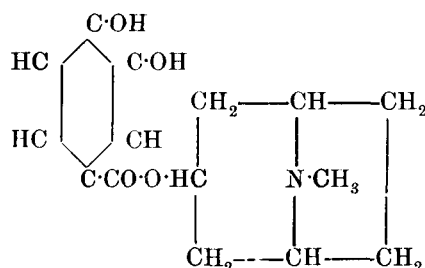


## XII.—The Pharmacological Action of Protocatechyl-Tropeine.\*

By Professor C. R. Marshall.

(MS. received November 20, 1909. Read June 21, 1909. Issued separately January 7, 1910.)

Protocatechyl-tropeine is one of a series of new tropeines investigated primarily with the object of determining the difference in pharmacological action between a lactone and the corresponding hydroxy-acid.† Its constitution is shown in the following formula :—



Like most other tropeines, it paralyses the vagal nerve endings in the heart. It also diminishes the irritability of voluntary muscle and its myo-neural junctions, and paralyses the respiratory centre.

## ACTION ON THE RESPIRATION.

When 0·01 g. protocatechyl-tropeine hydrochloride is injected into the external jugular vein of an anæsthetised rabbit or cat the respiration is rapidly paralysed (fig. 1). It generally ceases within ten seconds of the commencement of the injection, and may or may not recommence spontaneously. If it does not recommence, artificial respiration performed for  $\frac{1}{2}$ –1 min. will fully re-establish it. After larger doses (*e.g.* 0·02 g.) it may be necessary to resort to short periods of artificial respiration three or even four times before the respiration is permanently established, and then it may remain somewhat shallower than at first. (In one animal in which the uncut sciatic or crural nerve was being stimulated at intervals, the respiration restarted spontaneously after the injection of this dose, but it failed again later.) Doses of 0·005 g. intravenously may also paralyse the respiration, but it recommences with a shorter period of artificial respiration than is the case after larger doses. Smaller doses produce only shallower and less frequent respirations, the effect being roughly proportional to the dose. The smallest effective dose is 0·001 g. intravenously.

\* I am indebted to Mr H. A. D. JOWETT, D.Sc., for his kindness in providing me with this substance. Its preparation and characters have been described by him in conjunction with Mr HANN (*Trans. Chem. Soc.*, vol. 89, p. 364).

† *Arch. f. exp. Path. u. Pharm.*, 1908, Supplem. Bd., p. 389.

Division of both vagi has relatively little effect on the respiratory action of protocatechyl-tropeine. In many cases the respiration seemed to recover less readily than in animals with uncut vagi; and in a few cases the respiration did not recommence spontaneously, as it probably would have done if the vagi had been intact. I have observed the same effect after the administration of tetramethyl-ammonium chloride, a substance which acts on the respiration in a manner similar to protocatechyl-tropeine.

The experiments were made on etherised animals. The blood-pressure was taken from the common carotid artery, and the injection made into the external jugular vein in cats and the facial vein in rabbits. The respiration was recorded in most experiments by means of a phrenograph with a tube connection to a tambour.

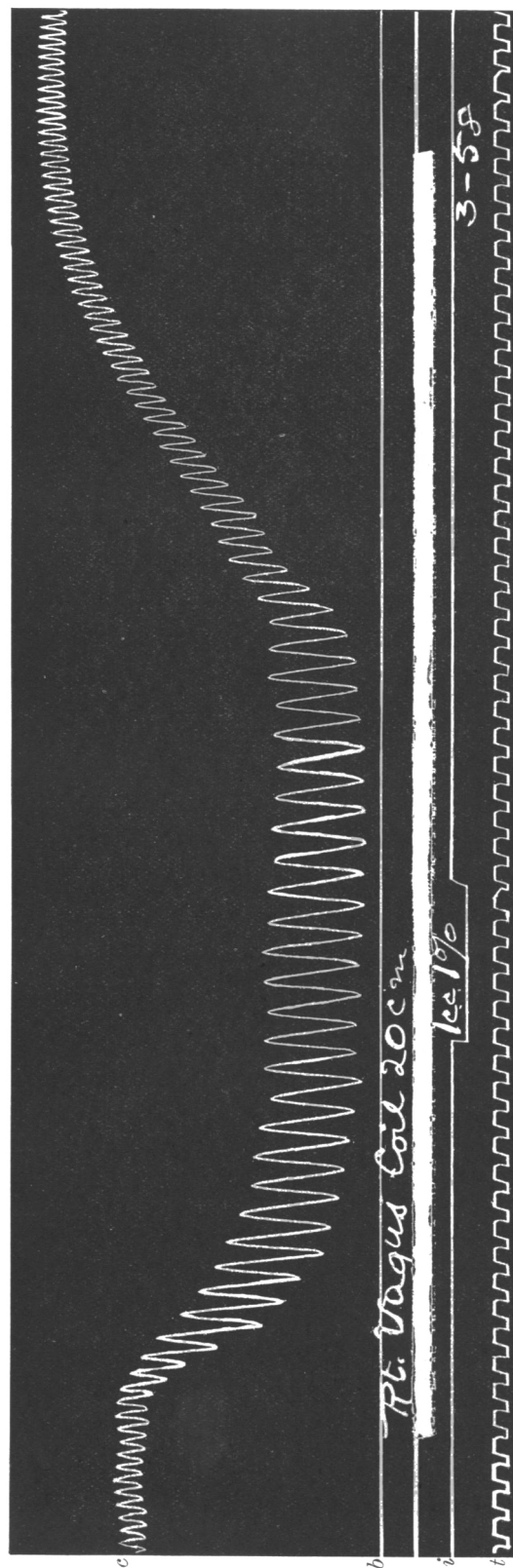
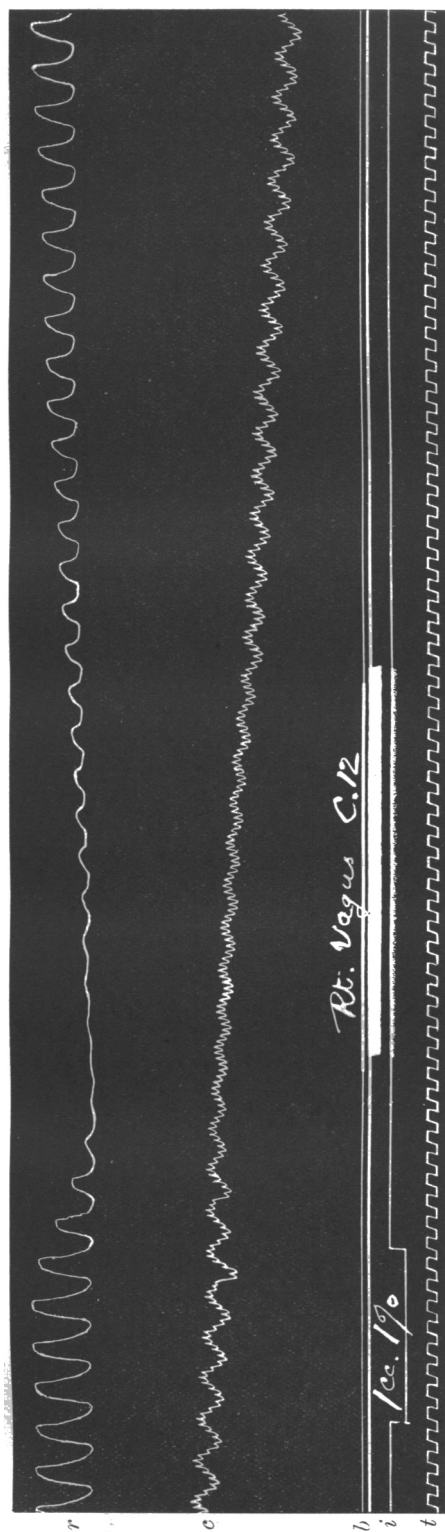
In a normal animal the largest dose I have been able to give, namely, 0.045 g. intraperitoneally to a rabbit weighing 720 g., produced only dyspnoea. The duration of action of this dose and its influence on the frequency of the respiration is shown in the following table:—

Time in minutes after injection	}	0	5	10	20	25	30	40	50	60	90	120
No. of respirations per minute	}	54	84	87	153	165	135	129	117	105	78	54

When injected into the dorsal lymph sac of winter frogs, 0.04 mg. per gramme body-weight caused slight slowing of respiration, but no other obvious symptoms; 0.08 mg. per gramme body-weight induced marked slowing of the respiration, which also took on a periodic character, groups of about six respirations being followed by an interval up to half-minute duration of no breathing; there was also some muscular depression; 0.16 mg. per gramme body-weight caused almost complete cessation of respiration and muscular paralysis; and 0.24 mg. per gramme body-weight eventually produced complete paralysis of the respiration and death. As an example, the effect after the injection of 0.16 mg. per gramme body-weight may be taken. In this experiment the frequency of the respirations fell to one-half in ten minutes, to one-eighth in twenty minutes, and to one-twentieth in seventy-two minutes after the injection; the frog was then pithed.

#### ACTION ON VAGAL ENDINGS.

This was determined by observing on the blood-pressure the effect of electrical stimulation of a divided vagus before and after injection of the drug, or the effect of the drug after the injection of pilocarpine. When electrical stimulation was employed the procedure was as follows: the vagus was stimulated at intervals until a practically constant effect was obtained, the drug was then injected into the external jugular or facial vein, and the vagus again stimulated at intervals until an effect as near as possible identical with that previously obtained was reached; or the injection was made during continued stimulation of the vagus (fig. 2).



By these methods 0·01 g. protocatechyl-tropeine hydrochloride was found to paralyse the terminations of the vagus in the heart for five minutes. At the end of this period stimulation of the vagus generally produced a slight effect, and the effect gradually increased with succeeding stimulations until the former normal condition was reached, usually about twelve minutes after the injection. Occasionally the same strength of stimulus failed to induce any action, and consequently it had to be slightly increased. Thus, after the injection shown in fig. 2, stimulation with the secondary coil at 20 cm. produced no effect up to eight minutes after the injection, whereas stimulation with the coil at 16 cm. produced at this time a very good effect. I have obtained the same result with other tropeines.

When pilocarpine is used as a stimulus the paralysis of the vagal terminations does not last so long. Thus the injection of 0·01 g. protocatechyl-tropeine hydrochloride, after a previous injection of 0·01 g. pilocarpine, totally abolished the pilocarpine effect for one and a half minutes only. The pilocarpine action then reappeared and in three minutes had reached its previous form. The shorter period of paralysis in these experiments as compared with that obtained when the vagus is stimulated electrically is due to the fact that pilocarpine and protocatechyl-tropeine are to some extent mutually antagonistic.

#### EFFECT ON BLOOD-PRESSURE.

The commonest effect on the blood-pressure is a gradual fall, usually commencing after the effect on the respiration has begun, and continuing when the respiration spontaneously recovers, after this has become practically normal (*cf.* figs. 1 and 4). The fall of blood-pressure continues for  $1\frac{1}{2}$ –3 minutes, rarely more, and then the pressure gradually returns to its previous height. It is not usually severe in extent in rabbits; after a dose of 0·01 g. intravenously it generally amounts to about one-third the normal blood-pressure. In cats the fall is often greater, and not infrequently is preceded by a slight rise. The extent of the fall in the last-named animals is shown in the following table, which expresses the result of two successive injections:—

Minutes after injection . . . . .	0	3	9
0·004 g. Bp. in Mm. Hg. . . . .	135	79	130
0·002 g. Bp. in Mm. Hg. . . . .	136	111	130

Occasionally in cats a rise of blood-pressure has been the most prominent feature. This effect is seen in fig. 3, which illustrates the greatest rise of blood-pressure I have obtained with this substance. There was no fall below the normal subsequently. The vagal terminations in the heart were found to be paralysed between A and B, and to be again irritable between B and C. Two injections of 0·01 g. each were made in the same animal later, and in both instances a rise of blood-pressure to nearly the height of that shown occurred. The rise was more prolonged in each case, and the vagal endings were paralysed for a longer time than after the injection illustrated. The respiration was not graphically recorded in this experiment.

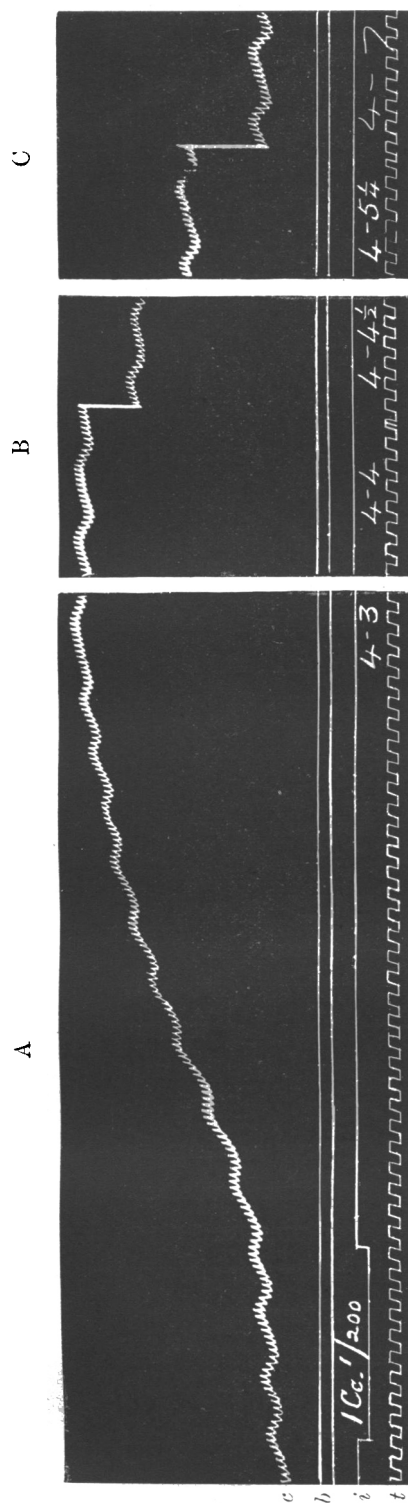


FIG. 3.—Occasional effect of 0.005 g. protocatechyl-tropeine hydrochloride intravenously on blood-pressure Cat. 3225 g. Ether. Right vagus cut. Vagus unirritable between A and B, slightly irritable between B and C. Letters as in previous figures. Base line raised 53 mm.  $\times \frac{1}{3}$  linear.

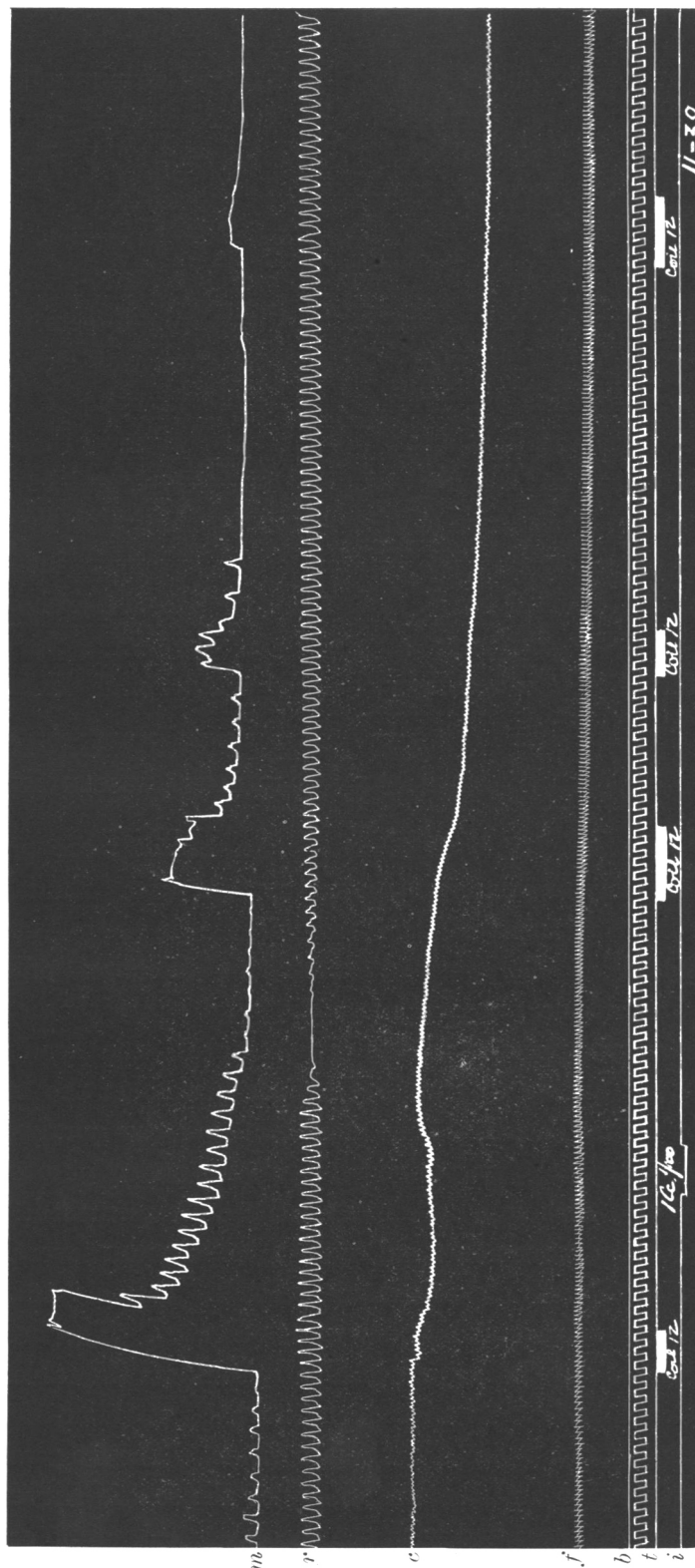


FIG. 4.—Effect of 0.01 g. protocatechyl-tropeine hydrochloride intravenously on motor nerve endings. Rabbit. 2400 g. Ether. Left crural nerve exposed. Heavy white lines indicate time of stimulation of nerve with secondary coil at 12 cm.  $m$  = effect on limb; lever  $\times 2\frac{1}{2}$  times. (First part of tracing shows terminal effect of a stimulation practically identical with first one shown, 35 seconds before commencement of tracing.)  $f$  = tracing by feder-manometer. Other letters as in previous figures. At 11.19 the same dose of protocatechyl-tropeine had been given with the same result.  $\times \frac{1}{3}$  linear.

When the respiration is paralysed and does not recover spontaneously the blood-pressure after a brief interval falls rapidly to a few millimetres. That this fall is mainly asphyxial is proved by artificial respiration, which quickly raises the pressure to the level it would probably have reached if respiration had recommenced. If the substance is injected after the administration of pilocarpine or during stimulation of the vagus a rise of blood-pressure always occurs.

The fall in blood-pressure is probably cardiac in origin, since it is accompanied by a diminution in the frequency of the heart-beats; and as the vagus nerve endings are paralysed, the action of the drug would seem to be on the muscular tissue of the heart itself. The rise of blood-pressure seen occasionally in experiments with cats is accompanied by an increase in the number of the heart-beats due to paralysis of the vagal terminations. The cardiac muscle in these cases is not depressed sufficiently to counteract the effect of paralysing the vagus, but that some depression is produced is shown by the rise of blood-pressure being less than that obtained with a corresponding physiological dose of atropine. Moreover, increase in dose leads to a somewhat smaller rise of pressure. Why this prolonged rise should occur in isolated cases is difficult to explain. Probably a certain concentration of the drug in the heart acting for a brief interval only is necessary, but the condition of the heart itself may also be a factor.

#### ACTION ON VOLUNTARY MUSCLE AND MOTOR NERVES.

The activity both of motor nerves, or more probably their terminations, and of voluntary muscle, is depressed by this drug. In rabbits the nerve endings appear to be more susceptible than the muscle; in frogs the muscle is at least as powerfully affected as the nerves. After an injection of 0.24 mg. protocatechyl-tropeine hydrochloride per gramme body-weight into the dorsal lymph sac of a frog, muscular weakness appeared within five minutes—the head began to droop and the animal became unable to turn over when placed on the back. A few minutes later the frog was quite flaccid. This condition and the paralysis of the respiration referred to previously was maintained during the period of observation (the frog died during the night). Although apparently completely paralysed, the frog occasionally made a slight voluntary movement, and a slight reflex was several times obtained on pinching a toe moderately strongly for some seconds. After 0.16 mg. per gramme body-weight was injected similar symptoms were observed. The head commenced to droop in twenty minutes and the animal gradually sank on the table. The reflexes, however, remained distinct, and when placed on the back an hour after the injection the frog recovered once, but not twice, from this position. The frog was pithed seventy-two minutes after the injection and the irritability of the sciatic nerves and gastrocnemii muscles tested. The sciatics reacted with the secondary coil at 35 cm., the muscles with the coil at 28 cm. The injection of 0.08 mg. per gramme body-weight produced only slight muscular depression.

On immersing a nerve-muscle preparation (gastrocnemius) in a 1-1000 solution of protocatechyl-tropeine hydrochloride in 0.6 per cent. sodium chloride and stimulating (one Daniell's cell) the nerve and muscle alternately every three minutes, the contractions were found to fall with the same regularity in each case, and both muscle and nerve became inexcitable forty-five minutes after immersion.

In a rabbit no muscular paresis was observed after 0.062 g. p. kg. intraperitoneally. Depression but not always paralysis of the nerve endings is obtained after intravenous administration to an anæsthetised animal. This is shown in fig. 4. The rabbit was prepared in the manner described, the right crural nerve was laid bare, and a hook was put into the right foot and connected by means of a thread working over pulleys to a weighted lever. After a practically constant effect had been obtained from stimulation of the nerve (one accumulator cell; secondary coil 12 cm.), 0.01 g. protocatechyl-tropeine hydrochloride was injected into the right facial vein. The contraction of the muscles produced by stimulation of the nerve gradually diminished until it disappeared two minutes after the commencement of the injection. Two and a half minutes later the limb muscles again responded to stimulation of the nerve, but the contractions did not assume their previous (normal) form until ten minutes after the injection of the drug. The tracing reproduced records a second injection of the drug; the same dose was administered at 11.19 and produced a similar effect.

In a second experiment, in which both the right crural and sciatic nerves were exposed, it was found that the muscles, when stimulated directly, contracted in the neighbourhood of the electrodes at a time when the nerves were inexcitable. It would seem, therefore, that in the rabbit the nerve endings are more susceptible to this compound than the muscular substance.

An interesting point is the want of correlation between the respiratory and the neuro-muscular effects; at a time when the latter are most manifest the respiration is practically normal. The explanation is probably to be found in the stimulus of the respiratory centre being physiologically more powerful than the electrical stimulus used, and thus able to overcome any tendency towards paresis of the respiratory muscles. As bearing upon this point, evidence was obtained showing that the paralysis of the muscles and nerve endings was only relative, *i.e.* only for minimal or moderate stimuli. The effects on the blood-pressure and the neuro-muscular system, on the other hand, are correlative, the fall of blood-pressure being mainly, if not solely, due to an action on the cardiac muscle.

#### REMARKS ON THE ACTION OF THE DRUG ON THE RESPIRATION.

Rapid cessation of respiration in the expiratory phase has been described by TAPPEINER\* after the intravenous injection of methyl-phenyl-isoxazol-methochloride, diphenyl-methyl-pyrazol-methochloride, dimethyl-phenyl-pyrazol-methochloride,

\* *Arch. f. exp. Path. u. Pharm.*, xxxvii., p. 325 [1896].

and tetra-methyl-ammonium chloride; and by POHL\* after the intravenous injection of papaverin-methochloride, papaveraldin-methochloride, and papaverinol-methochloride. None of these substances produced the effect when administered hypodermically.

As the result of his experiments, TAPPEINER came to the conclusion that methyl-phenyl-isoxazol-methochloride stimulated the terminations of the trigeminal nerve, and that the effect produced was, in reality, a Kratschmer-Hering reflex. Thus he found that cocainisation of the nasal mucous membrane prevented the respiratory paralysis; and that while cocaine administered intravenously also antagonised the action of the isoxazol, the dose required was larger than when the cocaine was applied directly to the nose. The action of tetramethyl-ammonium chloride and the other substances investigated by him was explained in the same way. IODLBAUER,† who investigated tetramethyl-ammonium chloride more minutely under TAPPEINER's direction, came to the same conclusion. POHL, however, still obtained the characteristic stoppage of the respiration

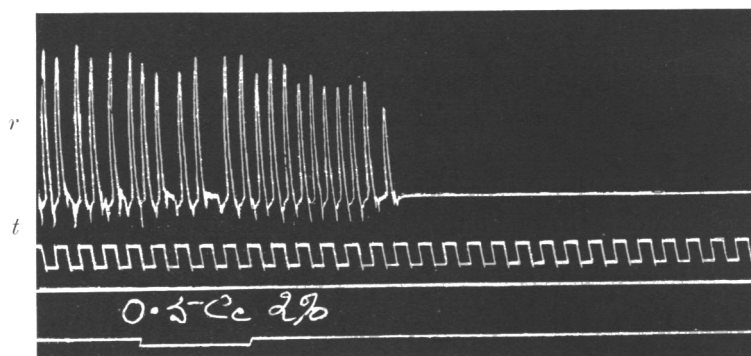


FIG. 5.—Effect of 0.01 g. protocatechyl-tropeine hydrochloride intravenously on decerebrate rabbit with both fifth cranial nerves cut. Tracing of respiration taken by connecting one limb of tracheal cannula to a tambour; other limb left open. Time in seconds.

after cocainisation of the nose and after division of the ophthalmic branch of the fifth nerves, both in the case of papaveraldin-methochloride and of tetramethyl-ammonium chloride, and he therefore maintains that the action is a central one. The action of protocatechyl-tropeine is also upon the centre. The typical effect on the respiration is still obtained when the brain above the pons is excised and both the fifth cranial nerves are cut within the cranium (fig. 5). Moreover, the same action is obtained in cats (fig. 1), animals in which the typical Kratschmer-Hering reflex is not present. And since the effect on the neuro-muscular system is not coincident in time with the effect on the respiration, the cause of the latter would seem not to be peripheral. It has, however, been shown that the motor nerve endings in the diaphragm may be affected differently, either as regards time or degree, from those of many other voluntary muscles, and it therefore seemed desirable to determine whether the diaphragm played any part in producing the respiratory paralysis. Accordingly, in an anæsthetised

\* *Arch. Internat. de Pharmacol.*, xiii., p. 479 [1904].

† *Ibid.*, vii., p. 183 [1900].



animal, both phrenic nerves were cut and the respiration registered by a connection with the tracheotomy tube. On injecting 0.01 g. protocatechyl-tropeine hydrochloride into the external jugular vein the respiration ceased thirteen seconds after the commencement of the injection (fig. 6).

In connection with the production of temporary cessation of the respiration, the question of dose is of paramount importance. The concentration of the drug producing this effect in the blood supplying the medulla can apparently vary only within narrow limits. Hence not only the amount of drug injected but also the time occupied by the injection is of moment. This explains why the effect does not result from hypodermic or intraperitoneal administration. It is probably owing to this fact that the effect has not been observed more frequently. It can certainly be produced by a number of

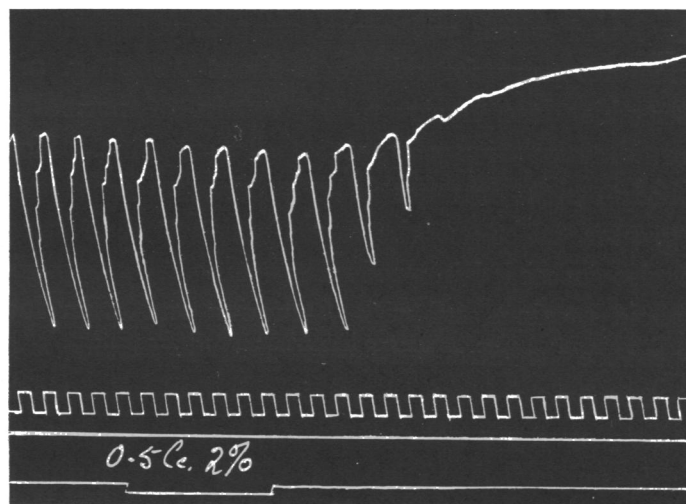


FIG. 6.—Effect of 0.01 g. protocatechyl-tropeine hydrochloride on respiration of rabbit with both phrenic nerves divided. Tracing taken as fig. 5, but with air-exits closed. Time in seconds.

drugs, but the doses of those which induce it fall within very narrow limits. In many of these cases the effect is probably merely that of a protoplasmic poison, and the respiration is most obviously affected because the respiratory centre is the most sensitive of the medullary centres to this class of substances. This hypothesis, however, does not seem sufficient to explain the actions of the substances already mentioned.

In a preliminary report on the physiological action of pukateine, an alkaloid isolated by ASTON\* from pukatea bark, MALCOLM says: "Intravenous injection of 10 mg. into an anæsthetised rabbit caused sudden stoppage of respiration without convulsions: the heart continued to beat vigorously for a long time afterwards." As Mr ASTON had given me some years ago a specimen of the mixed alkaloids isolated by him from pukatea bark, I was able to investigate this point. The alkaloids were first converted into the hydrochlorides. On injecting 0.01 g. intravenously (time occupied by injection, seven seconds) into a rabbit (wt. 2100 g.) the respiration was not

\* Annual Rep., New Zealand Dept. of Agriculture, 1908, Chemistry Division, p. 226.

paralysed; it began to get shallower ten seconds after the commencement of the injection, and reached its lowest point five seconds later, from which time it very gradually returned to the normal. The blood-pressure commenced to fall before the respiration was affected, and fell from 87 mm. before the injection to 58 mm. twelve seconds after the commencement of the injection. From this point it gradually rose in three minutes to 107 mm. The effect of a subsequent injection of 0.02 g. caused almost complete cessation of respiration for half a minute, and then a very gradual return to normal breathing. The fall in the respiratory curve, however, was less abrupt, the blood-pressure was more quickly and more powerfully influenced, and the return of normal respiration was later than occurs after protocatechyl-tropeine.

The other synthetic tropeines I have investigated do not distinctly influence the respiration in doses which depress the vagal endings, but doses of both atropine and homatropine may be found which will cause temporary cessation of the respiration. The dose of atropine necessary for rabbits is about 0.0001 g. per kg. body-weight intravenously. After this dose, however, the return of normal respiration is less rapid than after the administration of protocatechyl-tropeine. Homatropine, in doses of 0.005 g. per kg. body-weight intravenously, produces a more transient effect on the respiration and a greater effect on the blood-pressure than atropine in the dose mentioned. I have also succeeded in producing temporary stoppage of the respiration with the allied alkaloid cocaine, and with  $\beta$ -eucaine and other local anæsthetics. I failed, however, to produce the effect with ammonium hydroxide. A certain degree of recovery may, with appropriate doses, be obtained after intravenous administration of this substance, but this recovery is not maintained, and the respiration fails again unless artificial respiration is performed. The best effect I have obtained was from the injection of 0.025 g. ammonium hydroxide per kilogramme body-weight. Larger amounts of ammonium hydroxide may be followed by a few spontaneous respirations, but they paralyse the respiration permanently unless it is restored by artificial means. Doses less than 0.01 g. per kilogramme generally increase the respiratory movements; above this dose the movements are diminished.

#### COMPARISON OF EFFECTS ON BLOOD-PRESSURE.

All the drugs previously mentioned, in doses which temporarily abolish the respiration, diminish in rabbits the frequency of the heart-beats. The effect is greatest in the case of methyl-phenyl-isoxazol-methochloride and tetramethyl-ammonium chloride, and least in that of the tropeines. In most cases there is also a fall in blood-pressure. Methyl-phenyl-isoxazol-methochloride, however, notwithstanding the marked slowing of the heart produced by it, causes, after a preliminary slight fall, a rise of blood-pressure, which is due, according to TAPPEINER,\* to stimulation of the medullary centres. The slowing of the heart and fall of blood-pressure produced by tetramethyl-ammonium

\* *Loc. cit.*

chloride, and probably also by the alkaloid pukateine, are due mainly to stimulation of the vagal terminations. According to IODLBAUER,\* the effect of tetramethyl-ammonium chloride is less after section of both vagi, and consequently he concludes that its action on the circulation is partly, if not mainly, central. He also obtained a marked rise of blood-pressure when this drug was injected after atropine, a result he attributes to stimulation of the vasomotor centre. I have obtained a rise of blood-pressure on cutting both vagi a few minutes after the injection of tetramethyl-ammonium chloride, but have not observed any difference on the frequency of the heart-beats after injection of this substance whether the vagi were divided or not. After atropine had been given, the usual slowing of the heart did not occur, nor was there any rise of blood-pressure.

The slowing of the heart's frequency and the fall of blood-pressure produced by the papaverin derivatives investigated by POHL are attributed by him to the stoppage of the respiration. He does not, however, refer to any investigations bearing on this point in his paper, and he gives no tracings from which the action on the circulation might be inferred.

The action of protocatechyl-tropeine on the circulation differs from that of most substances producing temporary paralysis of the respiration, in that it paralyses the vagal endings within the heart. Hence the diminution in the frequency of the heart-beats and the fall of blood-pressure are less than are produced by most members of this class of respiratory paralytics. As previously stated, the fall of blood-pressure caused by these tropeines is probably due to a depressant action on the cardiac muscle, an action which in all probability is present in the case of the other substances also.

From these statements it is evident that no uniformity, such as exists in the case of the respiration, characterises the action of these different substances on the circulation, and this further supports the statement made previously that their action on the two systems is not correlated.

#### REMARKS ON THE RELATION BETWEEN CHEMICAL CONSTITUTION AND PHARMACOLOGICAL ACTION.

Protocatechyl-tropeine, as previously stated, was one of a series of tropeines investigated for the purpose of determining the difference between a lactone and the corresponding hydroxy-acid. As it is not a lactone it was used as one of the control substances, and it was found that, unlike pilocarpine and the lactone-tropeines, it does not lose its action when a molecular quantity of caustic alkali is added to its aqueous solutions. Even the addition of distinct excess of caustic alkali and prolonged standing do not influence its pharmacological action to any appreciable degree. It is evident, therefore, that the replacement of the hydrogen of the phenolic hydroxyls by an alkali metal is of no pharmacological importance.

A point of interest on which the action of protocatechyl-tropeine throws a little

\* *Loc. cit.*

light is the part which the constituent groupings play in the pharmacological action of tropeines. BUCHHEIM,\* LADENBURG,† and others have found that various aromatic acidic groups could be attached to the base tropine, and an atropine-like action be obtained; whereas CRUM BROWN and FRASER,‡ and more recent observers, have shown that alterations in the tropanyl radical generally produce profound changes in the pharmacological action of a tropeine. This suggests that the fundamental action of these tropeines depends on the tropanyl radical, and that the interaction with the so-called nerve endings occurs through the mediation of the acidic grouping. Whether the acidic group has any other action than a connecting or haptophoric one with the tissues is difficult to decide. Many of the tropeines, in so far as they have been investigated, differ little except quantitatively in pharmacological action from atropine, and it is open to assume that in these compounds the acidic groupings are purely haptophoric in character, since their different quantitative effects might be explained by differences in the power with which the acid group is able to attach the tropanyl group to the nerve endings. GOTTLIEB,§ however, showed that certain tropeines act very differently from atropine—acetyl-tropeine causes convulsions and succinyl-tropeine paralysis, and neither affects the vagus endings or the pupil; and in view of the comparatively simple nature of the acid groups of these compounds, it seems questionable whether any distinctive action can be attributed to the constituent groupings of tropeines. In the case of protocatechyl-tropeine we have a compound which differs materially in action from other tropeines, yet most of its actions can be demonstrated with atropine. But while it acts much less powerfully than atropine upon the vagal endings in the heart, it acts more powerfully on voluntary muscle, and has an action on the respiratory centre which atropine shares to a relatively slight degree. It may be that these differences might be explained by the presence of different receptive substances in the different tissues, but this view would scarcely explain why, in small doses, atropine exerts a stimulating effect on the respiratory centre, and protocatechyl-tropeine no such stimulant action. Unfortunately, it is not possible to determine the action of the two constituent groups of these compounds by investigating the products of their hydrolysis. It was early shown by FRASER¶ that tropine and tropic acid produce no atropine-like action, and it was consequently not surprising to find that simple protocatechyl compounds possess no action like that of protocatechyl-tropeine. The substances I investigated were protocatechyl-aldehyde,|| methyl-protocatechyl-aldehyde (vanillin), and di-methyl-protocatechyl-aldehyde (piperonal). Intravenous injections of these compounds produced no effect on the respiration resembling that produced by protocatechyl-tropeine. There is thus no evidence leading us to assume that the actions of protocatechyl-tropeine can be attributed with any certainty to the two constituent groupings individually.

\* *Arch. f. exp. Path. u. Pharm.*, v., p. 463 [1876].

† *Annalen d. Chemie*, Bd. 217, p. 82 [1883].

‡ *Trans. Roy. Soc. Edin.*, xxv., p. 693 [1869].

§ *Arch. f. exp. Path. u. Pharm.*, xxxvii., p. 218 [1896].

¶ *Proc. Roy. Soc. Edin.*, 1869, p. 558.

|| Prepared by acting on piperonal with phosphorus pentachloride.

All the substances previously investigated which have been shown to paralyse temporarily the respiration are quaternary bases. The tertiary bases corresponding to these did not, where tried, affect the respiration. Protocatechyl-tropeine, however, is a tertiary base, and chemically has nothing in common with the other substances producing the same respiratory effect. But it possesses another physiological action common to many of them, namely, the power of paralysing the motor nerve endings to voluntary muscle. It is questionable, however, if this connection is more than a coincidence, since trimethyl-ammonium chloride, triethyl-ammonium chloride, and tetraethyl-ammonium chloride, which paralyse motor nerve endings, have no paralysing action on the respiratory centre;\* and the papaverin bases which do produce respiratory paralysis do not paralyse motor nerve endings.

#### SUMMARY.

Protocatechyl-tropeine paralyses the vagal endings in the heart, but is much less powerful than atropine, or even homatropine.

It depresses muscular activity, especially in frogs, and interferes with the conductivity of motor nerves, or more probably the myo-neural junctions, in rabbits.

In certain doses, it paralyses temporarily the respiration, and causes a gradual fall of blood-pressure; but the two effects are not apparently correlated. In cats, a rise of blood-pressure sometimes occurs, owing to the paralysis of the vagal endings.

The temporary stoppage of the respiration is due to paralysis of the respiratory centre, and not to a peripheral action.

No evidence indicating separate pharmacological actions of the two component groupings of the compound was obtained.

\* TAPPEINER, *loc. cit.*