THE PART PLAYED BY THE ALA CINEREA IN VASO-MOTOR REFLEXES.

By J. M. DUNCAN SCOTT.

(*From the Physiological Laboratories of Cambridge and St Bartholomew's Hospital and Medical College.*)

ROBERTS and I(1) have confirmed the results obtained by Ranson and Billingsley(2) that a vaso-depressor effect is obtained on electrical stimulation of a point close to the calamus scriptorius (the depressor point) and we have discussed the question whether it represents merely a point on the depressor arc or is the supreme vaso-dilator centre. The present paper offers additional evidence as to the nature of this point. I owe the suggestion that I should try the effect of application of strychnine to the floor of the fourth ventricle to Prof. Langley, to whom my thanks for this and other help are due.

Application of 1 *p.c. strychnine to the depressor points.*

In 1888 Rey and Aducco(3) showed that strychnine paralysed the depressor in the rabbit and the vagus in the cat and dog. Bayliss(4) in 1908 described reversal after injection of strychnine of the normal effect obtained from the depressor in the rabbit and the vagus in the cat. Langley(5) contested this in 1912, saying that the effect of strychnine is, after a preliminary stage of increase of excitability, to decrease reflex vascular effects whether pressor or depressor.

Experiments were performed on cats, the anæsthetics used being either C.E. mixture or urethane. The results obtained do not depend on the anæsthetic. Two experiments were also performed on rabbits, urethane being used as the anæsthetic. The procedure was that, a tracheal cannula having been inserted, the right carotid artery and depressor nerve (or, if it could not be separated, the vagus) and then the right sciatic nerve or the brachial nerves were isolated. The floor of the fourth ventricle was exposed by the operation already described(1). A blood-pressure record was taken from the carotid and the optimum strengths of faradic stimulation (2 volts in primary) for a good effect from the depressor and good pressor and depressor effects from the sciatic were noted. Strychnine nitrate in 1 p.c. solution in distilled water warmed to body temperature

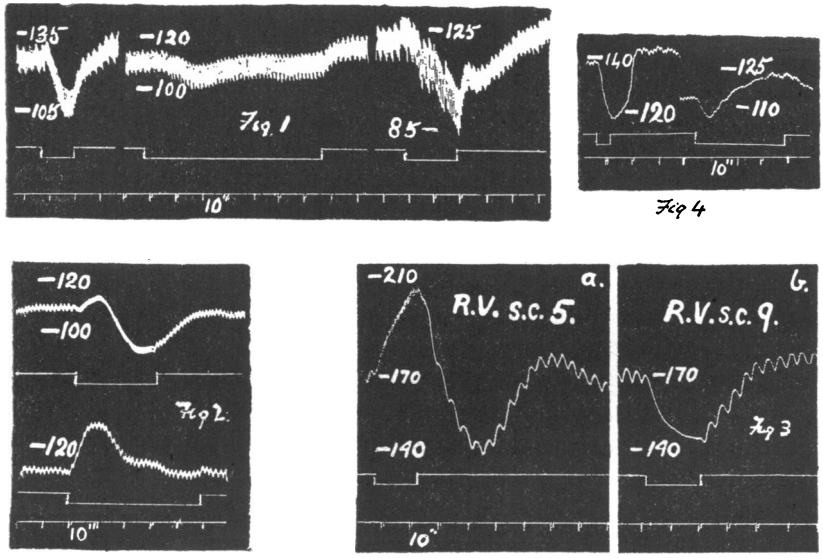
was now applied on a minute pledget of wool to the posterior part of the floor of the fourth ventricle; the application was confined as nearly as possible to the posterior part of the alæ cinereæ (depressor points); the amount of fluid used would contain about ·05 mgm. of the salt. During this application graphic records were obtained at intervals of the results of stimulation of the above nerves with the same strengths of stimuli as had previously been used.

Stimulation of the depressor nerve and of the vagus. On applying the strychnine there is a transient period in which the depressor effect may be increased, followed sometimes by an interval in which it can be observed to diminish progressively; it then practically disappears (Fig. 1). Reflex cardiac and respiratory effects from the vagus are blocked at the same time. Then vagal reflexes slowly reappear provided the application has been of short duration. The reappearance may be marked by a stage in which the depressor effect is exaggerated. A reversal of effect, such as described by Bayliss(4) with the depressor in the rabbit, was not obtained. The nearest approximation to his result is shown in Fig. 2. This was obtained once only. As will be seen, the slight primary pressor effect was much increased by strychnine and the depressor effect was abolished. In this experiment, after recovery from strychnine, I split the vagus into two bundles (there was no separate depressor nerve). One bundle caused mainly a pressor effect, the other mainly a depressor effect. The nerve therefore contained pressor as well as depressor fibres. Most observers who have stimulated the vagus in the cat have found that occasionally it causes a rise instead of a fall of blood-pressure. As a demonstration that both pressor and depressor fibres may be contained in the vagus of the cat a fortunate tracing (Fig. 3), showing the result of stimulation of the vagus in one animal, is appended. In this isolated case when the secondary coil was at 5 a pressor effect followed by an after-fall was obtained; while, when the secondary coil was at 9, a pure fall was given.

An apparent "reversal" of effect of the depressor after application of strychnine to the alæ cinereæ, was obtained in the rabbits (Fig. 4), but in both cases there was some evidence, as indicated by a slight initial rise or an after-rise, that the depressor contained some pressor fibres. It may be noted that Stewart and Pike(6) found the first reflex effect obtainable from the depressor of the rabbit (and vagus in the cat) in resuscitation from cerebral anæmia to be a rise of blood-pressure.

The results, I think, corroborate Langley's explanation(5) that the substitution of the depressor by a pressor effect (Bayliss' result), when

it is obtained, depends upon the presence of pressor elements in the nerve stimulated.



Figs. 1–6. Effects of application of strychnine to the lower part of the floor of the fourth ventricle (approximately to the depressor points).

Fig. 1. Stimulation of left vagus of cat (right vagus intact) before, during, and in recovery from, strychnine.

Fig. 2. Stimulation of left vagus of cat (right vagus cut) before and after strychnine. Increase of pressor, abolition of depressor effect ("Reversal").

Fig. 3. Stimulation of right vagus of cat (left vagus intact). Pressor and depressor effect from the same nerve: (*a*) sec. coil at 5; (*b*) sec. coil at 9 cm.

Fig. 4. Partial reversal of depressor reflex in the rabbit. Stimulation of left depressor nerve before and after strychnine.

Stimulation of sciatic nerve. Some difficulty was experienced in getting from the central end of the cut sciatic nerve a depressor reaction of such magnitude and constancy as to be perfectly reliable. Unless one could produce this reaction with certainty one would not be justified in attributing its absence on any occasion to a specific agency. Various methods were tried. Weak faradic currents as well as partial blocking of the stimulus were used, as described by Reid Hunt(7); I was not satisfied that the depressor reflex obtained by this means was constant enough for my purpose. Bilateral section of the pressor path in the region of the posterior horns of the cord was tried, as described by Ranson and

Billingsley(8); this had to be combined with exposure of the floor of the fourth ventricle in one acute operation, which was found to be too severe for the animal. Gruber(9), Gruber and Kretschner(10), and Vincent and Ogata(11), laid stress on the use of very low rates of faradic stimulation for the production of a depressor response. I have been able to produce this effect with certainty by the same means, provided that a few minutes (2–5) were allowed to elapse before repeating the excitation, care also being taken to avoid any asphyxia(12). Under these circumstances one could feel confident that if the depressor response disappeared during the course of the experiment, its disappearance was due to something occurring at that time. Fig. 5 shows a graphic record of the normal depressor response obtained from the sciatic under such conditions; the primary current was interrupted by a rod vibrating twice a second and the secondary coil was at 5 cm. 1 p.c. strychnine nitrate in distilled water warmed to body temperature was then applied on a minute pledget of wool to the depressor points, and tracings were taken at intervals with the same frequency and strength of stimulus. The depressor response soon disappeared (cp. Fig. 5); the blocking was commonly preceded by

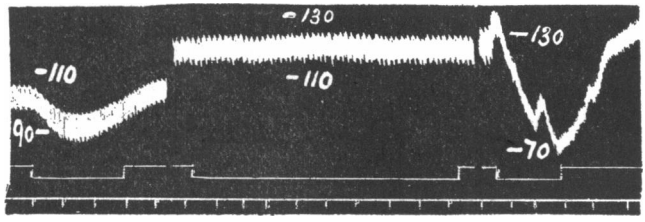


Fig. 5.

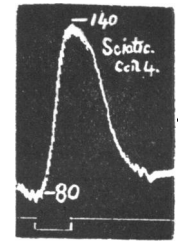


Fig. 6.

Fig. 5. Stimulation of sciatic of cat, as in text, sec. coil at 9 (one vagus intact), before application of strychnine, during application and during recovery.

Fig. 6. Pressor reflex from sciatic, tetanising current, 12 secs., sec. coil at 4, during abolition of depressor reflex by strychnine.

first an exaggeration and then a rapid lessening of the response. Respiratory reflexes from the sciatic were abolished at the same time. After removal of the strychnine pledget the depressor and respiratory reflexes reappear at about the same time as does the depressor reflex from the vagus. The reappearance of the sciatic depressor response is accompanied by a stage in which it is exaggerated (as shown in the figure), after which it returns to normal.

During the absence of depressor effect noted above, pressor reflexes

can still be obtained from the sciatic (Fig. 6). The effect of strychnine in these experiments is not due to a general action on the cord after absorption into the blood stream, for depressor responses can be abolished without the occurrence of convulsions, and injection of the total amount in the pledget does not abolish depressor responses. The result, I think, shows that in the normal animal the depressor impulses from the sciatic pass through the lower part of the spinal bulb and do not, or only to a trifling extent, depend on a spinal reflex. It is possible, however, that the simultaneous abolition by strychnine of the bulbar respiratory reflexes may aid the abolition of the sciatic depressor response, in the causation of which the rapid shallow respiration occurring on sciatic stimulation has sometimes been said to play a part (13).

Stimulation of the depressor points. It might be supposed that the action of strychnine on the depressor point is due to an effect on the superficial nerve cells of the region, *i.e.* to cells forming part of the dorsal nucleus of the vagus. But paralysis of the nerve cells (or of their synapses) would not prevent their axons from being stimulated at the point where they leave the cell. In fact, however, strychnine also diminishes the effect of direct stimulation of the depressor point (Fig. 7). Its effect on the cells must therefore be associated with either abolition of excitability of the superficial nerve fibres or an action on neighbouring or more deeply lying nerve cells.

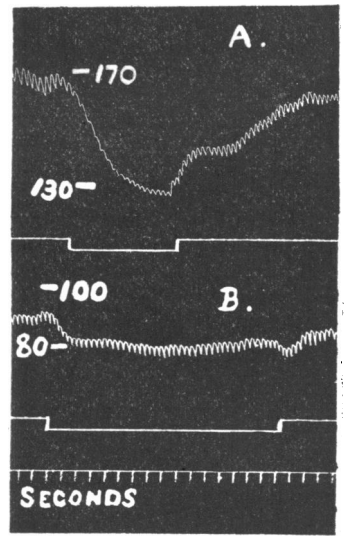


Fig. 7. Stimulation of left depressor point, cat; both vagi intact; (A) normal, (B) after strychnine.

Provided the strychnine is not allowed to act on the medulla for too long the depressor points recover their excitability to direct stimulation (Fig. 8); this recovery is coincident with the return of the depressor reflex from the vagus.

The question discussed by Ranson and Billingsley (8), by Bayliss, and by Roberts and myself, whether the depressor point is a supreme vaso-dilator centre, does not in any case arise; observations detailed in the next section show that the depressor points may be destroyed by cauterisation without diminishing the depressor effect from the sciatic, so that the depressor point cannot be a supreme vaso-dilator centre, for

not all dilator reflexes are transmitted through it. It may be that the abolition of sciatic depressor effect is due to diffusion to the vaso-constrictor (or pressor) centre, causing predominance of pressor action by

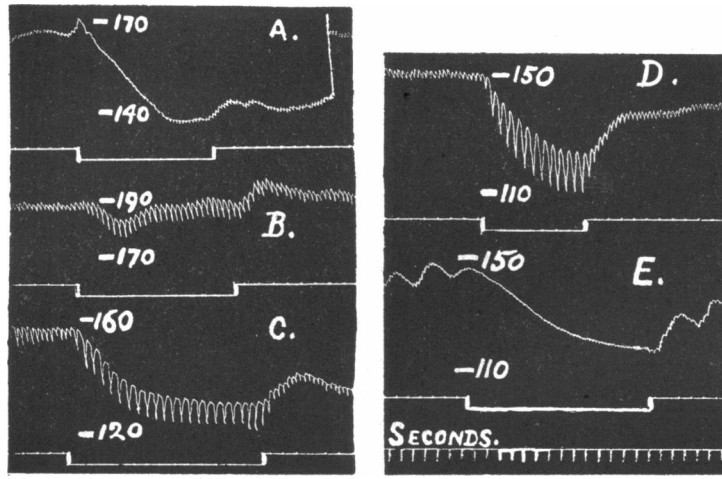


Fig. 8. Increased cardio-inhibition occurring during recovery from strychnine; stimulation of right depressor point; vagi intact; s.c. 12 throughout. A. Normal: strychnine was then applied for 10 mins. B. Stim. 5 mins. later. C. 20 mins. after B. D. 50 mins. later. E. Stim. after section of vagi.

increasing its excitability. But I believe that strychnine acts on the cells and possibly the fibres of the depressor point and that it diffuses to, and acts on, a nucleus or part of a nucleus[1] through which depressor reflexes from the sciatic are transmitted—a nucleus which is in no wise affected by cauterisation of the depressor points; but till the true nature of the depressor reflex from the sciatic is established no definite conclusions can be reached.

Cauterisation of the pressor and depressor points.

In this series of experiments, which deals with cats anæsthetised with urethane, the floor of the fourth ventricle was exposed in the way already described, and blood-pressure tracings were taken of the depressor effect from the vagus or depressor nerve and of the pressor and depressor effects from the brachial nerves at the elbow or the sciatic nerve.

The depressor points were then identified by electrical stimulation;

[1] In this connection one thinks naturally of the posterior extension of the dorsal accessory-vagus nucleus into the "closed" medulla.

they were cauterised by applying the end of a hot copper wire three times to them and the nerve stimulation was repeated with the same strengths of current as before. The pressor points were then identified, and cauterised in the same way; artificial respiration was started, for the latter procedure interfered with normal respiration, and the nerve stimulation was repeated. A complete series of tracings is shown in Fig. 9.

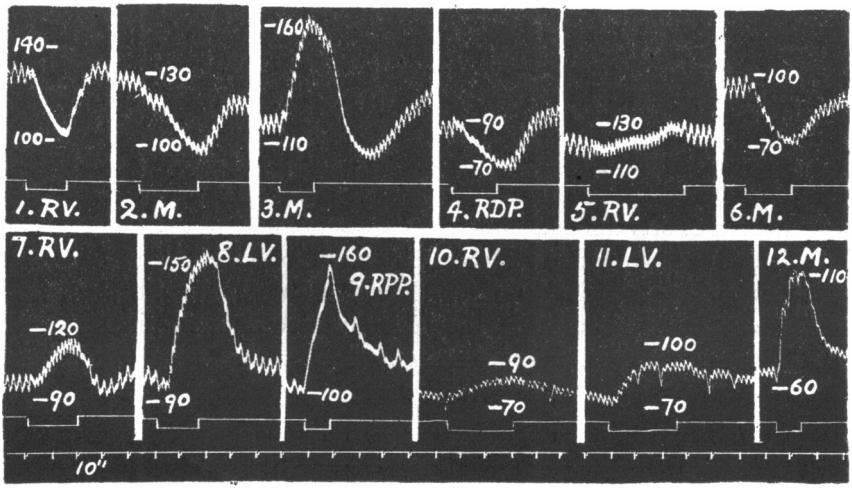


Fig. 9. Effect of cauterisation, cat. 1. Stim. R. vagus (L. vagus intact, s.c. 8). 2. Stim. R. median (s.c. 9; 2 per sec.). 3. Stim. R. median (s.c. 4, magnetic interruptor). 4. Stim. R. depressor point (s.c. 10).

Depressor points cauterised.

5. Stim. R. vagus (s.c. 8). 6. Stim. R. median nerve as in 2. 7. Stim. R. vagus as in 3. 8. The L. vagus was cut and stim. as in 3. 9. Stim. R. pressor point (s.c. 10).

Pressor points cauterised.

Artificial respiration. 10 and 11. Stim. R. and L. vagi as in 7 and 8. 12. Stim. median as in 3.

Cauterisation of the depressor points caused a fall followed by a rise of blood-pressure. After cauterisation, or indeed any injury, of the depressor points, direct stimulation of the injured area did not evoke any depressor effect.

From the depressor nerve after cauterisation of the depressor points either no effect or, if the strength of the stimulus was increased, a pressor reflex was obtained instead of the usual depressor one. The "reversal" was obtained every time. The difference between this result and the partial reversal, occasionally observed after application of strychnine

to the depressor point, may be explained by the hypothesis that in the case of strychnine, diffusion to, and paralysis of, the connections of some, at least, of the pressor as well as the depressor fibres of the vagus may occur. The phenomenon of reversal after cauterisation of the depressor points can only be due to destruction of depressor and unmasking of pressor fibres. The close resemblance between the effect occasionally produced by strychnine and that of cauterisation is suggestive evidence that in the former as in the latter case, "reversal," when it occurs, is due to the unmasking of pressor fibres. The diffusion hypothesis mentioned earlier will account for another and more striking difference between the effects of cauterisation and those of application of strychnine. After cauterisation appropriate stimulation of the median nerves or sciatic still causes a fall of blood-pressure, an effect which is abolished by local application of strychnine.

The facts recorded in the preceding paragraph clearly indicate that the depressor points are points on the reflex depressor arc of the vagus and are not essential for the production of vaso-dilatation. In the course of his experiments on animals decerebrated by the injection of starch Langley(5) has made observations which he interprets as possibly indicating that the centres for reflex depressor effects from the vagus are distinct from those involved in depressor effects from the sciatic. This dissociation may be due to the blocking by starch of an arteriole serving one capillary district within the area of a "centre," while another district close by is not so blocked off. It might well be produced if the depressor point or a cell station on the vagal depressor arc were blocked off without interfering with the nutrition of the neighbouring point which is not affected by cauterisation of the depressor points, but which is affected by the diffusion of strychnine applied thereto; or *vice versa*.

It has been shown earlier(1) that the pressor points are not constant in position. Their situation was therefore determined in each case by experiment. Cauterisation of the pressor points caused a rise of blood-pressure followed by a fall. After cauterisation of the depressor points, pressor reflexes only, as has been said, can be obtained from the central end of the cut vagus. If now the pressor points are cauterised these vagal pressor effects are reduced to about one-third. At the same time the pressor effect from the median is almost unchanged, this in spite of the fact that after cauterisation of the pressor points, which are close to the fasciculus solitarius, there is considerable interference with respiration and artificial respiration may have to be employed. Here we have similar direct proof that the pressor points do not represent the bulbar vaso-

motor centres, but are merely points on the reflex pressor arcs of the vagi. Since the response from the vagus was only reduced to one-third of what it was originally, there must be pressor fibres in the vagus other than those which traverse the pressor point. When I attempted to cauterise the pressor points more deeply in the hope of completely abolishing pressor reflexes from the vagus, I found that there was a fall of blood-pressure to under 30 mm. of mercury, such a fall as results from an incomplete lateral section of the medulla as practised in Dittmar's operation.

After completion of this work I found that in 1880 Laffont had performed somewhat similar experiments (14). He observed, as the result of puncturing the floor of the fourth ventricle, dilatation of the hepatic vessels, which he interpreted as dependent not on the destruction but on the stimulation of a vaso-dilator centre. On the following day stimulation of the depressors in the same animal failed to produce the customary fall of blood-pressure, probably, he thought, in consequence of paralysis due to the after-effects of the puncture.

Application of smaller doses of strychnine to the depressor and pressor points.

The fact that the paralysis of the depressor reflex by strychnine was preceded and followed by stages in which that reflex was exaggerated suggested that smaller doses of strychnine would result in exaggeration alone without the subsequent occurrence of paralysis. This idea was now tested; in three experiments on cats anæsthetised with urethane about a square millimetre of filter paper, soaked in a 0·1 p.c. solution of strychnine nitrate in distilled water warmed to body temperature, was laid upon both depressor points; the amount of the salt so applied would be about ·005 mgm. This application was followed in about 5 minutes by a definite increase in the size of the depressor reflex sometimes accompanied by increased cardio-inhibition (Fig. 10). The filter paper was removed in about 15 minutes and the increase lasted for from 1 to 1½ hours. Distilled water, similarly applied, had no effect on the size of the reflex, but it is of interest to note that ordinary Ringer's solution warmed to body temperature also increased the depressor reflex over approximately the same interval of time. Application of these small doses of strychnine also increased the effect obtained on direct stimulation of the depressor points.

The increase of the depressor reflex by this means naturally suggested investigation as to whether pressor reflexes were similarly increased. In

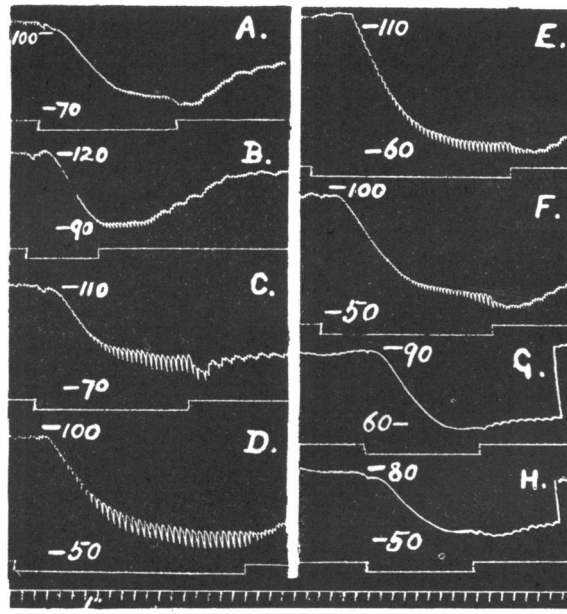


Fig. 10. Stim. of L. vagus (R. vagus intact, s.c. 8). A. Before applying ·1 p.c. strychnine to depressor points; B. to E. at intervals during application (about 1 hour). F. 10 mins. after removing strychnine. G. 30 mins. H. 80 mins.

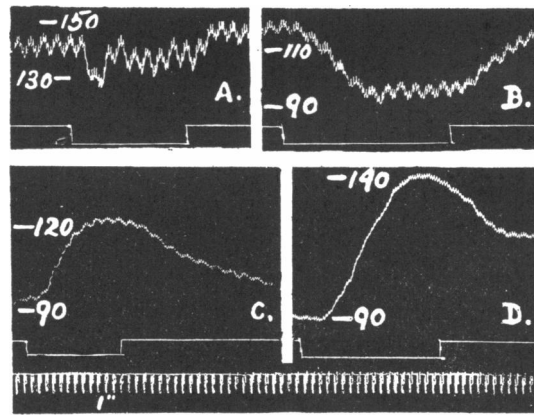


Fig. 11. A. Minimal depressor reflex obtained from L. depressor of cat; L. vagus cut, R. vagus intact; s.c. 29·5. B. Increased reflex obtained after application of ·1 p.c. strychnine to depressor points with same strength of stimulus. Half an hour after removal of strychnine the minimal stimulus which gave a depressor reflex was 38. After an interval of 2 hours the depressor points were cauterised. Vagal pressor response: C. before strychnine; D. after strychnine.

three other experiments, after cauterisation of the depressor points, the "reversal" of the depressor reflex from the vagus into a pressor reflex was demonstrated, and then the minimal strength of stimulus which would just give a pressor reflex from the vagus was determined. A square millimetre of filter paper soaked in warm 0·1 p.c. strychnine nitrate, was then applied to the upper end of each ala cinerea, where the pressor point is normally found, and in each case, after the lapse of about 5 minutes, a definite increase in the size of the pressor reflex from the vagus was noted, this increase lasting for about the same period after removal of the strychnine plug (Figs. 11, 12). Distilled water had no such effect. The effect of Ringer was not tried. It may therefore be concluded that the action of small doses of strychnine nitrate of the order of about ·005 mgm. locally applied to the appropriate sites is to increase vascular reflexes whether pressor or depressor.

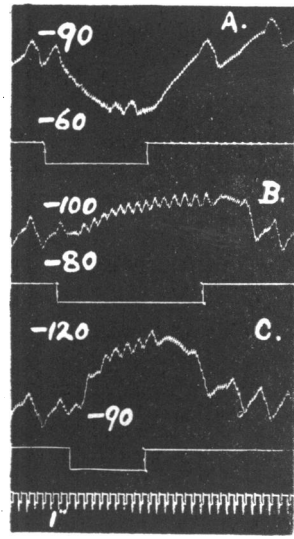


Fig. 12. Cat, both vagi cut; stim. of L. vagus; s.c. 8 throughout. A. Normal. B. After cauterisation of depressor points. C. After application of ·1 p.c. strychnine to pressor points.

Conclusions.

1. The application of 1 p.c. strychnine nitrate in doses of about ·05 mgm. in distilled water to the depressor points of the cat's spinal bulb blocks the depressor reflex on vagal stimulation and prevents direct stimulation of the depressor point from having any effect.

2. A fall of blood-pressure can be obtained in the cat by stimulating the sciatic or median nerve with induction shocks repeated two to four times a second. This fall of blood-pressure and the reflex effect of the sciatic on respiration are prevented by the local application of strychnine, as described above.

3. The amount of strychnine applied is too small to paralyse structures elsewhere than in the approximate region to which it is applied, so that normally vagus reflexes and depressor somatic reflexes depend upon some structure or structures in the lower portion of the bulb.

4. The above application of strychnine does not abolish the pressor effect of somatic nerve stimulation.

5. An increase in the above-mentioned reflexes occurs in the early stage of the action of 1 p.c. strychnine, in recovery from the paralysis produced by it, and when 0·1 p.c. strychnine is applied instead of 1 p.c.

6. Destruction of the depressor points by cauterisation has the same effects as applying 1 p.c. strychnine to them, *except* that (*a*) the depressor effect of somatic nerve stimulation is not altered, from which it is concluded that 1 p.c. strychnine diffuses to some structure in the course of somatic depressor reflexes and paralyses it; and (*b*) that strong stimulation of the vagus may have a pressor effect, though no depressor one can be produced.

7. The occurrence of a rise of blood-pressure on vagus stimulation after destruction of the depressor point is definite evidence that pressor fibres are present in the vagus. This fact, and the effect on the vascular reflexes obtained by local application of strychnine to the depressor points, confirms the view put forward by Langley that strychnine does not cause any reversal of nerve impulses, *i.e.* does not convert inhibitory into vaso-constrictor impulses.

8. Cauterisation of the pressor area following cauterisation of the depressor points, reduces the pressor action of the vagus but leaves uninfluenced the pressor action of somatic nerves.

The expenses of this work were defrayed in part by a Government Grant from the Royal Society, in part by a grant from the British Association, and in part by a grant from the British Medical Association.

REFERENCES.

(1) Scott and Roberts. This Journ. 58. 168. 1923.
(2) Ranson and Billingsley. Amer. Journ. Physiol. 41. 85. 1916.
(3) Rey and Aducco. Zntrlb. f. Physiol. 1. 586. 1888.
(4) Bayliss. Proc. Roy. Soc. B. 80. 353. 1908.
(5) Langley. This Journ. 45. 239. 1912; 53. 158. 1919.
(6) Stewart and Pike. Amer. Journ. Physiol. 19. 346. 1907.
(7) Reid Hunt. This Journ. 18. 383. 1895.
(8) Ranson and Billingsley. Amer. Journ. Physiol. 42. 20. 1916–17.
(9) Gruber. Ibid. 42. 214. 1916–17.
(10) Gruber and Kretschner. Ibid. 46. 222. 1918.
(11) Vincent and Ogata. Journ. Comp. Neurol. 30. 355. 1918–19.
(12) Ranson and Hess. Amer. Journ. Physiol. 38. 132. 1915.
(13) Vincent and Cameron. Quart. Journ. Exp. Physiol. 9. 45. 1915. But cp. Gruber and Kretschner, loc. cit.
(14) Laffont. C. R. Acad. de Sci. 90. 705. 1880.