The physiological action of cytisine, the active alkaloid of laburnum (cytisus-laburnum) / by H.H. Dale and P.P. Laidlaw.

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THE PHYSIOLOGICAL ACTION OF CYTISINE, THE ACTIVE ALKALOID OF LABURNUM (CYTISUS-LABURNUM)

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I. HISTORICAL AND INTRODUCTORY

Cytisine is an alkaloid, present in a number of plants, which was first isolated from the seeds and other parts of the common Laburnum tree (Cytisus laburnum): its presence in the latter has led to numerous cases of accidental poisoning.[1]

Most of the cases occur in children, who eat the seeds in play. Radziwillowicz[1] in 1888 collected accounts of 131 cases, including five fatal ones. The most recent detailed account of the symptoms which we have seen was given by Vallette,[1] who in 1908 attended three women who had eaten a dish in which laburnum flowers had been used as a flavoring agent, in mistake for those of Robinia pseudacacia. The most constant symptom appears to be vomiting, succeeded by prostration and torpor, which may or may not be preceded by a stage of excitement. Other symptoms described are delirium, hallucinations, mydriasis, muscular twitchings, convulsions, salivation, diarrhoea, vertigo, pallor and cold sweats. In Vallette's patients the first symptom was a feeling of numbness in the hands. Death, when it occurs, is due to respiratory paralysis.

[1] Cf. Radziwillowicz: Arb. d. pharm. Inst. z., Dorpat II, p. 56, 1888. Vallette: Rev. med. de la Suisse Romande,—1908, p. 366. Also various authors in The Lancet, 1877, ii, pp. 341 and 414; 1901, ii, p. 491; 1905, ii, p. 635; and the Brit. Med. Journ., 1870, i. p, 79; 1882, i, p. 199, 1883, i, p. 1117.

The alkaloid was first prepared and named by Gray,[2] isolated pure by Husemann and Marmé,[3] and further studied by others, including Partheil,[4] who assigned to it the accepted formula $C_{11}H_{14}N_2O$, and more recently, Freund and his pupils.[5]

Its action on animals has been described by Gray, Husemann and Marmé,[6] Cornevin,[7] Prevost and Binet,[8] and Radziwillowicz.[1] Bradford[9] also described the action of "ulexine," an alkaloid obtained by Gerrard from the seeds of the common gorse, and since shown to be identical with Cytisine. Most of the accounts agree as to the obvious symptoms of poisoning by Cytisine. These are described as a stimulation of medullary centres resulting in dyspnoea, salivation and vomiting, and a very large rise of blood-pressure, muscular twitchings and tremors, partly central, partly peripheral in origin, succeeded by weakness, lethargy and narcosis. With intravenous injection of a few milligrammes the stage of excitation is said to be succeeded by paralysis of the centres, death being due to paralysis of the respiratory centre, so that life can be prolonged indefinitely by the application of artificial respiration. Bradford obtained the rise of blood-pressure in the dog after section of the cervical cord. Most observers describe a curare-like action, which, according to Radziwillowicz, is produced with relative ease in the cat and dog, as compared with the frog. According to Bradford the muscular tremors are at least partly of peripheral origin, as they continue after response to motor nerves is abolished, and persist for some time in a completely severed limb. Increased diuresis is mentioned by Bradford and by Radziwillowicz. Rodents are relatively very insensitive to the poison (Prevost and Binet, Radziwillowicz). On some points there is lack of agreement between different observ-

[2] Edinburgh Med. Journ., VII, ii, pp. 908, 1025, 1862.

[3] Zeitsch. f. Chem., I, p. 161, 1865.

[4] Berichte d. deutsch. Chem. Gesell., XXIII, p. 3201, 1890.

[5] Ibid., XXXIV, p. 615, 1901; XXXVII, p. 16, 1904; XXXIX, p. 814, 1906.

[6] Loc. cit. Also Marmé: Nachr. d. kön. Gesell. z. Wissensch., z. Göttingen, 1887 (Ref. Therap. Monatsh., 1887, p. 156).

[7] Comptes Rendus, 1886, p. 777.

[8] Rev. med. de la Suisse Romande, 1887, pp. 516 and 553, and 1888, p. 670.

[9] Journ. of Physiol., VIII, p. 79, 1887.

ers. Thus Prevost and Binet noted the absence of effect on intestinal peristalsis, though a stimulant effect on this is described by Radziwillowicz. Prevost and Binet, again, describe the motor nerves in the frog as being paralysed before the vagus effect on the heart. The reverse relation was, apparently, observed by Radziwillowicz, who emphasises the fact that the curare-action is not obtained in the frog with small doses, though larger doses produce it. His description of the comparatively early paralysis of the fore-limbs in the frog, which show a cataleptic[10] condition while the hind-limbs are still capable of feeble movement, is very suggestive. The same observer found that 10 mgms. of Cytisine nitrate, given subcutaneously, caused stiff extension of the hind-limbs in a fowl; 12 mgms. killed it. He also observed powerful, peristaltic contraction of the uterus of a pregnant cat as the result of injecting 1 mgm. intravenously. Both Marmé and Radziwillowicz found that the alkaloid was excreted unchanged in the urine.

It is evident that the description given by these observers of the action of Cytisine might be transferred to that of nicotine[11] without any essential alteration. The general comparison was not made, however, though Prevost and Binet remark that, on direct application of Cytisine to the frog's heart, a momentary arrest is produced "similar to that produced by nicotine." Its pharmacological affinities were regarded as being rather with curare and, for no very clear reason, strychnine; Radziwillowicz concluding that its action is intermediate between those of strychnine and curare, but nearer that of the former.

Our own experiments confirm the impression made by perusal of the accounts of previous workers that the action of Cytisine is closely similar to that of nicotine. It may be recalled that a

[10] The statement is that the fore-limbs "wie gelähmt verharren bei jeder Lageveränderung in derselben Stellung." The meaning is not clear, but we imagine that a description is intended of the cataleptic condition, which is very easily observed.

[11] We have not attempted to give the individual authority for the different details of the action of nicotine to which reference is made. Most of the points to which we refer will be found in the paper by Langley and Dickinson, Journ. of Physiol., XI, p. 265, 1890, in which full references to earlier literature are given.

similarly close or even closer resemblance to nicotine in action was observed by Edmunds[12] in the case of Lobeline.

II. EXPERIMENTAL

For our supply of Cytisine we are indebted to our colleague, Mr. Ewins, who extracted it from Laburnum seeds. For our experiments the alkaloid was dissolved in water, in which it is readily soluble, the strongly alkaline solution being then exactly neutralised with HCl and diluted to contain 1 per cent of the base. Further dilutions were made with physiological saline from this stock solution. Our observations on the general toxic effects of Cytisine correspond in the main with those of previous observers. Points of difference can be noted in dealing with the separate systems.

Skeletal muscles. Cytisine, like nicotine, causes muscular tremors in mammals when injected intravenously. These are doubtless partly central in origin, being depressed by chloroform or other anaesthetic and by pithing the cord. The characteristic twitching of the cat's ears, which is one of the first visible effects of an intravenous injection of nicotine, lobeline or hordenine-methiodide in that animal, is not produced by Cytisine. After doses varying from 6 to 10 mgms. in different experiments we found stimulation of the sciatic nerve in the anaesthetised cat quite ineffective: the muscles still responded well to direct faradisation. In curare-like action on the cat, therefore, Cytisine is about as powerful as nicotine. The rabbit, as noted by previous observers, is relatively resistant. Five milligrammes intravenously, in a rabbit of $2\frac{1}{2}$ kilos, produced a mere trace of muscular twitching. Ten milligrammes subsequently caused violent general twitching, passing into fatal convulsions. The jaw muscles continued to twitch long after the death of the animal.

We have noted that a stiff extension of the legs, recalling that produced by nicotine, was observed by Radziwillowicz in the fowl as the effect of injecting Cytisine. In a fowl anaesthetised with ether, with the gastrocnemius tendon of one leg isolated and

[12] American Journ. of Physiol., xi, p. 79, 1904.

attached to a lever as described by Langley,[13] we observed a marked and persistent tonic contraction of the muscle when 2 mgms. of Cytisine were injected intravenously. Our impression is that the effect was less than that which a corresponding injection of nicotine would have produced. It is impossible, however, to be certain of this, since the effect of either alkaloid is reduced or abolished by a previous injection of the other, so that the two cannot be compared on the same animal. The effect of Cytisine on the frog is strongly reminiscent of that of nicotine. One-half milligramme injected into the dorsal lymph-sac caused slowness of movement in four minutes. In five minutes the fore-limbs were paralysed, being trailed alongside the body when the animal attempted to jump, so that the nose was thrust against the table. In six minutes a pronounced cataleptic condition of the fore-limbs was present: respiration had also ceased. Slight power of voluntary movement of the hind-limbs was retained long after this, however, and they still exhibited weak twitches thirty minutes after the injection. The frog was then pithed and dissected, when it was found that the muscles of the hind-limbs responded well to stimulation of the sciatic plexus. In another frog 2 mgms. produced a complete curare-like effect, the muscles being, however, still fully responsive to direct excitation. The action on isolated muscles of the frog was compared with that of nicotine. Pairs of sartorii were isolated from several frogs and placed in tap-water saline (0.6 per cent). They were fixed in turn in a Keith-Lucas[14] muscle-trough filled with saline, and records taken of the contraction produced when the saline was replaced by 0.1 per cent solution of nicotine or Cytisine made up with saline. In each case the action of nicotine on one sartorius was compared with that of Cytisine on the other muscle from the same frog. One-tenth per cent Cytisine always produced a well-marked tonic contraction, but this was in every instance slower in onset, lower in maximum and more evanescent than the effect of nicotine on the corresponding muscle. Nicotine, added subsequently to

[13] Journ. of Physiol., XXXIII, p. 380, 1905.

[14] Journ. of Physiol., XL, p. lxiv (Proc. Phys. Soc.), 1910.

subsidence of the Cytisine contraction, or Cytisine after nicotine, produced no effect. Similar results were obtained with the gastrocnemius and the flexor longus digitorum.

The excitatory action of Cytisine on skeletal muscle is, on the whole, therefore, similar to but weaker than that of nicotine: in curare-like action the two appear to be nearly identical.

Respiration. Previous observers have described a stimulant followed by a paralytic action on the respiratory centre. This is easily observed in the anaesthetised cat, in which animal the intravenous injection of 1 to 2 mgms. causes violent respiratory movements followed by cessation of respiration. If artificial respiration be applied the normal respiration begins again in a few minutes. In a rabbit, on the other hand, in which we made the injection by the ear-vein without anaesthesia, we observed no primary stimulation of the respiratory centre. Immediately after the injection the respiration ceased: with the smaller doses (up to 5 mgms.) it was soon gradually resumed; after an additional dose of 10 mgms. it was permanently abolished, the convulsions ensuing being possibly due in part to asphyxial stimulation of the cord.

Heart and circulation. The rise of blood-pressure recorded by all previous observers,[15] has by them been generally attributed to stimulation of the medullary vaso-motor centre. Bradford pointed out that a rise of blood-pressure was still produced by ulexine after section of the cervical cord. We find that after extirpation of the whole cord of a cat by pithing, the pressor effect is obtained practically unimpaired. The first effect on the circulatory mechanism of injecting 0.25 to 1 mgm. of Cytisine intravenously, even with the vagi cut, is inhibition of the heart: this may pass off rapidly as the blood-pressure begins to rise, or, especially with larger doses, may persist for a large part of the ascending limb of the pressure-curve. Sooner or later it gives way to pronounced acceleration. The combined cardio-acceleration and vaso-constriction produced by 0.25 mgm. drive the

[15] The effect was denied by Prevost and Binet in their first and main paper, but they subsequently observed it.

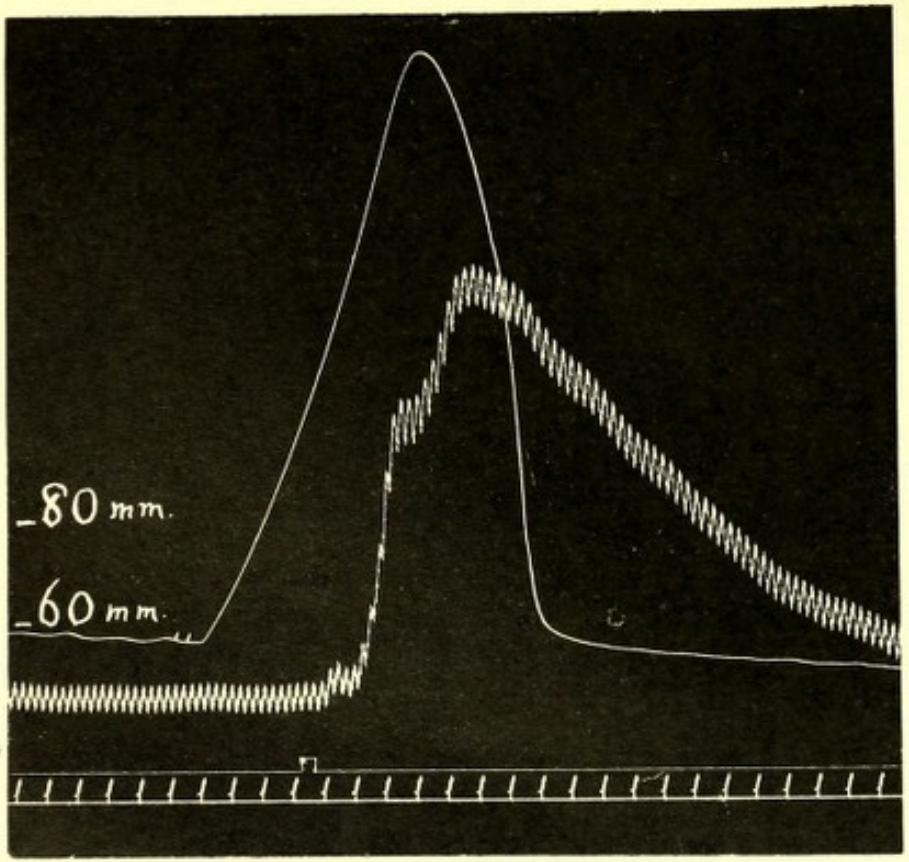

FIG. 1. Cat: brain and cord pithed. Bladder volume-record and carotid blood pressure. Effect of 0.25 mgm. nicotine intravenously. (0.25 mgm. nicotine and 0.25 mgm. Cytisine injected previously.)

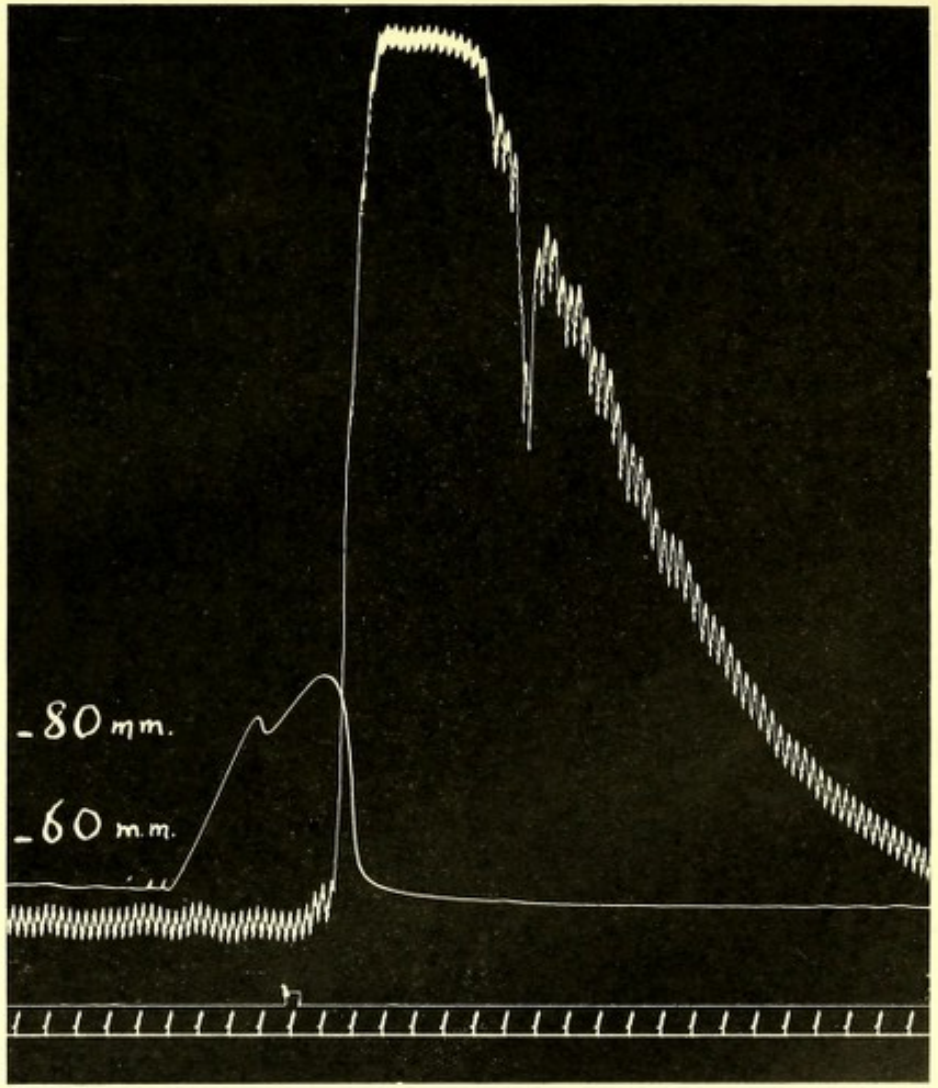

FIG. 2. Continuation of experiment shown in fig. 1. Effect of 0.25 mgm. Cytisine intravenously. Note that the effect on the blood pressure is much greater, that on the bladder much less than in fig. 1.

pressure up to the maximum possible to the cat under the conditions of the experiment. The effect is evanescent, and reproduced in diminishing degrees by successive doses. After 20 to 30 mgms. in all have been given further injections produce no effect on the blood-pressure.

After sufficient nicotine to render a cat irresponsive to further nicotine injection, Cytisine is without effect on the blood-pressure; an animal similarly paralysed by Cytisine is unaffected by nicotine. Each, therefore, in sufficient quantity paralyses the structures which the other stimulates. After a sufficient dose of ergotoxine (about 4 mgms. is usually needed in a cat) Cytisine produces a fall in place of a rise of blood-pressure.

For the comparison of the pressor activities of the two alkaloids small doses must be employed. In a cat with completely pithed central nervous system 0.25 mgm. of Cytisine is found always to produce a more rapid and greater rise of pressure than that produced by the same dose of nicotine, in whichever order they are given. As a first injection of this quantity of Cytisine frequently produces a supra-maximal effect, the difference becomes more marked with later injections, the effect of nicotine thus appearing to be more rapidly paralysed (see figs. 1 and 2). The effect of a given submaximal dose of Cytisine can, however, still be surpassed in height by that of a sufficiently large dose of nicotine, and as soon as sufficient nicotine, or Cytisine, has been given to annul the effect of further injections of nicotine on the blood-pressure altogether, no amount of Cytisine will produce any further rise. In primary stimulant action, then, on peripheral sympathetic neurones concerned with cardio-acceleration and vaso-constriction, Cytisine is considerably more active than nicotine: in secondary paralytic action on the same structures the two are apparently about equal. We hope to study the relation between the two actions in greater detail: there are certain points arising in the comparison of which the meaning is not yet clear. The initial stimulation of the vagus inhibitor mechanism is succeeded, when larger doses (e.g., 10 mgms.) are given, by paralysis of the effect of excitation of the vagus trunk. In this respect again, the action is like that of nicotine;

the likeness is rendered more striking by the production after 2 mgms. of Cytisine, and especially in a cat under paraldehyde, of the phenomenon of reversed vagus action on the heart (fig. 3) which we described in a recent paper,[16] and which was likewise produced by about 2 mgms. of nicotine.

Application of a few drops of 1 per cent Cytisine to the frog's heart causes transitory inhibition followed by return to the normal or slightly accelerated rate. Stimulation of the vagus then produces only acceleration or augmentation of the heart-beat.

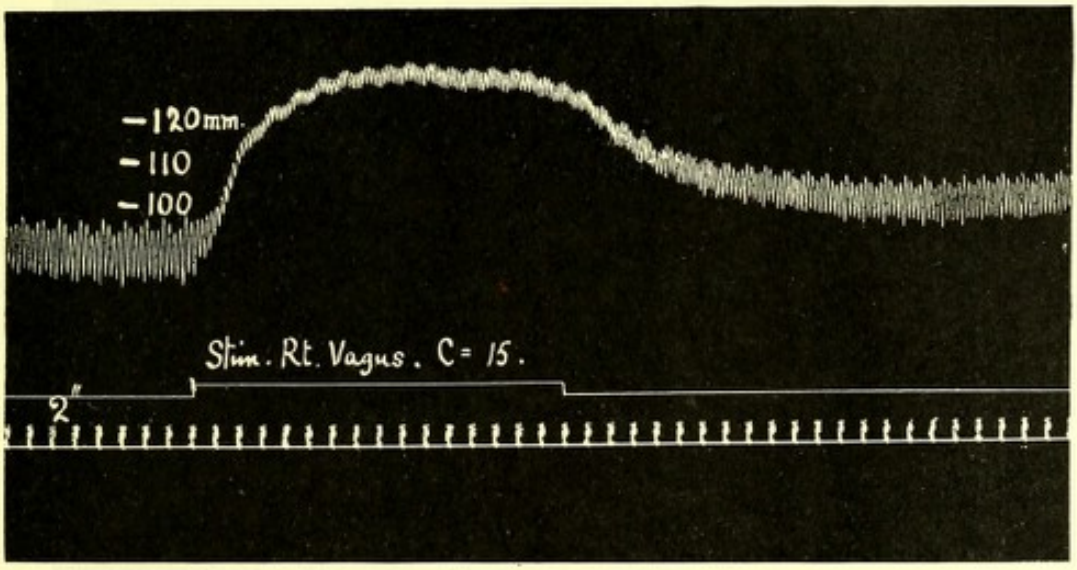

FIG. 3. Cat: Paraldehyde. Carotid blood-pressure. Reversed effect of the vagus on the rate of the heart-beat after 2 mgms. Cytisine.

Alimentary canal. Vomiting is one of the earliest and most characteristic symptoms of the action of Cytisine on the dog or cat. It is incompletely suppressed by anaesthesia, vomiting efforts of some vigour being produced in a cat under ether by the injection of 2 mgms. intravenously. Sometimes they are effective to the extent of producing regurgitation of part of the more fluid contents of the stomach.

The small intestine of the cat exhibits inhibition during the rise of pressure produced by Cytisine, followed by some exagger-

[16] Journ. of Physiol., XLI, p. 1, 1910.

ation of the normal pendulum movement as the pressure returns to the normal (fig. 4). The effect, like that on the blood-pressure, becomes progressively weaker with repeated injections. The whole effect is qualitatively indistinguishable from that produced by nicotine under the same conditions: a quantitative comparison

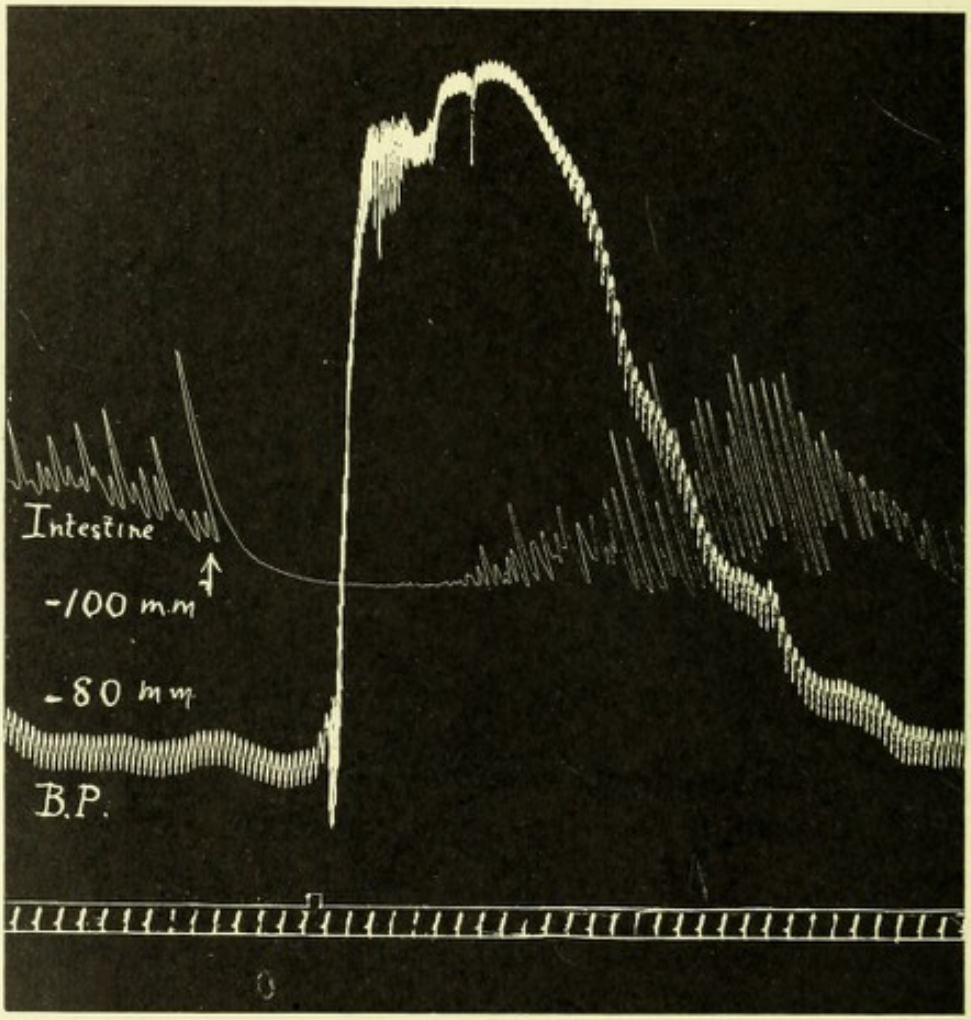

FIG. 4. Cat: Brain pithed. Balloon record from jejunum: carotid blood-pressure. Effect of 2 mgms. Cytisine intravenously. (Note the initial inhibitor effect on the rate of the heart-beat.)

was not made in this instance. In the rabbit, the effect of Cytisine on the bowel, again like that of nicotine, is predominantly motor. Intravenous injection of 2 mgm. into the jugular vein of a small rabbit, with pithed brain, caused a pronounced writhing

peristalsis of the whole of the small and large intestines, including the caecum.

By recording the longitudinal contractions of an isolated loop of rabbit's jejunum we observed, however, a distinct quantitative difference in the action of the two alkaloids. Two milligrammes of Cytisine added to the bath of 250 cc. Ringer's solution, caused momentary inhibition of pendulum movement, followed by increase of tonus and rhythm, which after about 30 seconds was succeeded by weak inhibition of both (fig. 5). On changing the Ringer's solution, the tonus and rhythm were slowly recovered. Two milligrammes of nicotine were then added, and caused, after a slight transient inhibition, a very much larger and more persistent tonic-contraction, also succeeded by an inhibitor phase (fig. 6). After recovery from this, in clean Ringer's solution, a further dose of 5 mgms. of Cytisine caused but weak motor and inhibitor effects, much weaker than those produced by a subsequent 2 mgms. of nicotine. Cystine, therefore, is much weaker than nicotine in motor action on the rabbit's intestine.

We shall see that the same is true of the motor effects of the two alkaloids on the cat's bladder.

Salivary glands. Salivation has been mentioned by several observers as a prominent symptom of poisoning by Cytisine in the cat and dog. The fact that vomiting is also one of its most constant effects suggests the probability that the salivation may be largely reflex, or at any rate central in origin. It is not, however, wholly so, since Cytisine again resembles nicotine in producing some flow of saliva in the anaesthetised dog or cat after section of the chorda tympani. Unless the first dose is very small, subsequent injections produce little or no flow.

The effect of the first small dose of nicotine or Cytisine depresses to such an extent the effect of subsequent similarly small doses of either alkaloid on the salivary flow, that we found it impossible to establish a comparison between their activities in this direction.

We found the effects of chorda stimulation in the dog only slightly reduced after intravenous injections amounting to 3 mgms. After 18 mgms. in all the immediate effect of stimulation was very

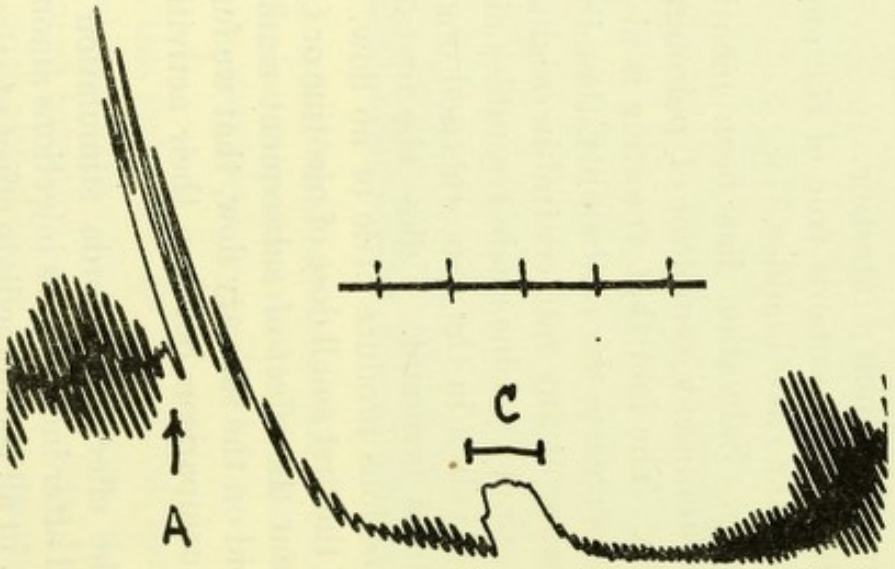

FIG. 5. Isolated loop of rabbit's small intestine, suspended in 250 cc warm oxygenated Ringer's solution, recording longitudinal contractions. At *A* added 2 mgms. Cytisine to the bath. At *C* fresh Ringer.

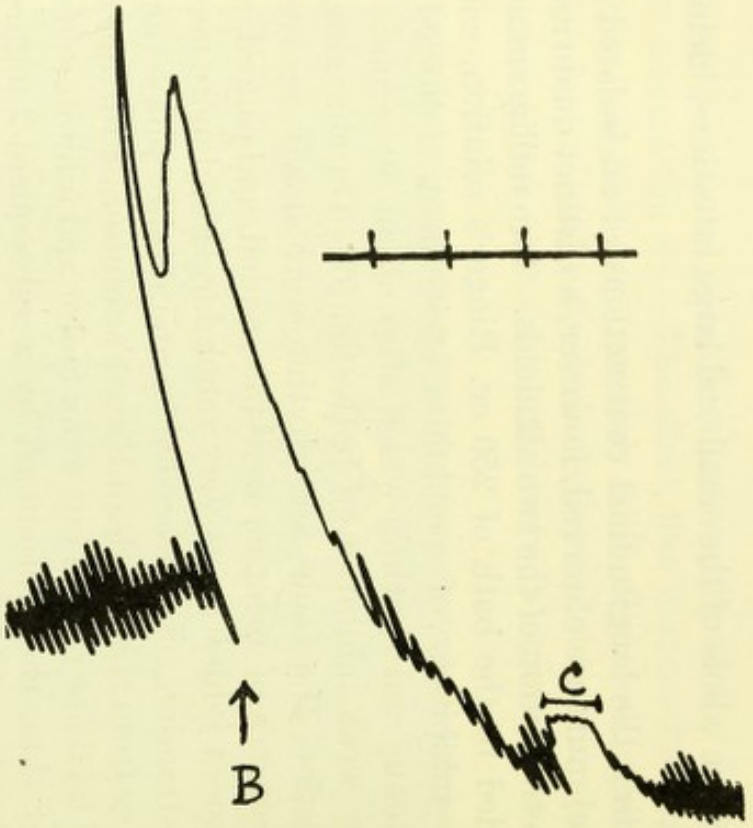

FIG 6. Continuation of record shown in fig. 5. At *B* added 2 mgms. nicotine to bath. At *C* fresh Ringer.

slight. The ganglion-cells, however, were not completely paralysed; for not only was a slight secretion produced during the stimulation, but after the stimulation was stopped, secretion continued for some time and at a considerably greater rate. Renewal of chorda stimulation during this after-period promptly reduced the rate, which again became accelerated as soon as the stimulation was stopped. The reversed action when once obtained could apparently be repeated indefinitely, though the effect of the Cytisine would doubtless have passed off in time if the experiment had been continued long enough. If a prolonged stimulation were given the flow became gradually accelerated during its progress, but there was a further and more sudden acceleration when the stimulation ceased.

A similar reversal of chorda action was observed in the cat with smaller doses of Cytisine.

The details of some of these experiments have been published elsewhere.[18] The fact that the secreto-motor effect of the chorda may be mainly an after effect, after incompletely paralytic doses of nicotine, was shown by Langley in 1890.[17] The inhibition of the delayed secretion by restimulation is clearly an analogous phenomenon to the reversed vagus effect on the cat's heart, which we described as occurring after nicotine, tropine, curare, hordenine-methiodide,[15] and now after Cytisine, and the similarly reversed effect of the pelvic nerve on the cat's bladder after curare described by Langley.[19] The immediate interest of the matter for us is the addition of another point of similarity between the action of Cytisine and that of nicotine.

The eye. In the dog and cat the primary effect on the eye, of an injection of Cytisine, like that of nicotine, is similar to that of stimulating the cervical sympathetic—dilatation of the pupil, retraction of the nictitating membrane and widening of the palpebral fissure. The retraction of the nictitating membrane is brief, and is soon succeeded by a movement forward, so that the membrane, after several milligrammes of the alkaloid, covers

[17] Journ. of Phys., XI, p. 123, 1890.

[18] Journ. of Phys., XLIII, p. 196, 1911.

[19] Journ. of Phys., XL, proc. Phys. Soc., p. lxii, 1910. Also XLIII, p. 125, 1911.

one-half to two-thirds of the visible portion of the eyeball. With doses up to 10 mgms. in the cat the pupils remain large. In the rabbit, on which we only made one experiment, and that on the intact unanesthetised animal, 2 to 5 mgms. by the ear-vein caused constriction of the pupil and retraction of the nictitating membrane. In a dog, which received 30 mgms. hypodermically, the pupils dilated and the nictitating membranes gradually became greatly prolapsed, so that the eyes must be rotated upwards and outwards to permit vision. In all these respects the action is again closely parallel to that of nicotine. So also is the paralytic effect on the cells of the superior cervical ganglion. Application of 1 per cent Cytisine to the superior cervical ganglion of a cat under ether caused a brief effect of sympathetic stimulation on the eye followed by complete paralysis of the cervical sympathetic nerve to electrical stimulation up to the ganglion. Stimulation of the branches from the ganglion to the internal carotid produced the normal effect. The same effect, as the result of intravenous injections, is shown in the following record, which illustrates incidentally other features of the action of the alkaloid.

Cat.

11.10 a.m. Chloroform. Then A. C. E. throughout. Tracheotomy. Cannula in femoral vein, by which all injections were made.

11.30 a.m. Pupils medium: nictitating membrane partly forward. 1 mgm. Cytisine. Widening of pupil and retraction of memb. nict. The latter then moved forward with continued widening of the pupil. A few deep respirations: then normal again.

11.35 a.m. Pupils nearly maximal: memb. nict. three-quarters prolapsed.

11.37 a.m. Two milligrams. A very few deep respirations. Then vomiting movements during which respiration ceases. After a short period of artificial respiration it is resumed normally. Heart-beat very slow. Right cervical sympathetic cut and isolated for stimulation.

11.52 a.m. Cat having artificial respiration with A. C. E. Pupil practically maximal. Stimulate cervical sympathetic with coil at 20 cm. Good retraction of nictitating membrane.

11.54 a.m. Five milligrams Cytisine. Memb. nict. retracts slightly and then returns. Pupils maximal. Slight tremors of paws.

11.55 a.m. Stimulate cervical sympathetic with coil at 20 and 15 cm. No effect. With coil at 10 cm. trace of retraction of memb. nict.

11.57 a.m. Stimulate sciatic (coil at 10 cm.)—feeble twitches of foot.

11.58 a.m. Stimulate cervical sympathetic (coil at 15 cm.)—memb. nict. retracts very slightly and then returns during stimulation, retracting again on cessation of stimulus. Repeated with identical effect.

12.2 p.m. Five milligrams Cytisine.

12.4 p.m. Stimulate sciatic, coil at 10 cm. No effect. Same stimulus directly to thigh muscles—normal contraction.

12.6 p.m. Stimulate cervical sympathetic, coil at 10 cm.—very weak and slow retraction of memb. nict. Repeat—no effect. Isolate branches from ganglion to internal carotid and stimulate with coil at 20 cm.—normal retraction of nictitating membrane.

Cytisine, therefore, like nicotine, produces its stimulant effects when directly applied to the ganglion-cells which it ultimately paralyses. On the other hand we find that its dilator action on the pupil, at any rate, is, again like that of nicotine, not wholly due to action on the superior cervical ganglion, since the pupil still dilates when Cytisine is injected intravenously after the ganglion has been removed.

The uterus. We have experimented with Cytisine on the uterus of the cat only. In this animal, as might be expected, the action of Cytisine changes like that of the sympathetic nerve supply and of adrenine or nicotine, being inhibitor in the virgin organ, motor in the pregnant, when the uterus is in its natural relations and the alkaloid administered intravenously. Like nicotine, Cytisine in small doses has practically no effect on the cat's uterus isolated from the body.

The urinary bladder. We have examined the effect on the cat's bladder. In all our experiments on this organ the central nervous system of the cat was destroyed completely by pithing. This excluded indirect effects from stimulation of centres in the cord; but the bladder under these conditions having but little initial tone, the effect obtained was only that on the motor ganglia connected with the pelvic nerves. Probably, as in the case of nicotine, a secondary inhibition from the sympathetic ganglia could be demonstrated under more favorable conditions of initial tonus. Our main object was to compare the extent of the main motor effect produced by Cytisine with that produced by an equal dose of nicotine. The comparison reveals a curious contrast. When small alternating doses of the two alkaloids are given at regular intervals, the contractions of the bladder produced by Cytisine are found to be regularly much less than those produced by nicotine, whereas Cytisine, as mentioned above, regularly produces a quicker and greater rise of blood-pressure (see figs. 1 and 2).

III. SUMMARY AND DISCUSSION

The results of this investigation may be roughly summarised in the statement that, in nearly every respect, the action of Cytisine is qualitatively indistinguishable from that of nicotine. Such small points of difference as its failure to produce the characteristic twitching of the ears in the cat have possibly a diagnostic, but at present no great theoretical importance. We have indicated certain quantitative differences in the action of the two alkaloids, such as the more powerful pressor action of Cytisine in the cat, and its less powerful action on the rabbit's intestine and the cat's bladder. In one case in which we compared the two, nicotine produced a more marked primary inhibition (vagus) effect on the cat's heart than Cytisine. The fact that both alkaloids paralyse ganglia in succession to their stimulation makes it useless to attempt to give numerical expression to their relative stimulant activities on any particular organ. We have contented ourselves, therefore, with this mere indication of the order of

their activities in these few instances. Still more difficult would be a comparison of their potency in producing secondary paralysis of ganglia, since, for obvious reasons, the two cannot be compared in this respect on the same animal. As far as individual differences permit us to judge, we should say that their activities in this direction on the cat and dog are of the same order. The affinity of the action of Cytisine with that of nicotine is further shown in the production of a reversed action of certain autonomic nerves under the influence of incompletely paralytic doses, such as has previously been demonstrated with nicotine, curare and other alkaloids of the same group.

One of us has previously shown the resemblance of the action of hordenine-methiodide[20] to that of nicotine, with which it has no obvious points of chemical similarity. The similarity with nicotine in action is very much closer, however, in the case of Cytisine: so close, indeed, that we doubt whether any instance of such exact parallelism is known to exist in the case of substances which are not close chemical relatives, except in the case of the apparently still closer resemblance in action to nicotine exhibited by Lobeline. At present but little is known of the constitution of Cytisine, though there are indications that its structure in some points resembles that of nicotine. An exact knowledge of its structure may give interest to the small points of difference between the two actions as well as to their general similarity.

On the basis of less complete pharmacological investigations certain therapeutic uses have been suggested and tried for Cytisine. Thus Radziwillowicz tried it in cases of migraine with low blood-pressure, and Bradford tried ulexine as a diuretic. Our experiments lend no support to the suggestion of its being therapeutically valuable. For physiological investigations it could be used in place of nicotine, and would have certain advantages in its easy preparation, with large yield, from the readily and cheaply obtainable Laburnum seeds; in the ease with which it can be purified—the alkaloid itself crystallises well and can be distilled under reduced pressure; and in its comparatively great stability.

[20] Barger and Dale: Journ of Phys., XLI, p. 35, 1910.