IV.—The Pharmacological Action of Harmine.

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CONTENTS.

Introductory.

The seeds of *Peganum Harmala* contain two alkaloids, Harmaline and Harmine. The pharmacological actions of the former alkaloid have been described in a previous communication to this Society;* in this paper an account is given of the pharmacology of the second alkaloid, Harmine.

Harmine ($C_{13}H_{12}N_2O$) was discovered by Fritche in 1847. Apart from a few observations by Tappeiner, its pharmacology has not been investigated. Tappeiner† states that, in mammals at least, the general nature of poisoning by harmine is qualitatively the same as by harmaline, but that the former alkaloid is weaker in action. He found that a dose of 0·2 gramme per kilo of harmine is fatal to the guinea-pig in about 12 hours, while the same dose is fatal to the rabbit in about 1 hour, and that a frog is killed in about 7 hours by a dose of 0·03 gramme (per kilo?). He states further that there appears to be one qualitative difference between the actions of the two alkaloids, in that harmine produces paralysis of reflex excitability before arrest of the heart. It may be stated here that this does not constitute a qualitative difference between the actions of harmaline and harmine, because the same effect is produced by harmaline.

My investigation of harmaline having shown that the actions of this alkaloid very intimately resemble those of quinine, a more extended investigation seemed

* Gunn, *Trans. Roy. Soc. Edin.*, xlvii., 1909, pp. 245–272.

† Tappeiner, *Archiv für exper. Pathol. u. Pharmakologie*, Bd. xxxv., 1895, p. 69.

desirable also of the pharmacology of harmine, especially as there seems some prospect of the alkaloids being of therapeutic value.

I am much indebted to Dr J. F. THORPE, F.R.S., for his great kindness in giving me several grammes of pure harmine for pharmacological investigation. From the base I prepared, according to his directions, the hydrochloride of the alkaloid, and with this salt all the experiments to be described were performed.

A. LETHALITY OF HARMINE.

The lethality of harmine was determined for frogs, guinea-pigs, rabbits, rats, and pigeons, with the following results :—

TABLE I.—MINIMUM LETHAL DOSE BY SUBCUTANEOUS INJECTION FOR FROGS.

No. of Experiment.	Weight of Frog in Grammes.	Dose per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
1	18	0·4	0·0072	Recovery.
2	20	0·5	0·01	,,
3	16	0·6	0·0096	Death in about 6½ hours.
4	23	0·8	0·0184	,, ,, ,,

TABLE II.—MINIMUM LETHAL DOSE BY SUBCUTANEOUS INJECTION FOR GUINEA-PIGS.

No. of Experiment.	Weight of Guinea-pig in Grammes.	Dose per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
5	620	0·08	0·05	Recovery.
6	750	0·1	0·075	,,
7	700	0·12	0·084	Death in 2 hours.

TABLE III.—MINIMUM LETHAL DOSE BY SUBCUTANEOUS INJECTION FOR RABBITS.

No. of Experiment.	Weight of Rabbit in Grammes.	Dose per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
8	1200	0·15	0·18	Recovery.
9	1750	0·2	0·35	,,
10	1600	0·23	0·368	Death in 2 hours 40 minutes.
11	1550	0·3	0·465	,, 1 hour 12 minutes.

TABLE IV.—MINIMUM LETHAL DOSE BY SUBCUTANEOUS INJECTION FOR RATS.

No. of Experiment.	Weight of Rat in Grammes.	Dose per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
12	155	0·1	0·0155	Recovery.
13	100	0·15	0·015	,,
14	150	0·2	0·03	,,
15	100	0·2	0·02	Death in 3 days.
16	115	0·3	0·035	,, 5–20 hours.
17	115	0·4	0·046	,, 7–20 ,,

TABLE V.—MINIMUM LETHAL DOSE BY SUBCUTANEOUS INJECTION FOR PIGEONS.

No. of Experiment.	Weight of Pigeon in Grammes.	Dose per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
18	300	0·1	0·03	Recovery.
19	430	0·12	0·051	,,
20	420	0·15	0·063	Death in 10 minutes.

For determination of the minimum lethal dose in frogs, and for all subsequent experiments on frogs, the species *Rana temporaria* was used. In frogs, injections were made into the dorsal lymph sac, in mammals under the skin of the right flank, and in pigeons under the skin of the right thigh.

From the above tables it is seen that the minimum lethal dose by subcutaneous injection per kilogramme is, for the frog, 0·6 gramme; for the guinea-pig, 0·12 gramme; for the rabbit, 0·23 gramme; for the rat, about 0·2 gramme; and for the pigeon, 0·15 gramme.

B. SYMPTOMS PRODUCED BY HARMINE.

(*a*) *In Frogs.*

Experiment 3.—*Rana temporaria*, male, weight 16 grammes. At 12.30 p.m. the throat respirations were twenty in ten seconds and the cardiac impacts seven in ten seconds.

At 12.40, 0·0096 gramme of harmine hydrochloride dissolved in 0·48 c.c. of saline solution was injected into the dorsal lymph sac. This was equivalent to 0·6 gramme per kilogramme.

At 1.40 the respirations were feebler and somewhat irregular, the average rate being about 14 per ten seconds. The cardiac impacts were five in ten seconds and less distinct than before injection. The back was stiff owing to rigidity of the back muscles. The frog was unable to jump, and turned over with difficulty when placed on

its back, an effect partly due to some stiffness of the thigh muscles caused by diffusion of the injected solution. The conjunctival reflex was sluggish, and there was some impairment of the reflex excitability of the cord as determined by electrical stimulation.

At 2.30 the frog was unable to jump, and could not recover the ventral posture when laid on its back.

At 3.0 the respirations had ceased and the cardiac impacts were not visible; but, when the web of the foot was examined under the microscope, the blood was found to be circulating sluggishly. Stimulation of the skin of one leg produced no movements of the opposite leg, even with the coil at 30 mm.; but stimulation of the skin over the sciatic nerve produced a contraction of the gastrocnemius muscle of the same side, with the coil at 120 mm.

At 4.30 the circulation was found to be arrested in the web. The brain was pithed and the heart exposed. The heart was beating feebly at the rate of 2 in ten seconds. It ceased beating in ten minutes. No reflex movements could be elicited even by direct stimulation of the sciatic nerve with the secondary coil at 20 mm., but contraction of the gastrocnemius muscle of the same side was induced by stimulation of the nerve at 100 mm.

(*b*) *In Mammals.*

Experiment 11.—Rabbit, 1550 grammes. At 10.55 a.m. the cardiac impacts were 46, and the respirations 34, in ten seconds. The temperature was 99° C.

At 11.0, 0·465 gramme dissolved in 10 c.c. of warm saline solution was injected under the skin of the right flank. This was equivalent to 0·3 gramme per kilogramme.

At 11.5 there were marked tremors of the head and fore part of the body, and the hind limbs were extended so that the abdomen touched the ground. Three minutes later the tremors were more violent and the animal made frequent spasmodic movements forwards, the hind limbs being unable properly to support or propel the body.

At 11.12 a slight epileptiform convulsion occurred, marked especially by clonic movements of the limbs, after which the animal lay quiet. A similar but more violent convulsion occurred a minute later, during which the animal fell on its side and rolled over sideways two or three times. After this the rabbit lay on its side with feeble pawing movements of the limbs. The respirations were 20, and the cardiac impacts 35, in ten seconds. The temperature was 100° C.

Up to 11.30 the symptoms were similar, but the convulsive movements became gradually less violent. At the end of that time the respirations were 12 in ten seconds, regular and deep. The cardiac impacts were palpated with difficulty, and were about 28 in ten seconds. The skin was colder.

At 11.50 there was almost complete motor paralysis, the animal lying continuously on its side and making feeble running movements occasionally. When held up by the ears it made no movements. Pinching the skin evoked no reflex movements, and the conjunctival reflex was sluggish.

At 11.55 the conjunctival reflex was with difficulty elicitable. The thigh muscles and muscles of the right flank were stiff. The temperature was 96·4° C.

At 12.9 the animal made no movements, apart from those of respiration which were feeble and irregular, the rate being about 9 in ten seconds. The heart beats were feeble, irregular, and infrequent.

At 12.12 the respirations ceased. The thorax was opened, and at 12.13 the heart found to be beating very feebly. It ceased beating in the diastolic position at 12.15. The muscles round the seat of injection were rigid and inexcitable. The muscles of the fore limbs reacted to weak stimulation of their nerves, as also did the diaphragm to stimulation of the phrenic nerve.

C. Action on the Central Nervous System.

(*a*) *In Frogs.*—The description given of the symptoms produced by lethal doses of harmine in the frog has shown that the chief effects referable to an action on the central nervous system are loss of co-ordination and of the power of jumping, arrest of respiration, and paralysis of reflex excitability. Since these effects come on at a time when they cannot be accounted for by paralysis of the peripheral neuro-muscular mechanism, they indicate that harmine paralyses the mid-brain, medulla oblongata, and spinal cord.

(*b*) *In Mammals and Pigeons.*—Epileptiform convulsions form the most conspicuous symptom produced by large doses of harmine in warm-blooded animals. They are clonic in nature and are usually intermittent, intervals of quiescence ensuing between the convulsions. They are generally aggravated by any voluntary movement. All the facts observed in regard to these convulsions, among which may be mentioned their clonic nature, their occurrence apart from any marked increase of spinal reflex excitability, and their absence in frogs, point to their being due to an exciting action on the cerebrum.

In regard to this action of harmine on the cerebrum, it is of interest to observe that the minimum lethal dose per kilogramme for a series of animals is roughly in inverse proportion to the amount of grammes of brain per kilogramme of body weight in those animals. A somewhat similar relationship occurs with cocaine, which also produces cerebral convulsions.*

The clonic convulsions produced by harmine are not directly fatal to the animal, as they do not markedly interfere with respirations. When the dose is lethal, the convulsions are followed for a short time before death by a condition of motor paralysis due to a depressing action on the central nervous system. If the dose be not lethal, the convulsions are usually entirely recovered from within one or two hours.

* Dixon, *Manual of Pharmacology*, 1906, p. 145.

D. Action on Skeletal Muscle.

To ascertain the effects produced by harmine on voluntary muscle, experiments were made on the isolated gastrocnemius muscles of the frog, one muscle being immersed in a solution of the alkaloid, the other muscle in Ringer's solution. A modified Wild's method was employed, and to stimulate the muscles the secondary current passed simultaneously through both muscles. Tracings were taken on a slowly revolving drum.

Experiment 21 (figs. 1 and 2).—Strength of solution, 1 in 2000. Normal twitches resulting from stimulation with break shocks are shown at 11.28, both muscles being in Ringer's solution. At 11.30 Ringer's solution was withdrawn from muscle B and replaced by a solution of harmine hydrochloride 1 in 2000 in Ringer's solution.

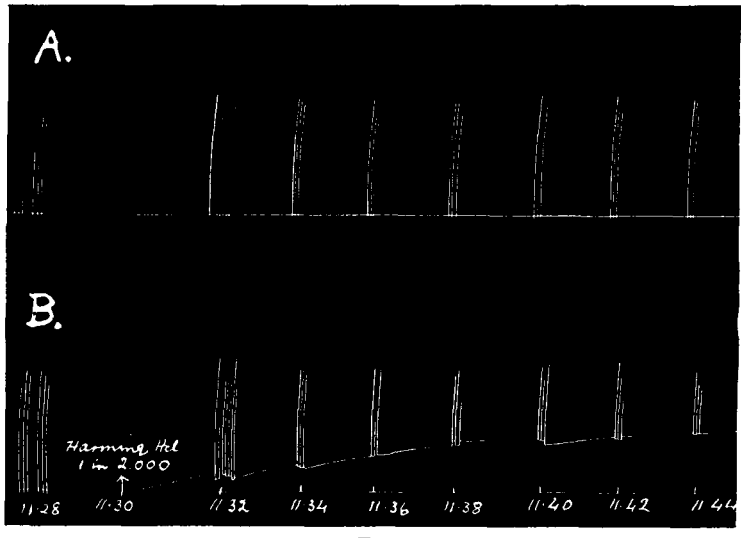

Fig. 1.

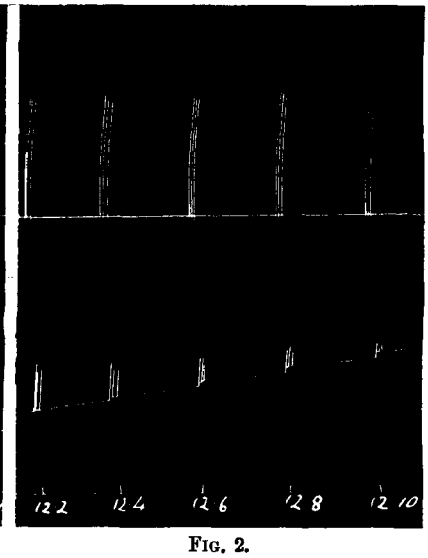

Fig. 2.

Muscle twitches (generally three in succession) were thereafter taken at intervals of two minutes, with the secondary coil at 100 mm. throughout.

As the tracing shows, harmine causes the muscle gradually to pass into a condition of rigor with diminishing excitability and extent of contraction, so that in forty minutes the muscle had raised the lever above the level of the summit of a single twitch and no longer responded to the stimulus. The control muscle was unaffected.

This effect on muscle is always produced by solutions of harmine when not less dilute than 1 in 5000, sometimes even by solutions of 1 in 10,000. Results of this action on muscle are exemplified in the general effects of poisoning by harmine by the occurrence of rigidity and impaired excitability of the muscles round the seat of injection, and also by the unusually rapid onset of rigor mortis after lethal doses.

E. Action on the Circulation.

(*a*) *Heart.*

A series of experiments was performed in which the isolated frog's ventricle was perfused by means of Schafer's frog-heart plethysmograph. A mixture of defibrinated

ox-blood (one part) and Ringer's solution (two parts) was used as the nutrient solution and as the solvent for harmine. The bulb of the plethysmograph which contained the heart was filled with Ringer's solution, and the contractions of the ventricle were recorded by means of an air-piston recorder attached by a rubber tube to the brass cylinder.

Experiment 22 (figs. 3 to 5).—Strength of solution, 1 in 10,000. This strength of

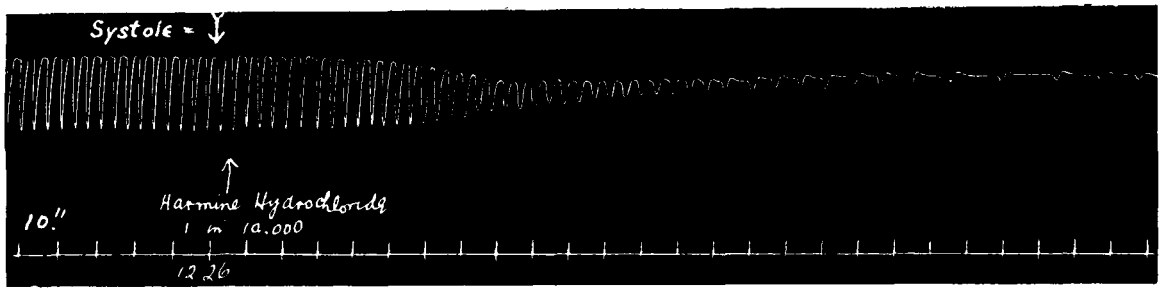

FIG. 3.

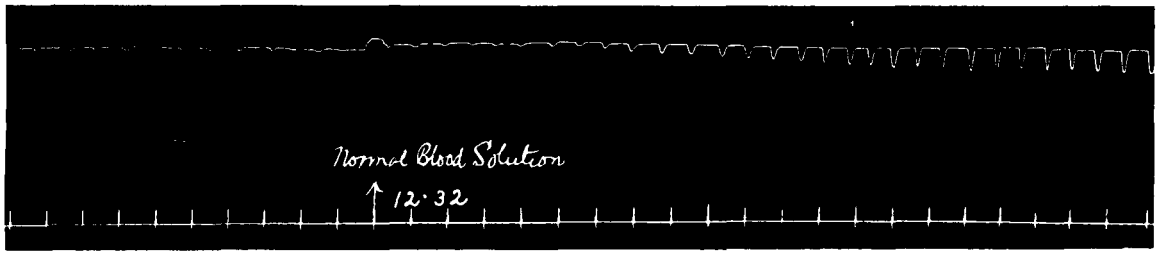

FIG. 4.

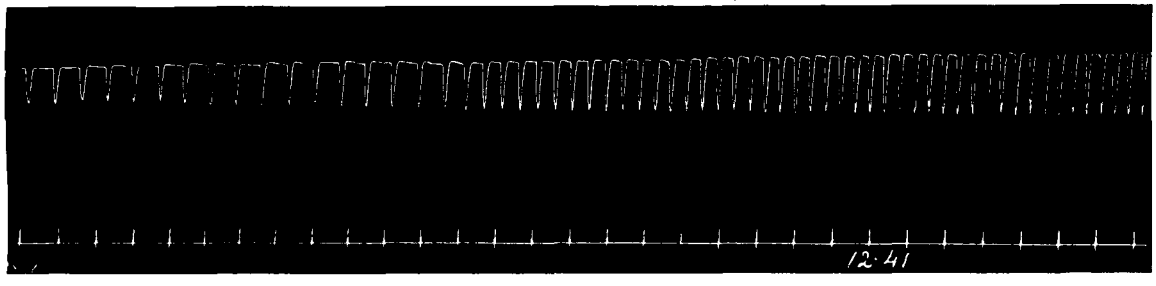

FIG. 5.

solution rapidly reduced both the rate of beat of the heart and also the amplitude of its excursus, the diminution of excursus being due mainly to less complete systole, but also to incomplete relaxation (fig. 3). Thus, in three minutes the rate fell from 18 to 6 contractions per minute, while the excursus was reduced from 9 to 2 millimetres. In six minutes the ventricle was arrested in a position of almost complete diastole, and the normal solution was thereupon substituted for the harmine solution (fig. 4). This so quickly restored the heart, that in ten minutes the rate and the excursus were practically the same as before harmine (fig. 5).

Experiment 23 (figs. 6, 7, and 8).—Strength of solution, 1 in 25,000. The conditions and result of this experiment are detailed in the following table:—

TABLE VI.—EXPERIMENT 23.

Time.	Rate per Minute.	Amplitude of Excursus.	Solution Perfused.
4.10	28	17 mm.	Normal solution.
4.20	30	16 „	
4.22	..	...	Harmine solution turned on (fig. 6).
4.25	17	11 mm.	
4.34	13	10 „	Fig. 7.
4.44	14	10 „	
5.4	11	14 „	Fig. 8.
5.11	...	...	Normal solution turned on.
5.13	20	17 mm.	
5.16	26	17 „	

This solution, therefore, produced considerable slowing and some weakening of the heart, but did not arrest it in fifty minutes. Recovery was rapid on reperfusion with the normal solution.

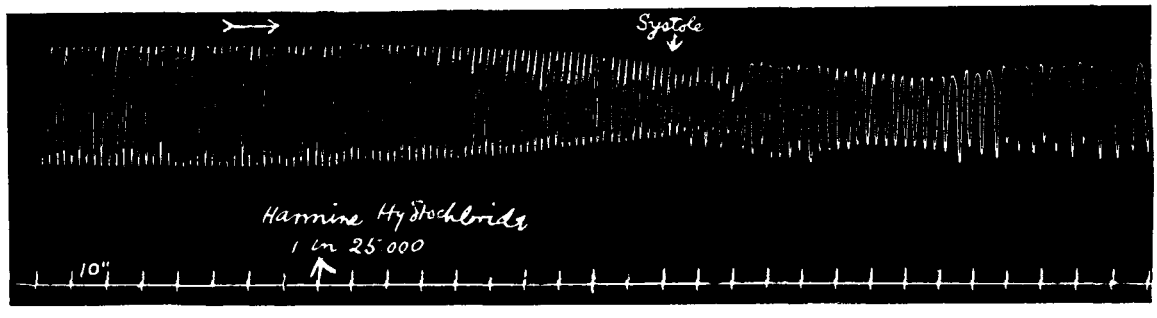

FIG. 6.

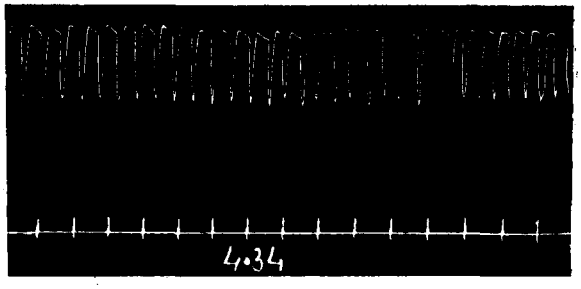

FIG. 7.

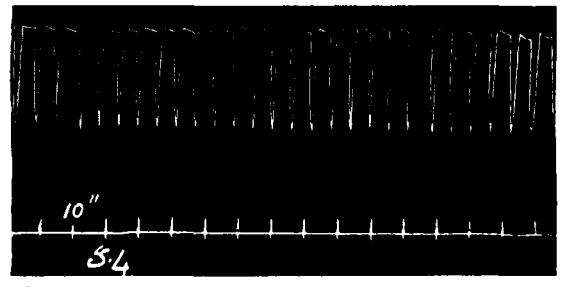

FIG. 8.

These two experiments illustrate the chief effects of harmine on the frog's heart, which may now be summarised. Solutions of 1 in 10,000 or more concentrated solutions rapidly slow the heart and arrest it in a position of complete, or almost complete, diastole. Solutions of 1 in 15,000 to 1 in 30,000 produce slowing of the heart, and also

some reduction in the amplitude of its excursus due to less complete systolic contraction. Solutions of 1 in 50,000, or weaker solutions, have no effect on the heart.

A point of some interest, when taken into consideration with the effect of harmine on blood pressure in mammals, is the extreme readiness with which the heart recovers when the harmine is removed from the circulation.

Other experiments have shown that the slowing of the heart produced by harmine is not prevented by simultaneous perfusion with atropine sulphate, and is therefore due to an action on the cardiac muscle.

(*b*) *Blood-vessels.*

To ascertain any changes produced by harmine on the blood-vessels of the frog, the following method was used. After the frog was pithed and the heart exposed, the venæ cavæ were cut across, and a fine cannula was tied into the left aorta, the right aorta being ligatured. This cannula was connected with two Marriotte's flasks containing the fluids to be perfused. A record was taken of the amount of fluid exuding per minute from the cut venæ cavæ. Ringer's solution was used as the normal solution and as the solvent for harmine.

Perfusion of the vessels for thirty minutes with solutions of harmine of varying strengths gave the following results:—A solution of 1 in 1000 reduced the flow from 1·8 c.c. per minute to 0·9 c.c. per minute; a solution of 1 in 2500 reduced the flow from 2·4 c.c. per minute to 1·7 c.c. per minute; a solution of 1 in 5000 reduced the flow from 2·7 c.c. per minute to 2·0 c.c. per minute; while a solution of 1 in 7500 had no effect on the flow through the vessels. Harmine has therefore a slight constricting action on the frog's blood-vessels.

(*c*) *Heart and Blood-vessels.* (*Blood Pressure.*)

In all blood-pressure experiments the animals (rabbits or cats) were first anæsthetised with chloroform; the trachea was then exposed, and a cannula tied into it through which diluted ether was thereafter inhaled. A cannula in the left carotid artery was connected with the manometer. Respirations were recorded by means of a double stethograph attached by a band round the thorax and connected with a Marey's tambour. Injections were made into the right jugular vein. It was found in preliminary experiments that the minimum lethal dose of harmine injected in this way is about 0·03 gramme per kilo.

Experiment 24 (Table VII., figs. 9 and 10).—Rabbit, 2400 grammes. The first injection of 0·01 grm. per kilo, equivalent to one-third of the intravenous minimum lethal dose, produced a somewhat transient fall of blood pressure, the normal level being restored in about ten minutes. The fall of pressure was accompanied by a slowing of the heart, which was evidently, in part at least, a causal factor. Recovery of blood pressure occurred in spite of further slowing of the heart. It is noteworthy

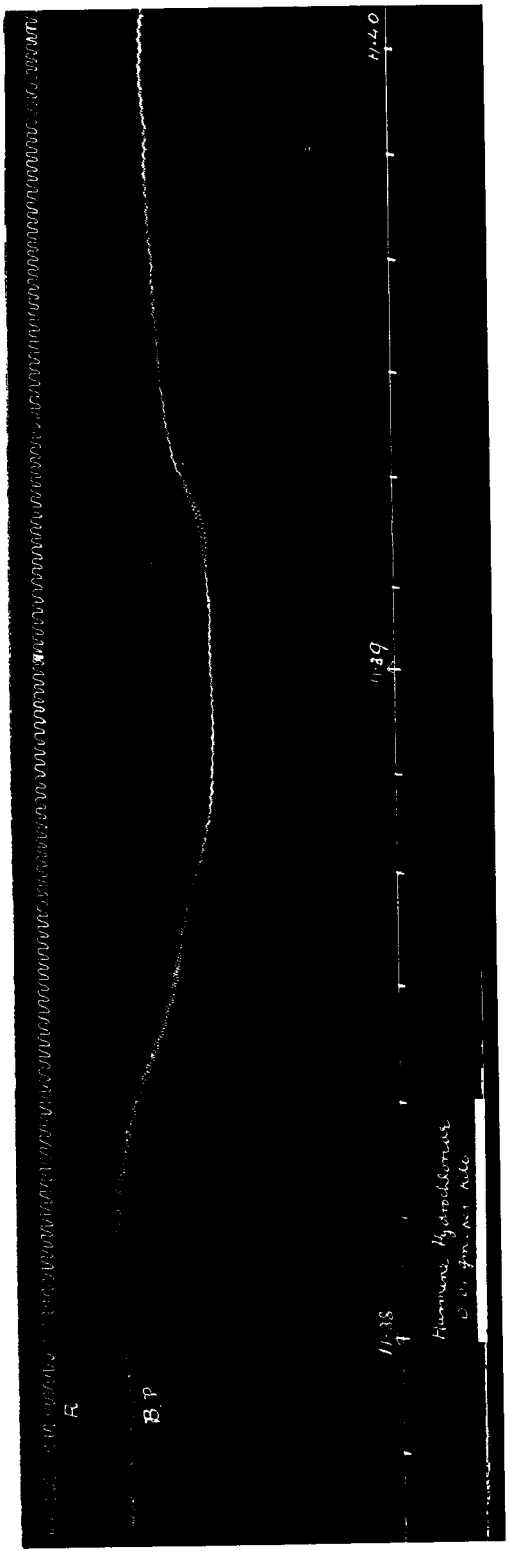
R.
B.P.
11·38
11·39
11·40
Human Hydrochloride
0·01 gm. per Kilo.

FIG. 9.

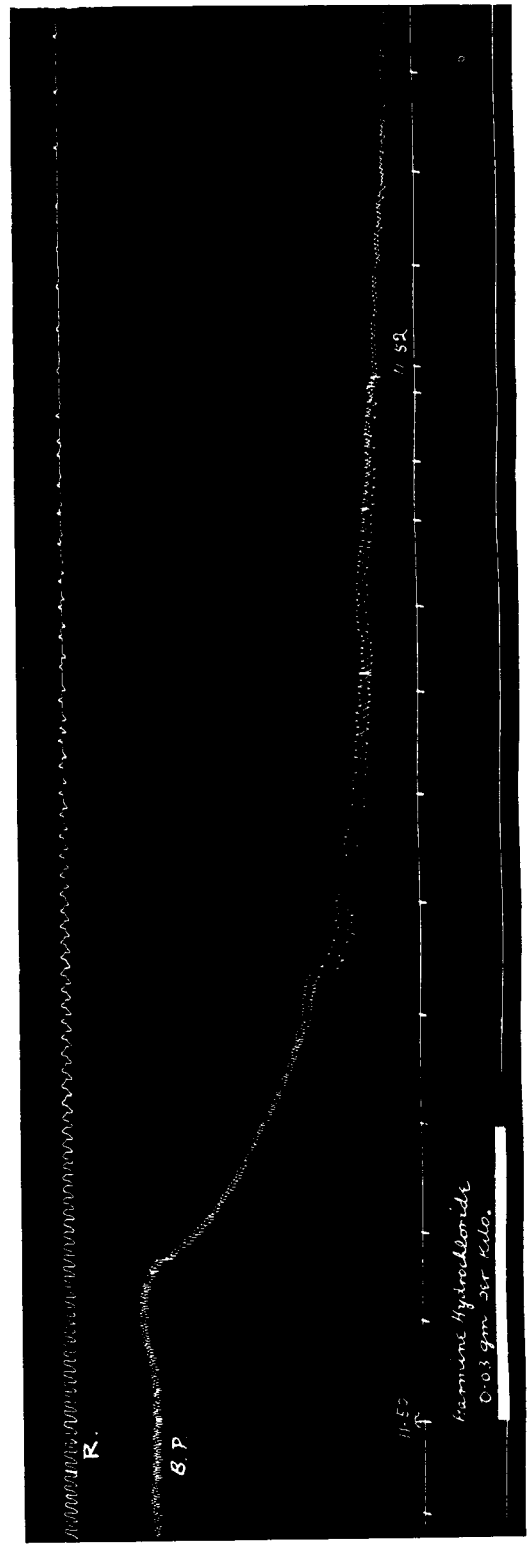
R.
B.P.
11·52
Human Hydrochloride
0·01 gm. per Kilo.

FIG. 10.

that, though the dose injected in this case was so large as one-third of the minimum lethal, no effect was produced on respiration.

The second injection produced a rapid decline of blood pressure, accompanied by slowing, and later by great feebleness, of the heart's contractions. Respiration was not much affected until the blood pressure reached a very low level. This, together with the facts that respirations continue as long as the heart beats and that respirations are unaffected except by doses which produce a grave fall of blood pressure, goes to show that death from intravenous injection of harmine is mainly, if not solely, due to cardiac failure.

TABLE VII.—EXPERIMENT 24.

Time.	Dose of Harmine intravenously.	Average B.P. in mm.	Pulse Rate per 10 seconds.	Rate of Respirations per 10 seconds.	Respiration Excursus.	Notes.
11.37	...	100	48	10	2 mm.	
11.38	0·01 grm. per kilo.	...	...	...	...	Fig. 9.
11.38.30″	...	82	42	10	2 mm.	
11.40	...	92	46	10	2 ,,	
11.48	...	98	40	10	2 ,,	
11.50	0·03 grm. per kilo.	...	...	...	...	Fig. 10.
11.50.30″	...	60	37	7	2 mm.	
11.51	...	50	14	5	1 ,,	
11.52	...	35	16	3	0·5 ,,	Pulse waves very small.
11.54	...	28	10	3	...	,,
11.56	...	0	0	0	...	

The effects of harmine on blood pressure, as deduced from this and other experiments, may be briefly summarised. Apart from very small doses, which sometimes produce an insignificant rise of blood pressure, the chief action of harmine is to produce a fall of blood pressure, due to slowing of the heart, and, in the case of lethal doses, also to enfeeblement of the heart's contractions. The slowing of the heart is not prevented by previous administration of a dose of atropine sufficient to paralyse the vagal endings, so that it is due to an action on the cardiac muscle, as was found also in the case of the frog's heart.

The only point of importance which remains to be discussed is whether the fall of pressure is due solely to cardiac causes or is due partly to vascular dilatation. To determine this, several experiments were made in which a record was taken of the blood pressure and also of the volume of the kidney or of a loop of intestine.

Experiment 25 (fig. 11).—Cat, 2700 grammes. Blood pressure was recorded as in the previous experiment, and the kidney volume was recorded by an oncometer and air-piston recorder. An injection of 0·004 gramme per kilo was given, about one-eighth of the minimum lethal dose. This reduced the blood pressure in one minute from 120 mm. to 88 mm., and the pulse rate from 18 to 13 per ten seconds. There

was meantime a considerable reduction in the volume of the kidney, showing that there was no dilatation of its blood-vessels. Similar results were obtained with the

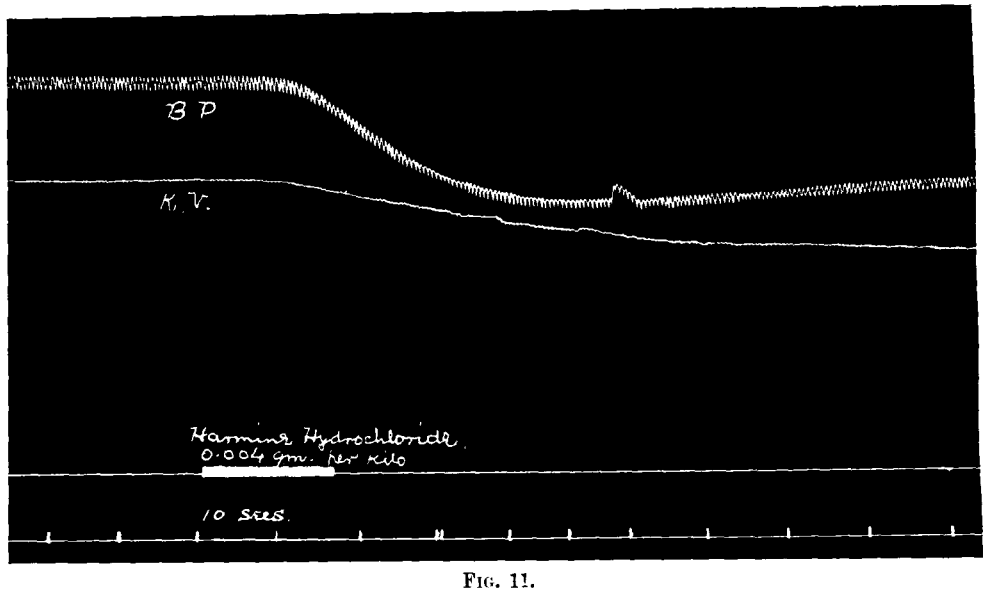

FIG. 11.

intestinal volume. It would appear, therefore, that the fall of blood pressure is due chiefly to diminished output from the heart, and not to dilatation of the abdominal vessels, though experiments on the intact animal gave indications of some dilatation of the vessels of the skin.

F. ACTION ON THE RESPIRATION.

Lethal doses of harmine paralyse the respiration in frogs a short time before cessation of the heart beats, but at a time when there is great feebleness of the circulation. In mammals the same effect is obtained with small lethal doses; but with rapidly lethal doses, especially if intravenously injected, the heart beats and respirations cease at the same time. At the time of death the diaphragm reacts to weak stimulation of the phrenic nerve, and respiratory failure is probably partly due to a direct depressing action of harmine on the respiratory centre, and is partly consequent upon circulatory failure.

In the unanæsthetised mammal sublethal doses produce a distinct stimulation of respiration. This does not occur if the animal is anæsthetised with chloroform or ether, a very common phenomenon with respiratory stimulants.

G. ACTION ON TEMPERATURE.

Large doses of harmine cause a fall of temperature in mammals, an effect which has been shown by HARNACK* to be generally true of convulsant poisons. The fall of temperature is sometimes preceded by a slight transient rise.

* HARNACK, *Archiv für exper. Path. u. Pharmakol.*, 1897, Bd. xxxviii.

H. Action on the Uterus.

Rabbits were used for these experiments. They were anæsthetised as for blood-pressure experiments and kept during the experiment in a bath of saline solution at 38° C., enough of the body being submerged to ensure that the uterus was never exposed to the air. The abdomen was then opened in the middle line, and the uterus, isolated from the surrounding viscera, was connected with a lever writing on a slowly revolving drum.

Experiment 26 (figs. 12 to 14).—Rabbit, 2350 grammes, parous, non-pregnant. Slight spontaneous contractions occurred regularly at the rate of about 2 per minute.

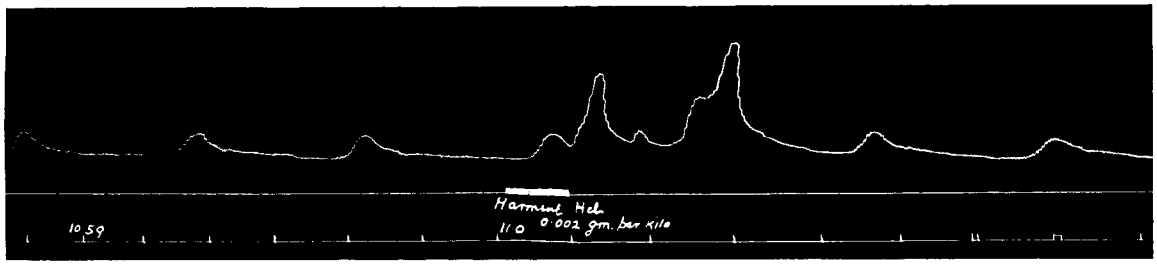

Fig. 12.

At 11.0, 0·002 gramme per kilogramme of harmine hydrochloride was injected intravenously, and this produced a marked augmentation of the uterine contractions, which, however, soon passed off. At 11.15 a second injection of twice the former amount was

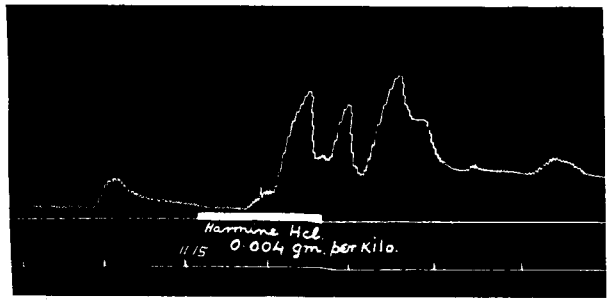

Fig. 13.

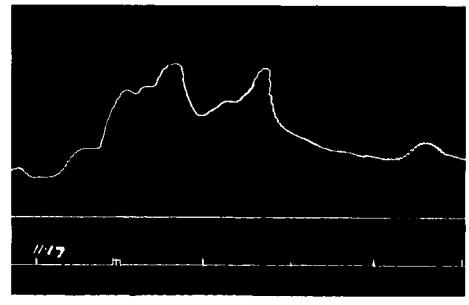

Fig. 14.

given, and this produced very powerful uterine contractions (fig. 13), which were repeated at intervals afterwards (fig. 14). The resting tone of the uterine muscle was also increased.

It is evident, therefore, that harmine exerts a decided stimulating effect on the uterine contractions.

General Summary.

The minimum lethal dose of harmine hydrochloride per kilogramme by subcutaneous injection is, for the frog, 0·6 gramme; for the guinea-pig, 0·12 gramme; for the rabbit, 0·23 gramme; for the rat, 0·2 gramme; and for the pigeon, 0·15 gramme.

In frogs, lethal doses of harmine paralyse the mid-brain, medulla oblongata, and

spinal cord. Abolition of reflex excitability occurs before arrest of the heart, and before paralysis of the voluntary muscles. In mammals large doses cause epileptiform convulsions, cerebral in origin. If the dose be non-lethal these are soon recovered from; if the dose be lethal, they give place to a condition of paralysis of the central nervous system, which endures for a short time before death.

Harmine produces rigor and inexcitability of an isolated muscle, but, even with lethal doses, the concentration of harmine in the blood is not sufficient to render this action of importance in the general effects of this alkaloid.

Strong solutions of harmine perfused through the frog's heart slow the heart and arrest it in a position of almost complete diastole; weaker solutions slow the heart and diminish the completeness of systolic contraction. The effects are due to an action on the cardiac muscle.

Harmine has a slight peripheral constricting action on the frog's blood-vessels.

In mammals, harmine, in doses which have any marked effect on blood pressure, produces a fall of blood pressure due chiefly to slowing, or, in the case of large doses, to slowing and weakening, of the heart's contractions. Cardiac failure is the chief cause of death from harmine poisoning.

Sublethal doses of harmine stimulate respiration; lethal doses paralyse respiration, partly from a direct action on the respiratory centre and partly as a consequence of circulatory failure.

Like many convulsant poisons, harmine in large doses produces a fall of temperature in mammals. Even in small doses it stimulates the contractions and augments the tone of uterine muscle.

Comparison of the Actions of Harmine and Harmaline.

The pharmacological actions of harmine resemble very closely those of harmaline in so far as the symptoms produced in the intact animal and the effects produced on the various systems and on isolated tissues are qualitatively the same in the case of both alkaloids. For this reason the pharmacology of the former alkaloid has been discussed more briefly. Harmine is, however, only about half as toxic as harmaline; and probably the chief reason for the relatively lower toxicity of harmine is that the primary stimulating action on the central nervous system less readily gives place to paralysis, and hence respiratory paralysis plays a less important part in the production of its lethal effects than is the case with harmaline.

As the alkaloids can easily be obtained from the seeds in a mixed form, whereas their separation from one another is, I understand, a difficult and tedious process, this close similarity in their pharmacological actions possesses this importance, that the mixed alkaloids would apparently be as effective therapeutically as either alkaloid alone, should a therapeutic use for them be found.