus fasciatus*, Experiment IV.).—Cat. *B. fasciatus* venom. 10 mg. per kilogramme, intravenously.

was performed to see if the same occurred in the case of the venom of the *Bungarus fasciatus*.

Experiment V.—A Cat, weighing 3½ kg., was given chloroform followed by ether, and 3·5 cg. (10 mg. per kilogramme) of the venom of *Bungarus fasciatus*, which had previously been heated in solution in 0·5 cub. centim. normal salt solution to a temperature of 90° C. for ½ minute in a water-bath, was injected intravenously.

Time.	Blood pressure.	Respirations per ½ minute.	Remarks.
	millims.		
Before injection . . .	135	17	
After ½ min.	100	20	
„ 1 „	60	8	Respirations stopped.
„ 1½ mins	75	15	Respirations recommenced.
„ 2 „	90	10	
„ 2½ „	95	8	
„ 3 „	95	6	
„ 3½ „	95	1	Respirations stopped.
„ 4 „	60	0	Blood pressure falling. Artificial respiration begun.
„ 5 „	90	0	
„ 7 „	70	—	Artificial respiration left off.
„ 8 „	55	—	

The pressure rose again on recommencing artificial respiration, and was kept up by its means until the 15th minute, but on then leaving it off an asphyxial rise followed rapidly by a final fall occurred. After death the phrenic nerves were found to be partially paralysed, while the blood collected immediately after death in a test-tube clotted firmly, and the next day a quantity of clear serum had exuded, showing that no marked hæmolysis had resulted from the action of the poison.

It is evident from the above data that the raising of the temperature of a solution of the venom to 90° C. for a very short time—opalescence resulting from the coagulation of some albuminous body present—had the effect of greatly lessening the action of the poison in causing a fall of blood pressure, while it did not reduce its action on the respiratory centre. It is also worthy of note that in this experiment artificial respiration had a much more marked effect in maintaining the blood pressure than in Experiment IV. with unheated venom. These facts confirm the supposition that the venom of the *Bungarus fasciatus* contains a mixture of Viperine and Colubrine poisons, the former being much more readily destroyed by heat, and thus closely resembles the venom of the Pseudechis in its general characters. It differs, however, from the last named in not having any powerful paralysing action on the heart, for I found that even a solution of the strength of 1 in 50 produced no effect on the beat of a frog's heart to which it was directly applied, while Martin (4) found Pseudechis venom to stop the frog's heart in diastole when applied in strong solution.

As Lamb (5) has shown that Daboia venom in a weak solution is completely destroyed by a temperature of 73–75° C. for ½ hour, while Cobra venom is little if at all affected by such treatment, I treated some *Bungarus fasciatus* venom in this way, and in Experiment VI. injected a cat under chloroform intravenously with the same dose as in the previous cases (10 mg. per kilogramme), but at the end of 1 hour it had produced no effect on either the blood pressure or the respiratory rate. This fact is of considerable interest, for the main action of the venom is undoubtedly of the Colubrine type causing paralysis of respiration, and the symptoms produced on birds, rats and mice are precisely similar to those of Cobra venom itself, yet the poison is rendered inert by heating to 73–75° C., and in the case of mice twenty times a minimal lethal dose thus heated proved harmless. It is evident then that Lamb and Hanna's (5) contention that Daboia venom contains no element of the Colubrine type is not proved by his experiments showing an absolute loss of virulence by heating to 73–75° C., for there might be such an element present which is destroyed by that temperature; as in the case of the Banded Krait venom.

III.—Bungarus cœruleus, *or Krait.*

This is one of the commonest and most dreaded of the poisonous Indian snakes, being very deadly in spite of its comparatively small size as compared with the Cobra, &c., and on account of its wide distribution it is the cause of a large amount of mortality. Thanks to the kindness of Dr. V. W. Shaw in giving me a few milligrammes of the venom of this snake, I have been able to get one tracing and to do some other experiments with its poison. It is slightly more virulent than Cobra venom, the minimal lethal dose for pigeons being 0·25 mg. per kilogramme, while the symptoms it produces are identical with those of the Cobra, as pointed out by Fayrer (2), and Wall (3), with whose observations on this point my own agree.

Experiment I.—Rabbit, weighing 1½ kg., under chloroform followed by ether. Injected intravenously with 8 mg. of Krait venom (4 mg. per kilogramme). The phrenic nerve was exposed in the neck and stimulated with induction shocks at intervals of 1 minute.

Time.	Blood pressure.	Respirations.		Phrenic nerve.	
		Per minute.	Amplitude.	Coil at	Contraction.
	millims.		millims.	millims.	
Before injection. .	60	63	5	30	Good.
After 1 min. . .	40	61	5	30	Good.
,, 2 mins. . .	40	56	3	30	Good.
,, 3 ,, . .	40	50	2	30	Fairly well.
,, 4 ,, . .	80	21	1	30	Feebly.
,, 5 ,, . .	30	0	—	30	Nil.
				25	Fairly well.
,, 6 ,, . .	20	—	—	25	Weaker.
,, 7 ,, . .	20	—	—	25	Feebly.
,, 8 ,, . .	15	—	—	20	Fairly well.
,, 9 ,, . .	10	—	—	—	

Here we have the typical paralysis of the respiratory centre, quickly followed by partial paralysis of the phrenic end-plates. In birds after death from this poison the sciatic nerves were also paralysed, just as in Cobra poisoning. The blood pressure showed a slight fall, followed by a marked rise with the advancing respiratory failure and a final fall after complete cessation of respiration. Artificial respiration was not tried, but there can be little doubt that it would be as efficacious in Krait poisoning as in that due to Cobra or Hamadriad and Enhydrina venoms. It is noteworthy that the end-plates of the phrenic nerves were not paralysed completely at the time death occurred, this effect being somewhat less than with the Cobra, Hamadriad and Enhydrina venoms, so that in the case of the Krait it is still more clear that the respiratory failure occurs before that of the phrenic end-plates.

Hæmolytic Action.—In the case of pigeon's blood, when 5 cub. centims. was added to 1 cub. centim. of a 1-in-10,000 solution of Krait venom in 0·9 salt solution complete hæmolysis took place within 6 hours. Similarly, with a 1-in-100,000 solution three-fourths of the red corpuscles were dissolved in 24 hours, while after 2 days it was nearly complete. With human blood the effect was not quite so great, as when the same quantity of blood was added to a 1 cub. centim. of a 1-in-10,000 solution the hæmolysis was not quite complete after 24 hours, although it was nearly so.

If we compare these data with those obtained in the same way for other snake venoms we find the hæmolytic action of Krait venom to be much less than that of Cobra poison; but, on the other hand, it is somewhat greater than that of Hamadriad or Enhydrina venoms, and also than that of the Banded Krait, being intermediate between these last three and Cobra venom.

Conclusions as to the Actions of the Indian Colubrine Poisons.

The physiological action of the three Colubrine Snake poisons dealt with, namely, the Hamadriad, Banded Krait and Common Krait, can be briefly summarised as follows :—

I. *Action on the Respiratory Centre.*—The essential lethal action of all these venoms, like that of the Cobra and the Hydrophidæ, is one of paralysing the respiratory centre, the respirations becoming both fewer in number and less in amplitude minute by minute until they cease when a large dose of the poison is administered intravenously. With smaller doses a very temporary stimulation of the respiratory centre is produced first.

II. *Action on the Motor End-Plates of the Phrenic and other Nerves.*—Next in importance is the paralysis of the end-plates of the phrenic nerves producing paralysis of the diaphragm, which follows very closely on the failure of the respiratory centre. This effect appears to be somewhat less marked in the case of the Krait venom than with the other two. If a large and rapidly fatal dose is given then the end-plates of the sciatic nerves are also paralysed before death occurs, but with smaller doses they usually only show partial paralysis at a time when the phrenic nerves are completely paralysed.

III. *Hæmolytic Action.*—The power of these venoms in dissolving the red corpuscles is very much less than that of Cobra venom, being about one hundred times less powerful in the case of the Hamadriad and Banded Krait, and about ten times less so in that of the Common Krait. Yet these venoms produce precisely the same symptoms as Cobra poison, so that the lethal effects of the latter cannot be in any degree due to its hæmolytic action, which becomes a very secondary property of Colubrine venoms in view of these results.

IV. *Action on the Blood Pressure.*—The blood pressure always rises during the asphyxial stage following the cessation of respiration, and subsequently falls again at

the time of death. The circulation, however, can be kept going for a long time after complete failure of the breathing if artificial respiration is kept up in the case of the Hamadriad, as well as in the Cobra, as first shown by LAUDER BRUNTON and FAYRER (6). In the case of *Bungarus fasciatus*, however, this is not the case, and in this instance marked primary fall of blood pressure occurs very shortly after intravenous injections of the venom. This we have seen is due to an added Viperine element, which may cause intravascular clotting in the portal system and in small animals throughout the body. This primary fall of pressure is similar to those always produced by Viperine poisons, and may be greatly lessened by heating the venom to 90° C. for a short time. In the case of Cobra and Krait venoms also slight primary falls of blood pressure are met with, which may possibly also be due to very minute amounts of the Viperine element in these venoms. It is only in the case of *Bungarus fasciatus* that this primary fall of pressure is of much importance.

The Relative Antidotal powers of Antivenin (CALMETTE'S), *prepared mainly by the injection of Cobra Venom, against the Poisons of the Hydrophidæ and Indian Colubrine Snakes.*

The facts recorded in the first part of this paper, and in a previous one (1), show that the physiological action of the Hydrophidæ, the Hamadriad and the Krait, as well as the most important element in the venom of the Banded Krait (*Bungarus fasciatus*), are all similar to that of the Cobra. Further, we have in CALMETTE'S antivenin an efficient antidote to the venom of the Cobra when it is given in sufficient doses, this serum being obtained from horses which have been actively immunised to a very high degree by frequent injections of a mixture of venoms which is mainly composed of Cobra poison. It becomes, then, a matter of great practical importance to ascertain whether CALMETTE'S antivenin is efficient against the other venoms mentioned, and if so, in what doses it must be used for curative purposes. Through the kindness of M. CALMETTE in placing at my disposal the necessary serum, I have been able to make a series of experiments on this point with results of some interest. The method adopted was that recommended by C. J. MARTIN (7), namely, the mixing at least ten minimal lethal doses of the poison with given quantities of the serum and leaving them in contact for at least $\frac{1}{2}$ hour at room temperature (about 18–20° C.), before injecting them subcutaneously, pigeons and rats being used for the experiments.

The first thing was to test the action of the antidote against Cobra venom, so as to standardise it and to get a term for comparison with other venoms. But there are two common varieties of Cobras in Bengal, one of which is much more frequently met with than the other, and consequently its venom was mainly used for the production of antivenin. As I had poison from these two kinds separately collected by Assistant-Surgeon DALY, in Calcutta, I have tested each of them with the following

results. The common variety is called by the natives the Keautiah, and the rarer one the Gokurrah, the former having one ocellus, or rounded mark, on the hood, and the latter having a double ocellus resembling a pair of spectacles.

I. *Cobra* (*Keautiah*).

The minimal lethal dose per kilogramme weight of the poison used was 0·5 mg. Rats of about 150 grammes in weight were used, the minimal lethal dose for which would be 0·075 mg., so as ten minimal lethal doses were to be given, each received 0·75 mg. of the dried venom, which had been dissolved in a fraction of a cubic centimetre of normal salt solution and added to varying quantities of the serum to be tested ½ hour before injection at room temperature (18–20° C). The results are shown in the following table :—

TABLE III.

Number.	Animal.	Weight.	Dose.	Minimal lethal doses.	Serum.	Result.
		grammes.	mg.		cub. centims.	
1	Rat . .	150	0·75	10	0·5	Died in 2¼ hours.
2	„ . .	150	0·75	10	1·0	Died in night.
3	„ . .	150	0·75	10	1·2	Recovered.
4	„ . .	150	0·75	10	1·4	Recovered.
5	„ . .	150	0·75	10	1·5	Recovered.

As recovery would take place if just over nine of the ten minimal lethal doses had been neutralised (the remaining quantity being then less than a minimal lethal dose), we see that 1·2 cub. centims. of the serum neutralised 0·675 cub. centim. of the venom (0·75–0·075 mg.). One cub. centim. would, therefore, neutralise 0·5625 mg., so that it would take 17·7 cub. centims. to neutralise 10 mg. of the venom. LAMB and HANNA (5) had obtained a very similar result, as they found 1 cub. centim. fresh CALMETTE'S antivenin neutralised 0·6–0·7 mg. of dried Cobra venom.

II. *Cobra* (*Gokurrah*).

In a similar manner the action of the antivenin was tested against the poison of the other variety of Cobra, the same quantity being used as in the above, namely, 0·75 mg. in each experiment, although the minimal lethal dose of this poison worked out at 0 4 mg. per kilogramme. The number of minimal lethal doses given, therefore, was 12·5. The results are shown in Table IV.

TABLE IV.

Number.	Animal.	Weight.	Dose.	Minimal lethal doses.	Serum.	Result.
		grammes.	mg.		cub. centims.	
1	Rat . .	150	0·75	12·5	0·5	Died in 1½ hours.
2	,, . .	150	0·75	12·5	1·0	Died in 1¾ hours.
3	,, . .	150	0·75	12·5	1·5	Died in 2 hours.
4	,, . .	150	0·75	12·5	2·0	Died in the night.
5	,, . .	150	0·75	12·5	2·5	Recovered.
6	,, . .	150	0·75	12·5	3·0	Recovered.
7	,, . .	150	0·75	12·5	3·5	Recovered.

In this case we find that 2·5 cub. centims. of the serum neutralised 0·69 cub. centim. (0·75–0·06 mg.) of the poison. One cub. centim. would, therefore, neutralise 0·276 mg., so that it would require 36·2 cub. centims. to neutralise 10 mg. of this venom, or twice as much as in the case of the former variety of Cobra, a difference which is only in a slight degree accounted for by the somewhat greater virulence of the latter kind, as shown by its lower minimal lethal dose. This is a remarkable point, which will be returned to after the tables for the other venoms have been given.

III. Naia Bungarus, *or Hamadriad.*

The minimal lethal dose of this venom worked out at 0·6 mg. per kilogramme weight, while as pigeons of about approximately 250 grammes were used in the experiments (on account of a difficulty in obtaining white rats) the minimal lethal dose was 0·15 mg., and ten doses equalled 1·5 mg. of venom.

TABLE V.

Number.	Animal.	Weight.	Dose.	Minimal lethal doses.	Serum.	Result.
		grammes.	mg.		cub. centims.	
1	Pigeon .	250	1·5	10	1	Died in 1 hour.
2	,, .	250	1·5	10	2	Died in the night.
3	,, .	250	1·5	10	3	Died in the night.
4	,, .	250	1·5	10	4	Recovered.
5	,, .	250	1·5	10	5	Recovered.
6	,, .	250	1·5	10	6	Recovered.

Here we find that 4 cub. centims. of serum neutralised 1·35 mg. (1·5–0·15) of the Hamadriad venom, so that 1 cub. centim. would neutralise 0·3475 mg., and it would require 28·8 cub. centims. of the serum to neutralise 10 mg. of the poison. It

is very interesting to observe that the antivenin made by injecting Cobra venom has an undoubted effect in neutralising the venom of a different kind of snake, although a nearly allied one, in only a slightly less degree than in the case of one variety of Cobra, namely, that called by the natives the Gokurrah.

IV. Bungarus cœruleus, *or Krait.*

The minimal lethal dose of this poison was found to be 0·25 mg. per kilogramme, being thus stronger than Cobra venom, although not so strong as the Sea-snake *Enhydrina Bengalensis.* Rats of approximately 80 grammes in weight were used, the minimal lethal dose for which would be 0·02 mg., and 0·2 mg. or ten mimimal lethal doses were injected after mixing with the serum as usual.

TABLE VI.

Number.	Animals.	Weight.	Dose.	Minimal lethal doses.	Serum.	Result.
		grammes.	mg.		cub. centims.	
1	Rat . .	80	0·2	10	1	Died in 7 hours.
2	,, . .	80	0·2	10	2	Died in the night.
3	,, . .	80	0·2	10	2·5	Recovered.
4	,, . .	80	0·2	10	3·0	Recovered.
5	,, . .	80	0·2	10	5	Died in two days.*

* Great inflammatory changes at seat of injection, no symptoms of Colubrine poisoning observed. Death due to septic changes.

In this instance it took 2·5 cub. centims. of the serum to neutralise 0·18 mg. (0·2–0·02) of Krait venom. One cub. centim. would therefore neutralise 0·072 mg., and it would take 138·8 cub. centims. of the serum to neutralise 10 mg. As the strength of the venom was twice as great as that of the Keautiah venom, this amount of serum would have to be halved when comparing the effect of the serum on these two poisons. Even then the serum will be about four times as effective against the Cobra venom as against that of the Krait.

V. Bungarus fasciatus, *or Banded Krait.*

We have seen that FAYRER (2) pointed out years ago that this snake, although a large one, is much less deadly than the Cobra, and WALL came to a similar conclusion (3), but I am not aware that its exact minimal lethal dose has been accurately worked out. The following table shows the results of inoculating pigeons with varying doses of the venom :—

TABLE VII.

Number.	Animal.	Dose per kilogramme.	Result.
		mg.	
1	Pigeon . .	1	Recovered. No symptoms.
2	,, . .	2	Recovered. No symptoms.
3	,, . .	3	Recovered. Slight symptoms.
4	,, . .	5	Recovered. Slight symptoms.
5	,, . .	6	Recovered. Marked symptoms.
6	,, . .	7	Died in 8 hours.
7	,, . .	8	Died in 1 hour.

Thus we find that the minimal lethal dose of this venom for birds is 7 mg. per kilogramme, or fourteen times as great as that of Cobra venom, and twenty-eight times as great as that of its near relation *Bungarus cæruleus*, or ordinary Krait, and no less than 140 times as great as that of the Enhydrina. This explains the generally acknowledged lesser degree of virulence of the Banded Krait. Such great differences in the toxicity of the venoms of different Colubrine and Sea-snakes, the physiological action of which are identical (with the exception of the added Viperine element in the case of *Bungarus fasciatus*, which probably accounts for the much smaller proportion of the Colubrine element in its venom), are presumably due to varying proportions of the active respiratory poisons in their compositions; a factor which must be taken into account in estimating the amount of antivenin which is required to neutralise the effects of any given snake, together with the amount of the poison ejected by it at a single bite. The markedly small virulence of the poison of *B. fasciatus* as compared with that of the other Indian Colubrine snakes is of great interest in connection with the presence of a Viperine element in this venom, as I have shown in the first part of this paper; for this element, although less toxic than the Colubrine portion, nevertheless is of some bulk, as shown by the marked coagulum produced by heating for a few moments to 90° C., which we have seen above reduces considerably the effect of the Viperine element without affecting the Colubrine portion. This fact no doubt accounts to some extent for the greater minimal lethal dose of this poison.

The experiments on the action of the serum on this poison were carried out with rats, but owing to the small amount of venom in hand, only 3 mg. were used for each rat, of approximately 60 grammes, which amounted to seven minimal lethal doses. The results are shown in the following table:—

TABLE VIII.

Number.	Animal.	Weight.	Dose.	Minimal lethal doses.	Serum.	Result.
		grammes.	mg.		cub. centims.	
1	Rat . .	60	3	7	1	Died in night. Ill after 2 hours.
2	,, . .	60	3	7	1·5	Died in night.
3	,, . .	60	3	7	2	Died after 3 days.
4	,, . .	60	3	7	3	Died after 4 days.
5	,, . .	60	3	7	5	Died after 4 days.

The first two animals died with the typical symptoms of Colubrine poisoning, but the remaining three died with signs of chronic Viperine poisoning only, the Colubrine element alone having been neutralised by the antivenin.

VI. *Enhydrina Bengalensis.*

The very virulent poison of this Sea-snake I have shown in a previous paper (1) to have identically the same physiological action as Cobra venom. It therefore becomes a matter of interest and practical importance to ascertain whether CALMETTE'S serum has any effect against it. The following series of experiments were carried out in the same way as the foregoing, pigeons of approximately 300 grammes in weight being used, and ten minimal lethal doses being injected. The minimal lethal dose of this virus is 0·05 mg. per kilogramme, or one-tenth of that of Cobra venom, and one-fifth of that of Krait venom, the strongest of the Indian Colubrine snake venoms. A pigeon injected with this dose as a control to the following series with serum added to the virus, died in $2\frac{1}{2}$ hours :—

TABLE IX.

Number.	Animal.	Weight.	Dose.	Minimal lethal doses.	Serum.	Result.
		grammes.	mg.		cub. centims.	
1	Pigeon . .	300	0·15	10	1	Died in $1\frac{1}{2}$ hours.
2	,, . .	300	0·15	10	2	Died in $6\frac{1}{2}$ hours.
3	,, . .	300	0·15	10	3	Died in 30 hours.
4	,, . .	300	0·15	10	4	Died in 32 to 40 hours.
5	,, . .	300	0·15	10	5	Died in the night.
6	,, . .	300	0·15	10	6	Recovered.
7	,, . .	300	0·15	10	7	Recovered.

Here we find that, although smaller doses caused great retardation of the onset of the symptoms and prolongation of life, yet 6 cub. centims. of serum were required

to neutralise 0·135 mg. of the poison (0·15–0·015), so that 1 cub. centim would neutralise 0·025 mg., while 444 cub. centims. would be required to neutralise 10 mg., which I have found to be the average quantity ejected at one bite by this Sea-snake. The venom of this snake, however, is ten times as powerful, weight for weight, as Cobra venom, presumably owing to its containing ten times as large a proportion of the toxic principle, so that in order to compare the action of the serum on the two it will be necessary to divide the figure just given by ten, which gives 44 cub. centims. for the Enhydrina venom against 17·7 and 28·9 cub. centims. respectively for the two varieties of Cobra venoms. Considering the Enhydrina belongs to a different class of poisonous snakes to the Cobras, it is somewhat remarkable that the antivenin prepared from Cobra venom should have so marked an effect on it, and this fact agrees with the results I have obtained showing the physiological action of the Colubrine and the Sea-snakes is identical. In a few unsuccessful experiments with the antivenin in Calcutta only 0·5 cub. centim. of serum was used (1).

The Relative Value of Calmette's *Serum against the Venoms of the Hydrophidæ and Indian Colubrine Snakes.*

We now have the necessary data for comparing the action of Calmette's antivenin on the venoms of the Enhydrina and the Indian Colubrine snakes, for the above six series of experiments were carried out with the same serum of the same date. In order to know how much serum would be required to neutralise a natural dose of virus in a man we require to know how much venom different kinds of snakes inject at a single bite. Again, in the above experiments the serum was mixed with the venom for $\frac{1}{2}$ hour before injection, but it would require a larger quantity to counteract a given amount of venom when it is injected after the bite, how much more could only be found out by experiments, which I have not yet been able to undertake. The data, as far as they are available, are embodied in Table X. (p. 147). The first column shows the minimal lethal dose, per kilogramme weight for a warm-blooded animal, of each poison; while the second shows the number of cubic centimetres of serum required to neutralise *in vitro* 10 mg. of each venom. As, however, some of the poisons contain very different proportions of the respiratory poison, as shown by their greatly different minimal lethal doses, this factor must be taken into account in estimating the action of the antitoxin on the actual toxin of the venoms. Thus the poison of *Bungarus fasciatus* has a minimal lethal dose which is fourteen times as great as the common form of Cobra (the Keautiah), so that it must contain only one-fourteenth of the toxin that is present in an equal weight of Cobra venom; and in order to compare the action of the serum on the toxin of each, it will be necessary to multiply by fourteen the amount which neutralises 10 mg. of *B. fasciatus* poison in order to make the figure comparable with that found for the Cobra venom.

Similarly, as the venom of the Enhydrina is ten times as powerful as that of the Cobra, the amount of serum which will neutralise 10 mg. of this venom must be divided by ten before it can be compared with the quantity required to neutralise 10 mg. of Cobra venom. Similarly, the figure for Krait venom must be divided by two, and so on with the others. In this way the figures of Column 3 have been arrived at, to show the relative action of the antitoxin on the equivalent quantities of the active respiratory paralysing toxin of the different venoms.

Next, we must know how much of the serum is necessary to neutralise a minimal lethal dose of the venoms for a man of, let us say, 50 kilos. weight (about the average for natives of India). In the case of the Cobra, with a minimal lethal dose of 0·5 mg. per kilogramme this will be 25 mg., so if we multiply the figures in Column 3, which represents the serum to neutralise 10 mg., by two and a-half, we shall obtain the required results. Lastly, we must know the number of minimal lethal doses for a man of 50 kilos. ejected by the different snakes at a single bite, in order to be able to estimate the amount of serum required to completely neutralise this amount of venom *in vitro*.

In the case of the Cobra, LAMB (8) quotes CALMETTE as giving the average amount of venom ejected by a Cobra at 0·03–0·045 gramme, but, on the other hand, D. D. CUNNINGHAM gives the amount at the much higher figure of 0·254 gramme of dried venom, which would amount to ten minimal lethal doses for a man of 50 kilos., requiring over 400 cub. centims. of serum to neutralise it *in vitro*, and correspondingly more if injected after the poison. Again, I found the average amount of venom to be obtained from an Enhydrina at a single bite to be 10 mg., with a toxicity equivalent to 100 mg. of Cobra venom, or four minimal lethal doses. To completely neutralise *in vitro* this amount (for in the case of man it would not be advisable to be content with reducing the virus to just below a minimal lethal dose) 444 cub. centims. of the serum would be necessary. The Hamadriad, being a much larger snake than the Cobra, would presumably eject a much larger dose of venom, but exact figures are not available as far as I know. In a single specimen, from which my poison was obtained, the amount got was not much larger than a Cobra ejects, but it would not be safe to draw any conclusions from this solitary observation. As, moreover, the serum is only half as active against this venom as against that of the common form of Cobra, it is evident that something like 1000 cub. centims. of the serum would be required to neutralise a natural dose of Hamadriad venom.

In the case of *Bungarus cæruleus*, or common Krait, the dose ejected is much smaller than in the case of the Cobra; but this is largely compensated by its greater toxicity, while the serum has a very feeble action against this poison as compared with Cobra venom, so that several hundred cubic centimetres would be necessary to neutralise *in vitro* a natural dose of this venom. In the case of

B. fasciatus, or Banded Krait, the large size of the snake is compensated by the small toxicity of the venom; but, on the other hand, the serum has only a slight action against the respiratory paralysing toxic body present, while it has no action against the Viperine element, or the tendency for septic conditions to ensue, probably due to a loss of bactericidal properties of the blood (a point which I hope to examine shortly). On the whole, although the serum is well worthy of use in these cases, especially as the dose ejected is often only slightly above a minimal lethal one, yet too much must not be expected from its action.

The data summarised in Table IX., then, are somewhat disappointing, in so far as they point to the present available serum being not strong enough to be of very great value in the case of poisoning by the Hydrophidæ and Indian Colubrine snakes when a full dose has been injected by them, yet it is encouraging to find that it has a very definite action against the venoms of all of them, which will make it of service in large doses, especially where only a slightly *supra*-minimal lethal dose may have been injected, while if the serums could be made stronger than they are at present they would be of inestimable service in the treatment of these classes of snake bites. I would suggest that a mixture of Colubrine poisons should be used in the preparation of the antivenom as likely to yield a more generally useful serum.

On the other hand, in the case of the Viperine poisons my experience agrees with that of others in showing that CALMETTE'S serum has no action whatever in neutralising them, and it will be necessary to prepare a separate serum for use against the Vipers.

TABLE X.

Snake.	Minimal lethal dose in mg.	CALMETTE'S Serum to neutralise 10 mg.	Serum to neutralise toxine equivalent to 10 mg. of Cobra.	Serum to neutralise one lethal dose for 50 kg. in man.	Grammes of venom ejected at one bite.	Lethal doses ejected at one bite.	Serum to neutralise amount ejected at one bite *in vitro*.
							cub. centims.
1. Cobra (Keautiah) . .	0·5	17·7	17·7	44·25	0·030* 0·254†	10	442
2. Cobra (Gokurrah) . .	0·4	36·2	28·9	72·25	0·254	10	722
3. Hamadriad	0·6	28·8	34·5	86·25	?	10	862
4. *Bungarus cæruleus* . .	0·25	166·0	83·0	207·5	?	(3) ?	(600) ?
5. *Bungarus fasciatus* . .	7·0	No effect.	—	—	?	—	—
6. Enhydrina (Sea-snake)	0·05	444·4	44·4	111·0	0·010	4	444

* D. D. CUNNINGHAM. † LAMB, quoting CALMETTE.

Part II.—Vipers and Pit Vipers.

A. Viperidæ.

During recent years a great deal of work has been done on the action of Viperine poisons on the blood, and their lethal action has mainly been attributed to such action. Thus, in the case of the Rattlesnake Weir Mitchell and Reichert (9) long ago described the loss of coagulability and hæmorrhages which form the most marked features of poisoning by the American Pit Vipers, although they also attributed the lethal effect in part to the paralysis of the respiratory centre and the heart. Flexner (10), who more recently has closely examined the blood changes, has supported these views, and described separate toxic bodies, which he calls hæmorrhagin, hæmolysin, and neurotoxin respectively; the latter being similar in nature to the principal constituent of Cobra venom, acting by paralysing the respiratory centre. C. J. Martin (4), working in Australia, discovered the intravascular clotting of the blood produced by the Pseudechis (a Colubrine snake), and he suggested that the rapid death with convulsions produced by the Indian (Russell's) Viper is produced by such clotting in the blood vessels, while Lamb and Hanna (5), working in Bombay, have since found this to be the case, and have carefully studied the blood changes produced by the Indian Viper, coming to the conclusion that clotting of the blood in the case of rapid deaths, and loss of coagulability and hæmolytic effects in the slow ones, are the essential action of the poison, and that this Viperine venom has no primary action on the respiratory centre. D. D. Cunningham (11) had previously published careful observations on the effect of Russell's Viper on the blood, and attributed the convulsions to a direct action on the central nervous system.

Whilst working recently at the action of the poisons of the Hydrophidæ and Indian poisonous Colubrine snakes on the respiration and circulation, I made some tracings illustrating the action of Russell's Viper, which soon led me to think that there must be some important factor, other than the blood changes, which had previously escaped notice, namely, a rapid failure of the circulation in the absence of any intravascular clotting. Through the kindness of several friends I have been able to extend my inquiry, with important results, from *Daboia Russellii* to the African Puff Adder, the *Crotalus horridus*, or Rattlesnake, and to one of the Indian representatives of the last named, viz., *Trimeresurus anamallensis.*

I. *Daboia Russellii.*

This snake is very common in the thickly populated parts of Bengal and Assam, and after the Cobra probably causes more loss of life than any other in India, while we have as yet no efficient antivenin for use in the treatment of its bites. In man great extravasation of bloody serum takes place throughout the limb affected, together with haemorrhage from the bowel, and death does not usually take place

until after several hours or even a day or two, when the blood within the body is fluid, as first pointed out by FAYRER (2), and no intravascular clotting is found, as, relatively to the small size of the animals usually killed by this snake, man is a very large one. In smaller animals even subcutaneous injections of the venom produce, after a time varying inversely with the dose, violent convulsions and rapid death, while very minute amounts given intravenously produce the same effects. In both cases the blood is found to be clotted within, especially the portal veins, the pulmonary arteries and the right side of the heart, as shown by LAMB (5). D. D. CUNNINGHAM (11), however, showed some years ago that by repeated injections of slightly sub-minimal lethal doses at intervals of 20 minutes or so, a slow form of poisoning without convulsions, but with haemorrhages similar to those which occur in man, could be produced. After death in such a case there will be no intravascular clotting found. Again, WALL (3) pointed out years ago that if Daboia venom is heated for a short time to 100 F. its action appears to be altered, the primary convulsions no longer appearing, but a gradual failure of respiration occurs terminating in respiratory convulsions of a secondary nature, much as in many cases of poisoning by the venom of the Rattlesnake. The above references suffice to show what different opinions have been held as to the action of the Daboia venom, while the whole of the known facts appear to be difficult to satisfactorily explain on any hypothesis yet put forward. In order to try and throw some light on the question I have taken simultaneous tracings of the respirations and blood pressure curves with interesting and instructive results.

Blood Pressure and Respiratory Curves.

EXPERIMENT I.—In the first experiment a sufficient dose was given intravenously to produce rapid death with primary convulsions. A Cat, weighing 2 kg., was chloroformed and 2 mg. (1 mg. per kilogramme) was injected into the external jugular vein, the blood pressure of the carotid artery and the respirations, by means of a tracheal tube connected with a SANDSTRÖM'S recorder, being taken.

Time.	Blood pressure.	Respirations.		Remarks.
		Per ½ minute.	Amplitude.	
	millims.		millims.	
Before injection	90	16	8	
After ½ min.	50	24	9	
„ 1 „	25	33	4	
„ 1½ „	10	7	5	Convulsions.
„ 2 „	5	2	—	
„ 3 „	5	2	—	Terminal respiratory gasps.

Post-mortem.—The portal vein and its tributaries were solid with blood clot. The blood in the venæ cavæ and their tributaries, as well as in the right side of the heart and the pulmonary arteries was also clotted, but the left side of the heart was free from it. The diaphragm contracted well when the phrenic nerves were stimulated with the secondary coil at a distance of 45 millims. and the sciatics responded at 23 millims. showing no paralysis of the motor end-plates, as occurs in poisoning by the Hydrophidæ and Colubrine snakes.

Here we have a typical example of rapid death from Daboia poisoning with a vascular clotting, and the tracing shows precisely the opposite effects to those produced by the Cobra class of venoms, namely, a primary failure of the circulation with temporary increased rapidity of the respirations, followed by secondary respiratory failure and terminal respiratory convulsions, whereas in Cobra poisoning the respiration fails first and the circulation only secondarily to the cessation of the breathing. The intravascular clotting found *post-mortem* would appear to be sufficient to account for the symptoms here seen.

EXPERIMENT II.—In this case a sufficient dose to kill fairly rapidly, when injected subcutaneously, was used. A Rabbit, weighing 1 kg., was chloroformed and injected subcutaneously in the muscles of the right thigh with 5 cg. of Daboia venom, dissolved in 1 cub. centim. of 0·9 per cent. NaCl solution, records being taken, as before, of the blood pressure and respirations.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection . . .	85	80	
After 1 min.	85	81	
„ 2 mins.	85	82	
„ 3 „	80	81	
„ 4 „	75	79	Blood pressure falling.
„ 5 „	65	79	
„ 6 „	55	78	
„ 8 „	40	88	
„ 10 „	40	80	
„ 12 „	40	80	
„ 16 „	50	78	
„ 20 „	40	—	
„ 24 „	35	70	Respiration slowing.
„ 30 „	30	64	
„ 32 „	20	60	
„ 33 „	10	56	
„ 34 „	0	23	
„ 35 „	0	0	

Post-mortem.—Clots were found in both the portal and systemic veins, the right heart and pulmonary arteries and a little in the left auricle and thoracic aorta.

Only a few drops of blood could be obtained from the large veins, and it did not clot after 24 hours. The phrenic nerves were not paralysed.

Here, again, the circulation failed, but in a much more gradual manner than in the first case where the poison was injected intravenously. The respirations remained unaffected until after the blood pressure had become greatly decreased, when they became reduced in number minute by minute until they ceased If no blood-pressure tracing had been taken and the vessels had not been searched for intravascular clotting after death, it might easily have been regarded as a case of primary respiratory failure, instead of one of primary failure of the circulation produced by intravascular clotting, followed by secondary affection of the respiration due to deficient supply of blood to the medullary centres.

EXPERIMENT III.—WALL'S experiment of heating Daboia venom to 100° C. for a short time was repeated, in order to see how far the respiratory failure thus produced is primary or secondary. A Cat, weighing 2·8 kg., was chloroformed, and 2·8 cg. of Daboia venom (1 cg. per kilogramme), which had previously been heated for one minute to 100° C., was injected into the external jugular vein, and records taken as before.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection . . .	150	41	
After ½ min.	125	—	Blood pressure falling.
„ 1 „	90	43	
„ 2 mins.	75	43	
„ 3 „	70	35	
„ 4 „	65	35	
„ 6 „	60	30	Respirations slowing.
„ 10 „	55	21	
„ 15 „	52	16	
„ 20 „	55	8	
„ 29 „	50	7	
„ 30 „	25	3	
„ 31 „	10	0	

Post-mortem.—There was much black clot in the portal and systemic veins, all the cavities of the heart, and in the pulmonary and aortic arteries. Blood from the carotid artery clotted only feebly and imperfectly, forming a soft clot after some hours. The phrenic nerves were not paralysed.

Here we have just the same gradual failure of respiration as WALL described under the same conditions, but with the addition of a blood-pressure tracing, which clearly shows that the circulatory failure was the primary affection, a fall to one-half having been registered within 2 minutes of the injection, while the respiratory failure did

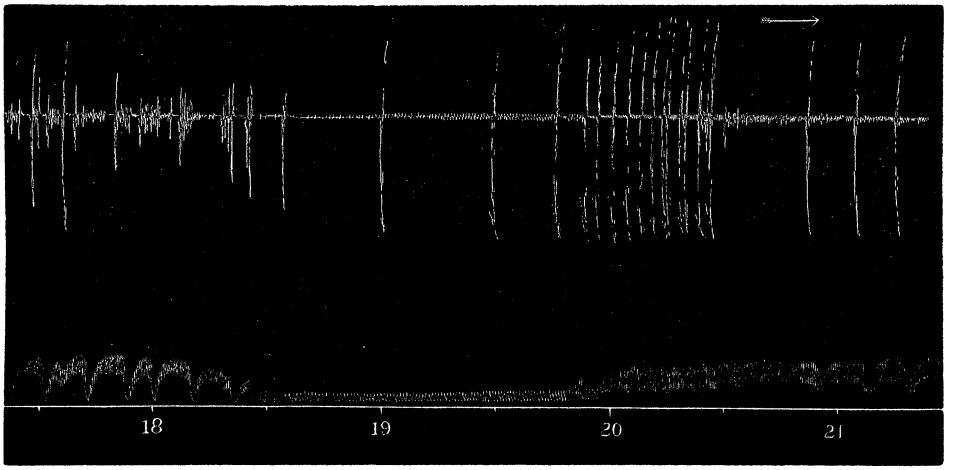
not begin until after that time, and was evidently secondary to the circulatory failure.

So far, then, the conditions met with in the three preceding experiments can be explained as the result of intravascular clotting, and they afford no evidence of any direct effect of the poison on the respiratory centre. We have seen, however, that in man this intravascular clotting has not been found, but a loss of coagulability and hæmorrhages constitute the essential symptoms observed, and the question arises whether such deaths can be fully accounted for by the effects of the poison on the blood, namely, the loss of coagulability and a less marked hæmolytic action, or whether there is any other factor present. In order to simulate this condition, CUNNINGHAM'S method of giving repeated slightly sub-minimal lethal doses must be used, or small doses may be given subcutaneously, which are not sufficient to produce intravascular clotting, but will bring about the negative phase of diminished coagulability of the blood, and then a small lethal dose may be given intravenously. In the following experiments these methods have been used with most instructive results.

EXPERIMENT IV.—A Cat, weighing 2·25 kg., was given chloroform followed by ether, and 0·225 mg. of Daboia venom (0·1 mg. per kilogramme) was injected into the external jugular vein, and records taken as before.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection . . .	110	35	
After 1 min.	110	32	
„ 3 mins.	110	33	
„ 6 „	110	30	
„ 7 „	80	23	Blood pressure falling.
„ 8 „	40	7	Respirations stopped.
„ 9 „	40	—	Respiratory convulsions.
„ 10 „	125	—	Blood pressure rising.
„ 11 „	40–130	16	Traube-Hering curves.
„ 13 „	70–110	21	
„ 14 „	30	14	Fall of blood pressure.
„ 15 „	30	1	Respirations stopped again.
„ 16 „	100	—	Respiratory convulsions. Blood pressure rising.
„ 18 „	25–110	15	Traube-Hering curves.
„ 19 „	30	—	3rd fall of pressure.
„ 20 „	75	—	Respiratory convulsions.
„ 22 „	50–120	—	Traube-Hering curves.
„ 25–26 mins. . . .	25	—	4th fall of pressure.
„ 27 mins.	80	—	Repiratory convulsions.
„ 28 „	50–100	—	Traube-Hering curves.
„ 30–31 mins. . . .	20	—	5th fall of pressure.
„ 33 mins.	80	—	Respiratory convulsions.
„ 35 „	85	—	Rise of blood pressure.
„ 37 „	45	—	Final fall of pressure.
„ 38 „	10	—	Death.

(See Tracing III. for 18–22 minutes and 34–38 minutes.)



Tracing III. (*Daboia Russellii*, Experiment IV.).—Cat. Daboia venom. 0·1 mg. per kilogramme; intravenously. 18–21 minutes.

Post-mortem.—A few minutes after the final fall of blood pressure and cessation of respiration the body was opened. A few drops of blood only were obtained from the carotid artery, which was very dark, but clotted well and gave out fairly clear serum. The large systemic veins were greatly distended with dark fluid blood, which clotted fairly well in test-tubes. The portal system was full of fluid blood, but there were no clots in it or in the systemic veins. The heart continued to beat, the right side being distended with blood, and the left empty. The pulmonary and aortic arteries were free from blood clot, but on opening up the branches of the pulmonary artery within the lung a tiny clot was found in one small branch only. The brain was normal, and there was no sign of hæmorrhage in the medulla or elsewhere. Stimulation of the phrenic nerves with the secondary coil at 45 millims. produced good contraction of the diaphragm.

The above experiment presents several points of interest. In the first place death clearly due to circulatory failure resulted from a very small dose of the venom given intravenously, without there being any marked intravascular clotting which could account for it. The first fall of blood pressure, however, did not occur until after 6 minutes, instead of within a few seconds as in the first experiment, when ten times as large a dose was given. Immediately after the fall in blood pressure the respirations rapidly failed, and after another minute, what appeared to be terminal respiratory convulsions, commenced. During this interval of very low blood pressure (40 millims.) the heart continued to beat slowly, each beat being clearly recorded, showing that the heart itself was not paralysed. After a few convulsive respirations had taken place the blood pressure began to rise again and the heart to beat more rapidly, while less deep, but irregular, respirations began once more, and at the same time very marked waves of alternately rising and falling of the blood pressure, resembling Traube-Hering curves, appeared.

A close comparison of the curves showed that the rises of pressure immediately

followed a deep respiration or group of respirations, while the falls corresponded with temporary cessation of the breaths, as if the pressure was pumped up with each convulsive respiratory effort. In the middle of the 18th minute the pressure sank again, this time to only 30 millims., and the respirations ceased, but at the end of the 20th minute another series of convulsive respirations was followed by a second rise of the blood pressure and another series of waves with a very definite relationship to the now infrequent inspirations. This sequence of events was repeated three times more, as the figures above given show, but the amplitude of the pressure waves became less each time, and at the end of the 37th minute the pressure finally fell, the succeeding convulsive inspirations failing to improve it, and death ensued. At each of the pressure failures the record of the pulse beat became less and less marked, and was no longer evident in the final fall.

The absence of the intravascular clotting (except very slight in the pulmonary vessels), *post-mortem* in this case was somewhat surprising, and made it very difficult to account for the facts observed on the theory that they were due to the blood changes known to be produced by Daboia venom, unless it might be that there was clotting in the capillary vessels of the lung producing obstruction of the circulation, which was temporarily overcome by the greatly increased intrathoracic pressure produced by the respiratory convulsions. This appeared to me the most probable explanation of the curve, and it became necessary to devise some means of testing its truth. In order to do this I determined to repeat the experiment and after death to see what pressure was required to pass fluids through the pulmonary circulation, so as to be able to form a rough estimate of the degree of obstruction, if any, present in them, which might possibly be due to capillary clotting.

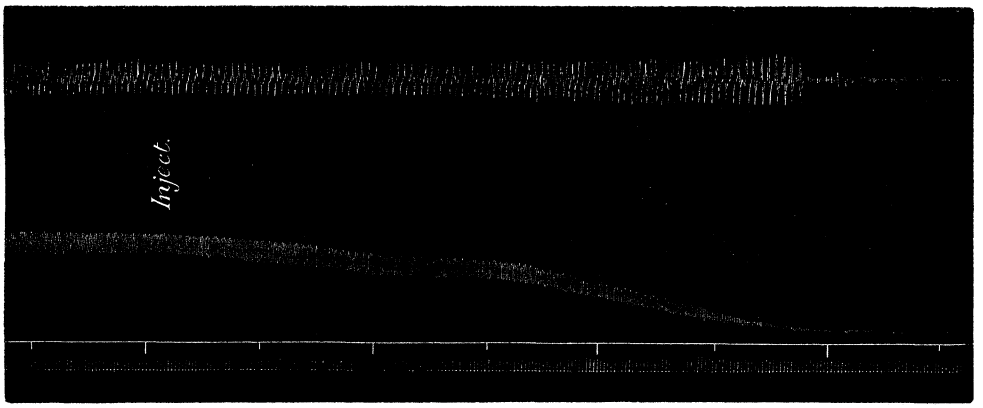
EXPERIMENT V.—A Cat, weighing $3\frac{1}{4}$ kg., was chloroformed and 0·325 mg. of Daboia venom (0·1 mg. per kilogramme) injected into the jugular vein.

Time.	Blood pressure.	Respirations per minute.
	millims.	
Before injection . . .	160	57
After 2 mins	140	58
„ 6 „	135	54
„ 11 „	150	44
„ 21 „	180	36
„ 33 „	165	32
„ 44 „	170	38

At this point a second dose of 0·1 mg. per kilogramme was injected into the jugular vein with the following result :—

Time.	Blood pressure.	Respirations per minute.
	millims.	
After ½ min.	160	—
„ 1 „	145	32
„ 1½ mins. . . .	140	—
„ 2 „	115	38
„ 2½ „	75	—
„ 3 „	40	31
„ 4 „	30	0
„ 7 „	20	—

(See Tracing IV. for 44–48 minutes.)



Tracing IV. (*Daboia Russellii*, Experiment V.).—Cat. Daboia venom. 0·1 mg. per kilogramme, intravenously, repeated after 44 minutes. 44–47 minutes.

Post-mortem.—On opening the chest the heart was beating, the right side being distended with blood and the left nearly empty. The systemic veins were also distended with fluid blood, which was very dark and did not clot in a test-tube. No clots could be found in the portal, pulmonary or systemic vessels, or in the heart. The diaphragm contracted well when the phrenic nerves were stimulated with the secondary coil at 45 millims. In order to test if there was any capillary clotting in the portal or pulmonary systems, normal salt solution was transfused through them from measured heights above the liver and lung respectively, with the result that it passed through readily at a pressure of 20 millims. of water in the case of the portal circulation, and of 30 millims. in that of the pulmonary vessels. It was therefore evident that there could be no obstruction of the capillaries of either organ such as could account for the circulatory failure recorded above.

In the foregoing experiment only a slight and temporary reduction of blood pressure followed the first very small intravenous dose, but on repeating it a rapid circulatory failure ensued, followed by the usual secondary failure of respiration. Yet there was absolutely no intravascular clotting, and the blood remained completely fluid after removal from the veins for over 24 hours.

Capillary clotting in the pulmonary or portal circulations was also excluded. The first dose evidently produced the negative phase of reduced coagulability of the blood, while the second one acting cumulatively brought about a rapid failure of the circulation. The accumulation of blood in the venous system, and the emptiness of the left heart and systemic arteries, were the most marked *post-mortem* features, while death had occurred far too rapidly to allow of the hæmorrhages, which are the characteristic feature of the chronic form of Daboia poisoning. It was now clear that there was some important factor present other than the mere changes in the coagulability of the blood, and further experiments were undertaken to see if, by first inducing the negative phase of reduced coagulability by repeated subcutaneous injections of sub-minimal lethal doses, rapid circulatory failure could be easily obtained by small intravenous doses without any intravascular clotting.

EXPERIMENT VI.—A Cat, weighing 3 kg., was given chloroform followed by ether, and 6 mg. of Daboia venom (2 mg. per kilogramme) was injected subcutaneously into the thigh.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	180	53	
After 2 mins. . .	180	49	
„ 12 „ . .	195	38	Respirations less frequent.
„ 28 „ . .	195	28	
„ 30 „ . .	—	—	
2nd subcutaneous injection of 2 mg. per kilogramme.			
After 36 „ . .	175	28	
„ 46 „ . .	165	30	
3rd injection of 0·3 mg. (0·1 mg. per kilogramme) intravenously.			
After 1 min. . .	150	32	
„ 3 mins. . .	160	34	
„ 5 „ . .	150	23	
4th injection of 0·6 mg. (0·2 mg. per kilogramme) intravenously.			
After 1 min. . .	110	28	
„ 2 mins. . .	70	41	Fall of blood pressure.
„ 3 „ . .	60	34	
„ 5 „ . .	40	25	
„ 6 „ . .	30	8	
„ 7 „ . .	30	3	Respirations stopped. Terminal respiratory convulsions.

Post-mortem.—The portal, pulmonary and systemic circulations, together with the heart, were all found to be free from blood clot. There were local extravasations

of blood-stained serum at the seats of subcutaneous injection. The phrenic nerves were not paralysed.

Here, again, a rapid failure of the circulation was produced by a very small dose of the poison intravenously after subminimal lethal doses subcutaneously, while the respirations, although much reduced in frequency after the first doses, only failed subsequently to the final marked fall of blood pressure; yet there was no intravascular clotting to account for the result. In the next experiment, repeated and increasing doses of Daboia venom were given subcutaneously to see if a marked reduction in the blood pressure could be induced by this mode of administration, which is the natural one.

EXPERIMENT VII.—A Cat, weighing 3·5 kg., was given chloroform followed by ether, and 2 mg. per kilogramme of Daboia venom injected subcutaneously.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	100	33	
After 10 mins. . .	115	24	
„ 20 „ . .	125	20	Respirations less frequent.
2nd subcutaneous injection of 5 mg. per kilogramme.			
After 40 „ . .	120	20	
3rd subcutaneous injection of 5 mg. per kilogramme.			
After 50 „ . .	120	24	
„ 69 „ . .	120	22	
4th subcutaneous injection of 10 mg. per kilogramme.			
After 79 „ . .	100	22	
„ 89 „ . .	90	20	Blood pressure falling.
„ 97 „ . .	85	20	
5th subcutaneous injection of 20 mg. per kilogramme.			
After 108 „ . .	65	20	Blood pressure falling.
„ 144 „ . .	65	22	
„ 152 „ . .	70	24	
6th injection of 0·1 mg. per kilogramme intravenously.			
After 1 min. . .	65	24	
„ 2 mins. . .	55	23	
„ 3 „ . .	30	37	
„ 4 „ . .	25	32	
„ 6 „ . .	25	26	
7th injection of 0·1 mg. per kilogramme intravenously.			
After 8 „ . .	25	21	
„ 9 „ . .	20	10	
„ 10 „ . .	20	0	Respiration stopped.

Post-mortem.—There was no intravascular clotting anywhere. The blood on removal formed only a very loose clot after some time, which exuded only slightly hæmoglobin-stained serum. The phrenic nerves were normal. On carrying out transfusion with normal salt solution it was found to pass readily through the pulmonary circulation at a pressure of 30–40 millims., through the portal system at one of 30 millims., and through the abdominal aorta and back by the inferior vena cava at one of 30 millims., all water pressure, proving that the failure of the circulation was not due to any intravascular clotting in the capillary vessels.

Here, again, we have death from primary circulatory failure without any clotting in the vessels to account for it. The first three small subcutaneous doses no doubt produce a condition of reduced coagulability which prevented the subsequent ones from causing intravascular clotting. The fourth and fifth larger subcutaneous ones produced a marked fall of pressure of a very gradual nature until it reached about half the normal, so that there is little reason for doubt that in time fatal circulatory failure without any clotting could be brought about in this way (as was done in a later experiment, namely No. XI.). In order to terminate the experiment more quickly, very small intravascular doses were given, when a similar rapid circulatory failure to those of the previous experiments resulted.

The above experiments were sufficient to show that if steps are taken to produce a reduced coagulability of the blood by small doses, then a fatal circulatory failure independent of any intravascular clotting can readily and constantly be induced, which will be of a rapid nature if the later dose be introduced into the circulation directly, and of a much slower character if they be given subcutaneously as in nature. It remained to ascertain the exact nature of the circulatory failure, and if it will account for the hæmorrhages which constitute the essential symptoms of the slow form of poisoning by Daboia venom which occurs in the case of man. At first sight the rapid fall of blood pressure following very small intravenous injections of the poison seemed to indicate a direct action on the heart, but against this interpretation was the remarkable recovery of the pressure with the onset of respiratory convulsions which repeatedly occurred in Experiment III. and to a less extent in some others, together with the evidence of the records of the continuance of the pulse beats during and sometimes for minutes after the fall of the blood pressure. Further, the marked Traube-Hering curves pointed to vaso-motor action, and a paralysis of the vaso-motor centre would equally well explain the blood-pressure fall.

Direct Action on the Heart.

The effect of direct applications of solutions of Daboia venom in normal salt solution to excised frogs' hearts was therefore tried, with the result that even solutions of a strength of 1 in 50 produced no definitely retarding effect on the contractions of the organ, which made it difficult to conceive how the injection of 0·1 mg. per

kilogramme weight could cause an immediate great fall of blood pressure by the direct action of the venom on the heart. Attention was then turned to the question whether the effects recorded above could be explained as a result of a direct paralysing effect of the poison on the vaso-motor centre in the medulla, for which purpose the following experiments were performed.

Action on the Central Vaso-Motor Centre.

Experiment VIII.—A Dog, weighing 10 kg., was given chloroform followed by ether, the spinal cord cut in the cervical region, and artificial respiration performed. The blood pressure before the section was 135 millims. of mercury, and it fell afterwards to 65 millims. A first subcutaneous injection of 2 cg. of Daboia venom (2 mg. per kilogramme, a sub-minimal lethal dose) was now injected into the thigh, in order to produce a reduction in the coagulability of the blood and prevent a second intravenous dose from killing immediately by clotting the blood in the vessels, so as to allow of the effect of this second dose on the pulse and blood pressure being observed. The second dose consisted of 1 mg. per kilogramme (1 cg.) in 0·2 cub. centim. salt solution, and was injected into the external jugular vein. The following table shows the result of the intravenous injection :—

Time.	Blood pressure.	Pulse rate per minute.	Respiration.
	millims.		
Before injection . . .	50	72	Artificial.
After 1 min.	50	68	Artificial.
„ 2 mins.	45	49	Artificial.
„ 3 „	45	47	Artificial.
„ 4 „	40	—	Artificial.
„ 5 „	30	—	Artificial.
„ 6 „	20	—	Artificial.
„ 7 „	10	—	Artificial.

Post-mortem.—The heart was still beating feebly. There was extensive clotting in the portal veins, pulmonary arteries and systemic veins, as well as some in the right heart. Here the slow steady failure of the circulation was doubtless due to intravascular clotting, which would have taken place in a few seconds with the dose used, but for the first subcutaneous injection of venom. The absence of any sudden fall of blood pressure and the continuation of the pulse after this large intravenous dose shows that the venom does not produce the falls always caused by it when the cord is intact by direct action on the heart, and the fact that the production of vaso-dilatation by section of the cord prevents any sudden marked fall of pressure due to the intravenous injection of the venom indicates that its action is one of paralysing the central vaso-motor centre in the medulla, and not a direct one on the heart.

If this is the case, then section of the cord after a very marked fall of pressure produced by Daboia poison should not cause any further very marked fall of pressure. Further, if central vaso-motor paralysis is the cause of the pressure fall, then it ought to be possible to observe the dilatation of the blood vessels of the portal area in the mesentery and omentum. In order to test these points the following experiment was performed.

Experiment IX.—A cat, weighing 3 kg., was given chloroform followed by ether. Two subminimal lethal subcutaneous doses of Daboia venom were injected, in order to produce the negative phase of reduced coagulability of the blood before giving an intravenous dose. They were as follows: First injection, 6 mg. in 0·5 cub. centim. salt solution (2 mg. per kilogramme), and after 15 minutes a second injection of 12 mg. (4 mg. per kilogramme). No definite effect on either the blood pressure or respiratory rate was produced by these small doses. At 42½ minutes after the first dose, 0·3 mg. (0·1 mg. per kilogramme) was injected into the external jugular vein with the following result. Just before this last dose a piece of the omentum was withdrawn from the abdominal cavity, and, protected by cotton wool soaked in warm normal saline solution, was placed under the microscope and the circulation watched during and after the fall in blood pressure produced by the intravenous injection. The field under observation included a small artery and vein, from which two or three small vessels containing circulating blood came off. With the rapid fall in pressure, which occurred within 2 minutes of the third injection, a very marked dilatation of both the large and the small vessels was noted, while numerous capillaries, which had previously been invisible, were now seen with blood streams actively flowing through them. The circulation continued actively until after the cord was cut 11 minutes after the third injection. The effect on the circulation is shown in the following figures:—

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before 3rd injection . .	150	48	
After ½ min.	140	—	
„ 1 „	70	56	Rapid fall of blood pressure.
„ 2 mins.	50	56	
„ 8 „	50	45	
„ 11 „	50	37	
Spinal cord cut in the cervical region. Artificial respiration.			
„ 12 „	30	—	
„ 15 „	30	—	
„ 17 „	40	—	
„ 18 „	50	—	Artificial respiration left off.
„ 20 „	40	—	
„ 22 „	10	—	

Post-mortem.—The large veins were distended with incoagulable blood. There was a blood clot in the external jugular vein just below the seat of injection only, while a very small clot was found in one of the tributaries of the superior mesenteric vein. The portal vein and its distributory vessels within the liver were quite free from clots, as was the pulmonary circulation and the cavities of the heart. The small clots noted must almost certainly have been formed as a result of the preliminary subcutaneous injections, and even if they were formed after the third intravenous one they would in no way account for the rapid fall of blood pressure from 150–50 millims. within 2 minutes of the last injection. On section of the cervical cord there was a slight further fall of pressure, which was completely recovered from after artificial respiration had been kept up for a few minutes, so it must have been solely due to shock. It is evident, therefore, that complete vaso-motor paralysis must have resulted from the action of the intravenous injection of the Daboia venom, for the heart continued to beat steadily until several minutes after the artificial respiration was finally stopped. The observation of the very marked dilatation of the vessels of the omentum confirms the view that the fall of pressure was due to a vaso-motor dilatation of very marked degree. Immediately after death the blood was transfused through the portal and pulmonary circulations, and was found to pass easily from a height of 40 millims., showing that there was neither capillary clotting or any change in the viscosity of the blood which could account for the failure of the circulation.

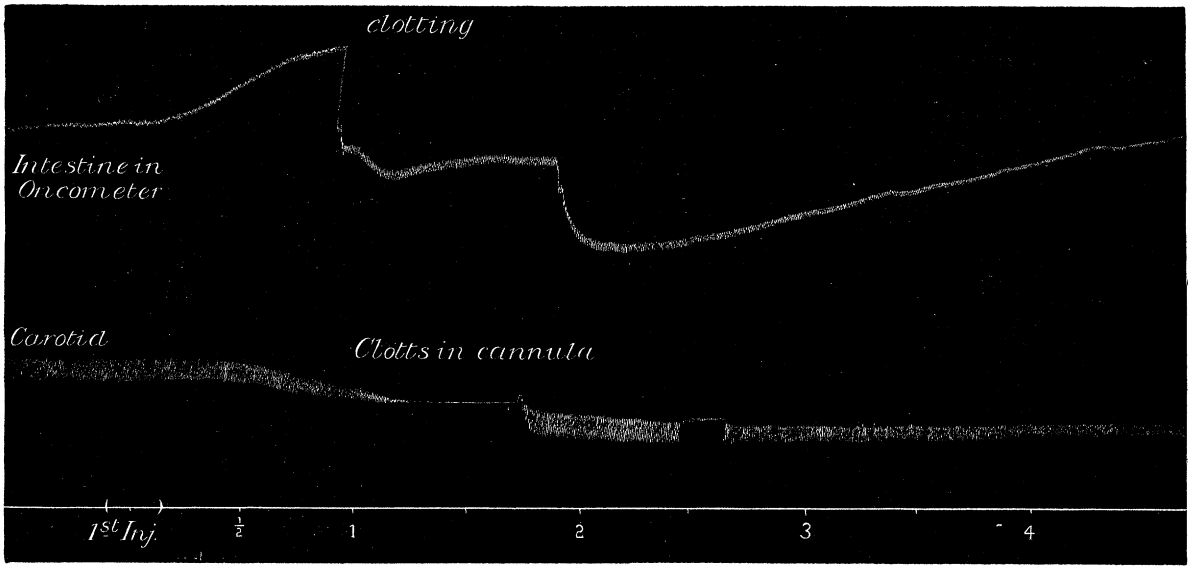
Simultaneous General Blood-Pressure Fall and Portal Vaso-Dilatation.

In order to obtain an absolute demonstration of the vaso-dilatation of the portal vessels, simultaneous tracings of the general blood pressure and of the variations in the amount of blood in a large loop of the small intestine placed in an oncometer connected up with a Sandström recorder were taken in cases of poisoning with different Viperine venoms, Dr. T. G. Brodie very kindly helping me with the first (that with the Puff Adder venom).

EXPERIMENT X.—A Cat, weighing 4 kg., was chloroformed and a cannula in the carotid artery was connected up with a GAD'S manometer. The abdomen was then opened and a large loop of intestine was isolated by ligaturing in two places on either side, and placed in an oncometer connected up with a SANDSTRÖM'S recorder. Any vaso-dilatation would cause the lever to rise, and any cause of diminished blood entry would cause it to fall. The following is the record of the experiment :—

Time.	Blood pressure.	Oncometer lever.	Remarks.
	millims.		
Before 1st injection .	160		
1st injection of 0·1 mg. per kilogramme intravenously in 0·5 cub. centim. normal saline.			
After ½ min. . . .	150	Rising very fast.	Vaso-dilatation.
,, 1 ,, . . .	125	Rising very fast.	Vaso-dilatation.
,, 2 mins. . . .	87	Sudden fall.	Clotting in arterial cannula. Fall due to clotting in mesenteric vein.
,, 3 ,, . . .	85	Rising fast.	Vaso-dilatation.
,, 6 ,, . . .	85	Rising steadily.	Vaso-dilatation.
,, 9 ,, . . .	87	Rising steadily.	Vaso-dilatation.
2nd injection of 0·2 mg. per kilogramme intravenously in 0·5 cub. centim. normal saline.			
After 10 mins. . . .	87	Rising slowly.	
,, 11 ,, . . .	75	Slight fall.	
,, 12 ,, . . .	70	Rising slowly.	
,, 15 ,, . . .	87	Rising slowly.	
,, 18 ,, . . .	90	Stationary.	
,, 23 ,, . . .	80–125	Rising steadily.	Traube-Hering curves well marked.
,, 25 ,, . . .	90–100	Rising steadily.	Traube-Hering curves less marked.
,, 28 ,, . . .	70	Rising slowly.	
,, 30 ,, . . .	65	Stationary.	

(See Tracing V. for 1–3½ minutes.)



Tracing V. (*Daboia Russellii*, Experiment X.).—Cat. Daboia venom. 0·1 mg. per kilogramme, intravenously. First 4½ minutes.

The pulsation of the vessels in the loop of intestine became very feeble by this time, so the record was stopped.

Post-mortem, slight clotting was found in the external jugular vein below the seat of injection. The portal vein and its branches in the liver were free from clot, as was the pulmonary circulation. Careful search showed a small thread of clot in one of the tributaries of the mesenteric vein within the oncometer. This accounts for the sudden fall of pressure in the oncometer at the end of the 2nd minute, at the same time that clotting occurred in the carotid artery cannula. Except for this, marked vaso-dilatation of the portal vessels occurred throughout the 10 minutes following the first injection of the Daboia venom, and to a somewhat less extent after the second one, the entry of which was probably retarded by the clot in the external jugular vein just below the cannula through which the injections were made. The secondary marked vaso-dilatation, which occurred with the onset of the Traube-Hering curves at the 23rd minute, is also of great interest, as these curves always make their appearance before the final fall of blood pressure, and are doubtless due to the struggles of the enfeebled vaso-motor centre to keep up its tonic contraction of the peripheral vessels.

This experiment, then, proves that marked vaso-dilatation of the portal system does occur coincidently with the general fall of blood pressure for which it accounts. In view, however, of the effect of Viperine poisons in causing hæmorrhages, which in the case of the Rattlesnake in particular has been shown by Weir Mitchell and Reichert (9), and more recently by Flexner (10), to be largely due to a destructive effect of the poison on the endothelial lining of the blood vessels, it becomes of importance to determine if the vaso-dilatation produced by the Daboia venom is due in part at least to an action on the peripheral vessels and not entirely to a paralysing action on the central vaso-motor centre in the medulla.

The Effect of Daboia and Cobra Venoms on the Calibre of the Systemic Vessel.

Dr. J. G. Brodie very kindly tested the action of these venoms on the peripheral mechanism, controlling the circulation through the blood vessels by means of his perfusion apparatus.

Experiment I.—The hind quarters of a freshly killed cat were perfused with defibrinated blood of cats through the abdominal aorta. Ten mg. of Cobra venom in 1 cub. centim. of 0·9 per cent. salt solution was injected into the circulating blood. A rapid and very marked vaso-constriction immediately occurred, and persisted for so long that no further experiments could be carried out with this animal.

Experiment II.—The small intestines of another cat were perfused with blood, and 0·3 mg. (0·1 mg. per kilogramme in 1 cub. centim. salt solution) were injected into the circulating blood. A very rapid and marked vaso-constriction appeared before the whole of the injection had been made. After some time a second injection of 3 mg.

in 1 cub. centim. salt solution was injected, and, although the vessels were still contracted to a considerable degree, a further marked constriction occurred, the amount of blood returning through the cannula in the inferior vena cava becoming visibly less.

Thus we have a large dose of Cobra venom and a small one of Daboia venom both causing a marked local vaso-constriction when perfused through blood vessels which were cut off from the influence of the vaso-motor centre. This effect is worthy of further study, but at least it is clear that the vaso-dilatation produced by the injection of Daboia venom is not due to any action on the peripheral mechanism, but solely to paralysis of the central control of the medulla, acting in spite of the opposite tendency to constriction due to the peripheral action of the venom. This conclusion is also supported by the action of drugs which produce local constriction of the blood vessels, of which the most powerful is adrenal extract. The following experiment will serve to illustrate this point :—

The Effect of Abdominal Pressure and Adrenal Extract on the Blood Pressure in Daboia Poisoning.

EXPERIMENT XI.—Cat, weighing $2\frac{1}{4}$ kg., was chloroformed and Daboia venom injected subcutaneously, small doses being first given to produce the negative phase of reduced coagulability. The first dose was 2 mg. per kilogramme.

Time.	Blood pressure.	Respirations per $\frac{1}{2}$ minute.	Remarks.
	millims.		
Before injection .	150	39	
After 10 mins. . .	140	32	
2nd injection of 5 mg. per kilogramme subcutaneously.			
After 20 ,, . .	150	32	
,, 40 ,, . .	150	22	Respiration less frequent.
,, 73 ,, . .	125	21	
3rd injection of 20 mg. per kilogramme subcutaneously.			
After 5 ,, . .	100	20	
,, 7 ,, . .	90	—	
,, 8 ,, . .	65	—	
,, 10 ,, . .	40	17	Respiration stopped.
,, 13 ,, . .	35	—	Infrequent convulsive respirations.
,, 20 ,, . .	40	—	Infrequent convulsive respiration.
,, 35 ,, . .	50	—	
,, 37 ,, . .	55	—	Abdominal binder applied.
,, 45 ,, . .	60	—	Abdominal binder applied.
,, 50 ,, . .	50	—	Binder relaxed.
,, 55 ,, . .	60	—	Binder tightened.
Adrenal chloride (1 in 1000), 0·3 cub. centim. in 1 cub. centim. salt solution injected intravenously.			
After 62 mins. . .	80	—	
,, 65 ,, . .	80	—	
,, 70 ,, . .	75	—	
,, 75 ,, . .	25	—	

This experiment is interesting from several points of view. In the first place we have a circulatory death produced entirely by subcutaneous doses of Daboia venom, the fall of pressure following the last large dose having been a rapid one of marked degree. *Post-mortem*, the blood was incoagulable as usual, the large veins being distended with it. There was some clotting in the portal system, together with fluid blood. The pulmonary circulation and heart were free from clot, as were the large systemic veins, with the exception of those near the seats of injection in the thighs and axilla, where there were also effusions of blood-stained fluid and petechiæ. The partial clotting in the portal circulation probably took place as a result of the first two injections, and would not account in any way for the failure of the general circulation. Secondly, the improvement of the blood pressure each time that pressure was applied to the abdomen by means of a binder was noteworthy, being no doubt due to the displacement of blood from the dilated portal vessels, and its being driven on to the heart. Lastly, the marked, although very temporary, improvement of the blood pressure immediately following the injection of the adrenal chloride, shows that the small arteries could still contract and raise the pressure even when it had reached a very low ebb.

We shall see later, when discussing the other Viperine poisons, that a very much more marked and prolonged effect on the pressure can be obtained by the use of this drug before the vaso-motor centre is completely paralysed, but the result above recorded supports the conclusion derived from the perfusion experiment that the peripheral vaso-motor mechanism is not destroyed by the Daboia venom, and that the fall in pressure noted must be due to paralysis of the central vaso-motor centre in the medulla. In the case of this venom, the difficulties due to the complications produced by the intravascular clotting it also produces rendered the demonstration of the paralysis of the vaso-motor centre a matter of considerable difficulty; but we shall see that with some of the other Vipers little or no intravascular clotting is produced, so that in them the circulatory failure can be much more easily studied. It will be well, then, to record some experiments with other Viperine poisons before summing up the effects of the Daboia venom, so as to be able to consider the physiological action of the Vipers as a whole.

II. *The African Puff Adder.*

Through the great kindness of Dr. J. W. W. Stephens, in placing at my disposal some venom of the Puff Adder, which he collected in Africa, while on the Malarial Commission of the Royal Society, and in allowing me to publish the records, I have been able to take some tracings illustrating the action of this venom for comparison with that of *Daboia Russellii*, with results of considerable interest. As in all the other experiments, the dried venom was used, and it has proved almost as deadly as Daboia venom itself when injected subcutaneously into pigeons, the symptoms being

also similar in the case of the two poisons, a lethal dose causing death with violent convulsions. *Post-mortem*, intravascular clotting was found most marked in the portal system, but also present in the pulmonary arteries, and in the systemic veins and heart, thus resembling again the changes found after acute Daboia poisoning. A dose of 5 mg. per kilogramme produced death in this way in 1 hour, and 4 mg. per kilogramme in 5 hours. The same result was obtained with 3 mg. of the Daboia venom with which I have worked. With a single lethal dose, then, there is no marked difference between the action of the two venoms, while in both there is much local extravasation of bloody serum, which is somewhat more extensive in the case of the Puff Adder.

A difference between the two is, however, noticed as soon as repeated sub-minimal lethal doses are given, in order to produce the chronic form of poisoning which the bites of vipers cause in man. As already stated, this chronic form of poisoning was produced in fowls by D. D. CUNNINGHAM by repeated small doses of Daboia venom, the negative phase of reduced or lost coagulability of the blood being caused, and death eventually resulting from repeated hæmorrhages from the bowel, &c. This chronic condition I have not found easy to produce in the case of pigeons, probably on account of their small size as compared with fowls, intravascular clotting being often produced by repeated injections of sub-minimal doses, although it may be limited to the portal circulation, and not sufficient to cause death by itself. In the case of the Puff Adder poison, on the other hand, it is quite easy to produce fatal results by repeated slightly sub-minimal lethal doses without the production of any intravascular clotting, but with a complete loss of coagulability of the blood, and accompanied by very marked pericardial, endocardial, sub-pleural, mesenteric, and other hæmorrhages as marked in degree as those produced by Rattlesnake venom. In these cases very marked portal congestion is present, pointing to a vaso-motor paralysis such as we have seen is the essential result of the action of the Daboia venom if intravascular clotting is avoided by any means.

Blood Pressure and Respiratory Curves.

As in the case of the Daboia venom, tracings have been taken of the respirations and of the carotid pressure, and the following will illustrate the effect of a single lethal dose given intravenously.

EXPERIMENT I.—A Cat, weighing 2½ kg., was chloroformed and a tracheal and a carotid cannula, respectively connected with recording apparatus, as in the former series of experiments. 5 mg. per kilogramme of Puff Adder poison were then injected intravenously.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection. .	140	41	
After ⅓ min.. . .	125	—	
„ ½ „ . . .	115	21	
„ ⅔ „ . . .	60	—	
„ 1 „ . . .	100	21	Respirations stopped.
„ 2 mins. . .	50	—	

Post-mortem.—There was clotting throughout the portal system, but it was not so complete as after one-fifth of the dose of Daboia venom, some fluid incoagulable blood being also present. The pulmonary arteries, right cavities of the heart and systemic veins also contained clotted blood together with a good deal of fluid blood. The phrenic nerves responded to a weak faradic stimulus. No hæmorrhages were found. Here we have intravascular clotting of a similar nature, although less marked in degree to that produced by the intravascular injection of one-fifth as much Daboia venom, although we have seen that there is but little difference in the minimal lethal dose of the two venoms when given subcutaneously. In the next experiment a small dose was first given, in order to produce the negative phase of reduced coagulability before injecting a larger dose.

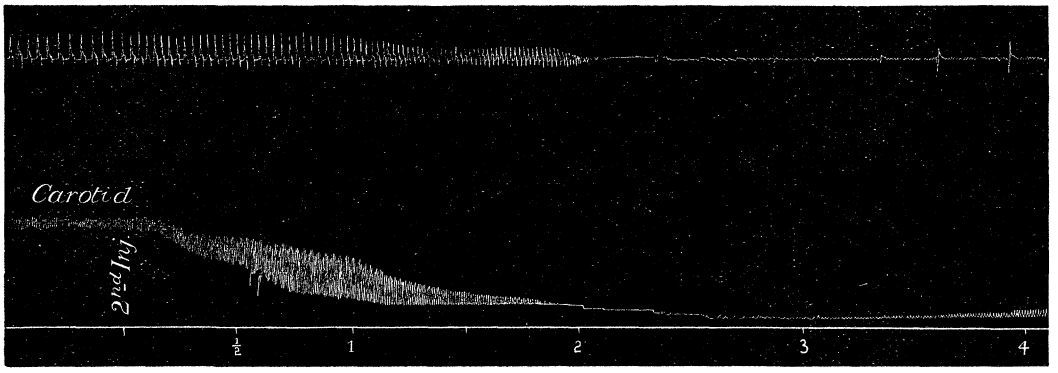
EXPERIMENT II.—A Cat, weighing 2·7 kg., was chloroformed and 0·3 mg. per kilogramme of Puff Adder poison injected intravenously, the usual records being taken.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	145	33	
After 1 min. . .	140	31	
„ 5 mins. . .	140	35	
„ 10 „ . .	125	30	Slight fall of blood pressure.
„ 24 „ . .	125	27	
2nd injection of 2 mg. per kilogramme intravenously.			
After ½ min. . .	95	—	Marked full of blood pressure.
„ 1 „ . .	70	29	
„ 1½ mins. .	55	—	
„ 2 „ . .	50	51	Respirations very shallow.
„ 3 „ . .	40	0	Respirations stopped.
„ 5 „ . .	50	2	Infrequent convulsive respirations.
„ 12 „ . .	50	4	Infrequent convulsive respirations.
„ 16 „ . .	53	15	Infrequent convulsive respirations.

EXPERIMENT II.—*continued.*

Time.	Blood pressure.	Respirations per minute.	Remarks.
Adrenal chloride (1 in 1000) 0·5 cub. centim. in 1 cub. centim. injected intravenously.			
	millims.		
After 17 mins. . .	60–125	4	Infrequent convulsive respirations.
„ 20 „ . .	55–100	3	Infrequent convulsive respirations.
„ 22 „ . .	55– 90	5	Infrequent convulsive respirations.
„ 27 „ . .	55	5	Infrequent convulsive respirations.
„ 37 „ . .	35	—	Infrequent convulsive respirations.
„ 47 „ . .	15	—	Infrequent convulsive respirations.
„ 57 „ . .	15	—	Respiratory convulsions ceased.

(See Tracing VI. for first 3 minutes.)



Tracing VI. (Puff Adder, Experiment II.).—Cat. Puff Adder venom. 2 mg. per kilogramme, intravenously. First 4 minutes.

Post-mortem.—The large veins were distended with incoagulable blood. No trace of clotting could be found in the portal, pulmonary or systemic circulations or in the heart. The pericardium contained blood-stained fluid, and there were very marked sub-pericardial hæmorrhages over the outer surface of the heart, as well as beneath the endocardium, especially of the left ventricle. The mesentery, omentum and other parts of the peritoneum showed very numerous petechial hæmorrhages, such as commonly result from intravenous injections of Rattlesnake venom, but which I have never seen in the case of Daboia poisoning, except slight petechiæ in the left ventricle after prolonged poisoning.

In the above experiment we have the same circulatory failure without any intravascular clotting that has been obtained with Daboia venom injected after the establishment of the negative phase of reduced congulability of the blood, only it is much more easy to produce this state in the case of the Puff Adder poison. Further, after complete vaso-motor paralysis has occurred a marked and somewhat prolonged raising of the blood pressure was obtained by the injection of adrenal chloride. The

increased excursus of the lever during the fall of blood pressure is typical of that due to vaso-motor failure as opposed to cardiac failure, this venom having been found to have a slightly stimulating effect on excised frogs' heart having been obtained with strong solutions of Puff Adder venom (1 in 100). In another similar experiment the fall of pressure was more gradual, as will be seen from the following data.

EXPERIMENT III.—A Cat, weighing $3\frac{1}{2}$ kg., was chloroformed and 0·3 mg. per kilogramme of Puff Adder venom injected intravenously, the usual records being taken.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	130	—	
After 7 mins. . .	125	24	
2nd injection of 3 mg. per kilogramme intravenously.			
After 1 min. . .	100	32	Fall of pressure commencing.
„ 2 mins. . .	70–110	34	Greatly increased excursus of the pulse.
„ 3 „ . .	60–100	37	
„ 4 „ . .	55–85	40	
„ 5 „ . .	65	40	
„ 7 „ . .	55	33	
„ 11 „ . .	55	37	
Adrenal chloride (1 in 1000) 0·2 cub. centim. in 1 cub. centim. salt solution injected intravenously.			
After $12\frac{1}{2}$ mins. .	95	42	Marked rise in pressure.
„ 12 „ . .	80	42	
„ 13 „ . .	60	40	
„ 20 „ . .	50	23	Bled to death from carotid.

Post-mortem.—The portal, pulmonary and systemic circulations and the heart were free from any clotting. The blood was incoagulable and bright red in colour. There were well marked sub-pericardial, endocardial, sub-pleural and peritoneal hæmorrhages.

Here we have a steady fall of pressure with greatly increased excursus of the pulse, the heart continuing to beat steadily throughout, and was still contracting well at the end of the experiment. The adrenal chloride caused a marked but temporary rise of pressure. The usual slow failure of respiration secondary to the failure of the blood pressure was showing itself when the experiment was stopped. A central vaso-motor paralysis would account for all the facts observed, while the following experiment affords further strong support to this view of the action of the poison.

EXPERIMENT IV.—A Cat, weighing 2 kg., was chloroformed and 0·2 mg. of Puff Adder venom injected intravenously, the usual records being taken.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	140	—	
After 1 min. . .	130	—	
„ 10 mins. . .	135	57	
2nd injection of 2 mg. per kilogramme intravenously.			
After 1 min. . .	120	54	
„ 2 mins. . .	100	60	
„ 3 „ . .	70	60	
„ 4 „ . .	60	53	
„ 6 „ . .	52	57	
„ 8 „ . .	50	46	
„ 12 „ . .	50	45	Peripheral end of sciatic nerve stimulated by strong faradic current. No effect on blood pressure.
„ 13 „ . .	50	45	Central end of sciatic stimulated. No effect on blood pressure.
„ 18 „ . .	50	28	
Adrenal chloride (1 in 1000) 0·3 cub. centim. in 1 cub. centim. salt solution injected intravenously.			
After 19 mins. . .	125	35	Marked rise of blood pressure.
„ 20 „ . .	120	31	
„ 22 „ . .	95	31	Pressure falling again.
„ 24 „ . .	65	30	
„ 30 „ . .	50	33	
„ 40 „ . .	50	28	
Nicotine 1 mg. in 1 cub. centim. salt solution injected intravenously.			
After 41 mins. . .	110	—	Marked rise of pressure. Respirations very rapid.
„ 42 „ . .	75	56	
„ 43 „ . .	55	54	
„ 50 „ . .	45	34	
„ 60 „ . .	45	21	
Caffiene citrate 1 grain in 1 cub. centim. salt solution injected intravenously.			
After 61 mins. . .	55	31	
„ 63 „ . .	45	33	
„ 67 „ . .	35	29	
3rd injection of 2 mg. per kilogramme intravenously of Puff Adder venom.			
After 69 mins. . .	35	32	
„ 71 „ . .	35	26	
„ 72 „ .	35	29	Respirations very shallow.
„ 73 „ . .	35	0	Respirations ceased.
„ 76 „ . .	55	—	Respiratory convulsions.
„ 80 „ . .	45	—	
„ 90 „ . .	25	—	Convulsive respirations ceased.

Post-mortem.—The large veins were distended with incoagulable blood. There

were no clots in the portal, pulmonary or systemic circulations or in the cavities of the heart. The peri- and endo-cardium, mesentery and omentum showed numerous petechial hæmorrhages. The brain and medulla were examined, but no naked eye changes were found. The phrenic nerves when stimulated with a weak faradic current produced good contraction of the diaphragm.

Here, again, we have a steady fall in blood pressure as the essential action of the venom. When this had fallen to about 50 mg. of mercury, stimulation of the central end of the sciatic nerve produced no rise of blood pressure, proving that the central vaso-motor centre was by this time completely paralysed. Yet, after this, adrenal extract produced a very marked rise of blood pressure, showing that the peripheral vaso-motor system was intact. Nicotine (the trial of which was suggested to me by Sir Lauder Brunton) also produced a marked but temporary rise of pressure, and at the same time a marked stimulation of respiration was noted. Caffeine citrate had much less effect. The long persistence of the respirations, although of a feeble nature, after complete paralysis of the vaso-motor centre is also noteworthy, as was its rapid failure after the injection of the third dose of venom, for this points to the venom having some direct action on the respiratory centre in addition to its marked one on the vaso-motor one. The last three experiments, then, show that in the case of the Puff Adder poison the tendency to the production of intravascular clotting is a much less marked feature than it is with Daboia venom, as a small preliminary dose intravenously rapidly produces the negative phase of lost coagulability, and allows of uncomplicated vaso-motor paralysis being readily produced by a second larger dose. It only remained to demonstrate the dilatation of the portal system coincidently with the fall in blood pressure, for which purpose the following experiment was carried out :—

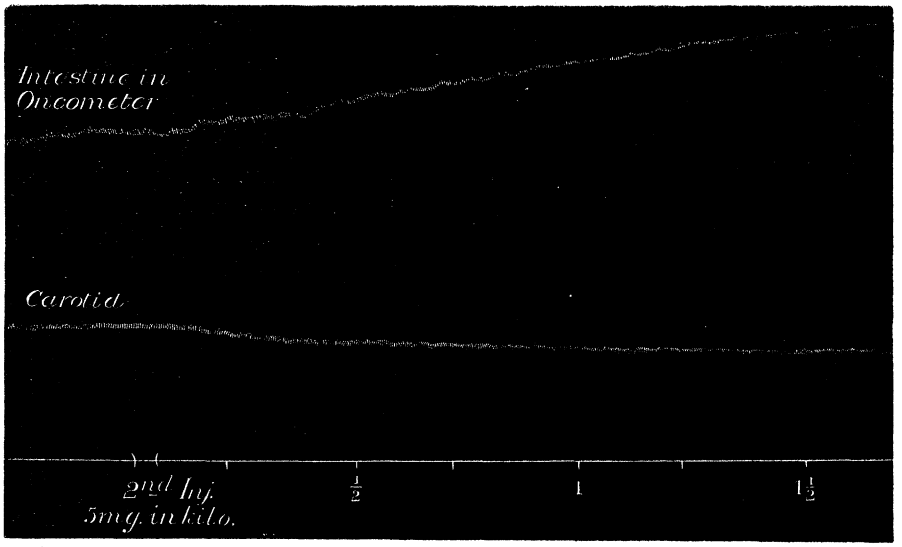
Experiment V.—A Cat, weighing 3 kg., was chloroformed, and after a cannula in the carotid artery had been connected up with a Gad's manometer, the abdomen was opened and a loop of small intestine, isolated and placed in an oncometer connected up with a Sandström's recorder, so that any increase in the blood entry due to vaso-motor dilatation would cause the lever to rise and *vice versâ*. A preliminary dose of 0·3 mg. per kilogramme was injected intravenously with the following results :—

Time.	Blood pressure.	Oncometer lever.	Remarks.
	millims.		
Before injection .	150	Level.	
After 1 min. . . .	150	Rising slowly.	Slight vaso-dilatation.
„ 2 mins. . .	140	Rising slowly.	Slight vaso-dilatation.
„ 4 „ . .	140	Level.	
„ 5 „ . .	150	Level.	

EXPERIMENT V—*continued.*

Time.	Blood pressure.	Oncometer lever.	Remarks.
	millims.		
2nd injection of 5 mg. per kilogramme intravenously.			
After ½ min. . .	125	Rising fast.	Marked vaso-dilatation.
„ 1 „ . .	120	Rising fast.	Marked vaso-dilatation.
„ 2 mins. . .	115	Rising fast.	Marked vaso-dilatation.
„ 3 „ . .	90	Rising fast.	Marked vaso-dilatation.
„ 4 „ . .	85	Rising slowly.	Slight vaso-dilatation.
„ 7 „ . .	60	Rising slowly.	Slight vaso-dilatation.
Adrenal chloride (1 in 1000) 0·3 cub. centim. in 1 cub. centim. salt solution injected intravenously.			
After 8 mins. . .	130	Rising fast.	Passive dilatation.
„ 12 „ . .	70	Falling slowly.	Passive contraction.

(See Tracing VII. for first 2 minutes.)



Tracing VII. (Puff Adder, Experiment V.).—Cat. Puff Adder venom. 5 mg. per kilogramme, intravenously.

By this time the pulsation of the oncometer lever had become very slight, and the experiment was terminated shortly after.

Post-mortem.—The blood was incoagulable, and no trace of clotting could be found in the mesenteric vessels, portal, pulmonary, and systemic circulations or in the cavities of the heart. Marked petechial hæmorrhages were found in the

pericardium, endocardium, especially of the left ventricle, and in the peritoneum, especially in the mesentery.

Here once more we have actual demonstration of a marked vaso-dilatation of the portal vessels occurring at the same times that the fall in the general blood pressure occurred and in proportion to its degree, both being slight after the first small injection, and both equally marked immediately after the second larger dose. Thus we have evidence of the same effect in paralysing the central vaso-motor centre by both Daboia and Puff Adder venoms, only, owing to the much less action of the latter in producing intravascular clotting of the blood, it is easier to demonstrate in the case of the Puff Adder.

B. Crotalidæ.

The Crotalidæ or Pit Vipers.

The best known poisonous snakes of this class are the American Rattlesnakes, while in India they are represented by the different species of *Trimeresurus*. I am indebted to Dr. J. Brunton Blaikie for some venom of *Crotalus horridus*, and to Dr. W. Dowson for that of *Trimeresurus anamallensis*, which will serve very well for comparison with the two true vipers already dealt with.

I. Crotalus horridus.

A few experiments on pigeons showed that the respirations were first increased in number, and the bird appeared watchful and anxious as in the early stages of Daboia poisoning. Then the respirations gradually slowed down, but there was none of the sleepiness and nodding of the head, which is so characteristic of Colubrine poisoning. Lastly, convulsions occurred, and death quickly ensued. Except that the convulsions were usually less violent than in the case of Daboia poisoning, there was little difference between the general symptoms observed. *Post-mortem*, even after death had been produced in less than an hour by the subcutaneous injection of over ten times a fatal dose, no clotting in the portal or other vessels could be found, but the blood was incoagulable. A dose of 5 mg. per kilogramme caused death in about 10 hours.

Circulatory and Respiratory Curves.

Circulatory and respiratory tracings were taken as in the former experiments with the following results :—

EXPERIMENT I.—A Cat, weighing $2\frac{1}{4}$ kg., was chloroformed and 1 mg. per kilogramme Rattlesnake venom injected intravenously, the usual records being taken. This dose in the case of Daboia venom produced very rapid death, with intravascular clotting; so it was first tried, as there is not much difference in the minimal lethal subcutaneous dose in pigeons of the two venoms.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	145	35	
After 1 min. . .	105	36	Marked fall in blood pressure.
„ 2 mins. . .	95	27	
„ 3 „ . .	85	20	Respirations less frequent.
„ 4 „ . .	75	24	
„ 5 „ . .	65	23	
„ 15 „ . .	60	21	Traube-Hering curves well marked.
„ 24 „ . .	65	15	Traube-Hering curves well marked.
„ 36 „ . .	60	28	Traube-Hering curves less marked.

At this point the experiment was stopped and the animal bled to death from the carotid artery. *Post-mortem*, stimulation of the phrenic nerves with a weak induction shock (secondary coil at 45 millims.) caused good contraction of the diaphragm. The blood was bright red and incoagulable. No trace of clotting could be found in the portal, pulmonary or systemic circulations or in the heart. There was some blood-stained serum exuding from the wound.

Here we have the same fall of blood pressure, following a single injection of Rattlesnake poison, without a trace of intravascular clotting, which was also obtained in the case of the true Vipers by the injection of a large dose after reduced coagulability of the blood had been produced by preliminary small doses. The reduced frequency of the respirations followed the reduction in blood pressure, being probably secondary to it. At the time the animal was killed there was some tendency to improvement in both the blood pressure and the respiratory rate, and recovery might have taken place.

EXPERIMENT II.—A Rabbit, weighing 1½ kg., was chloroformed, and 1 cg. per kilogramme of Rattlesnake venom injected intravenously.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	90	116	
After ½ min. . .	50	—	Marked fall of blood pressure.
„ 1 „ . .	60	113	
„ 2 mins. . .	50	123	Respirations increased.
„ 4 „ . .	40	116	
„ 6 „ . .	40	97	
„ 10 „ . .	35	80	Respirations slowing.
„ 14 „ . .	25	64	
„ 26 „ . .	25	54	
„ 36 „ . .	30	38	
„ 40 „ . .	30	13	
„ 42 „ . .	25	7	
„ 46 „ . .	15	3	Respirations ceased.

Post-mortem.—The blood was incoagulable. No clotting could be found in the portal, pulmonary or systemic circulation. The phrenic nerves were not paralysed. In order to see if there was any capillary obstruction, which could account for the failure of the circulation, the blood was transfused through both the pulmonary system and through the abdominal aorta, and was found to run through both readily from a height of 40 millims., proving that there was no capillary clotting present.

Here, again, we have a primary circulatory failure followed by slowing down and eventual failure of the respirations, due to the deficiency of blood circulating through the medulla, which seems to be sufficient to account for the respiratory failure without any direct effect of the poison on the breathing centre itself.

EXPERIMENT III.—A Rabbit, weighing 1·7 kg., was chloroformed and injected intravenously with 5 cg. per kilogramme.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	95	116	
After ½ min. . .	40	—	Marked fall in blood pressure.
„ 1 „ . .	35	145	Respiration quickened.
„ 2 mins. . .	25	115	
„ 3 „ . .	20	94	Respiration slowed and shallow.
„ 4 „ . .	15	84	
„ 6 „ . .	12	76	
„ 12 „ . .	10	42	
„ 14 „ . .	10	29	
„ 15 „ . .	0	4	Respiration ceased.

Post-mortem.—The heart was still beating feebly. The phrenics were not paralysed.

The blood was dark and incoagulable. A clot was found in the external jugular vein just below the seat of injection only, and not extending its whole length. No other clots could be found in the portal, pulmonary or systemic circulations or heart. The fluid blood was easily transfused through the lungs and through the abdominal aorta from a height of from 30–40 millims. Here, once more, we have a primary circulatory followed by a secondary respiratory failure, both being more marked and rapid than with the smaller doses used in the two preceding experiments.

EXPERIMENT IV.—A Cat, weighing 2½ kg., was chloroformed and injected intravenously with 5 cg. per kilogramme of Rattlesnake venom in 1 cub. centim. salt solution.

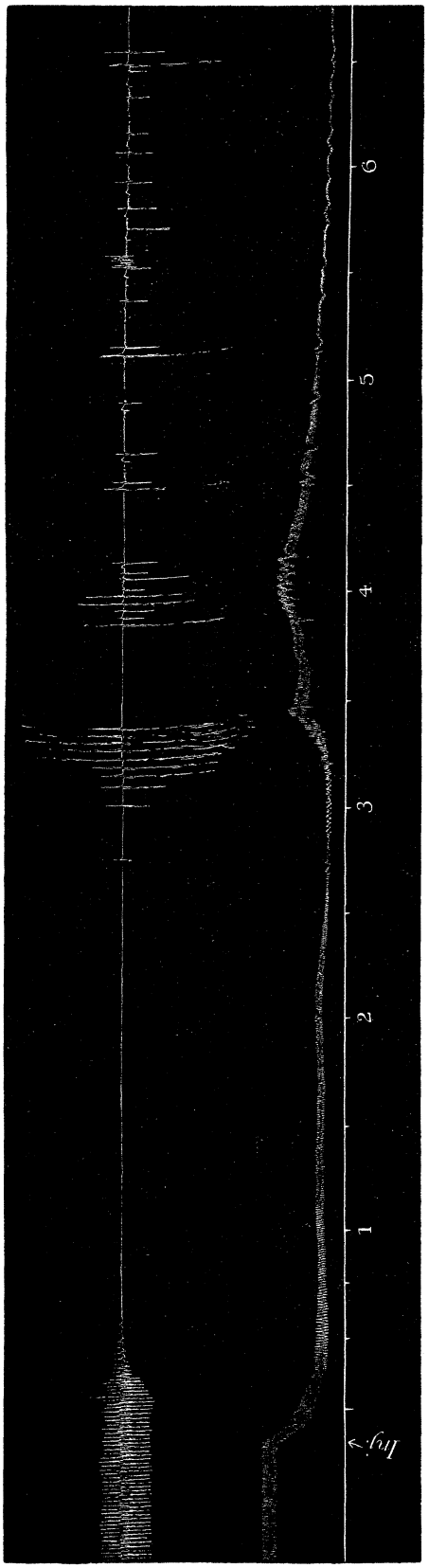
Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	145	55	
After ½ min. . .	55	27	Marked fall of blood pressure.
„ 1 „ . .	55	3	Respirations stopped.
After 2 mins. .	58	0	
„ 3 „ . .	40	1	
„ 4 „ . .	115	13	Convulsive respirations.
„ 5 „ . .	65	11	Convulsive respirations.
„ 6 „ . .	50	7	Convulsive respirations.
„ 8 „ . .	25	2	Convulsive respirations.
„ 12 „ . .	20	14	Convulsive respirations.
„ 14 „ . .	15	0	Respirations finally ceased.

(See Tracing VIII.)

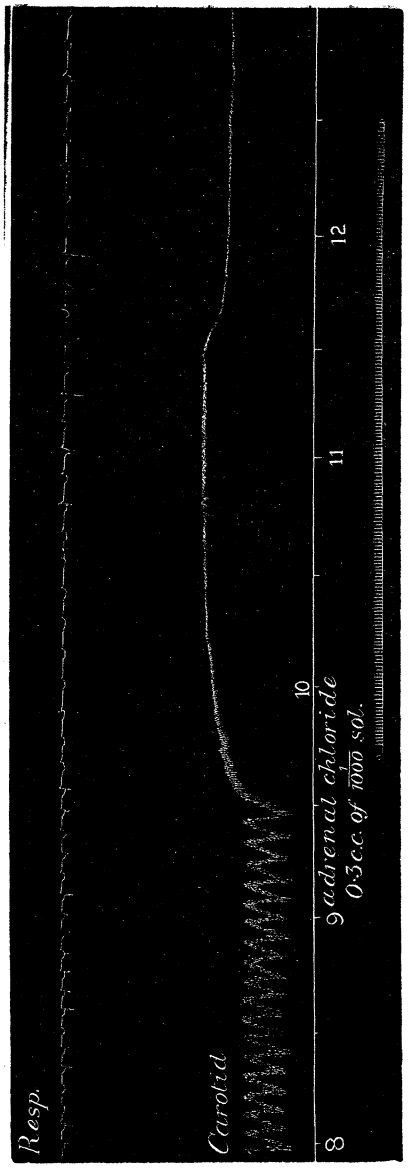
Before the injection of the venom the abdomen was opened, and a piece of omentum protected by cotton-wool soaked in warm normal salt solution was placed under the microscope and the circulation watched. Coincidently with the first fall in the blood pressure marked dilatation of the portal vessels was observed to take place, and in a few minutes red corpuscles were seen to be exuding through the walls of the small vessels and capillaries, and before the conclusion of the experiment small petechial hæmorrhages were visible both in the part of the membrane under the microscope and also in parts freshly withdrawn from the abdominal cavity.

Post-mortem.—No clotting was found in either the portal, pulmonary or systemic circulations or in the heart. The blood was fluid and incoagulable. Very marked petechial hæmorrhages were found in the peri- and endo-cardium, and in all parts of the peritoneum, but especially in the mesentery and omentum. A smaller number were also found in the pleura. The brain and medulla were carefully examined, but no hæmorrhages were found in them. The whole of the portal system was greatly congested, as it always is in cases of Viperine poisoning.

This experiment is a very interesting one, as it affords complete proof of marked vaso-dilatation of the portal system coincidently with the sudden fall in blood



Tracing VIII. (Crotalus, Experiment IV.).—Cat. Crotalus venom. 5 cg. per kilogramme, intravenously.



Tracing IX. (Crotalus, Experiment V.).—Cat. Crotalus venom. 1 cg. per kilogramme, intravenously. 8–13 minutes. Showing effect of adrenal extract.

pressure. Further it also shows the effect of respiratory convulsions in raising the blood pressure again, just as we found to occur in Daboia poisoning, although in the above experiment this effect was only temporary on account of the large dose of venom used. The tracing also well shows the continuance of the pulse after the sudden fall of pressure, so that this could not have been due to stopping of the heart, while there was absolutely no intravascular clotting to produce it. The cessation of respiration was doubtless due to the sudden deprivation of the medulla of blood by its being so rapidly drained into the capacious portal system. In the case of Experiments I. and II., in which smaller doses were used, the portal dilatation was less rapidly complete, and consequently the respiratory centre was able to hold out longer. As cats are much better than rabbits for studying blood pressure effects, the above experiment was repeated with a smaller dose.

Experiment V.—A Cat, weighing 3·2 kg., was chloroformed, and 1 cm. per kilogramme in 1 cub. centim. salt solution was injected intravenously, the respirations and the carotid pressure being accorded as in the previous experiments, and the effect of adrenal extract also tried.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	110	44	
After ½ min. . .	75	20	Marked fall of blood pressure.
„ 1 „ . .	40	8	Respiration stopped.
„ 2 mins. . .	15	0	
„ 4 „ . .	20	14	Respiratory convulsions.
„ 5 „ . .	95	13	Marked rise of pressure.
„ 6 „ . .	80	7	
„ 7 „ . .	65	20	Inspiratory gasps.
„ 8 „ . .	50–75	9	Traube-Hering curves well marked.
„ 9 „ . .	50–75	9	Traube-Hering curves well marked.
Adrenal chloride (1 in 1000) 0·3 cub. centim. in 1 cub. centim. salt solution injected intravenously.			
After 10 mins. . .	125	4	Marked rise in pressure. Respirations very shallow.
„ 11 „ . .	140	1	
„ 15 „ . .	115	9	
„ 23 „ . .	100	9	
„ 27 „ . .	55–100	6	Traube-Hering curves reappearing.
„ 33 „ . .	120	—	Respiratory convulsions.
„ 35 „ . .	70–100	6	
„ 37 „ . .	70–75	6	
„ 41 „ . .	60–70	—	Deep inspiratory gasps.
„ 44 „ . .	30	6	Respirations very shallow.
„ 45 „ . .	70	—	Respiratory convulsions.
„ 50 „ . .	40	—	Respiratory convulsions.
„ 52 „ . .	70	—	Respiratory convulsions. Central end of sciatic nerve stimulated.
„ 54 „ . .	50	—	Central end of sciatic nerve stimulated, no effect.
„ 58 „ . .	30	—	Respiratory convulsions feebler.
„ 60 „ . .	20	—	Respiratory convulsions ceased.

(See Tracing IX. for 9–13 minutes.)

Post-mortem.—The heart, portal, pulmonary and systemic circulations were free from clot, and the blood was incoagulable. There were extensive petechial hæmorrhages in the peri- and endo-cardium, the peritoneum and the pleura. The phrenic nerves were not paralysed.

This experiment presents several points of interest. The same circulatory failure and cessation of respiration, followed by respiratory convulsions and pumping-up again of the blood pressure, through the action of the diaphragm and other muscles on the dilated portal vessels, occurred as in Experiment IV. The dose, however, being smaller, the blood pressure recovered to a greater extent, and the Traube-Hering curves, indicative of the struggles of the partially paralysed vaso-motor centre, were well marked. At this point a single intravenous injection of a small dose of adrenal chloride produced a most marked effect on the blood pressure, raising it to above the original height before the injection of the poison. This effect was very much more lasting than in previous cases in which the drug was given after the paralysis of the vaso-motor centre had become complete, for in the present case a good pressure was maintained for 25 minutes, and it was not until the lapse of 40 minutes that the pressure again fell to the same point as before the injection. It is evident from this that much good may be expected to result from the use of this drug in cases of poisoning by the bites of Vipers by maintaining the circulation sufficiently to prevent the fatal secondary respiratory failure from want of blood supply to the medulla. Lastly, the slight rise of pressure on stimulation of the central end of the sciatic nerve after 52 minutes, and its failure to evoke any rise by this means, shortly before death, indicates that the complete paralysis of this centre was the cause of the final circulatory failure and the secondary cessation of respiration.

In order to demonstrate the dilatation of the portal vessels, coincidently with the fall in blood pressure due to the Rattlesnake venom, the following experiment was carried out.

EXPERIMENT VI.—A Cat, weighing 3 kg., was chloroformed and 1 cg. per kilogramme of Rattlesnake venom injected intravenously, a loop of small intestine having first been placed in an oncometer.

Time.	Blood pressure.	Oncometer lever.	Remarks.
	millims.		
Before injection .	150	Level.	
After ½ min. . .	130–150	Rising.	Vaso-dilatation.
„ 1 „ . .	130	Rising.	Vaso-dilatation.
„ 1½ mins. .	90–120	Slight fall.	Passive contraction.
„ 2 „ . .	100–120	Rising.	Vaso-dilatation.
„ 4 „ . .	105	Rising.	Vaso-dilatation.
„ 6 „ . .	90	Rising.	Vaso-dilatation.
„ 9 „ . .	85	Rising.	Vaso-dilatation.
„ 12 „ . .	75	Rising.	Vaso-dilatation.
„ 14 „ . .	75	Level.	

EXPERIMENT VI.—*continued.*

Time.	Blood pressure.	Oncometer lever.	Remarks.
	millims.		
2nd injection of 1 cg. per kilogramme in 0·5 cub. centim. salt solution.			
After 15 mins. . .	60	Very slight fall.	
„ 16 „ . .	55	Rising slowly.	
„ 18 „ . .	75	Rising.	Respiratory convulsions, passive dilatation.
„ 21 „ . .	60	Rising.	

By this time the pulsation of the oncometer lever had ceased.

Post-mortem, the blood was incoagulable, and no clotting could be found anywhere. Hæmorrhages were found as usual in the heart and peritoneum. The phrenic nerves were not paralysed.

In this experiment slight falls of the oncometer lever occurred for a very short time shortly after each injection, pointing to a momentary weakening of the heart as the injection passed through it. With this exception there was evidence of steady vaso-dilatation of the portal vessels occurring with the steady fall of pressure in the general circulation. Strong solutions of Rattlesnake venom, such as 2–10 per cent., I have found to cause temporary weakening of the contraction of excised frogs' hearts, while the doses used (1 cg. in 0·5 cub. centims.) were injected in a 2-per-cent. solution. This effect on the heart passes off, as the venom becomes immediately diluted in the blood stream, and the subsequent steady fall of pressure is due to vaso-dilatation, as shown by the marked rise of the oncometer lever in the above experiment. WEIR MITCHELL and REICHERT (9) also observed some effect of Rattlesnake venom in producing vaso-motor paralysis in their classical experiments, but they considered that the venom had a very marked effect in paralysing the respiration. If the latter is the main cause of death then artificial respiration ought to prolong life and assist the circulation, as it does in the case of the pure Colubrine snake poisons. In one experiment with Rattlesnake venom in a rabbit, in which the respirations appeared to be affected in a more marked manner than usual, I tried the effect of artificial respiration with the following result.

EXPERIMENT VII.—A Rabbit, weighing 1·75 kg., was chloroformed and 3·5 cg. (2 cg. per kilogramme) injected intravenously in 0·35 cub. centim. salt solution.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	50	86	
After 1 min. . .	50	83	
„ 2 mins. . .	40	85	Fall in blood pressure.
„ 3 „ . .	35	68	
„ 4 „ . .	30	60	
„ 6 „ . .	30	30	Respirations ceased. Artificial respiration started.
„ 7 „ . .	25	—	Artificial respiration.
„ 10 „ . .	25	—	Respiratory convulsions.
„ 11 „ . .	25	—	Artificial respiration.
„ 12 „ . .	20	—	Artificial respiration.
„ 13 „ . .	15	—	Artificial respiration. No effect.

Post-mortem, no clots could be found anywhere. The phrenic nerves were not paralysed. No good effect was produced by the artificial respiration, while the fact that the phrenic nerves were unaffected showed that no respiratory paralysis of a similar nature to that produced by pure Colubrine poisons had occurred.

II. *Trimeresurus anamallensis.*

Only three tracings illustrating the action of this venom have been obtained, but, read in the light of the results got with the other Viperine poisons, they suffice to afford a good idea of the action of this venom.

EXPERIMENT I.—A Rabbit, weighing 1½ kg., was chloroformed and 5 mg. per kilogramme (in 0·75 cub. centim. salt solution) was injected intravenously.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	40	108	
After ½ min. . .	25	—	Marked fall in blood pressure.
„ 1 „ . .	25	145	Respirations quickened.
„ 2 mins. . .	25	134	
„ 3 „ . .	25	99	
„ 4 „ . .	20	93	
„ 5 „ . .	20	83	Respirations slowed.
„ 6 „ . .	15	59	
„ 8 „ . .	15	24	
„ 10 „ . .	10	0	Respirations ceased.

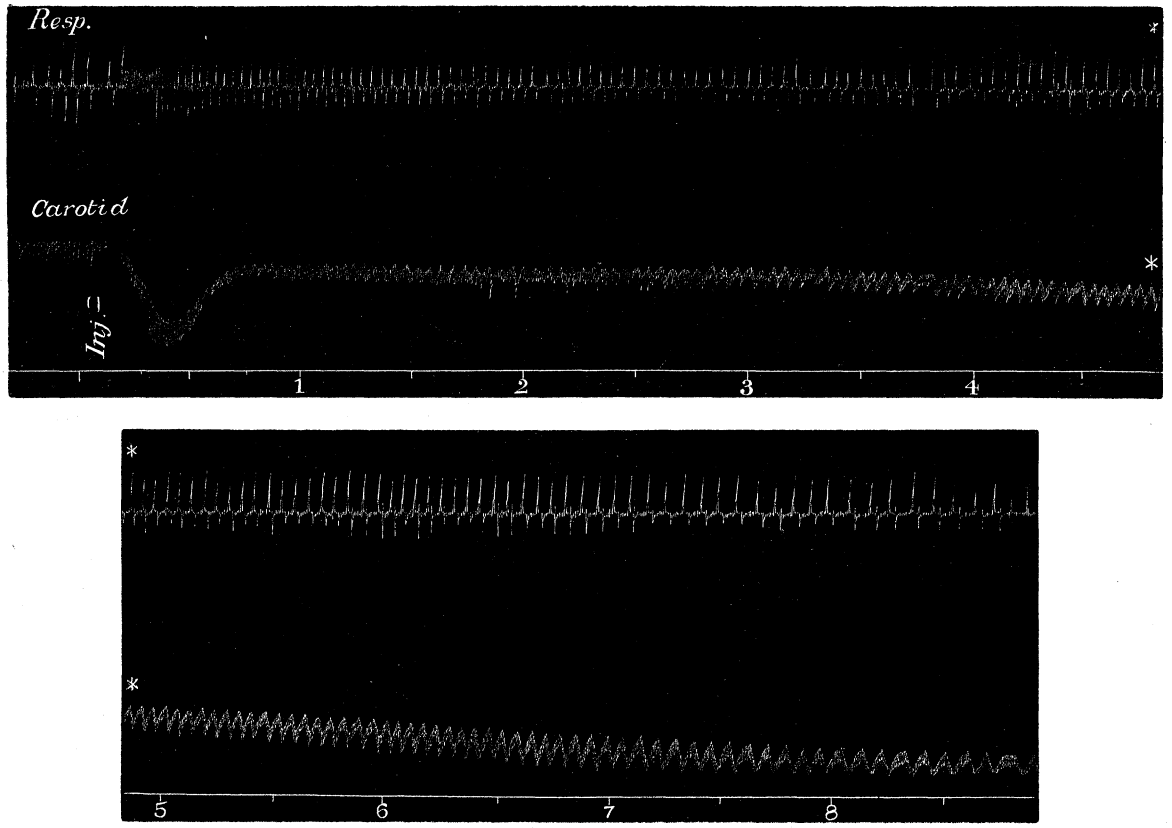
Post-mortem.—The phrenics were not paralysed, stimulation with a weak faradic current (secondary coil at 45 millims.) producing a good contraction of the diaphragm. The heart was beating when the chest was opened, and a very small clot was found in the right auricle. A small clot, $\frac{1}{2}$ inch in length, was found in the external jugular vein immediately below the point of injection, but no other trace of clotting could be found in either the portal, pulmonary or systemic circulations, including the heart. The blood when placed in a test-tube clotted very slowly and feebly, and on the following day some slightly hæmoglobin-stained serum had exuded, showing some hæmolytic action of the venom. The vessels of the portal system were greatly congested.

Here we have the same primary circulatory failure, followed by a slower failure of respiration, that we found in the case of the Rattlesnake. The stimulation of the respiratory centre in the early part of the experiment points to a direct effect of the venom on the respiration, and it is impossible to say how far the succeeding slowing down and stopping of the breathing was due to the direct action of the poison on the respiratory centre, and how far it was secondary to the failure of the respiration. The absence of any paralysis of the phrenic nerve proves that the respiratory failure was not of the same nature as that produced by Colubrine poisons, so that it appears to be more likely that the cessation of the breathing was purely brought about by deprivation of the medulla of sufficient blood by reason of the circulatory failure.

Experiment II.—A Cat, weighing 3 kg., was chloroformed and injected intravenously with 1·5 mg. (5 mg. per kilogramme) of Trimeresurus venom in 0·5 cub. centim. of salt solution.

Time.	Blood pressure.	Respirations per minute.	Remarks.
	millims.		
Before injection .	140	16	
After $\frac{1}{2}$ min. . .	60	—	Rapid fall in pressure.
„ 1 „ . .	100	21	Partial recovery of pressure.
„ 2 mins. . .	100	21	Respirations increased.
„ 3 „ . .	80–110	19	Traube-Hering curves appearing.
„ 4 „ . .	75–100	17	
„ 6 „ . .	60–80	17	
„ 8 „ . .	50–65	12	Respirations decreased.
„ 10 „ . .	50–60	8	
„ 12 „ . .	57	4	
„ 15 „ . .	85	—	Infrequent respiratory gasps.
„ 18 „ . .	65	—	Infrequent respiratory gasps.
„ 20 „ . .	100	—	Frequent respiratory convulsions.
„ 24 „ . .	70–90	9	Traube-Hering curves reappearing.
„ 28 „ . .	55–70	10	Infrequent deep respirations.
„ 34 „ . .	50–65	8	Infrequent deep respirations.
„ 44 „ . .	50–65	8	Infrequent deep respirations.
„ 55 „ . .	50–62	11	
„ 60 „ . .	52–65	13	Pressure and respirations improving.
„ 65 „ . .	55–70	16	Pressure and respirations improving.

(See Tracing X. for the 7th minute and the 16th to 23rd minutes.)



Tracing X. (*Trimeresurus anamallensis*, Experiment II.).—Cat. Trimeresurus venom. 5 mg. per kilogramme, intravenously.

At this point recovery was beginning to take place, the pupils, which had been widely dilated, were beginning to contract, and both the blood pressure and the frequency of the respirations were improving, so the animal was killed.

Post-mortem.—The phrenic nerves were not paralysed. The blood from the portal vein was incoagulable and after 24 hours the corpuscles had subsided, leaving slightly blood-stained fluid serum in the upper layers. The blood from the venæ cavæ clotted feebly, and after 24 hours had given out a small quantity of slightly blood-stained serum. No trace of clotting could be found in either the portal, pulmonary or systemic circulations or in the heart. There were a few small pericardial hæmorrhages on the surface of the heart, and also well-marked endocardial petechiæ in the left ventricle, but none could be found in the mesentery or omentum. These hæmorrhages were much less marked than that found in poisoning by the Rattlesnake or Puff Adder, but slightly more marked than Daboia venom causes.

This experiment is a very instructive one. The first sudden fall of blood pressure may possibly have been partly cardiac in origin, but the subsequent steady fall with well marked Traube-Hering curves was undoubtedly due to vaso-motor paralysis, as the tracing in all respects resembles those produced by the other Viperine poisons, which we have seen clearly cause vaso-motor paralysis. The pumping-up of the

blood pressure on the occurrence of respiratory convulsions was well shown in the curve. It is also of great interest to note that the Traube-Hering curves persisted throughout, and at the end of the experiment the animal showed evident signs of recovery, for we have already seen that as long as these curves remain the vaso-motor centre is not completely paralysed, for stimulation of the central end of the sciatic nerve causes a rise in the blood pressure, while drugs such as adrenal extract, which raise the pressure, have a much more lasting effect in this stage.

It is evident, then, that as long as the vaso-motor centre is not completely paralysed recovery may take place, and in borderland cases any treatment which raises the blood pressure sufficiently to keep the respiratory centre going will be of great service. The entire absence of intravascular clotting in this experiment is similar to the absence of that feature in poisoning by the other Crotalidæ examined, namely, the Rattlesnake. The respiratory failure in this case appears to have been entirely secondary to the failure of the circulation, for with the first signs of improvement in the latter the frequency of the respirations also increased. In the next experiment a larger dose was used, and a loop of the small intestine was also placed in an oncometer.

EXPERIMENT III.—A Cat, weighing 2 kg., was chloroformed, and after a loop of small intestine had been placed in an oncometer, 1 cg. per kilogramme in 0·5 cub. centim. salt solution was injected intravenously.

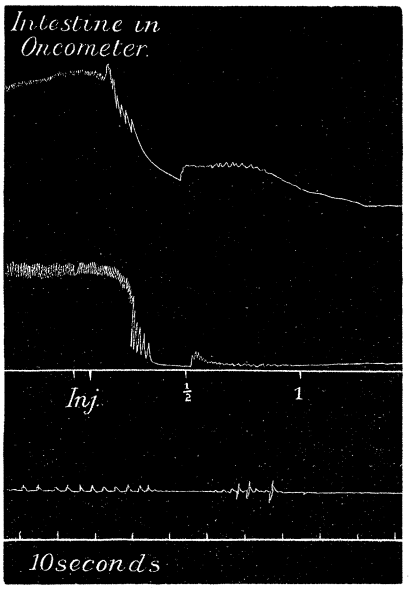
Time.	Blood pressure.	Respirations per minute.	Oncometer lever.	Remarks.
	millims.			
Before injection . .	100	18	Rising slowly	
After ½ min. . .	15	7	Sudden marked fall	
„ 3 mins. . .	25	—	Final respiratory convulsions	

(See Tracing XI.)

Post-mortem.—The phrenic nerves were not paralysed. There was extensive intravascular clotting throughout the portal circulation, the pulmonary arteries, the systemic veins, and the right side of the heart. The remaining blood clotted very feebly, and after 24 hours exuded a little blood-stained serum.

Here we have a typical death due to intravascular clotting, and it is interesting to observe the sudden fall of pressure in the portal circulation with the general fall of blood pressure, that is just the opposite to what occurs in Viperine poisoning without any intravascular clotting. We also have here one of the Crotalidæ producing in a large intravenous dose clotting in the blood vessels precisely similar to that produced by the pure Vipers, but which I have never obtained with the other Pit Viper, namely,

the Rattlesnake, except at the seat of injection of the venom. On the other hand, the Trimeresurus has much less effect than the Rattlesnake in producing hæmorrhages, in which respect it resembles the Daboia more closely than any of the other Vipers dealt with in this paper.



Tracing XI (*T. anamallensis*, Experiment III.). — Cat. Trimeresurus venom. 1 cg. per kilogramme, intravenously. Intestine tracing above, carotid below.

Comparison and Summary of the Action of the Vipers and Pit Vipers.

A comparison of the results obtained with the four Viperine poisons dealt with above shows a most striking general resemblance together with most marked differences in degree, more especially with regard to the effect on the coagulability of the blood as shown by intravascular clotting. This can be best brought out by comparing the effect of the different poisons on the various systems.

I. *Action on the Blood.*

1. *On the Coagulability.*—The action of Viperine poisons in producing intravascular clotting is the most striking factor met with. Yet we find it differs very greatly in degree in the different venoms examined. That of the *Daboia Russellii* nearly always kills the comparative small animals used by producing intravascular clotting of the blood whenever a single lethal dose is given either subcutaneously or intravascularly, the symptoms being of an acute and rapidly fatal character. The Puff Adder venom also in a single lethal dose either subcutaneously in pigeons, or intravenously in larger animals, produces intravascular clotting, but in proportion to its minimal lethal dose in pigeons it requires a larger dose of it to cause clotting than of Daboia venom. Next, passing on to the Pit Vipers we find that in the case of *Trimeresurus anamallensis* fatal failure of the circulation can be produced by a single small intravenous dose without any intravascular clotting other than locally in the vein through which the venom enters the circulation. Yet a larger dose may produce marked and rapidly fatal intravascular clotting as in Experiment III. with this venom. Lastly, in the case of the Rattlesnake venom I have never found any intravascular clotting, except once at the seat of injection, after death brought about by a single intravenous injection of the venom. These facts alone are sufficient to show that intravascular clotting is not an essential lethal action of the Viperine snakes as a class.

But we may go further, for the experiments recorded in this paper show that in

the case of all these venoms, by giving small preliminary doses either subcutaneously or intravenously, so as to bring about the negative phase of reduced coagulability, death due to circulatory failure can be readily produced without the occurrence of any intravascular clotting. The blood in such cases will remain fluid or clot only very feebly after death when placed in test-tubes. There is evidently, then, some important lethal action other than the intravascular clotting of the blood to be considered.

2. *Hæmolytic Action.*—In all of the four Viperine venoms dealt with there is evidence of fairly well-marked hæmolytic action, for if the fluid blood be allowed to stand in a test-tube for 24 hours the red corpuscles will settle, and the uppers layers will consist of hæmoglobin-stained serum. Lamb (12) has recently studied this effect and concludes that the hæmolytic action of Daboia venom is more marked *in vivo* than *in vitro*, while in the case of Cobra venom the reverse holds good. He regards the fact that the blood-stained discharges in Daboia poisoning contain few red corpuscles as evidence of marked hæmolytic action, but this must be largely due to the effusion of serum brought about by the vaso-motor paralysis, which I have found to be the most essential and constant action of Viperine poisons, and to their effect in dissolving the walls of the small vessels, which we have next to discuss.

3. *Hæmorrhagic Effects.*—In the records of the experiments recorded in this paper we have repeatedly come across marked petechial hæmorrhages, especially in the mesentery and omentum, and in the peri- and endo-cardium, as well as less frequently in the pleura. Here, again, we find great differences in degree in the case of the several Viperine poisons examined. Thus the greatest hæmorrhagic effects are undoubtedly produced by the Rattlesnake poison, for in Experiment IV., although the experiment only lasted 15 minutes, yet there were marked hæmorrhages at the end of that time. Flexner has recently studied this phenomenon and attributes it to a dissolution of the endothelial cells lining the small blood vessels and capillaries, which would largely account for the extreme rapidity of the process noted above, although I think the vaso-dilatation produced by all these venoms must materially aid it, for the changes are most marked in the distribution of the portal circulation, where the vaso-motor paralysis is most felt. The other Pit Viper, the Trimeresurus, has a much less marked action in this direction, although it is still a very definite one. On the other hand, the true Viper, the Puff Adder, has a very marked hæmorrhagic action, more marked indeed than the Trimeresurus, so that this property is in no way peculiar to the Pit Vipers. Lastly, the Daboia has a very slight action in producing these petechial hæmorrhages compared to that of the Rattlesnake or Puff Adder, yet endocardial petechiæ in the left ventricle result from its action in prolonged cases, so that the difference is one rather of degree than of kind, all of the Vipers yet examined showing it to some extent. Nevertheless the lethal effects of these poisons, at any rate in the case of the comparatively rapid deaths here dealt with, cannot be attributed to this hæmorrhagic action, although they doubtless play a large part in

the more chronic forms produced by slightly *supra*-minimal lethal doses such as are likely to be met with in man.

It has hitherto been thought that the fatal effects in man produced by Viperine poisons are due to the loss of coagulability of the blood and consequent hæmorrhages, but it is not quite clear how such fluidity of the blood can bring about a rapidly fatal termination, seeing that the coagulability may be enormously reduced in hæmophilia without any such rapid death with hæmorrhages, from the bowel more particularly, taking place as in Viperine poisoning. Further, we have seen that in the case of each of the venoms dealt with a rapidly fatal failure of the circulation can be produced without any intravascular clotting, and without sufficient hæmorrhages to in any way account for the fatal termination, and the factor which produces this must also be operative in the more chronic cases with more marked hæmorrhages. Further, we know from the researches of Weir Mitchell (9) that complete loss of coagulability of the blood, with very marked hæmorrhages from the bowel and other parts, of several days' duration, may yet be completely recovered from, while some of the cases recorded by Fayrer (2) of bites by Indian Vipers, including one by a Trimeresurus, presented similar remarkable recoveries. It is very difficult to account for these on the theory that the whole of the pathology of Viperine poisoning is summed up in the blood changes dealt with above.

If, on the other hand, there is in addition a more powerful circulatory effect produced by the poison, which is the real cause of the lethal results, and this condition may be recovered from after it has persisted for some time, the explanation will become much easier. In the case of intravenous injections of poisons not only will the symptoms be rapidly produced, but if the dose is insufficient to produce death, then recovery will be proportionally rapid. More than one example of this occurred in the experiments recorded in this paper. Take, for example, the Experiment II. with the Trimeresurus venom, in which at the end of an hour both recovery of the circulation and increased frequency of the respirations began to take place, yet on killing the animal the blood was completely incoagulable (no clotting taking place in 24 hours in a test-tube), while hæmorrhages had commencd to take place both in the peritoneum and in the heart. Here the commencing recovery was clearly due to improvement in the circulatory conditions in spite of the persistence of the blood alterations. Other similar instances might be given, but enough has been said to prove that the circulatory changes referred to afford a more satisfactory explanation of the lethal effects of these venoms than do the blood changes taken by themselves.

II. *The Circulatory Effects of the Venoms.*

1. *Action on the Heart.*—The first three venoms have been applied in solutions of varying strengths, directly to excised frogs' hearts, and the contractions recorded. In the case of Daboia venom, solutions as strong as any used in the injections did not

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retard the contractions of the heart. In that of the Puff Adder temporary stimulation was produced by strong solutions, while with Rattlesnake venom in very strong solutions the contractions of the heart were somewhat weakened for a short period, but in no case was it rapidly stopped. It is possible that a small part of the rapid circulatory failure may be due to a direct effect of the Rattlesnake venom in its passage through the heart, but it would immediately become diluted in the blood stream to such an extent as to lose this effect, while the continuance of the heart beats for long periods shows conclusively that the circulatory failure cannot be due to failure of the heart's action.

2. *Paralysis of the Central Vaso-Motor Centre.*—As the circulatory failure cannot be explained as due to any direct action of the venom on the heart itself, we must consider how far an effect on the vaso-motor mechanism will explain the facts recorded. Capillary clotting having been excluded by transfusion of the portal, pulmonary, and systemic circulations after death having demonstrated that there was no obstruction in them; we find that a paralysis of the central vaso-motor centre will fully account for all the phenomena met with. Thus, the increased excursus of the pulse, so constantly seen in the tracings, indicates diminished peripheral resistance; the pumping-up of the fallen blood pressure on the occurrence of respiratory convulsive efforts, which has formed such a remarkable feature of some of the charts of each of the venoms dealt with, can only be explained as the result of a mechanical aid to the circulation brought about by pressure on the dilated portal circulation, while the good effect of abdominal pressure is also accounted for on the same hypothesis; the remarkable Traube-Hering curves so frequently met with, and persisting as long as the central vaso-motor centre is not too completely paralysed to respond to strong stimulation of the central end of the sciatic nerve; the extreme portal dilatation met with after death, and the rapid dilatation of the vessels of the omentum and mesentery coincidently with the primary fall in pressure, which has been observed with the microscope in several instances; and lastly, and most conclusive of all, the demonstration of the portal dilatation by means of a large loop of small intestine in an oncometer, at the very time that the pressure in the general circulation is declining; all prove that the essential action common to all the four Viperine poisons dealt with is a vaso-motor paralysis, which is undoubtedly of central origin, for the action of Daboia venom on the vessels themselves has been found to be one of vaso-constriction, which can also be brought about by the action of such drugs as adrenal extract and nicotine after the vaso-motor centre itself is completely paralysed.

If the dose of venom given intravenously is sufficient to paralyse the vaso-motor centre very rapidly the circulatory failure will be too quick to be recovered from even temporarily. On the other hand, if a smaller dose be given, then the portal dilatation is more gradual, and time is given for the circulation to accommodate itself to the altered conditions sufficiently to allow of enough blood being sent to the

medulla to enable it to keep up infrequent and often convulsive respirations, accompanied by well-marked Traube-Hering curves. Close observation now shows the sequence of events to be as follows: A deep inspiration is taken, and the breath is held, during which time the blood pressure reaches and is maintained at the height of the curve. Then an expiration follows, and immediately the pressure gives way a little, to rise once more with the next inspiration. As the vaso-motor centre becomes more and more enfeebled these curves become less marked, and by the time the centre no longer responds to stimulation of the central end of the sciatic nerve they have disappeared, the centre being now completely paralysed, although adrenal extract will still produce a temporary rise of pressure by contracting the peripheral vessels. The respirations now grow less and less frequent, and are of a convulsive nature, and then finally cease, and then death takes place.

If, on the other hand, the dose is still less, and the vaso-motor centre begins to recover its tone, the blood pressure rises slowly once more, and coincidently the respirations improve in frequency, and recovery takes place in spite of complete incoagulability of the blood, and well-marked visceral hæmorrhages. All the facts recorded can, then, be explained as a result of paralysis of the central vaso-motor centre, and in no other way.

III. *Action on the Respiratory Centre.*

The failure of respiration occurring in the case of Viperine poisons can best be explained as being secondary to the failure of the circulation brought about by the central vaso-motor paralysis. Whether they have any direct action on the respiratory centre as well, as held by Weir Mitchell and Reichert and by Flexner in the case of the Rattlesnake, is open to doubt. In favour of such an action is the fact that in the cases in which small doses of Daboia venom were given, to induce the negative phase of reduced coagulability, the number of respirations were nearly always reduced very considerably before any marked fall of blood pressure had taken place. Further, in some instances when a second dose of venom was injected, after complete vaso-motor paralysis had taken place, the already much reduced respirations speedily failed altogether and death took place, as, for example, in the fourth Puff Adder experiment. In one experiment (not mentioned hitherto) two small subcutaneous doses of Daboia venom, which had been mixed for $\frac{1}{2}$ hour with Calmette's antivenin, were not followed by the usual slowing of the respiration, which would seem to point to a small amount of Colubrine poison present having been neutralised by the serum. On the other hand is the fact that in no case of Viperine poisoning was there any evidence of paralysis of the end-plates of the phrenic nerves. The evidence does not seem to be sufficient to decide the point either way, and it must be left to further experiments, on the lines of C. J. Martin's method of separating the Colubrine from the Viperine element by filtering through gelatine under pressure, to determine it.

Antidotes to Viperine Venoms.

If my conclusion is correct that the most essential lethal action of the Viperine poisons as a class is a paralysis of the central vaso-motor centre, much as that of the Colubrine class is a paralysis of the respiratory centre, then it would appear to be probable that an antivenin which would be effective against the vipers might be made on the same lines as CALMETTE's serum, which I have shown in the first part of this paper has a very definite, if not very powerful, action against all the purely Colubrine poisons tested. In support of this view it may be urged that D. D. CUNNINGHAM working in Calcutta did succeed in protecting a goat against a fatal dose of Daboia venom by means of repeated subcutaneous injections of this venom, so that it would be well worth while to attempt to make such a serum as that suggested.

Until, however, such a serum is prepared we must content ourselves with trying to counteract the physiological action of the Viperine poisons by such measures as appear likely to serve this purpose. The most promising of these which have been found to improve the blood pressure in my experiments are, firstly, mechanical pressure such as a binder applied to the abdomen, to which might be added bandages applied to the limbs so as to conserve as much blood as possible for the urgent needs of maintaining the circulation through the brain and medulla, and, secondly, such drugs as contract the peripheral vessels, of which the most powerful are adrenal extract and nicotine. The former in particular has a most beneficial and lasting effect, so long as the vaso-motor centre is not completely paralysed, as in Experiment V. with the Rattlesnake poison. In borderland cases there is good reason to hope that some lives may be saved by such rational lines of treatment based on the presence of vaso-motor paresis.

In conclusion, I have to express my great indebtedness to the Senate of the London University, for permission to work in their Physiological Laboratory, and to Dr. A. D. WALLER, Dr. T. G. BRODIE and Dr. N. H. ALCOCK for much very valuable advice and help in the course of the investigation.

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