XI.—The Pharmacological Action of Harmaline. By James A. Gunn, M.A., M.D.,
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INTRODUCTORY.

Harmaline is one of two alkaloids found in the seeds of *Peganum Harmala*, a strong-smelling herbaceous plant belonging to the order of Rutaceæ. This plant grows to a height of from 1 to 3 feet, is much branched, and profusely covered with leaves. It is found wild in S. Europe, Asia Minor, Egypt, Arabia, N.W. India, and Siberia. It is the *Πήγανον ἄγριον* (wild rue) of Dioscorides, *Πήγανον* being the name still applied in Greece to several species of *Ruta*.

The seeds were used medicinally by the ancient Greeks, as they are to this day in India, where they are known chiefly by the old Arabic name of *Harmal*. In Europe they were formerly much employed as *Semen Rutæ sylvestris*, and as such are enumerated among the simples of several of the early London Pharmacopœias.*

The seeds are of a dark brown colour, and contain (1) a red colouring matter, which was at one time imported into England from the Crimea as a dye; (2) oil; (3) a soft resin of a deep carmine lake colour, having a heavy odour like that of *Cannabis Indica*; (4) two alkaloids, harmaline and harmine.

Harmaline ($C_{13}H_{14}N_2O$) was discovered in 1837 by GÖBEL, and harmine ($C_{13}H_{12}N_2O$) in 1847 by FRITCHE. According to the latter, the total yield of alkaloid is 4 per cent., of which two-thirds is harmaline and one-third harmine.

Harmaline crystallises in yellow rhombic octahedra, neutralises acids, and forms

* FLÜCKIGER, *Year-book of Pharmacy*, 1871, p. 600.

with them salts which have a yellow colour and bitter taste. Harmaline hydrochloride ($C_{13}H_{14}N_2O$, HCl , $2H_2O$) forms long, fine yellow needles, easily soluble in water and in alcohol. Dilute solutions of harmaline exhibit a green fluorescence.*

The only observations hitherto made to determine experimentally the general action of harmaline were those of TAPPEINER in 1895.† His experiments were concerned chiefly with symptoms produced in frogs and mammals.

In frogs he found that harmaline produces paralysis of voluntary movement. Reflex excitability remains after loss of voluntary motion, and even until arrest of the heart and respiration; after its complete paralysis, nerve and muscle are quite excitable. No convulsions were observed.

In mammals he found that harmaline produces motor disturbances, convulsions followed by paralysis. Consciousness is retained during the convulsions, but the sensitiveness to pain is reduced throughout the poisoning. Respiration is accelerated, and the temperature slightly raised. He found the minimum lethal dose to be 0.11 gramme per kilogramme, death being due to the arrest of respiration, which occurs suddenly without any previous considerable reduction in frequency.

From two kymograph experiments on rabbits, he concluded that the blood pressure is at first considerably raised, especially during the convulsions. This rise is due to stimulation of the vasomotor centre, since the heart's action did not appear to be increased. Subsequently the blood pressure falls, owing to paralysis of the vasomotor centre and increased weakness of the heart.

He summed up as follows: "If we judge by the most apparent symptoms of poisoning—the convulsions—which seem to be direct, as they are due to disturbance neither of the respiration nor of the circulation, we can until further notice reckon harmaline and harmine as convulsive poisons, and, in so far as death is due to arrest of the respiration, also as respiratory poisons. This investigation gives no basis for its therapeutic uses."

In 1899 OSCAR RAAB‡ investigated the action on Infusoria of several substances which form fluorescent solutions, e.g. acridin, phosphine, quinine, and eosine. He found that all of these are much more toxic to *Paramecium caudatum* in light than in darkness, those light rays which most excite fluorescence being especially powerful in increasing the toxicity. In 1903 he extended these investigations to include harmaline,§ and found that a solution of 1 in 20,000 of harmaline kills paramœcia in 8 to 20 minutes, the presence or absence of light having no effect on the toxicity. Nor does the light effect come into play with 1 in 40,000; but when exposed to a solution of harmaline hydrochloride of 1 in 200,000, paramœcia remain quite healthy in the dark for 20 hours, while in the light they die in 1 to 3 hours. Exposure to light has by itself no injurious action on paramœcia.

* HUSEMANN, *Die Pflanzenstoffe*, 1871, p. 76.

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

‡ *Zeitschrift für Biologie*, Bd. xxxix., 1899, p. 524.

§ *Ibid.*, Bd. xlv., 1903, p. 16.

In 1901 JACOBSON* showed that, in regard to their toxic effect on ciliated epithelium, solutions of harmaline hydrochloride (among other fluorescent substances) act independently of light in stronger concentrations, while in weaker concentrations they are much more poisonous in light than in darkness.

In August 1908 I obtained from Dr J. F. THORPE, F.R.S., of Manchester University, 7 grammes of harmaline and 5 grammes of harmine for pharmacological investigation, for which kindness I take this opportunity of expressing my great indebtedness to him.

After performing a large number of experiments with harmaline, both with regard to its general effects and its effects on isolated tissues, I have come to the conclusion that the pharmacological actions of this alkaloid, almost without exception, resemble intimately those of quinine; and it is possible that this more extended investigation may give, contrary to TAPPEINER'S conclusion, some pharmacological basis for the therapeutic use of harmaline. Hence, in the course of the following account of the pharmacology of harmaline, its various actions will be compared in detail with those of quinine.

A. LETHALITY OF HARMALINE.

The lethality of harmaline was determined for frogs, guinea-pigs, rabbits, rats, and cats, 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	31	0·05	0·0015	Recovery.
2	34	0·1	0·0034	„
3	20	0·2	0·004	„
4	26	0·2	0·0052	„
5	38	0·25	0·0095	Death in 31–36 hours.
6	32	0·3	0·0096	„ before 20 „
7	28	0·4	0·011	„ in 6 hours.
8	22	0·45	0·01	„ „ 3 „

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

No. of Experiment.	Weight of Guinea pig in Grammes.	Does per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
9	500	0·01	0·005	Recovery—slight effects.
10	450	0·04	0·018	„ marked effects.
11	470	0·08	0·038	„ severe effects.
12	500	0·1	0·05	Death in 7 hours 40 minutes.
13	500	0·2	0·1	„ 33 minutes.

* *Zeitschrift für Biologie*, Bd. xli., 1901, p. 445.

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.
14	1120	0.02	0.022	Recovery—slight effects.
15	1650	0.08	0.132	„ severe effects.
16	1150	0.09	0.103	„ „ „
17	1000	0.1	0.1	Death in 1 hour 30 minutes.
18	1450	0.12	0.174	„ 3 hours.

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.
19	132	0.076	0.01	Recovery—severe effects.
20	150	0.09	0.0135	„ „ „
21	170	0.11	0.019	„ „ „
22	107	0.12	0.013	Death in 7½ hours.

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

No. of Experiment.	Weight of Cat in Grammes.	Dose per Kilogramme in Grammes.	Actual Dose in Grammes.	Result.
23	2700	0.09	0.243	Recovery—severe effects.
24	3000	0.1	0.3	Death in about 9 hours.
25	1730	0.13	0.225	„ 1½ hours.

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, and in mammals under the skin of the right flank.

Minimum Lethal Dose for Frogs.—Recovery followed from doses of 0.2 gramme per kilogramme and under; doses of 0.25 gramme per kilogramme and above proved fatal. The minimum lethal dose is therefore about 0.25 gramme per kilogramme.

Minimum Lethal Dose for Mammals.—In the cases of the guinea-pig, rabbit, and cat, doses of 0.09 gramme per kilogramme and under were followed by recovery; doses of 0.1 gramme per kilogramme and above proved fatal. The minimum lethal dose is therefore 0.1 gramme per kilogramme. In the case of the rat, recovery followed from doses of 0.11 gramme per kilogramme and under, while 0.12 gramme per kilogramme was the smallest dose to prove fatal. In this mammal the minimum lethal dose is therefore slightly higher, namely 0.12 gramme per kilogramme.

Harmaline resembles quinine in being relatively much more toxic to mammals than to frogs.

B. SYMPTOMS PRODUCED BY HARMALINE.

(a) *In Frogs.*

The following experiment will serve to illustrate the symptoms produced by a minimum-lethal dose of Harmaline.

Experiment 5.—*Rana temporaria*, male, weight 38 grammes. At 11.27 a.m. the throat respirations were 17 in ten seconds, deep and regular; the cardiac impacts were 7 in ten seconds, fairly easily seen. Faradic stimulation of the skin of the right leg with the secondary coil at 160 mm. elicited a slight kick of the same leg, and the animal moved away if the stimulation was prolonged; similar stimulation with the coil at 140 mm. caused immediate extension of both legs. Stimulation of the skin over the dorsal part of the spinal cord caused extension of the legs with the coil at 140 mm.

At 11.50, 0.0095 gramme of harmaline hydrochloride dissolved in 0.8 c.c. of Ringer's solution was injected into the dorsal lymph-sac. This was equivalent to 0.25 gramme per kilogramme.

At 11.58 the pupils, which had been medium before injection, were more contracted. The results of electrical stimulation were the same as before. There was persistent contraction of the muscles running from the skin to the side of the urostyle.

At 12.5 p.m. the respirations were 13 in ten seconds, and very feeble. The back was rigid, and curved in a direction concave upwards, due to rigidity of the back muscles. The frog jumped away when the skin of the leg was stimulated at 230 mm., and turned immediately when placed on its back.

At 12.14 the rate of the respirations had fallen to 9 in ten seconds. With the coil at 160 mm., stimulation of the skin of the right leg caused extension of both legs, while at 12.34 the coil required to be at 145 mm. to produce this effect.

At 1.50 the pupils were contracted. An area of skin overlying the dorsal lymph-sac was pale, contrasting markedly with the much darker colour of the skin of the rest of the body. The respirations were only 3 in ten seconds, and consisted of very feeble undulations of the anterior part of the floor of the mouth. The cardiac impacts were 3 in ten seconds. The reflex excitability as determined by electrical stimulation was unchanged. When the frog was laid on its back it made no effort to recover, but when the foot was now stimulated the frog turned over with difficulty. The animal jumped only if strongly stimulated, and when it alighted the hind limbs were not drawn up with normal rapidity.

At 2.25 the respirations had ceased, and the cardiac impacts were not visible, but when the web of the foot was examined under the microscope the circulation was seen to be active. At 3.15 the animal lay prone, with limbs extended. The conjunctival and nose reflexes were active.

At 6.30 p.m. no reaction resulted from either touching the conjunctiva or stroking the nose. The eyelids were fully open, and the pupils semi-dilated.

At 11 a.m. next day, as also at 12.30 p.m., with the coil at 100 mm., stimulation of the skin of either leg caused feeble movements of both legs, and stimulation of the skin over the dorsal part of the cord caused fairly vigorous extension of both legs. The circulation in the web of the foot was fairly active.

At 3.20 p.m. stimulation of the skin of either leg with the coil even at 40 mm. produced no movements of the opposite leg. Stimulation over the cord at 100 mm. still produced feeble extension of both legs.

The heart was now exposed by removing part of the sternum, and found to be beating moderately strongly at the rate of 2 in ten seconds; auricles and ventricle were beating synchronously.

The left sciatic nerve was exposed, and stimulation of it with the coil at 295 mm. induced contraction of the left gastrocnemius muscle, but no movement of the opposite limb ensued even with the coil at 40 mm. The muscles reacted to direct stimulation at 50 mm.

At 5.0 p.m. the heart was beating feebly at the rate of about 4 in 30 seconds. No crossed reflex movements could be obtained by stimulation either of the skin of the leg or the sciatic nerve. Stimulation over the cord with the coil at 80 mm. caused feeble localised movements of the leg muscles, and stimulation of the sciatic nerve at 130 mm. caused a feeble contraction of the gastrocnemius.

At 10.0 p.m. the heart was found to be arrested in diastole, and the muscles and nerves were irresponsive to electrical stimulation.

(b) *In Mammals.*

There is a close similarity in the effects produced by harmaline in different mammals. To illustrate the general nature of these effects, the following two experiments were selected; the former as an example of the symptoms produced by a minimum lethal dose, in the case of which death is postponed for several hours, the latter as an example of a rapidly fatal dose. They also illustrate differences in the symptoms in different animals.

1. *Guinea-pigs.*—*Experiment 12.*—Guinea-pig, male, weight 500 grammes. At 11.5 a.m. the cardiac impacts were 37, the respirations 21, in ten seconds.

At 11.45, 0.05 gramme of harmaline hydrochloride dissolved in 4 c.c. Ringer's solution was injected under the skin of the right flank. This was equivalent to 0.1 gramme per kilogramme.

At 11.50 the cardiac impacts were 30, the respirations 18, in ten seconds. There were slight tremors of the head, and the right hind limb was slipping on the tray. During the next five minutes the animal made several short, jerky rushes forward; in the quiet intervals the hind limbs were extended as if unable to support the body-weight. There were marked tremors of the head, and chewing movements of the jaws.

At 12.0 the cardiac impacts were 21, the respirations 18, in ten seconds. During the next fifteen minutes the animal remained usually with the fore part of the body upright, but with the hind-quarters lying on the side, there being frequent clonic movements of the hind legs. When it was disturbed it could run normally, and when laid on its back it turned over immediately. It uttered cries frequently.

At 12.20 the hind limbs were somewhat rigid, and in the extended position. Respirations seemed to be more panting, but their rate could not be counted owing to the incessant tremors and clonic movements.

At 12.32 the conjunctival reflex was duller, and the convulsive movements less violent. The animal generally lay on its side, occasionally assuming the upright position for short periods. Two minutes later it lay on its back, and from this time onwards usually remained lying on its back or side.

At 1.0 the cardiac impacts were 20 in ten seconds. There were frequent clonic movements of the limbs and jaws. The tongue was often quickly protruded and withdrawn. There were sometimes rapid movements of the eyelids and oscillations of the eyeballs. When the animal was placed in the upright position it made no effort to move forward but slowly fell over on to its side. There was apparently a definite diminution in reflex excitability, for even pricking the skin of the leg with a pin induced no reaction.

At 3.0 the limb movements were much feebler, though still almost constant. The conjunctival reflex was dull. The body was felt to be abnormally cold. The respirations were about 20, and the cardiac impacts about 18, in ten seconds, but they were difficult to count accurately. At 4.25 the rectal temperature was 26° C.

At 7.13 the animal was lying on its side gasping. The respirations were 2 or 3 in ten seconds, irregular in rate and accompanied by gaping of the mouth. The cardiac impacts could not be felt. There were feeble pawing movements of the fore limbs. The hind limbs were quite stiff, as if in rigor mortis. The conjunctival reflex was completely gone, but the animal moved its head feebly when the ear was pinched. The rectal temperature was 21° C.

At 7.25 all respiratory movements ceased. The thorax was then opened, and the heart was exposed at 7.29 and found to be beating slowly and feebly.

2. *Cats.*—*Experiment 25.*—Cat, male, 1730 grammes. At 11.35 the respirations were 6, the cardiac impacts 34, in ten seconds.

At 11.40, 0.225 gramme of harmaline hydrochloride dissolved in 2 c.c. Ringer's solution at about body temperature, was injected under the skin of the right flank. This was equal to 0.13 gramme per kilogramme.

At 11.43 the cat was timid and uneasy, and appeared to have hallucinations. He moved sometimes in a circle, trembling and with eyes staring. There were slight tremors of the body.

At 11.48 he stood mewing loudly, with back arched and limbs extended and upright. The mouth was widely opened, and saliva flowed from it.

At 11.55 he had a sudden, violent convulsion which lasted about thirty seconds, and during which he fell on his side. After this he remained lying on his side, mewing loudly. The respirations were then easily counted, and were 16 in ten seconds, deep and regular.

Thereafter the animal had convulsions at 12.1, 12.2, 12.3, 12.5, 12.9, 12.13, 12.20, 12.25, and 12.30. These convulsions conformed to a fairly definite type. They generally began by gaping of the mouth, followed suddenly by rapid clonic movements, involving especially the hind limbs; the animal generally fell on its side. Often ushered in by a cry, with occasionally a short tonic phase prior to the clonic movements, and followed by an interval of flaccidity during which the respirations were panting, these convulsions frequently bore a strong resemblance to attacks of *grand mal*. It is also seen that there is a tendency to gradual lengthening of the interval between the attacks. The later convulsions also became less violent, and the animal during the intervals more paretic. Up to 12.20 there was no impairment of the conjunctival reflex.

At 12.25 the respirations were 20 in ten seconds, regular and deep. The conjunctival reflex was duller, and pinching the tail evoked no reaction. The fore limbs were extended at right angles to the body, while the hind-quarters lay on the side.

At 12.30 the respirations were 14 in ten seconds, and much feebler. The cardiac impacts were 27 in ten seconds.

At 12.44 no reaction resulted from strongly pinching the limbs or tail; the conjunctival reflex was almost abolished, but the eyes were closed if blown upon.

At 1.3 the respirations were 15, the cardiac impacts 25, in ten seconds. The cat was lying quite quiet, and there were no tremors or convulsions.

At 1.10, apart from the movements of respiration, the animal appeared completely paralysed. When held up by the neck it hung quite limp, and when placed on the floor made no attempt to support itself.

At 1.13 the respirations were 4 in ten seconds, gasping in character; the cardiac impacts were 15 in ten seconds, feeble and irregular. At 1.14 respirations were reduced to an occasional gasp, and no cardiac impacts could be felt.

At 1.16 the respirations ceased, and the pupils, which had been medium both before injection and throughout the poisoning, dilated widely. The thorax was now opened and the heart exposed; there were no contractions of either auricle or ventricle. At 1.18, faradic stimulation of the phrenic nerve with the secondary coil at 550 mm. induced contraction of the diaphragm; at 1.22, stimulation of the sciatic nerve with the secondary coil at 370 mm. caused contraction of the gastrocnemius muscle.

C. ACTION ON THE CEREBRO-SPINAL NERVOUS SYSTEM.

(a) *Brain and Spinal Cord.*

1. *In Frogs.*—The frog is not a suitable animal for manifesting the action of drugs on the cerebrum, and no symptoms were observed which could be ascribed definitely

to an action of harmaline on this part of the brain. However, the onset of inco-ordination of movement, the loss of the power of jumping and of recovering the normal posture when the animal is laid on its back, and the cessation of respiration—occurring as these effects do at a time when the spinal reflexes and peripheral motor mechanism are slightly, if at all, impaired—indicate that harmaline first paralyses the functions of the mid brain and medulla oblongata.

With regard to the spinal cord, a transient stage of increased reflex excitability usually occurs, after which spinal reflexes become less and less easily elicitable. The voluntary muscles still readily respond to weak faradic stimulation of their nerves when the abolition of reflex excitability first occurs, showing that the paralysis is one involving the spinal cord.

As is the case with many poisons, the power of transmission of impulses across the spinal cord, *e.g.* from left to right leg, is lost much earlier than the power of conducting impulses down the spinal cord, rendering it probable that the block in conduction is due not to paralysis of the efferent nerve cells but to interference between the afferent and efferent nerve cells of the cord. Loss of reflex excitability occurs before arrest of the heart, if the heart be not exposed.

Harmaline resembles quinine very closely in its action on the central nervous system of the frog. Like harmaline, quinine in large doses paralyses the brain and respiratory centre, and later the reflex excitability of the spinal cord after a preliminary increase of excitability. In quinine poisoning too the heart continues to beat after paralysis of the spinal cord.

2. *In Mammals.*—Harmaline affects the central nervous system of mammals in a manner different from the central nervous system of frogs, in so far as symptoms of excitation are added to symptoms of paralysis. Convulsions do not occur in frogs, but are the most conspicuous effects produced in mammals.

In the cat these take the form of more or less violent convulsions of epileptiform character, occurring at irregular intervals and separated by quiescent periods. In the guinea-pig, clonic convulsions, less violent than those produced in the cat, and resembling running movements, occur almost without respite. In the rabbit, convulsive movements of an intermediate type are observed; and in the rat, spasticity of the limb muscles, with tremors and swaying of the head and body, is the most characteristic appearance, though the kind of clonic convulsions described in the guinea-pig occurs also in the rat.

Certain facts in regard to these convulsions aid in the localisation of the site of their production. In the first place, they are not due to asphyxia, because they occur before there is any impairment of respiration or any appearance of cyanosis. In the second place, the convulsions are cerebral in origin and not spinal. They are quite different from the convulsions produced by strychnine, for example; they are not evoked by any apparent external stimulus, opisthotonus is never seen, and the convulsions do not occur in frogs. Also it will be shown in kymograph experiments

that the convulsions do not occur in an animal anaesthetised by ether or chloroform. Apart from negative evidence, the epileptiform character of the convulsions points to the brain as the seat of their origin. It is, moreover, probable that they are due mainly to an exciting action on the cerebral cortex. The occurrence in cats of symptoms apparently due to hallucinations suggests an action on the cerebral cortex. Further, if the convulsions were due to an action on the lower part of the brain, they would probably occur in frogs, as in the case of the convulsions produced by picrotoxin.

Tremors or convulsions are not produced in rabbits by doses less than 0.02 gramme per kilogramme, *i.e.* one-fifth of the minimum lethal dose; in the guinea-pig, tremors occur after doses of above 0.01 gramme per kilogramme.

In none of my experiments were the convulsions observed to be fatal, probably because their clonic nature does not seriously interfere with respiration.

After a period, which varies with animal used and the dose given, the convulsions pass off, and in the case of smaller doses recovery ensues. In the case of larger doses the convulsions diminish in severity and are succeeded by a stage of exhaustion and, it may be, of complete motor paralysis, which may endure for some considerable time before failure of the heart or respiration. When this stage of motor paralysis supervenes, the symptoms referable to the central nervous system approximate closely to those described in frogs, and are probably due to like causes. There is possibly an increased excitability of the spinal reflexes in the early stages of poisoning in mammals as in frogs, but of this it is difficult to be certain. However, it is clear that the ultimate effect on the spinal cord, that of paralysis, is the same in mammals as in frogs. This is well seen in Experiment 25 described above, where the spinal reflexes were abolished some time before death, while the fact that the excitability of the peripheral neuromuscular mechanism was unimpaired even some minutes after death showed that this effect was central in origin. Owing to this paralysis of the spinal cord, the terminal phenomena of asphyxia are unattended by convulsions.

Though convulsions, due to an action on the cerebrum, may occur under certain circumstances also with quinine, they are more typical of some of the other cinchona alkaloids, *e.g.* cinchonamin. Harmaline and quinine are, however, alike in producing, in large doses, diminution of excitability of the spinal cord in mammals.

(b) *Nerve.*

To investigate the action of harmaline on nerve structure, the following method was employed. The muscle response was taken as an index of the condition of the nerve. The gastrocnemius muscle of the frog was used, with the sciatic nerve carefully removed leaving a small part of the spinal column attached. Two pairs of electrodes, proximal and distal, were used to stimulate the nerve, and a small part of the nerve between the proximal and distal electrodes was painted with a solution of harmaline.

A comparison was made, before and after the application of harmaline, of the muscle response evoked by proximal and distal stimulations.

It was found that nerve is very resistant to harmaline: even so strong a solution as 2 per cent. of harmaline hydrochloride impairs the conductivity only after several hours' application. This feeble action on nerve presents a marked contrast to the unusually toxic effect which harmaline exerts on striped muscle.

As in the case of the nerve trunks, so the motor nerve terminals are slightly if at all affected by harmaline. Thus in Experiment 5, in the course of impairment of the peripheral neuromuscular mechanism, stimulation of the sciatic nerve of the frog caused contraction of the gastrocnemius with the coil at 295 mm., while direct stimulation of the muscle required a strength of 50 mm. This relation of excitability appears to show that the peripheral paralysis, which occurs late in the course of poisoning, is due to paralysis of the muscle, the nerve and nerve-ends being slightly if at all affected. This opinion was confirmed by investigating the action of harmaline on the nerve-muscle by Claude Bernard's method, when it was found that diminution in excitability of muscle when stimulated through its nerve occurred only when there was a corresponding decrease in the excitability of the muscle to direct stimulation.

D. ACTION ON SKELETAL MUSCLE.

It has been shown that, after injection of harmaline, rigor and loss of excitability occur in those muscles to which the injected solution obtains more direct access. This produces an appearance of opisthotonos when the injection is made into the dorsal lymph-sac, of emprosthotonos when the injection is made under the skin of the abdomen. Arrangements were made to test further this action of harmaline by keeping a muscle directly in contact with solutions of varying strengths of the alkaloid. A modified Wild's method was employed; and when the muscles were stimulated, the current from the secondary coil passed simultaneously through both muscles. Tracings were taken on a slowly revolving drum.

Experiment 26 (figs. 1 and 2).—Strength of solution, 1 in 500. Normal twitches resulting from stimulation of the muscles with break shocks are shown at 11.40 (fig. 1). At 11.45, Ringer's solution was withdrawn from the upper tube, and a solution of harmaline hydrochloride (1 in 500 of Ringer's solution) was substituted. Almost immediately this caused the muscle to pass into rigor. This proceeded so rapidly that in five minutes this muscle had raised the lever above the level of the summit of a single twitch.

At 11.58, thirteen minutes after exposure to harmaline, the upper muscle ceased to respond to stimulation, whereas the control muscle contracted as before (fig. 2).

This strength of solution therefore very soon brings on rigor with loss of excitability of the muscle.

Rigor of frog's muscle is produced by solutions of harmaline even so dilute as 1 in

10,000, or sometimes 1 in 20,000. Harmaline produces rigor as rapidly and as completely in curarised muscle, so that the effect is probably due to an action on the muscle protoplasm. In respect of this action in producing shortening and loss of excitability of muscle, harmaline resembles quinine, but is more powerful. In none of the experiments did fibrillary twitchings of the poisoned muscle occur.

Solutions of harmaline which are too dilute to produce rigor of muscle do not

FIG. 1.

FIG. 2.

markedly diminish the excitability of the muscle. Thus a gastrocnemius-sciatic preparation was kept in a solution of harmaline 1 in 25,000 for eighteen hours, at the end of which time the muscle reacted to direct and indirect stimulation almost as well as a control preparation kept for the same time in Ringer's solution alone. This may explain why, in spite of the fact that actual rigor of muscle may be produced by a solution so dilute as 1 in 20,000, paralysis of the voluntary muscles plays a part relatively so unimportant among the general effects of harmaline poisoning, for the muscles respond to stimulation of their nerves for some hours after abolition of reflex excitability.

E. ACTION ON THE CIRCULATION.

(a) Heart.

The description given of the symptoms occurring in the frog after subcutaneous injection of harmaline has shown that this alkaloid at an early period causes slowing of the rate of the heart, but that the heart, though apparently much enfeebled, continues to beat until after cessation of respiration and paralysis of reflex excitability. In mammals too the rate of the heart-beats is reduced very soon after the injection of harmaline. With large doses, this reduction in rate is progressive, and arrest of the heart plays a part

almost as important as arrest of the respiration in causing death. In the case of smaller lethal doses, where death is clearly due to respiratory failure, the heart rate is diminished soon after injection to a certain extent, and tends to remain at this point till the respirations fail. For example, in Experiment 18, where a rabbit received a dose which killed in three hours, the cardiac impacts were reduced from 46 to 27 per ten seconds in twenty minutes, and were still 27 per ten seconds two hours later. The heart is always arrested in diastole. In several experiments in which the heart continued to beat after arrest of the respirations, the right vagus was exposed, and stimulation of it with the coil at 70 mm. to 90 mm. was found to arrest the heart-beats.

Further experiments were made to ascertain the action of harmaline on the isolated heart, the frog's heart being used.

In a first series of experiments the heart was perfused *in situ* through the hepatic vein, the perfused fluid escaping through the cut aorta; and in a second series the

FIG. 3.

isolated ventricle alone was perfused by means of Schäfer's frog-heart plethysmograph. Only the latter series need be described, as the results were similar in both. As the nutrient solution and as the solvent for harmaline a mixture of defibrinated ox blood (one part) and Ringer's solution (two parts) was used. 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 27 (fig. 3).—Strength of solution, 1 in 2000.

A solution of 1 in 2000 within one minute arrested the contractions of the ventricle in almost complete systole (fig. 3). Two minutes later the normal solution was turned on, and the heart slowly dilated till it reached the condition of relaxation normal to the end of diastole, whereupon it again resumed beating. The contractions gradually improved till in fifteen minutes the rate and excursus were practically the same as before harmaline. A second introduction of the harmaline solution produced the same effect as before.

Experiment 28 (figs. 4 to 7 inclusive).—Strength of solution, 1 in 10,000.

This solution very soon reduced the rate of beat of the ventricle, and to a less extent

FIG. 4.

the amplitude of its excursions (figs. 4, 5, and 6). In twenty-two minutes the ventricle ceased contracting altogether, in a position of almost complete relaxation. Two minutes

FIG. 5.

FIG. 6.

later the normal solution was turned on, and in five minutes this completely reinstated the ventricle to its normal action (fig. 7). A second introduction of the harmaline

FIG. 7.

solution produced the same poisoning effects more quickly, and the ventricle again completely recovered when this was replaced by the normal solution. The normal solution was now perfused through the ventricle for over two hours. To the harmaline solution was then added atropine sulphate in the proportion of 1 in 100,000. This

combined solution brought about arrest of the ventricle in the same way as was produced previously by the same strength of harmaline without atropine.

These effects are detailed in the following table :—

TABLE VI.—EXPERIMENT 28.

Time.	Rate per Minute.	Amplitude of Excursus.	Notes.
12.33	22	25	Solution of H.H. 1 in 10,000 turned on (fig. 4).
12.36.30"	...	...	
12.40	16	24	
12.48	13	19	
12.53	8	19	Fig. 6.
12.59	0	0	
1.1	...	...	Normal solution turned on (fig. 7).
1.2	11	15	
1.3	19	14	
1.7	23	25	
1.14	27	25	Solution of H.H. 1 in 10,000 turned on.
1.15	...	...	
1.17	7	25	
1.20	2	23	
1.22	1	20	Normal solution turned on.
1.23	0	0	
1.25	...	...	
1.26	11	18	
1.31	26	25	Solution containing H.H. 1 in 10,000 and A.S. 1 in 100,000 turned on.
3.48	27	24	
3.51	...	...	
3.53	2	20	
3.54	0	0	

Experiment 29.—Strength of solution, 1 in 20,000.

This solution, in three and a half hours, reduced the rate of beat from 25 to 9 per minute, and the amplitude of excursus from 28 mm. to 21 mm. Complete recovery was then brought about in fifteen minutes by re-introduction of the normal solution. The harmaline solution, to which had been added atropine sulphate in the proportion of 1 in 50,000, was then perfused, but the addition of atropine did not prevent the slowing of the ventricle produced by harmaline.

Experiment 30.—Strength of solution, 1 in 50,000.

Perfusion of the ventricle with this solution had practically no effect on the heart in two and a half hours.

These experiments show that very strong solutions of harmaline bring about abrupt systolic arrest of the heart, an effect probably similar in nature to the rigor of voluntary muscle which strong solutions of harmaline have been shown also to effect.

The characteristic action of harmaline on the heart, however, is to slow the rate

and diminish the completeness of systolic contraction, actual arrest in almost complete diastole being produced by a solution of 1 in 10,000.

The slowing of the heart is uninfluenced by simultaneous perfusion with atropine, and is therefore probably due to an action on the cardiac muscle, and not to stimulation of the vagal terminations.

In its action on the frog's heart, harmaline resembles quinine, which produces, in much the same concentrations, slowing of the heart (which is not prevented by atropine) and arrest in diastole.

(b) *Blood-vessels.*

To ascertain any changes produced by harmaline in the blood-vessels of the frog, the following method was used. After exposure of the heart of a pithed frog, the venæ

FIG. 8.

cavæ were cut across and a fine cannula was tied into the left aorta, the right aorta being ligatured. This cannula was connected with a series of Mariotte's flasks which contained the fluids to be perfused. The amount of fluid exuding per minute from the cut venæ cavæ was accurately measured. Ringer's solution was used as the normal solution and as the solvent for harmaline.

The results of these perfusion experiments may be shortly stated as follows:—

A solution of 1 in 1000 reduced the flow from 2.6 c.c. per minute to 0.6 c.c. per minute in thirty minutes; a solution of 1 in 5000 (see fig. 8) reduced the flow from 3.2 c.c. per minute to 0.9 c.c. per minute in thirty minutes; a solution of 1 in 10,000 reduced the flow from 2.5 c.c. per minute to 1.7 c.c. per minute in forty minutes; a solution of 1 in 20,000 reduced the flow from 2.1 c.c. per minute to 1.5 c.c. per minute in sixty minutes; while solutions of 1 in 25,000 and 1 in 40,000 had no effect on the vessels in forty minutes.

As there occurred in the frogs during these perfusions practically no œdema, it is

apparent that harmaline causes constriction of the arterioles : a marked constriction in the case of solutions not less dilute than 1 in 5000, and a still perceptible constriction with a solution of 1 in 20,000. I have recently shown * that quinine exerts a similar action on the blood-vessels of the frog.

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

In all blood-pressure experiments the animals (rabbits or cats) were first anaesthetised 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

FIG. 9.

stethograph attached by a band round the thorax and connected with a Marey's tambour. Injections were made into the right jugular vein.

Experiment 31 (fig. 9).—Rabbit, 2200 grammes.

At 12.35, 0.044 gramme of harmaline hydrochloride dissolved in 2 c.c. Ringer's solution was injected. This was equal to 0.02 gramme per kilogramme.

This experiment illustrates the effect of a rapidly lethal dose. Blood pressure, after a slight transient rise, rapidly falls. The respirations and heart-beats quickly decrease in rate. The pulsations in the carotid diminish in size in spite of the slowing of the heart. Death is due both to cardiac and respiratory failure.

Experiment 32 (Table VII., figs. 10 to 14 inclusive).—Rabbit, 2000 grammes.

Successive actual doses of 0.002 gm., 0.004 gm., 0.008 gm., and 0.016 gm., each dose being dissolved in 2 c.c. of Ringer's solution. This experiment shows the effects of increasing sub-lethal doses on the blood pressure and the respirations of the rabbit.

* *Archives internat. de Pharmacodynamie*, 1909, p. 319.

Doses of 0.001 grm. per kilo and 0.002 grm. per kilo (fig. 10) caused a rise of blood pressure. Doses of 0.004 grm. per kilo and 0.008 grm. per kilo (figs. 11 to 14) caused a preliminary fall, followed by a rise, with later again a fall of blood pressure.

The rise of blood pressure is in the case of all doses accompanied by slowing of the heart. The increase of blood pressure must therefore be due either to increased

TABLE VII.—EXPERIMENT 32.

Time.	Dose of Harmaline.	Average B.P. in mm.	Pulse Rate.	Rate of Respirations.	Respiration Excursus.	Notes.
1.0	...	104	40	12	3 mm.	Fig. 10.
1.0.50"	...	102	41	13	3 "	
1.1	0.001 grm. per kilo	...	...	...	...	
1.1.20"	...	106	35	11	3 mm.	
1.2	...	105	29	11	3 "	
1.3	...	102	29	10	3 "	
1.9	...	107	31	11	3 "	
1.11	...	106	32	10	2 "	
1.12	0.002 grm. per kilo	...	...	...	...	
1.13	...	110	27	9	2 mm.	
1.14	...	110	24	9	2 "	Fig. 11.
1.16	...	110	26	9	2 "	
1.21	...	114	26	8	2½ "	
1.25	...	114	30	8	2½ "	
1.29	...	112	28	7	2½ "	
1.30	0.004 grm. per kilo	...	...	...	...	
1.30.30"	...	108	26	7	2 mm.	
1.31	...	116	24	7	2 "	
1.33	...	112	24	6	2½ "	
1.35	...	106	26	7	2 "	
1.39	...	105	26	7	2 "	Fig. 12.
1.42	...	105	26	7	2 "	
1.44	...	106	25	7	2 "	
1.45	0.008 grm. per kilo	...	...	...	...	
1.45.30"	...	76	20	4	1 mm.	
1.46	...	76	18	6	1 "	
1.48	...	92	19	7	½ "	
1.50.30"	...	120	20	5	1 "	
1.52	...	114	20	5	1 "	
1.56	...	100	21	7	1½ "	Anæsthesia incomplete. Fig. 13. Fig. 14. Experiment discontinued.
1.59	...	101	20	6	2 "	
2.6	...	108	21	7	3 "	
2.8.10"	...	109	20	7	25 " ?	
2.9.40"	...	119	20	7	7 " ?	
2.22	...	102	18	6	2 "	

cardiac output per single beat or to contraction of the blood-vessels. Perfusions of the frog's heart give no indication of augmented action of the heart, whereas a solution of harmaline so dilute as 1 in 20,000 constricts the frog's blood-vessels. It is probable, therefore, that the rise of blood pressure is due to contraction of the blood-vessels. The fact that this rise of pressure tends to be gradual and persistent points to the contraction of the blood-vessels being due rather to an action on the arterioles them-

selves, as seen in the case of the frog, than to a stimulation of the vasomotor centre.

In this experiment a total amount of 0.015 grm. per kilo was injected in divided

FIG. 10.

doses—an amount which would immediately have been fatal if administered by a single injection. About forty minutes after the last injection, however, the blood pressure was still at the level normal to the animal, though the pulse rate had

FIG. 11.

diminished so greatly as from 42 to 18 per ten seconds. It would appear, therefore, that in the rabbit very large doses of harmaline may bring about a constriction of the arterioles so physiologically balanced that it may exactly maintain the level of blood pressure in spite of a profound fall of the pulse rate.

An important point, illustrated by this experiment and confirmed by all of a large number of blood-pressure experiments in rabbits and cats, is the complete absence of

FIG. 12.

convulsions in a properly anæsthetised animal. This was the only one of these experiments in which convulsions were ever observed; they lasted for about one

FIG. 13.

FIG. 14.

minute (see fig. 13), and were due to insufficient depth of anæsthesia. TAPPEINER, in his two experiments on blood pressure, observed convulsions during practically the whole time of these experiments. Unfortunately he does not state what anæsthetic, if any, he used. This occurrence of convulsions vitiated the value of his experiments

as a study of the uncomplicated action of harmaline on the blood pressure and respiration.

Experiment 33.—(Table VIII., fig. 15).—Cat, 3000 grammes. This experiment illustrates certain differences between the blood-pressure effects in the cat and those in the rabbit; it also shows the terminal phenomena in a case where respiratory failure definitely precedes arrest of the heart (contrast fig. 9).

At first, three injections were given, each of 0·001 gm. per kilo. The first and third injections caused a slight rise of blood pressure, the second a fall. The effects of small

TABLE VIII.—EXPERIMENT 33.

Time.	Dose of Harmaline.	Average B.P. in mm.	Pulse Rate.	Rate of Respirations.	Respiration Excursus.	Notes.
5.3	...	164	27	9	5 mm.	Fig. 15.
5.3.40"	0·001 gm. per kilo					
5.4	...	175	24	9	5 mm.	
5.5	...	166	24	7	4 "	
5.6	...	166	25	8	4 "	
5.7.30"	...	170	24	8	4 "	
5.8	0·001 gm. per kilo					
5.8.10"	...	154	22	8	4 mm.	
5.10	...	158	24	8		
5.10.50"	0·001 gm. per kilo				4 mm.	
5.11	...	162	25	9	4 "	
5.12	...	158	22	8	4½ "	
5.21	...	150	24	8	4 "	
5.21.30"	0·004 gm. per kilo					
5.21.50"	...	138	20	7	4 mm.	
5.23	...	146	20	6	4 "	
5.29	...	140	24	6	4 "	
5.37	...	116	30	7	4 "	
5.40	...	122	27	6	4 "	
5.40.30"	0·01 gm. per kilo	...	...	...	...	
5.50.30"	...	96	20	9	2 mm.	
5.51	...	64	19	4	2 "	
5.52	...	50	18	1	1 "	
5.53	...	36	16	0	0 "	
5.57	...	0	0	0	0 "	

doses are therefore inconstant, and it was found in other experiments that, in the cat in contrast to the rabbit, small doses of harmaline produce either a very slight rise, or sometimes no rise, of blood pressure.

When this experiment is compared with Experiment 32, it is also seen that in the cat, after a total dose of 0·007 gm. per kilo, there is a considerable and permanent fall of blood pressure, whereas in the rabbit after the same dose blood pressure, after a temporary fall, recovers to the normal level. These differences are probably due to the fact that changes in blood pressure which are due to an action on the arterioles are more marked in the rabbit than in the cat, owing to the much greater length of the intestinal

canal in the former animal.* In the cat the constriction of the arterioles is insufficient to counterbalance the slowing of the heart, and the blood pressure falls.

FIG. 15.

With these experiments as examples of the effects of small and large doses, an account may now be given of further experiments made to define more accurately the nature of the production of these effects.

The Cause of the Slowing of the Heart.

Experiment 34.—In this experiment, doses were given corresponding to those given in Experiment 32, with this difference, that sufficient quantities of atropine sulphate were administered during the experiment to ensure that, before each injection of harmaline, the terminations of the vagus nerves in the heart were paralysed. The conditions of the experiment are indicated in Table IX.

In this experiment the first injection of 0.001 gm. per kilo reduced the pulse rate from 36 to 31 per ten seconds as compared with a reduction of from 41 to 29 per ten seconds by the same dose in Experiment 32, where no atropine was given. It seems probable that, in case of the first injection of a small dose of harmaline, part of the slowing of the heart is due to reflex stimulation of the vagus by the rise of blood pressure.

On the other hand, doses of 0.002 gm. and 0.004 gm. per kilo produce an amount of slowing of the heart (when the terminations of the vagus are paralysed by atropine) quite commensurate with that produced by the same doses in Experiment 32, where the

* LAUDER BRUNTON, *Textbook of Pharmacology and Therapeutics*, 1887, p. 288.

vagal mechanism was intact. The last dose (0.008 grm. per kilo) proved fatal in this experiment probably because respiratory failure was caused by the added effects of harmaline and atropine on the respiratory centre. However, a sufficient comparison can

TABLE IX.—EXPERIMENT 34.

Time.	Injection.	Average B.P.	Pulse Rate.	Result of Stimulation of Left Vagus.
1.15	...	100	40	
1.16	...	...	...	130 mm.—arrest of heart.
...	...	...	...	140 „ slowing of heart.
...	...	...	...	150 „ nil.
1.18	A.S. 0.001 grm. per kilo	...	...	
1.20	...	...	...	140 mm.—nil.
...	...	...	...	120 „ „
1.39	...	...	...	140 „ arrest of heart.
1.40	A.S. 0.002 grm. per kilo	...	...	
1.40.30"	...	...	...	140 mm.—nil.
...	...	...	...	100 „ „
1.42	...	94	36	
1.43	H.H. 0.001 grm. per kilo	...	...	
1.43.30"	...	102	33	
1.44.20"	...	...	...	120 mm.—nil.
1.46	...	102	31	
2.15	...	...	...	120 mm.—slowing of heart.
2.25	...	...	...	120 „ „ „
2.26	A.S. 0.002 grm. per kilo	...	...	
2.29	...	...	...	120 mm.—nil.
2.29.30"	...	79	28	
2.30.10"	H.H. 0.002 grm. per kilo	...	...	
2.31	...	82	24	
2.33	...	90	23	
2.36	...	92	22	
2.37	...	...	...	120 mm.—nil.
2.38	H.H. 0.004 grm. per kilo	...	...	
2.38.30"	...	84	19	
2.39	...	88	20	
2.42	...	96	19	
2.45	...	...	...	120 mm.—slowing of heart.
2.52	A.S. 0.001 grm. per kilo	...	...	
2.55	...	88	22	
2.55.40"	...	...	...	120 mm.—nil.
2.56	H.H. 0.008 grm. per kilo	...	...	
2.56.40"	...	52	18	
2.58	...	30	13	
3.0	...	22	12	
3.3	...	0	0	

be made to allow the conclusion that, except in the case of the first injection, the slowing of the heart is not due to central or peripheral stimulation of the vagus, but to an action on the cardiac muscle. This result corresponds with that obtained in perfusion experiments on the frog's heart where the slowing of the heart produced by harmaline was not prevented by simultaneous perfusion with atropine.

The Cause of the Fall of Blood Pressure.

It has been already stated that the rise in blood pressure produced by smaller doses of harmaline is to be attributed to contraction of the arterioles; it remained to be determined whether the fall of blood pressure, when it occurs, is due to cardiac causes or to dilatation of the arterioles.

Experiment 35 (fig. 16).—Rabbit, 1900 grammes. In this experiment a record was taken of the blood pressure and of the changes in intestinal volume. About four inches of the rabbit's small intestine was enclosed in an oncometer, and the changes in its volume were recorded by an air-piston recorder. A dose of 0.008 gm. per kilo was injected, and in thirty seconds this lowered the blood pressure from 100 mm. to 78 mm., and the pulse rate from 19 to 16, per ten seconds. No increase of intestinal

FIG. 16.

volume occurred during this fall of pressure, which must therefore be ascribed to slowing or to slowing and weakening of the heart.

Experiment 36.—Cat, 3300 grammes. A record was taken of the blood pressure and volume of the left kidney. A dose of 0.005 gm. per kilo was given, and this reduced the blood pressure in one minute from 109 mm. to 78 mm., and the pulse rate from 21 to 15 per ten seconds. During this fall of blood pressure there occurred a distinct diminution of kidney volume, showing that there was certainly no dilatation of the kidney vessels. In the cat, therefore, as in the rabbit, it is probable that the fall of blood pressure produced by large doses of harmaline is due to slowing or to slowing and weakening of the heart's action.

The effects produced by harmaline on the blood pressure differ in some respects from those produced by quinine. With quinine "the heart is often accelerated at first, but is afterwards slow and weak, while the blood pressure, after a slight increase, declines progressively. The changes are caused by a preliminary contraction of the arterioles

and acceleration of the heart, followed by dilatation of the former and slowing and weakening of the latter."* Harmaline differs from quinine in its blood-pressure effects in that the preliminary rise of blood pressure is due only to contraction of the arterioles and not to acceleration of the heart, while the fall of blood pressure produced by large doses of harmaline is due, so far as my experiments have shown, only to cardiac slowing and weakening, and not to dilatation of the arterioles.

F. ACTION ON RESPIRATION.

Lethal doses of harmaline paralyse respiration both in frogs and in mammals. Since at the time of death in mammals faradic stimulation of the phrenic nerve causes tetanus of the diaphragm with a normally minimum stimulus (see Experiment 25), it is probable that respiratory failure is due to paralysis of the respiratory centre.

Especially during the time that convulsions occur, the rate and vigour of the respirations are often increased. In none of my blood-pressure experiments (when convulsions were prevented by anaesthesia) was an increase in the rate or amplitude of the respirations observed, such as was found by TAPPEINER.

In the case of slowly fatal doses, death is due to arrest of the respiration alone, and the heart may continue beating as long as ten minutes after respiration has ceased. With larger doses, however, the heart-beats and respirations fail about the same time; indeed, one or two respiratory gasps may occur after it is impossible to feel any cardiac impacts.

TAPPEINER stated that arrest of the respiration comes on somewhat suddenly, not being intimated by any previous considerable reduction in frequency. This is only partly true in the case of rapidly fatal doses, where the toxic effect on the heart attains greater prominence. In the case of smaller lethal doses, where heart failure does not so materially contribute to the cause of death, there is a gradual and progressive diminution in the rate of the respirations.

G. ACTION ON TEMPERATURE.

TAPPEINER stated that "the body temperature is rather heightened than lowered. In one case in a rabbit it was 40.4° C. and in a dog 39.7° C. in the rectum." It is unfortunate that he does not state with what doses or at what times after injection this elevation of temperature occurred, and also what was the temperature before injection. In the rabbit the normal temperature may be above 40.4° C.†

In my experiments I have not observed with any dose a definite rise of temperature, while large doses invariably produce a fall of temperature, in regard to which action harmaline resembles quinine.

* CUSHNY, *Textbook of Pharmacology*, 3rd edit., p. 360.

† SIMPSON and GALBRAITH, *Journal of Physiology*, 1905, p. 230.

In the case of sub-lethal doses the fall of temperature is comparatively slight, *e.g.* the temperature of a rabbit which received four-fifths of the minimum lethal dose fell from 39° C. to 37° C. in 1½ hours. The fall is greater in the case of lethal doses; *e.g.*, the temperature of a rabbit which received 1½ minimum lethal dose fell from 38° C. to 34° C. in one hour. However, the extent of the fall of temperature is not proportional to the dose in the case of lethal doses. The fall is progressive, and is the greater the longer the animal lives after injection. Thus, as was seen in the account of Experiment 12, the temperature of a guinea-pig which received a minimum lethal dose

FIG. 17.

was as low as 21° C. before death, which occurred 7 $\frac{2}{3}$ hours after injection. SIMPSON and HERRING* have shown that with such a low temperature a warm-blooded animal is narcotised by cold, and that when the temperature falls below 24° C. the animal cannot recover unless artificially warmed. Therefore in this case the profound fall of temperature is probably a contributory cause of death.

H. ACTION ON THE UTERUS.

In view of the employment of harmaline in India to procure abortion, it was interesting to ascertain whether experimental evidence could be found of an action on the uterine muscle. In some experiments made for this purpose the following method was used.

* *Journal of Physiology*, 1905, p. 305.

The animals (rabbits) were anaesthetised as for blood-pressure experiments, and kept during the experiment in a bath of saline solution at 39° C., just 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 37 (fig. 17).—Rabbit, 2100 grammes, non-pregnant. From 2.30 p.m. there were slight spontaneous contractions of the uterus, just sufficient to move the lever perceptibly. At 3.5 a dose of 0.001 gramme per kilogramme was given by the jugular vein (see fig. 17). This brought on almost immediately a very powerful tetanic contraction of the uterus lasting for about seven minutes, after which uterine contractions again remained in abeyance. At 3.25 a second injection was given of 0.0005 gramme per kilogramme, which produced a similar tetanic contraction lasting for four minutes.

This experiment shows that harmaline, in doses which previous experiments have shown to be the smallest to affect blood pressure, exerts a powerful action on the uterus in the direction of inducing vigorous and sustained tetanic contraction. This fact sufficiently explains the clinical observation that harmaline may cause abortion. It is an effect which is also, but less powerfully, produced by quinine.

GENERAL SUMMARY.

The minimum lethal dose of harmaline hydrochloride by subcutaneous injection is for frogs 0.25 gramme per kilogramme, and for mammals (guinea-pig, rabbit, rat, and cat) about 0.1 gramme per kilogramme.

In frogs, lethal doses of harmaline paralyse the mid-brain and medulla oblongata, and, at a much later period, the spinal cord. Abolition of reflex excitability occurs before arrest of the heart, and before paralysis of the voluntary muscles.

In mammals, large doses of harmaline cause epileptiform convulsions varying somewhat in character in different animals. The convulsions are due to an action on the cerebrum, probably especially affecting the cortex. Lethal doses paralyse the spinal cord also in mammals, and, as in the case of frogs, this occurs at a later stage than the action on the brain.

The conductivity of nerve is impaired only by prolonged direct application of strong solutions of harmaline, and the motor nerve-ends are slightly, if at all, affected by this alkaloid. On the other hand, harmaline in comparatively weak solutions causes rigor and excitability of voluntary muscle.

When perfused through the frog's heart, strong solutions of harmaline cause almost immediate systolic arrest of the heart; weaker solutions cause slowing of the heart and diminution of systolic contraction, and arrest of the heart, when it occurs, is in the diastolic position. The latter kind of action is the only one which is observed in frogs or mammals after subcutaneous administration of harmaline.

In the frog, after destruction of the central nervous system, harmaline constricts the blood-vessels when perfused through them.

In mammals, small doses of harmaline cause a rise of blood pressure—always in the rabbit, and sometimes in the cat. The rise is due to contraction of the arterioles, and is accompanied by a diminution in the rate of the heart. Large doses produce a fall of blood pressure due to slowing and weakening of the heart.

The slowing of the heart produced by an initial small dose is partly due to reflex stimulation of the vagus by the rise of blood pressure; that produced by larger doses is independent of vagus stimulation, and due to an action on cardiac muscle.

In frogs, paralysis of respiration is an early effect of lethal doses; and in mammals, arrest of respiration, due to paralysis of the respiratory centre, is the chief cause of death from harmaline poisoning. In the latter there is frequently an initial stage of increased respiratory activity.

Large doses of harmaline cause a fall of temperature in mammals; the fall is slight with non-lethal doses, but may be profound in the case of a slowly lethal dose.

Harmaline exerts a powerful action on uterine muscle in the direction of inducing sustained tetanic contraction.

Harmaline can therefore no longer be regarded merely as a respiratory and convulsant poison. It differs from most alkaloids in that it does not exert, to the same extent as they do, a selective action on one kind of tissue. It attacks not only highly specialised tissues such as voluntary muscle, muscle of the heart, blood-vessels, and uterus, and cells of the central nervous system, but also less highly differentiated cells, such as pigment cells, protozoa (RAAB), and ciliated epithelium (JACOBSON).

In this account of its pharmacology the actions of harmaline have been shown to resemble very closely those of another alkaloid, of which the above type non-selective action is also true, viz. quinine. As a pharmacological agent, harmaline ought to be grouped with quinine, and therefore with those substances which are conveniently, if somewhat indefinitely, termed "protoplasmic poisons."

Considering the close resemblance in the pharmacological actions of harmaline and quinine, one is led to anticipate some corresponding similarity in their therapeutic effects. With this subject I hope to deal on a future occasion.