On Reciprocal Innervation in Vaso-motor Reflexes and the Action of Strychnine and of Chloroform thereon.

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CONTENTS.

I. Introductory.

In a paper published in the year 1893, after describing various experimental results on vascular reflexes, I made use of the following words: "the simplest explanation of the above results is the hypothesis that the vaso-motor centre consists of a constrictor and a dilator part, the depressor nerve acting in an inhibitory manner on the former, and in an exciting manner on the latter, while pressor nerves act in an opposite way on both."*

The evidence brought forward at that time in support of this view was mainly indirect, and in no way comparable with the brilliant experimental proofs afforded by Sherrington's masterly researches on the similar phenomena in the case of the reflexes to voluntary muscles. These latter results have, however, given renewed interest to the question, and the following pages contain an investigation whose object was to obtain direct experimental evidence whether or not the phenomena of vascular reflexes can be brought into line with those affecting skeletal muscle.

Since the publication of my paper referred to, certain incidental observa-

* "On the Physiology of the Depressor Nerve," 'Journ. of Physiology,' vol. 14, p. 317, 1893.

tions have been brought forward at various times tending to confirm the above hypothesis. These will best be discussed under the separate headings of the next section.

Before proceeding to the experimental results, it will be advisable to make clear the meanings attached to some of the words used. By "vaso-motor" I intend to include not only vaso-constrictor effects, as is sometimes done, but also those of a vaso-dilator nature. Both actions are, in fact, vaso-*motor*, one producing movement in the sense of narrowing of vessels, the other widening. Similarly, by vaso-motor centre, or centres, I mean the centres from which are given off both the vaso-dilator and vaso-constrictor fibres, whatever may be the situation of these centres.

It is also necessary to remember that under normal conditions the arterioles are in a state of moderate contraction or tone, which may continue even when these vessels are separated from connection with the central nervous system. This tone is probably a normal characteristic of smooth muscular tissue; but, apart from this, it is kept up by the contractile reaction of the arterial muscle to the distending force of the heart-beat,* as well as by the effect of the internal secretion of the adrenals, in the case of those arterioles supplied with sympathetic nerve-fibres.†

This inherent muscular tone of the arterioles can be affected in two directions by impulses from the central nervous system, at all events in the case of most organs of the body. It can be increased by impulses down vaso-constrictor fibres or diminished (inhibited) by impulses down vaso-dilator fibres. Moreover, these impulses may be continuous, resulting from a state of tonic excitation of their respective centres, in all probability of reflex origin.

It is then obvious that, when we observe a vaso-dilatation in a particular organ in response to excitation of an afferent nerve, this result may be due to two things, either an excitation of vaso-dilator fibres or, supposing that the vaso-constrictor centre is in a condition of tonic excitation, to an inhibition of this centre, resulting in a cessation of the vaso-constrictor impulses previously producing increased contraction of the arterial muscle. Both results may be simultaneously brought about.

Conversely, when what is conveniently called a "pressor" reflex is brought about, that is, one associated with increased contraction of arterioles and consequent rise of arterial blood-pressure, we may have both excitation of vaso-constrictor fibres and inhibition of tone in the vaso-dilator centre.

Now, in order to investigate experimentally the various possibilities referred

* W. M. Bayliss, 'Journ. of Physiology,' vol. 28, p. 220, 1902.

† T. R. Elliott, 'Journ. of Physiology,' vol. 32, p. 401, 1905.

to, it is necessary to be able to make use of organs which are supplied with both vaso-constrictor and vaso-dilator nerves, and these two kinds of fibres must pass to the organ in anatomically distinct nerve-trunks. When this is the case, it is possible to decide by section of one or the other whether a particular result is due to one of these alone. For instance, if we observe a vascular dilatation in the sub-maxillary gland in response to excitation of the central end of the depressor nerve, we can decide by section of the cervical sympathetic nerve whether the effect is still present. If so, it cannot be due to inhibition of constrictors alone, there must be also excitation of dilators in the Chorda tympani nerve.

There are, unfortunately, very few organs, accessible to investigation, which satisfy these conditions. Such are the sub-maxillary gland, the tongue, the external ear in the rabbit, the penis in the dog and the limbs. On all of these organs I have made observations.

General Methods.—All animals used were anæsthetised with A.C.E. mixture and morphine, except in the case of rabbits, where ether was used instead of A.C.E. mixture for reasons which will be seen later. With the exception of the submaxillary gland, all the organs investigated were placed in oncometers of appropriate form and the changes of volume recorded by a piston-recorder. In the plethysmographic experiments curare was usually found to be necessary. The arterial blood-pressure was always traced simultaneously with the plethysmographic curve.

II. Reciprocal Innervation in the Normal Animal.

There are, in the investigation of this question, four cases to be considered. In a reflex producing fall of blood-pressure with general dilatation of arterioles, is there evidence of both excitation of vaso-dilator nerves and inhibition of central vaso-constrictor tone? In a reflex of the opposite kind, is there evidence of both excitation of vaso-constrictor nerves and inhibition of central vaso-dilator tone?

1. *Depressor Reflexes.*

These are to be obtained, as is well known, by excitation of the central end of the depressor nerve in the rabbit, also from the central end of the vagus in the cat, and, under certain conditions, not exactly definable, from the central end of the vagus in the dog.

The discoverers of the depressor nerve, Ludwig and Cyon, apparently regarded its action as purely inhibitory on the vaso-constrictor centre.* This was also the usual opinion of subsequent workers until the publication of my

* 'Ber. d. k. Sächs Ges.,' Math. phys. Classe, vol. 18, p. 318, 1866.

paper above referred to. Ostroumoff,* however, in his work on the dilatation of cutaneous vessels, had already expressed the view that, in this particular case, the action of the depressor nerve is due to an excitation of vaso-dilator fibres and not to an inhibition of constrictor tone. Biedl,† at a later date, came to the same conclusion with regard to the vascular innervation of the adrenals. Cyon,‡ himself, on the other hand, strenuously opposes this interpretation of the facts. None of these observers recognises the possibility of both effects being present at the same time.

(i) *Excitation of Dilators.*—All the vaso-dilator nerves to the posterior limbs are contained in the dorsal roots of the sacral plexus.§ All the constrictors are situated in the abdominal sympathetic, having left the spinal cord in the white rami from the eleventh thoracic to the third lumbar segments inclusive.‖ If, then, the spinal cord be transected at the fourth lumbar segment the hind-limbs will be, as regards their vaso-motor supply, in connection with the central nervous system by means of vaso-constrictor fibres only; and, if the abdominal sympathetic chain on both sides be extirpated, the dilators alone will be left. When this latter operation has been performed, it is found that dilatation of the limbs can still be obtained on exciting the depressor nerve. This can only be due to excitation of vaso-dilator fibres. The evidence for this statement is given in my paper above-mentioned. I will, therefore, merely refer to the experiment shown in fig. 10, p. 293, of that paper.¶

The objection may be made that the dilator impulses to the limbs are of a peculiar nature, being antidromic. It is, therefore, important to test the behaviour of organs, such as the submaxillary gland, the penis, or the tongue, where the dilators are of the recognised type.

The submaxillary gland suggests itself at once for this purpose, since it is easy to observe changes in the venous outflow by inserting a cannula in the peripheral end of the external jugular vein, after having tied all branches except that from the gland. Hirudin, in doses of about 0·02 gramme per kilogramme was found to be sufficient to prevent clotting in the cat. The drops of blood were allowed to fall on a slip of mica attached to the end of the lever of a Marey tambour, in connection with another tambour which recorded each drop on the smoked paper. The cervical sympathetic was cut on both sides, so that the gland was supplied with dilator fibres only, conveyed by the

* 'Arch. f. d. ges. Physiol.,' vol. 12, p. 277, 1876.

† 'Arch. f. d. ges. Physiol.,' vol. 67, p. 469, 1897.

‡ Article "Dépresseur (nerf)," Richet, 'Dictionnaire de Physiologie,' vol. 4, p. 786, 1900.

§ Bayliss, 'Journ. of Physiol.,' vol. 28, p. 276, 1902.

‖ Bayliss and Bradford, 'Journ. of Physiol.,' vol. 16, p. 10, 1894.

¶ 'Journ. of Physiol.,' vol. 28, p. 293, 1902.

Chorda tympani. The central end of the vagus, on the opposite side to the gland under observation, was arranged for excitation. As a rule, the animal was eviscerated, in order to diminish the effects of the mere fall of blood-pressure on the rate of flow through the gland. Fig. 1 is a tracing obtained in this way. It will be noted that, in spite of evisceration, there is a large fall of arterial pressure, which lasts for a long time after the excitation ceases. This is usually the case with vaso-motor reflexes in the cat. While the blood-pressure is falling, the drops greatly increase in number per unit time, but later, the effect of the low blood-pressure shows itself by a slowing of the flow. There is, apparently, no lasting vaso-dilatation, as seen in direct excitation of the chorda. The reason for this is, probably, that no saliva is secreted, so that the action of products of cell-activity on the arterioles is

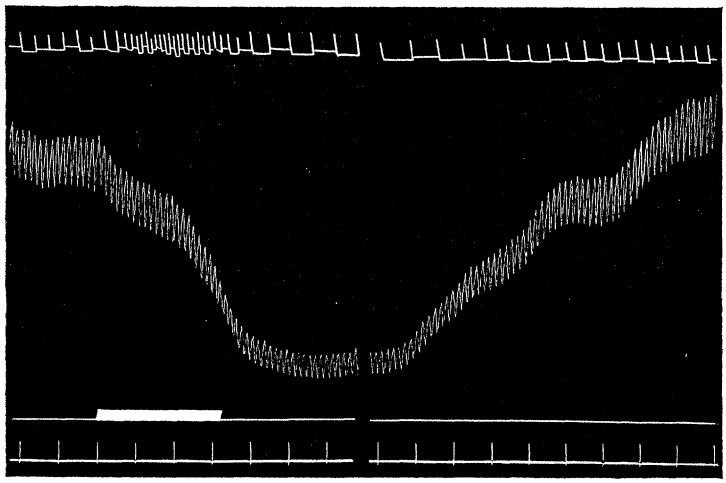

FIG. 1.—Excitation of chorda dilators in depressor reflex. Upper line, drops of blood from gland vein. Middle curve, arterial pressure. Bottom line, time in 10 sec. Zero of blood-pressure, 58 mm. below time line.

absent. In order to save space, the middle part of the tracing has been cut out, amounting to three minutes in time.

A circumstance may be mentioned here that makes the investigation of this, as of other vaso-dilator reflexes, a matter of peculiar difficulty: viz., they are only to be seen while the animal is in the best condition as regards temperature, blood-pressure, etc., *i.e.*, at the beginning of an experiment. It seems improbable that this loss of reflex excitability is due to fatigue, since it has no obvious relation to the number of times the reflex has been excited.

The effect on the submaxillary gland above described is abolished by section of the chorda, but considering the circumstance spoken of in the previous paragraph, too much importance must not be given to this result.

It appears to me that the only objection that can be brought against my interpretation of the experiment is that the increase of blood-flow may be in some way a consequence of the fall of general arterial pressure, the bulbar centres of gland-nerves may be excited by anæmia in a manner like that produced by the injection of extracts of duodenal mucous membrane,* or the rapid fall of pressure may induce a relaxation on the part of the arterioles themselves. Now, in the first place, the time at which the effect appears is not consistent with either of these suggestions. If the fall of pressure were the cause of the dilatation, this would be greatest during, or immediately after, the fall. On putting the question to the test of experiment, by the excitation of the peripheral end of the vagus nerve, I find that there is frequently a short period of increased rate of flow when the blood-pressure returns to normal. It was only seen when there was a rise of blood-pressure following the fall, and was absent after section of the chorda. It appears therefore, to be due to excitation of bulbar centres by anæmia. In order to be able to detect any secretion of saliva, which would only be small, I performed a similar experiment on a dog, but could not observe any secretion. Apparently the secretory centres were not excited by the degree of anæmia produced. It has been found difficult or impossible to excite reflexly electrical changes in glands.†

[*Note added May* 25, 1908.—Professor Langley thinks that objection may be taken to the interpretation of vaso-dilation in the submaxillary gland in response to excitation of the central end of the vagus as representative of a general depressor reflex. The vagus nerve contains afferent fibres from various digestive organs, so that the effect on the salivary gland may well be a special reflex associated with the taking of food and different in its mechanism from genuine depressor reflexes. In order to meet this objection, I have repeated the experiment, but exciting the depressor nerve in the rabbit. In this case also considerable increase of the rate of blood-flow through the gland deprived of constrictors was obtained on excitation. It seems, then, that the vagus effect in the cat may fairly be taken as a true depressor one. Moreover, as shown below, the reflex from the vagus in the cat consists, not only in the excitation of dilators, but also in inhibition of constrictors, so that, in any case, it shows the phenomenon of reciprocal innervation.

Professor Asher informs me that he has obtained excitation of vaso-dilators to the submaxillary gland of the rabbit on exciting the depressor nerve.]

* Bayliss and Starling, 'Journ. of Physiol.,' vol. 28, p. 348, 1902.

† Bayliss and Bradford, 'Journ. of Physiol.,' vol. 7, p. 224, 1886.

The tongue, especially in the dog, would be expected to be a favourable organ for investigation of vascular reflexes. To my disappointment it was found to give very poor plethysmographic records, so far as concerns changes in its own vessels of an active nature. On excitation of the central end of depressor or vagus there was occasionally to be seen a slight dilatation at the beginning of the fall of pressure, but this was soon overpowered by the passive effect of the lowered arterial pressure. In these experiments the cervical sympathetics were cut on both sides, so that the tongue was supplied only with vaso-dilators.

In the course of experiments made for another purpose two or three years ago, I noticed that in a depressor reflex, the abdominal sympathetics having been cut, there was increase of volume of the penis, enclosed in a plethysmograph. Since the rhythmic contractions shown by the curve were also inhibited, it might be that these contractions, probably due to the retractor penis, were responsible for the changes of volume. I have recently, therefore, repeated the experiment, three times in all.

In the first experiment, although there was a marked effect, it was found, *post mortem*, that only one of the sympathetics had been completely severed, the other was merely crushed. This latter was apparently incapable of conduction, since there was no contraction of the organ on excitation of a sensory nerve nor in asphyxia.

In the second experiment the vaso-dilatation did not appear until the arterial pressure had returned to its original level, so that it might be due to local reaction. This does not seem to have been the case, however, since an equally great and sudden fall produced by cardiac inhibition was not followed by any dilatation.

Fig. 2 was obtained in the third experiment. After a long latent period the blood-pressure begins to fall, and simultaneously there is an increase of volume of the penis. The curve has the appearance of having been cut off at the top; this is, no doubt, due to the piston recorder sticking slightly at this position.

The conclusion to be drawn is that when cut off from the vaso-constrictor centre the penis is still capable of reflex vascular dilatation, which can only be due to excitation of vaso-dilator nerves contained in the pelvic nerves of Langley, the *nervi erigentes* of Eckhard.

It was shown by Winkler,* with some degree of probability, that vaso-dilators to the external ear of the rabbit run in upper cervical nerve-roots. They are, perhaps, posterior root fibres, and, if so, the dilatation is antidromic in nature. The majority of the constrictor fibres run in the cervical

* 'Sitzungsberichte d. Wien Akad.,' Math.-Naturw. Klasse, vol. 111, June, 1902.

sympathetic, although it has been shown by Fletcher* that a few fibres for the tip of the ear run by way of the ramus vertebralis of the stellate ganglion and the third cervical nerve. If the cervical sympathetic is cut, there is, then, a small part of the ear left in connection with vaso-constrictors. I do not think that these fibres play any part in the reflexes obtained under experimental conditions. The ear soon becomes cold and

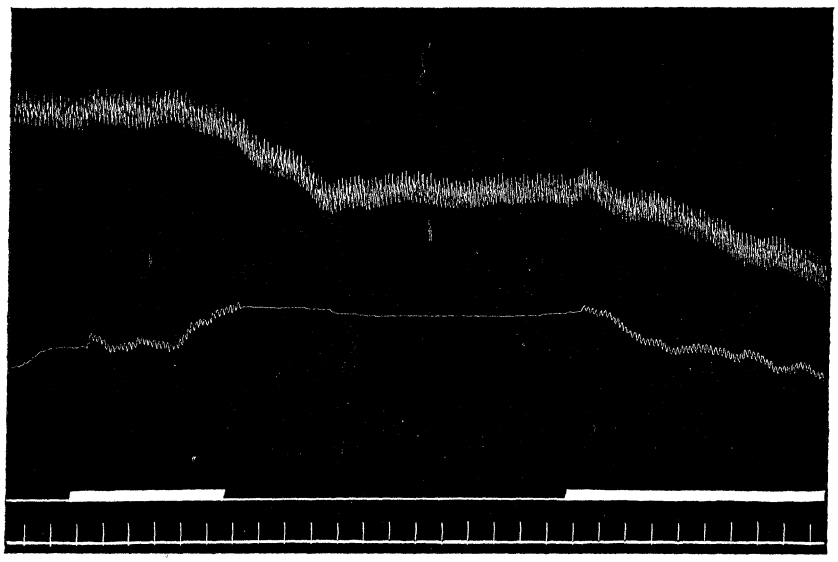

FIG. 2.—Excitation of dilators in pelvic nerves in depressor reflex. Upper curve, arterial pressure. Middle curve, volume of penis. Blood-pressure zero, level of excitation-signal. The second excitation of the vagus central end was without effect on the penis, probably following too closely after the preceding one.†

bloodless under anæsthetics and curare, so that only reflex effects of considerable magnitude are shown in the plethysmographic curve. In fig. 3 the result of exciting the central end of the vagus on the opposite side, which, in this case, contained more depressor fibres than the depressor nerve itself, is shown. The cervical sympathetic having been cut, the effect must be due to dilator nerves, apart from the problematic inhibition of Fletcher's fibres, above mentioned. Since the dilators in question are possibly

* 'Journ. of Physiol.,' vol. 22, p. 259, 1898.

† It will be noticed that in many of the plethysmographic curves given in the following pages small waves appear during the period of excitation. These are merely due to the fact that the exciting coil was placed on the table of the kymograph. The interrupter was in action only during the excitation-period and the slight shaking of the writing lever diminished the friction between it and the smoked paper so that the respiratory waves were traced. This is of use in that it serves to mark out exactly the period of excitation.

antidromic in nature, I did not think it worth while to devote much time to the detailed investigation of the case.

An indirect piece of evidence, tending to confirm the thesis of this section, is derived from consideration of the vascular reflexes in the "eviscerated" animal. In an animal from which all the abdominal viscera have been removed or tied off from the circulation, and in which, also, the abdominal and cervical sympathetics have been cut and the median nerve of one fore-limb prepared for excitation, it is surprising to find that the changes of blood-pressure in vascular reflexes are, in many cases, as large as in the normal animal. When we remember that the only organs retaining their constrictor supply are one fore-limb and part of the other, together with the walls and skin of the chest and upper part of the abdomen, it is difficult to conceive that this small fraction of the total vascular area remaining can be responsible for as large an effect as is obtained in the complete animal; of course, the capacity of the vascular system is very greatly diminished, but the proportion of the part supplied with constrictors to the whole is far less than in the normal animal. On the other hand, the dilator supply of the organs remaining, so far as they possess such, is not interfered with. It is, I think, difficult to avoid the conclusion that the dilators take part in the reflexes in such cases. Since I shall have frequently to refer to the state of affairs in animals in this condition, I shall, for the sake of brevity, speak of these as "dilator" animals. It should be mentioned that no change in the heart-beat could be detected in the reflexes referred to above. To put it shortly, the "dilator" animal possesses the following parts supplied with dilators and devoid of constrictors: head and neck (perhaps excluding brain), hind-limbs, and trunk from middle of abdomen; while the remaining parts have both dilators and constrictors, no part having constrictors only.

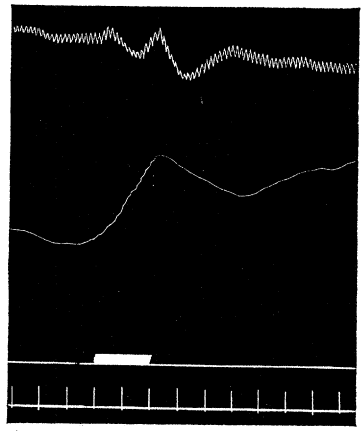

FIG. 3.—Excitation of dilators to ear in depressor reflex. Upper curve, arterial pressure. Middle curve, volume of ear. Time in 10 sec. intervals.

(ii) *Inhibition of Constrictors.*—As already stated, the general opinion is that depressor effects are brought about by inhibition of constrictor tone. But, so far as I am aware, the proof has not been yet given that vaso-dilatation is possible in the complete absence of dilators. Fig. 4 will serve as such a proof. This tracing was obtained from a dog in which, for other

purposes, the spinal cord had been transected at the third lumbar segment 27 hours previously. The hind-limbs were, therefore, in connection with vaso-motor centres by vaso-constrictor fibres only. The first excitation in the figure is of the central end of the vagus; a fall of arterial pressure follows, with considerable increase of volume of the limb. Between the two parts of the figure the abdominal sympathetic was cut on the side of the limb under

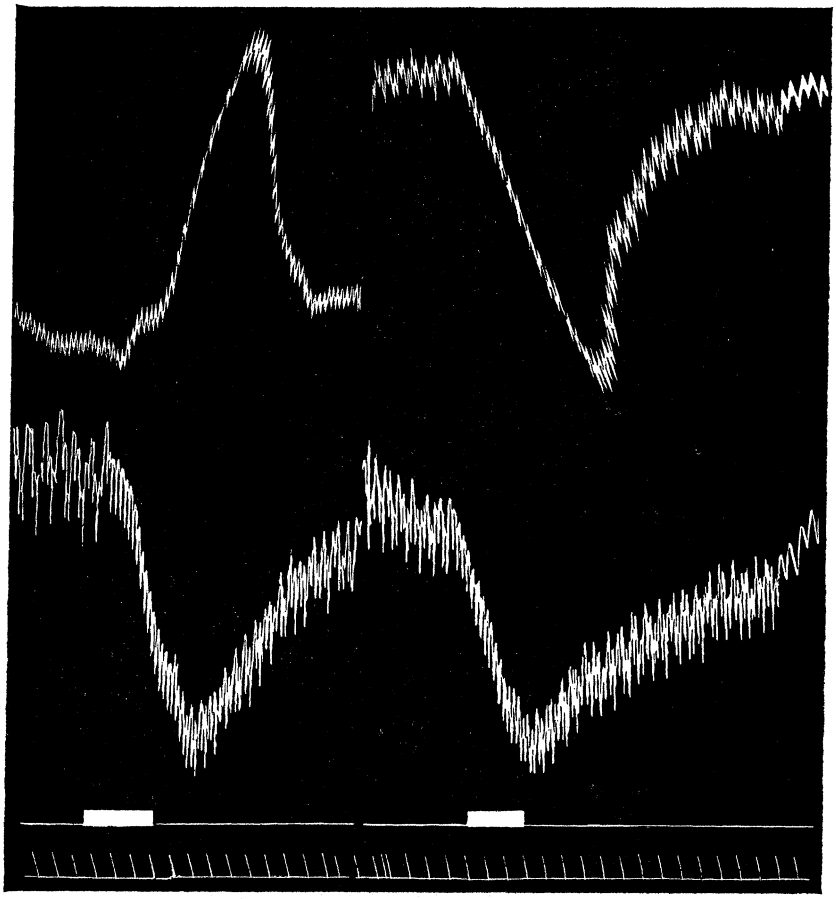

FIG. 4.—Dilatation by inhibition of constrictor tone. Upper curves, volume of hind-limb of dog. Lower curves, arterial pressure. Time in 10 sec. Zero of blood-pressure, 24 mm. below time-signal.

observation. Expansion of the limb is shown, due to cutting off tonic constrictor impulses. The central end of the vagus was again excited, a similar fall of arterial pressure being produced, but this time accompanied by passive *diminution* of volume of the limb. This result is, however, not always to be obtained; it appears that, at all events under experimental conditions, tone of

the abdominal sympathetic is sometimes absent, so that after section of the cord no reflex dilatation of the limb can be obtained.*

2. *Pressor Reflexes.*

(i) *Excitation of Constrictors.*—When the arterial pressure rises in response to excitation of the central end of a sensory nerve, it is universally admitted that the effect is due to excitation of vaso-constrictor fibres. But, as in the last case, the possible co-operation of dilators has not been taken into account. I have, therefore, taken a tracing of the change of volume in the hind-leg of a cat, in which the cord has been transected in the middle of the lumbar region, in order to cut off the dilator supply of the part. Fig. 5 reproduces this experiment. At the place indicated by the signal, the central end of the median nerve was excited. The arterial pressure rises, and, at the same time, the limb constricts. The effect is prolonged, as is usual in the cat. Further experiments were deemed unnecessary, as the phenomenon is undisputed.

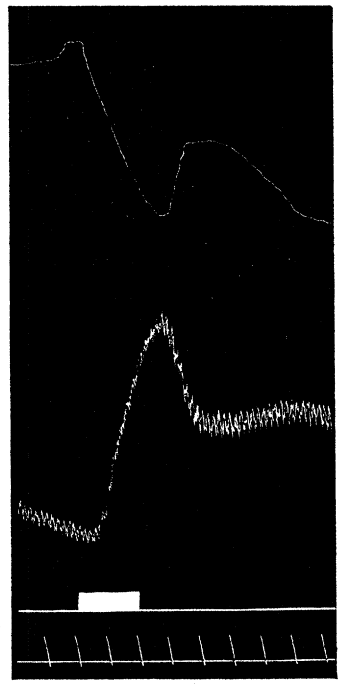

FIG. 5.—Constriction by excitation of vaso-constrictors. Upper curve, volume of leg. Lower curve, arterial pressure. Zero, 25 mm. below time-signal.

(ii) *Inhibition of Dilators.*—This case has proved to be the most difficult one of the four as regards experimental investigation. It is obvious that, in order to be able to show inhibition of tone in the vaso-dilator centre, this tone must first be in existence. Just as in the experiments of Sherrington, where extensor tone was usually produced by decerebration, in my experiments it was necessary to induce tone in the dilator centre by keeping the animal as warm as possible, and, in the eviscerated animal, with renal vessels tied, by the intravenous injection of warm saline, in order to raise the arterial pressure as high as possible. Nevertheless, a

* *Note added to Proof.*—I have recently observed another case of dilation by inhibition of constrictor tone in the absence of dilator fibres. The blood-flow through the sub-maxillary gland of the cat is increased in rate by exciting the central end of the vagus on the opposite side, even after section of the Chorda tympani nerve, if the cervical sympathetic is left intact. The effect, as far as it is possible to compare results on different animals, seems to be somewhat less than that obtained when the dilators are intact and the constrictors cut, as described in the previous section.

considerable number of experiments were of a negative character. At the same time those in which positive results were obtained were precisely such cases as would be expected to possess tone of dilators, viz., those with high temperature and blood-pressure; moreover, the effect was generally obtained, if at all, early in the course of the experiment.

Fig. 6 is an instance from the ear of the rabbit. The cervical sympathetic being cut, the vaso-motor supply was limited to dilators, with the exception of the few sympathetic fibres to the tip of the ear already referred to.

In fig. 7 an attempt was made to increase the tone of the dilator centre by

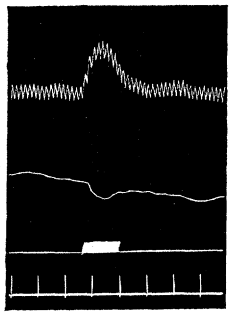

FIG. 6.—Vaso-constriction by inhibition of dilator tone. Median nerve excited. Upper curve, arterial pressure. Zero, 30 mm. below time-signal. Lower curve, volume of ear. Time in 10 sec.

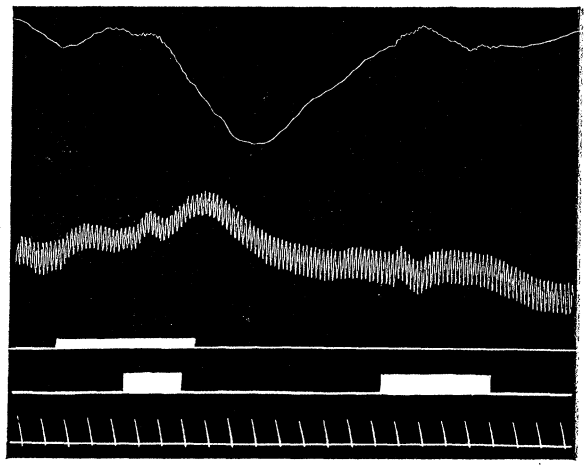

FIG. 7.—Inhibition of dilator tone. Upper curve, volume of hind-leg. Lower curve, arterial pressure. Zero, 40 mm. below time-signal. Uppermost signal, excitation of depressor. Middle signal, excitation of median nerve, twice.

excitation of the depressor. In order to lessen the effect of the fall of arterial pressure, the peripheral end of the cervical sympathetic was excited along with the depressor; this latter, however, did not seem to be very active, as judged by the change of arterial pressure. It did, apparently, increase the effect of excitation of the median nerve, shown by the difference between the first and second excitations on the tracing. The small effect of the later one may also be due to its following the previous one at too short an interval of time.

The tongue was disappointing, as before, showing mere passive changes

with the blood-pressure; perhaps these changes were rather less than would be expected from the amount of the rise of pressure obtained.

The sub-maxillary gland, with sympathetic cut, drops being recorded as before, showed a distinct slowing of the rate of flow at the beginning of the excitation of the median, but this was rapidly overpowered by the rise of arterial pressure increasing the circulation. It appears that this organ is very sensitive to changes in the general blood-pressure.

On the whole, it seems that, under experimental conditions, inhibition of dilator tone does not play a great part in pressor reflexes. No doubt, under more natural conditions, it has a greater importance. Moreover, from the theoretical point of view, it is of interest to be able to show that it does take place.

Indirect evidence similar to that referred to above, with regard to the magnitude of the vascular reflexes in the "dilator" animal, applies here also. It is rather difficult to find in literature measurements of rise of arterial pressure on exciting central ends of sensory nerves; but, on looking over several curves, I note that 70 mm. Hg is a high value. Bradford* states that the rise obtained from the central end of a dorsal root is of unusual magnitude; on measuring one of the curves he gives, I find that it amounts to 76 mm. Hg. To compare with this, in a "dilator" dog, on exciting the median nerve, there was a rise of 50 mm. Hg, viz., from 130 mm. to 180 mm., and the rise would probably have been greater if the arterial pressure had been lower to begin with, as it appears to have been in Bradford's experiments. It is difficult to avoid the conclusion that inhibition of vaso-dilator tone plays some part in the rise of pressure in the "dilator" animal.

3. *Lovén Reflexes.*

This type of reflex was first described by Lovén in the ear of the rabbit and in the hind-leg of the same animal. It has subsequently been found in various other organs, so that it may fairly be regarded as of general occurrence. Put briefly, when the afferent nerve from any particular organ is excited, there is produced, along with the usual pressor effect on the general blood-pressure, a vaso-dilatation in the organ itself. By this means the maximal supply of blood is sent to an active organ. I have previously shown† that dilator centres are excited, but, as yet, the proof is wanting that constrictor tone is inhibited.

To decide this point, I made the following experiment: In a dog, the dorsal roots of the lumbo-sacral plexus on the left side were divided, and the

* 'Journ. of Physiol.,' vol. 10, p. 400, 1889.

† 'Journ. of Physiol.,' vol. 28, p. 292, 1902.

cord itself transected immediately below the lowest root cut. It was found, *post mortem*, that the roots from the third to the seventh lumbar inclusive had been divided, and the cord was completely severed with the exception of a small piece of the anterior columns. The central end of the sixth root was prepared for excitation. The left hind-leg was placed in a plethysmograph. At first excitation of the central end of the dorsal root produced the usual pressor effect, a reflex *constriction* of the limb, precisely similar to that resulting from the median nerve, so that the Lovén effect appeared to be absent. On carefully raising the root well away from the tissues, however, a different result was obtained. With the same strength of exciting current the rise of blood-pressure was less, a fact indicating escape to the posterior columns of the cord in the previous case, while in the leg, instead of constriction, there was now well-marked *dilatation*. Fig. 8 shows the contrast between the effect of the median and that of a dorsal root carrying sensory

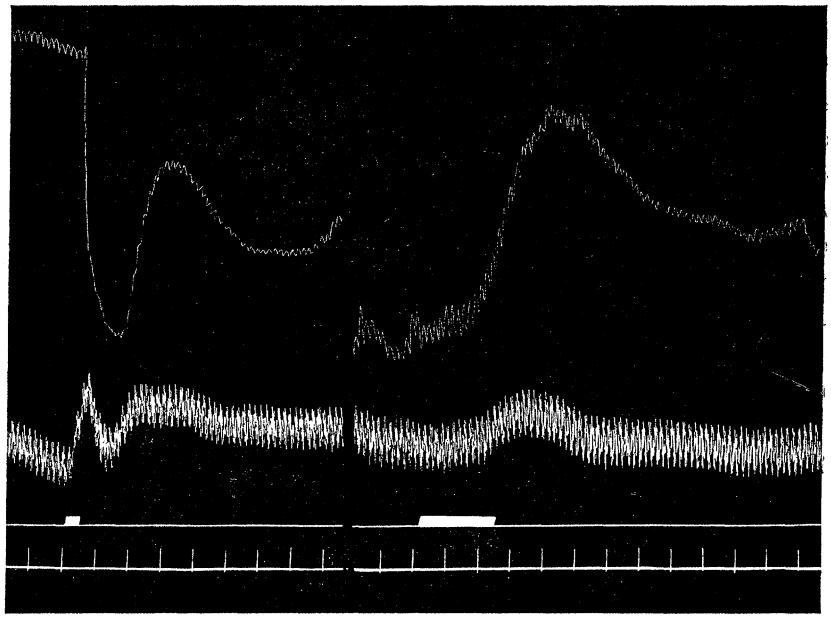

FIG. 8.—Inhibition of constrictors in Lovén reflex. Upper curves, volume of hind-limb. Lower curves, arterial pressure. Zero, 35 mm. below line of excitation-marker. First excitation, median nerve. Second ditto, central end of sixth lumbar dorsal root.

impulses from the limb itself. Since the dilators were cut, the effect was due to inhibition of constrictors. We see, then, that reciprocal innervation holds in the case of Lovén, or local, reflexes.

The question was also investigated on the tongue. Excitation of the central

end of one of the lingual nerves, the other being cut, while the cervical sympathetics were intact, was followed by constriction of the organ. Either the conditions were not favourable, or the Lovén reflex on the tongue is a matter of dilator excitation alone. The problem of these reflexes is still under investigation.

Piotrowski* has shown that excitation of the central end of the great auricular nerve causes dilatation in the ear, whether the sympathetic be divided or not. Since the latter normally possesses tone, there can be no doubt that in the full reflex there is also inhibition of this tone.†

III. The Action of Strychnine.

It was discovered by Sherrington‡ that the inhibitory component of the "flexion reflex" of the knee is converted by strychnine into an excitation. The phenomenon can only be satisfactorily explained by the hypothesis "that the action of the alkaloid is to convert in the spinal cord in these instances the process of inhibition—whatever that may essentially be—into the process of excitation—whatever that may essentially be."

As the depressor reflex is, at all events in great part, an inhibition of constrictors, Sherrington thought it of interest to test the action of strychnine on this; the result was that, in certain cases, a rise of arterial pressure was produced, instead of the usual fall. Thinking the fact worth further investigation, he suggested to me the continuation of the experiments.

The subject proved to be more complex than it seemed to be at first sight, but ultimately I found that all the various aspects of the action of strychnine could be readily explained on the lines of Sherrington's hypothesis, when the nature of vascular reflexes, as described in the preceding pages, is duly taken into consideration.

The effects of the actual injection of progressive doses of the alkaloid will be discussed in the first place.

It is well known that a considerable rise of arterial pressure is caused by the intravenous injection of a small dose. This is, no doubt, correctly

* 'Centralbl. f. Physiol.,' vol. 6, p. 464, 1892.

† *Note added to Proof.*—It is possible, according to a suggestion made by Professor Langley, that the dilator reflex in the submaxillary gland of the cat in response to excitation of the central end of the vagus, may be of the nature of a local, rather than of a general, reflex. The vagus contains afferent fibres from the alimentary canal and it may be in response to excitation of these fibres that the vessels of the salivary gland are dilated. If this is so, it should, perhaps, be referred to in the present section. In any case, the reflex in question exhibits the phenomenon of reciprocal innervation, as shown in a previous page.

‡ 'Roy. Soc. Proc.,' vol. 76, B, p. 288, 1905.

attributed to excitation of the vaso-constrictor centre.* Fig. 9 shows, indeed, that this statement is correct. Vaso-constriction in the intestine is seen coincident with the rise of blood-pressure.

Supposing that the first dose was not too small, say 5 milligrammes per kilogramme, the injection of a further dose is followed by a *fall* of arterial pressure with a peripheral *vaso-dilatation*. Each subsequent dose is accom-

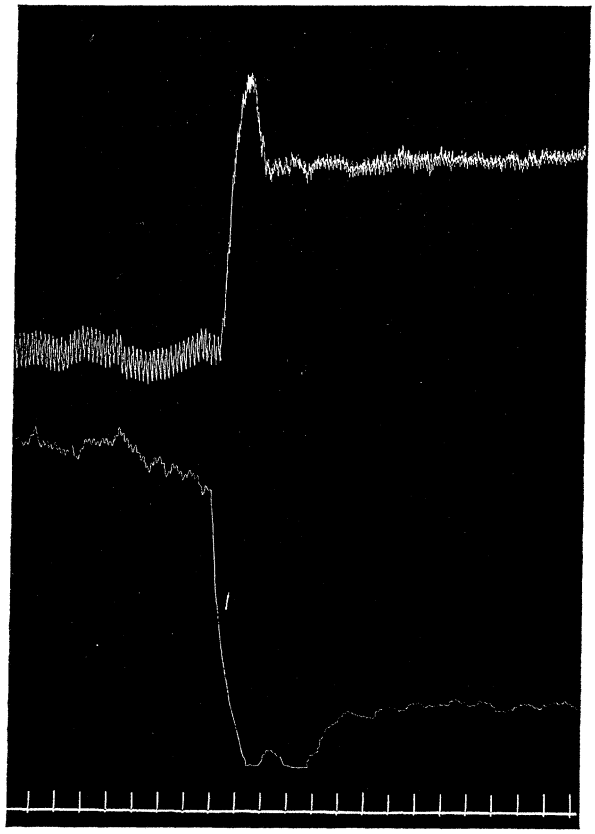

FIG. 9.—Effect of first injection of strychnine. Upper curve, arterial pressure. Lower curve, volume of intestine.

panied by the same effect, until complete paralysis of the centres ensues. Fig. 10 is a tracing of the intestinal volume.

Now what is this fall of pressure due to? There are several reasons for the belief that it is an excitation of dilators. In the first place, the action of strychnine in general is exciting, rather than inhibitory, so that it is quite probable that dilators should share in the general excitation.† Secondly, when

* *Vide* Cushny, 'Pharmacology,' 4th ed., p. 201, 1906.

† *Vide* Cushny, *loc. cit.*, p. 202.

the cord is cut in the lumbar region, so that the limbs are deprived of vaso-dilator supply, there is no dilatation in them when a second dose of strychnine is given. But the strongest evidence is the behaviour of the "dilator" animal.

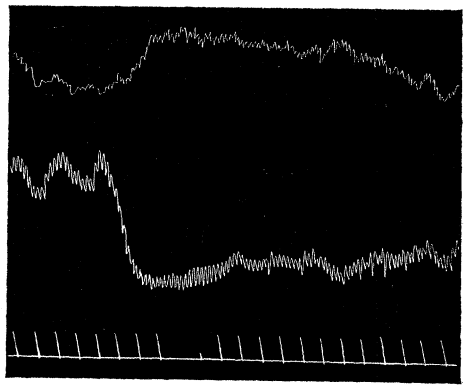

FIG. 10.—Action of a dose of strychnine subsequent to the first. Upper curve, volume of intestine (Cat). Lower curve, arterial pressure. Time in 10 sec.

Here the *first* dose produces *fall* of pressure and *vaso-dilatation* (figs. 11 and 12). In fig. 12 the fall of pressure is preceded by a small rise. In both these cases

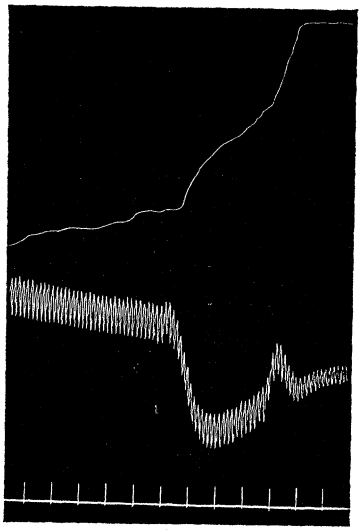

FIG. 11.—Effect of *first* dose in "dilator" animal. Upper curve, volume of ear. Lower curve, arterial pressure.

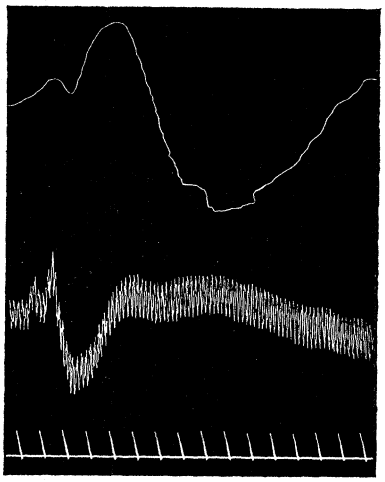

FIG. 12.—As fig. 11, but hind-leg in place of ear.

the organ under observation was deprived of its constrictor supply, so that the increase of volume must be due to excitation of dilators. The drug, in fact, excites both dilators and constrictors indiscriminately, the effect on the

arterial pressure being due to those in the majority. The reason why the effect, in the complete animal, of the first and second doses is opposite is, in all probability, that the alkaloid, after strongly exciting the constrictor mechanism, paralyses this earlier than it does the dilator. It will be shown later that the toxic action is not on the efferent vaso-constrictor neurone; it may be on the synapse of the pressor fibre or of an intermediate neurone with the cell-body of the former, or even earlier on the afferent side.

In this connection the fact is of interest that, after strychnine, there is no rise of blood-pressure in asphyxia; there is, on the contrary, an excitation of dilators, as shown by fig. 13. The dilatation seen comes on too early to be an effect of raised venous pressure. Since the constrictor neurone itself is not

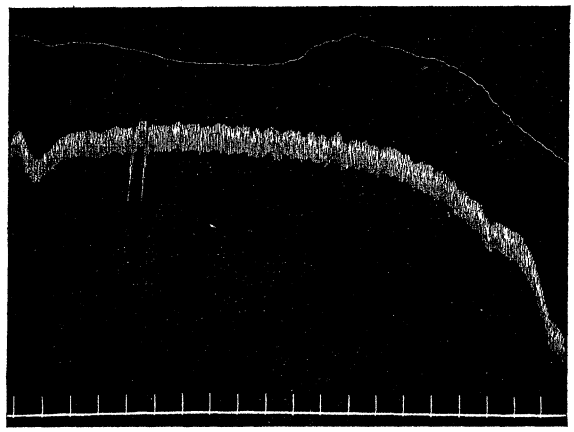

FIG. 13.—Asphyxia after strychnine. Upper curve, volume of penis. Lower curve, arterial pressure. At the time when the tracing begins the artificial respiration was stopped.

attacked, a fact shown by the persistence of vaso-constrictor effects from the depressor, it follows that the action of asphyxial blood in exciting constrictors is not exerted directly on the efferent neurone itself. In normal animals, I at times observed dilator effects in asphyxia. These do not appear to be due to the direct action of carbon dioxide on the blood-vessels,* since they were not to be seen in organs deprived of their dilator supply.

That the constrictor mechanism, or rather the afferent excitor part, is paralysed by strychnine in smaller dose than is required by the dilator mechanism, is also confirmed by the fact that the first dose of the drug is usually sufficient to abolish all pressor effects from the central end of an ordinary sensory nerve.

Cocaine produces a rise of arterial pressure by central excitation of con-

* Bayliss, 'Physiol. Soc. Proc.,' 1901, p. xxxii. In 'Journ. of Physiol.,' vol. 26, 1901.

strictors, as usually stated. Accordingly, I find that this drug, injected subsequently to a dose of strychnine, causes a *fall* of pressure, just as a second dose of strychnine itself would have done. On the other hand, bodies acting peripherally, like adrenaline, still produce a rise after strychnine, apparently as great as normally.

Vascular Reflexes under Strychnine.

The effect of a small dose is to increase general excitability, not only as regards pressor, but also depressor, reflexes. Fig. 14 is an interesting case of this. In my work on the causes of the depressor fall of arterial pressure, I was never able to obtain a dilatation of the renal vessels of sufficient magnitude to counteract the effect of the fall of blood-pressure so as to produce an actual increase of volume of the organ. In the experiment of which the tracing of fig. 14 forms a part, a similar passive diminution in renal volume was seen on depressor excitation at the beginning. After injection of 0·013 gramme of strychnine, the depressor gave rise to an actual *increase of volume*. As will be seen later, this dilatation is probably due to excitation of dilators, rather than to increased excitability to inhibitory influences.

Fig. 14.—Effect of the depressor nerve on the kidney after a small dose of strychnine. Upper curve, volume of kidney. Lower curve, arterial pressure.

As the dose is progressively increased, the depressor nerve being excited between each dose, a change in its effect on the arterial pressure is seen to make its appearance, step by step. The first sign of this change is that the fall of pressure is of short duration only and is followed by a slight rise, which becomes, as the dose is increased, greater in relation to the fall, until it alone is left and finally itself disappears, owing to abolition of all reflex excitability. Fig. 15 gives a series of such curves from the rabbit.

It was necessary in this case to inject 7 centigrammes of the sulphate, in order to produce complete conversion of the fall into a rise. This would be a colossal dose for man, but the rabbit is very insensitive to strychnine. In cats and dogs the effect is brought about by a fifth of this dose. Individual animals, of each species, vary as to the dose required; probably age is the factor concerned.

Although there can be no reasonable doubt that the cause of the rise of

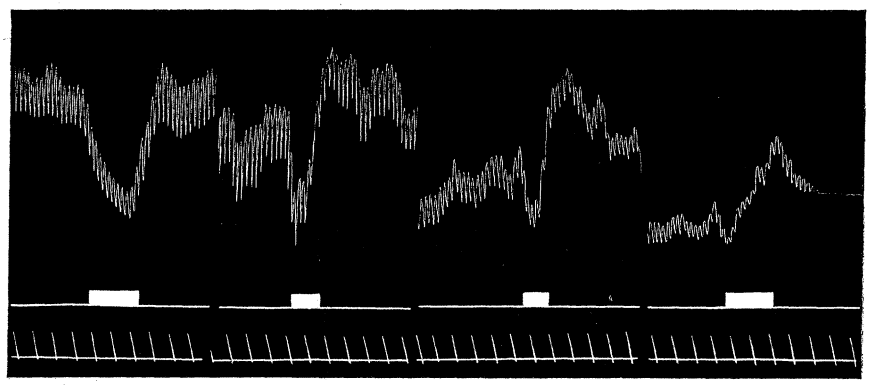

FIG. 15.—Effect of increasing dose of strychnine on the depressor fall in the rabbit.

blood-pressure on excitation of depressor nerves under the action of strychnine is constriction of peripheral arterioles, it is well, at the outset, to make no error as to this fact. Fig. 16 shows that, coincidently with the rise of arterial pressure, there is a constriction of the intestine. Before the injection of the drug, this cat gave the result always obtained on excitation

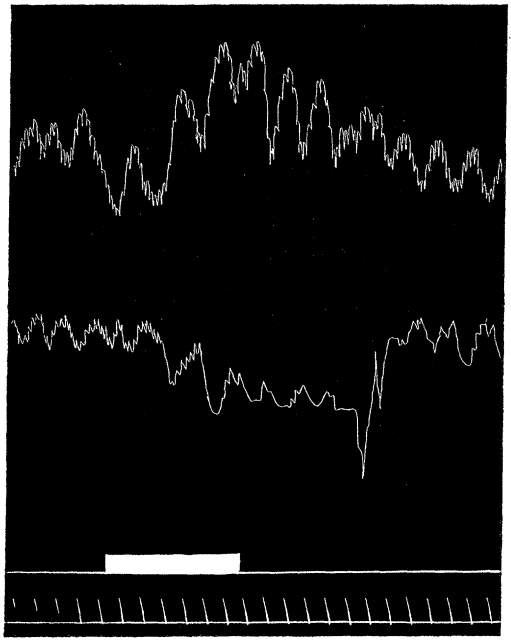

FIG. 16.—Peripheral vaso-constriction produced by depressor excitation after strychnine (Cat). Upper curve, blood-pressure. Lower curve, volume of intestine.

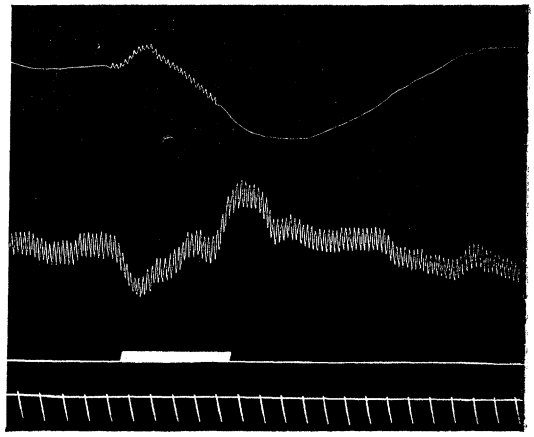

FIG. 17.—Vaso-constriction in spleen produced by depressor excitation after strychnine. Upper curve, volume of spleen. Lower curve, arterial pressure. Zero, 32 mm. below signal of excitation.

of the central end of the vagus, viz., fall of pressure and dilatation in the intestinal vessels. The dose was, as will be seen, not quite sufficient to completely convert the fall into a rise, but the intestinal dilatation is now replaced by constriction. In fig. 17, a similar tracing from the spleen, it is interesting to note that the preliminary short fall of pressure is accompanied by vaso-dilatation.

Although these tracings show that lessening of calibre in arterioles occurs, they do not exclude the possibility of this change being caused by inhibition of dilators, improbable as this may be. For this reason it was necessary to repeat the experiment on an organ in which the dilators can be excluded, such as the hind-leg, which can be deprived of dilators by section of the lumbar cord. Most of these experiments, however, were devoid of result, for a reason which was made clear by subsequent experiments. The animals, in fact, were eviscerated, in order to reduce the effect of the mere change in blood-pressure on the volume of the limb, and at that time I had not sufficiently realised the peculiarity of the vascular reflexes in the "dilator" animal. Finding, as a rule, that it was impossible to obtain the typical reversal of the depressor effect by the usual dose of strychnine, I continued to inject more and more of the drug, only to put an end to all reflexes. The cause of this phenomenon is that dilator excitation, as I have shown, is an integral part of the depressor reflex, indeed, the main part in the "dilator" animal, and this component is not reversed in sign by strychnine, but merely ultimately reduced to zero. In the "dilator" animal, therefore, there will be a fall of pressure as long as any effect is obtained. It sometimes happens, however, by a lucky chance, that the dose of strychnine falls just within the narrow limits between paralysis of the dilator excitation and that of the constrictor effect due to reversal of the normal inhibition. This is a somewhat important fact, since the normal constrictor effect of pressor reflexes is abolished by a small dose of strychnine, as will be seen later. The fact that the constrictor effect due to reversal of normal inhibition is the last to disappear shows that it is a different thing from the ordinary constriction; but our present knowledge is insufficient to explain the difference. In the experiment of fig. 18 the spinal cord was transected in the lumbar region, in order to cut off the vaso-dilators; evisceration was performed and a large dose of strychnine injected. Notwithstanding the bad condition of the animal, excitation of the depressor produced a rise of arterial pressure, accompanied by diminution of volume of the limb, which was later overpowered by the rise of pressure. The result is quite definite, although small.

It did not seem to me worth while to repeat the experiment, without

attempting to completely reverse the depressor action. For, supposing that before strychnine the usual effect on the limb was obtained, viz., a dilatation, and that after a certain dose of the drug there was a diminution of volume of the limb but coincident with a fall of arterial pressure, the objection would justly be made that the diminution of the leg-volume was merely the passive effect of the fall of pressure, the proper depressor effect of dilatation being paralysed. Moreover, the absence of a dilator reflex on repetition of the stimulus is by no means uncommon. For this reason I am unable to admit that the mere non-appearance of a dilator reflex is of any value as evidence.

The result of the experiment of fig. 18 is conclusive in showing that the reversal of the normal depressor fall into a rise is a matter effected by the constrictor system and since in normal conditions the depressor inhibits this system, it inevitably follows that, by some means or other, the inhibitory action is changed into an excitatory one.

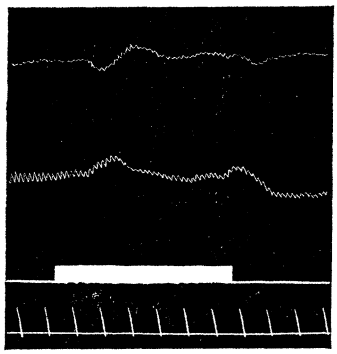

FIG. 18.—Excitation of vaso-constrictors to leg by depressor after strychnine. Upper curve, volume of leg. Lower curve, arterial pressure.

When I demonstrated the rise of pressure from the depressor after strychnine at the International Congress of Physiologists at Heidelberg in 1907, Professor Hans Meyer made the criticism that the result might be due to escape of exciting current to neighbouring tissues, whose reflexes would be more easily evoked under the alkaloid, while the action of the drug on the depressor reflex might be merely that of paralysis. I was able to show that the same result was obtained by pinching the nerve with forceps. It is also easy, by placing electrodes on the surrounding tissues, to show that the suggested explanation is not the correct one; this has no effect at all when the reversal is at its maximum. Indeed, excitation of the trunk of a nerve such as the median at this stage, or even earlier, has no effect on the blood-pressure, a fact which disposes also of another possible explanation of the reversal. This consists in the hypothesis that there are in the depressor trunk a certain number of pressor fibres which come into effect when the depressor fibres are paralysed by the drug.

On proceeding to further investigate the action of strychnine on pressor reflexes, some interesting facts came out. I have already mentioned that very early in the progressive poisoning these reflexes are abolished, so that no effect of any kind is produced in the curarised animal by exciting a pressor nerve. This statement, however, only applies to the complete animal.

Having adopted as a working hypothesis that of Sherrington, I was somewhat surprised, not to say disconcerted, to find that in the "dilator" animal there is, at a particular stage in the action of the drug, a *fall* of blood-pressure on exciting the central end of the median nerve. It is difficult to specify the exact stage, except that a large dose does not seem necessary. Of course, in these experiments care was taken to compare the action of stimuli of the same strength, since it sometimes happens that weak stimuli may cause fall of arterial pressure in the normal animal. This fact is, as yet, unexplained; perhaps it may depend on the presence of depressor fibres which are more excitable. In my experiments this effect was not often met with, perhaps because curare was used. It seems to have some relation to the reflex contractions of voluntary muscle.

Fall of arterial pressure from excitation of a pressor nerve is a characteristic of an advanced stage of the action of chloroform, and is due, in this case, to conversion of excitation of constrictors to inhibition of their centre. Since the general action of strychnine is antagonistic to that of chloroform, it is puzzling to find the same effect produced.

The clue is given by the plethysmograph. Fig. 19 shows that dilatation of the kidney is produced after strychnine under conditions which ordinarily cause constriction and fig. 20 that, under the same conditions, excitation of

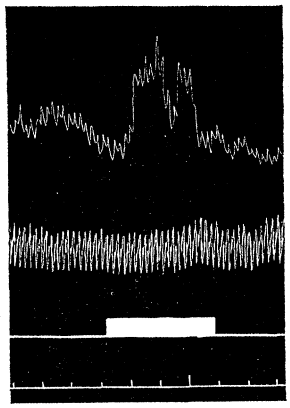

FIG. 19.—Vaso-dilatation in kidney from excitation of the median nerve after strychnine. Upper curve, volume of the organ. Lower curve, arterial pressure.

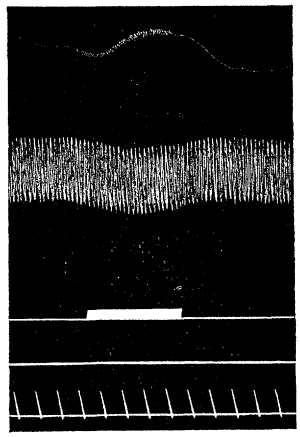

FIG. 20.—Excitation of dilators to ear by "pressor" reflex after strychnine, which has converted the reflex into a depressor one. Upper curve, volume of ear. Lower curve, arterial pressure.

dilators results. In this experiment, the cervical sympathetic having been cut, the large expansion observed on excitation of the median must be due to

the dilator nerves. Fig. 21 is, perhaps, important, since it shows a similar phenomenon in the hind-limb, after section of both abdominal sympathetics, so that there is no possibility of constrictors playing any part.

These results at once suggest the meaning of the conversion of the "pressor" rise into a fall and of its cause, excitation of vaso-dilators. In the earlier part of this paper I have shown that in the normal pressor reflex there is, along with excitation of constrictors, an inhibition of dilator tone; now, by hypothesis, the action of strychnine is to change in some way a process resulting in inhibition into one of excitation; so that it was really to be expected that the drug would effect such a change that dilator excitation would result from ordinary sensory nerves. Figs. 22 and 23 show the effect

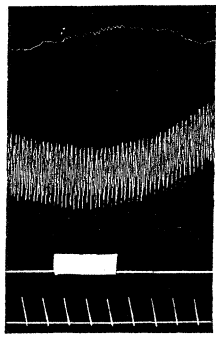

FIG. 21.—Excitation of dilators to hind-leg by reflex from median nerve after strychnine. Upper curve, volume of limb. Lower curve, arterial pressure.

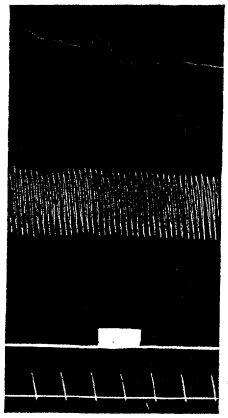

FIG. 22.—Inhibition of dilator tone before strychnine.

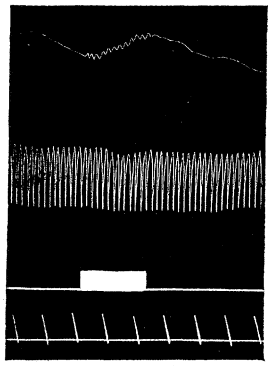

FIG. 23.—Excitation of dilators after injection of the drug. In both figures the upper curves are the volume of the ear, the lower curves are the arterial pressure.

of excitation of the median nerve, on the rabbit's ear deprived of constrictors, before and after the injection of strychnine.

In view of this fact it seems possible that the absence of pressor effects from sensory nerves in the "complete" animal after a comparatively small dose of the alkaloid may not mean total paralysis of the constrictors but a diminution of their excitability only, and that the simultaneous excitation of dilators suffices to antagonise their effect on the general blood-pressure.

The apparent anomaly of conversion of rise of pressure into fall by the action of strychnine turns out to be, in reality, a confirmation of the hypothesis adopted.

With respect to the effect of the drug on the excitation phase of the two kinds of vascular reflex there is little to be said. I have been unable to detect any indication of change of sign before disappearance; which abolition takes place with a less dose of the drug in the case of the constrictor centres than of the dilator centres. It seems also that both the above are paralysed in respect of response to the normal excitation by a less dose than in respect of response to the reversed inhibition, now acting as excitation.

It remains to refer briefly to the action of strychnine on the Lovén reflexes. In the experiment of fig. 8 it was found, after section of all dorsal roots supplying dilators to one limb, that a dilator reflex could still be obtained by exciting the central end of one of these roots. This proves that inhibition of constrictor tone is a factor in these reflexes. In this same experiment, later on, a small dose of strychnine was injected into a vein. On exciting again the same root which had given, previously, dilatation of the leg, a constriction was observed. Accordingly, reversal is produced here as in the general vascular reflexes. The only point to be noted is that the dose of the drug was not sufficient to completely abolish the pressor reflex from the median nerve; it is to be remembered, however, that the dog is very sensitive to strychnine.

Evidence has already been adduced to show that the rise of arterial pressure on excitation of the depressor after strychnine, although caused by excitation of the vaso-constrictor centre, is of a somewhat different nature from that due to excitation of a pressor nerve under normal conditions. In order to obtain more decisive evidence on this point, which seemed of some importance, the following experiment was performed. In a cat the spinal cord was transected at the second lumbar segment, to cut off the hind limbs, one of which was in a plethysmograph, from the dilator centre. Excitation of the median nerve produced the usual result of rise of blood-pressure and constriction of the leg. Five milligrammes of strychnine were now given intravenously. On repeating the excitation of the median nerve no effect whatever was produced on the arterial pressure, although the nerve was dissected out further and the electrodes placed on a fresh spot. If this absence of effect were due to simultaneous excitation of dilators, rather than to paralysis of the pressor synapse with the constrictor centre, the constriction should have shown itself in the limb, where there were no dilators to mask it. Nothing of the kind was seen, however; the limb remained stationary. The conclusion seems justified that the paralysis is a genuine one, although I admit that the result, being of a negative character, is not absolutely cogent. At this stage of strychnine action, it was found that the central end of the vagus still produced fall of pressure, although less than

normal, not followed by a rise. Accordingly, a further dose of the drug, 3 milligrammes, was given; this had the effect of completely converting the depressor effect into a considerable rise. At a time, therefore, when the constrictor centre is inaccessible to the normal excitations, it can still respond to the excitatory action of what were previously inhibitory impulses. It appears as if the drug is in some way used up or taken into combination in the inhibitory synapse, in order to perform its function of reversal.

In this connection it is advisable to refer to what may seem a simpler explanation of the strychnine reversal than that given by Sherrington. The usual account of the action of the drug is that it acts upon synapses so as to render those permeable which were previously closed. If we assume that the depressor has connections with the constrictor centre which only became permeable under the action of the alkaloid, and that these are excitatory in nature, the result may be explained. The hypothesis is not in agreement with experimental facts. We have seen that the connections with the constrictor centre are always open in the normal state, but that their mode of action is not excitatory but inhibitory. Moreover, it seems rather that, at all events in this particular case, the action of the drug is of the nature of a block. In the experiment described above, what was especially noticeable was the long latent period of the constriction from the reversed depressor. The rise of pressure from the median commenced, at most, two seconds after the beginning of excitation, whereas that from the depressor under strychnine, in the first excitation, was 22 seconds; in fact I thought that the second dose had been followed by paralysis, so long a time elapsed before any effect was produced. The second excitation had a somewhat shorter latent time, viz., 18 seconds, so that something of the nature of "facilitation" took place. The third excitation had the same latent time as the second. This fact, on the face of it, looks more like obstruction than the breaking down of barriers. It is worth mentioning that this rise of pressure was accompanied by constriction in the limb, so that it was a real excitation of the vaso-constrictor centre.

With respect to the mode of action of the drug, there is one more point worth calling attention to. As shown in fig. 15, this is not done by first abolishing the inhibition and then replacing it by excitation, but by producing, as an intermediate stage, a double effect, so that opposite processes seem to be consecutively induced by one and the same exciting cause. It is possible that this fact may ultimately give a clue to an explanation of the mechanism of the reversal, but at present I am unable to suggest any such.

It has been already pointed out that asphyxial excitation of constrictors is abolished by strychnine in a less dose than that required to abolish the constrictor effect from reversed depressor action. A larger dose is necessary,

however, to paralyse the action of asphyxial blood than that which puts an end to the constrictor excitation from the median nerve. The following is the order in which the various effects dealt with in the preceding pages are attacked by the drug:—

1. Constrictor excitation by median or other sensitory nerve.
2. Asphyxial excitation of constrictors.
3. Dilator excitation by depressor.
4. Constrictor excitation by reversed depressor.

My experiments do not enable me to assign a place to the excitation of dilators by reversed median nerve effect.

As to whether this difference of sensitiveness to strychnine implies a different point of attack in each case, I do not feel that we have yet sufficient knowledge of the way the result is produced to warrant an expression of opinion.

IV. The Action of Chloroform.

In many of the early researches on vascular reflexes it was thought that the action of sensory nerves was of a depressor nature in the rabbit, until Cyon* showed that chloral, used as anæsthetic for these animals, was responsible for the difference in behaviour compared with dogs. This observer, indeed, considered that the action of the drug was due to abolition of function of the cerebral cortex. The view cannot be maintained, since a far larger dose is required to convert the vaso-motor reflex than to paralyse the cortex. I have previously pointed out† that chloroform has the same effect, and is more convenient in practice, since the experiment can be commenced under ether, in order to obtain the pressor reflex, which can then be converted by administration of chloroform; if desired, ether can be returned to and the original form of the reflex obtained.

In experiments with chloroform, the difficulty to be contended with is the paralysing action of the drug on the heart, and, in fact, on all protoplasmic activities. The arterial pressure being low, the centres suffer from anæmia, so that the reflexes obtained are usually small.

Fig. 24 was obtained from a rabbit, in which a plethysmographic tracing was given by the kidney. In the first curve, under ether, excitation of the median produced the typical pressor effect of rise of blood-pressure with constriction of the kidney. Chloroform was now given until the arterial pressure was reduced from 110 mm. Hg to 64 mm.; on repeating the excitation a fall of pressure was seen, accompanied by dilatation of the

* 'Bulletin de l'Acad. des Sciences de St. Petersburg,' December 22, 1870.

† 'Journ. of Physiol.,' vol. 14, p. 316, 1893.

kidney. In the third curve, ether was resumed and the median excited before complete recovery; there was a diphasic effect in both kidney and blood-pressure—the latter had risen to 88 mm. before the excitation was made.

This experiment shows that the fall of blood-pressure obtained from sensory nerves under chloroform is caused by dilatation of arterioles, but does not decide whether this is due to inhibition of constrictors or to excitation of dilators. This point is only to be settled by observing the effect on an organ,

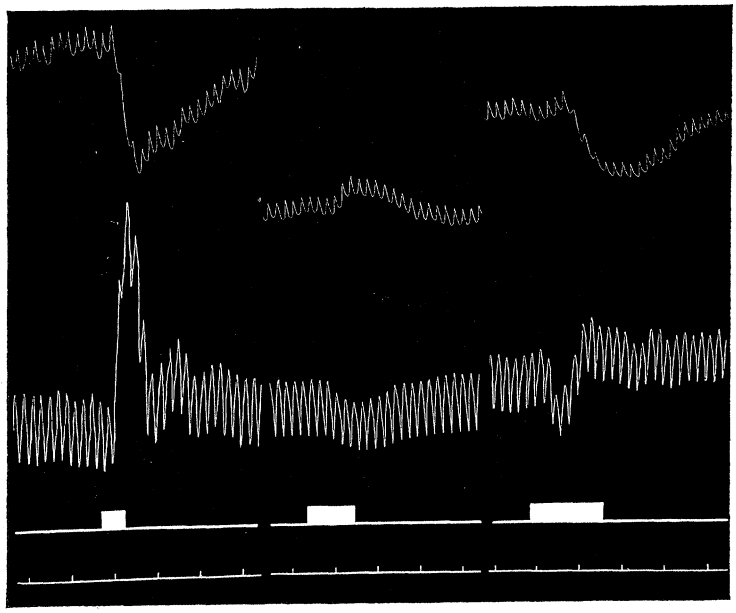

FIG. 24.—Action of chloroform on result of excitation of median on blood-pressure and on kidney. Upper curves, volume of kidney. Lower curves, arterial pressure. Zero is not the same in the three tracings, see text. First tracing, before chloroform. Second, under full influence of the drug. Third, after partial recovery.

such as the leg, in which the dilators have been cut. Since the results are much more easily interpreted when the passive effects are reduced to a minimum by evisceration, it is necessary first to describe the action of chloroform in the "dilator" animal. Now, a similar fate befell my early experiments with this drug to that of the analogous experiments with strychnine; I lost several by pushing the chloroform to total abolition of all vascular reflexes in the vain attempt to obtain a depressor effect from the median nerve. Although it seems difficult to believe, I can see no other alternative but to interpret the rise of arterial pressure seen under maximal

doses of chloroform in the "dilator" animal, as due to inhibition of dilator tone.

The first curve of fig. 25 shows the ordinary result of exciting the median nerve in the eviscerated rabbit under ether; rise of blood-pressure and constriction of the limb of which the dilators had been cut. Chloroform was then given in as great an amount as possible without lethal results; the blood-pressure fell by 70 mm. Hg. Excitation of the median still gave a rise of pressure, but now accompanied by *dilatation* of the limb. This means that the process which previously resulted in excitation now results in inhibition. At the same time there are too few constrictors left in the body to counteract by their inhibition the opposite effect on the blood-pressure of the inhibition

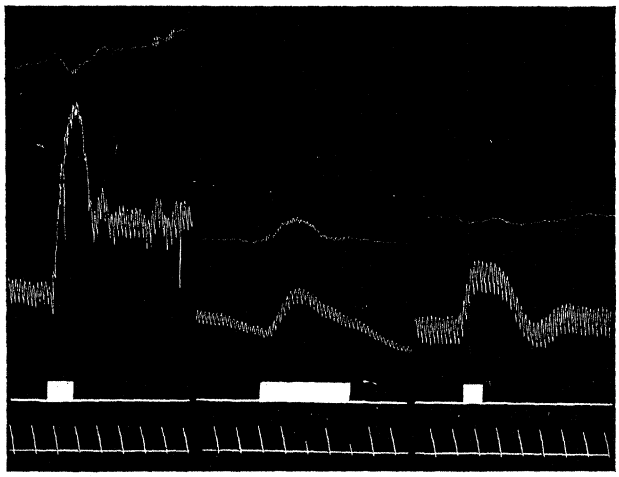

FIG. 25.—Inhibition of constrictor tone by excitation of a pressor nerve under chloroform, etc. Upper curves in each, volume of hind-limb, vaso-dilators cut. Lower curves, arterial pressure. Zero different for each.

of dilators present as a normal constituent of the reflex and left intact by the chloroform, which apparently only attacks excitation processes in such a way as to reverse them, while inhibitory processes are unchanged in sign until finally paralysed. The result is that a rise of blood-pressure occurs, produced, not by excitation of constrictors, but by inhibition of dilator tone. The third curve was obtained after return to ether anæsthesia and partial recovery, the arterial pressure having risen by 25 mm. Hg. Excitation of constrictors is commencing to return as a part of the reflex from median nerve.

The result of this experiment shows the incorrectness of a statement made by me in a former paper to the effect that the depressor reflex from sensory nerves under chloroform differed from the true one from the depressor nerve

in that the former was confined to the viscera; in all probability, the experiments on which this statement was based happened to be on subjects devoid of tone in the constrictors to the leg, as often occurs under experimental conditions. This erroneous conclusion serves as a warning against reliance on negative results.

As far as conversion of excitation into inhibition is concerned, we see that the action of chloroform is the opposite to that of strychnine. Since these drugs are regarded as antagonists in general, some experimental results with respect to the action of chloroform on the vaso-motor system will throw some light on the question.

Since in the normal depressor reflex excitation of dilators takes place, it would be expected that chloroform would reverse this effect; so that, in the "dilator" animal, the depressor should cause a rise of pressure by inhibiting dilator tone. Up to the present I have been unable to obtain this result, the normal fall gradually disappears as the chloroform is slowly increased, without giving place to a rise. Whether this is due to the paralytic action of the drug on the centre, or whether the action of reversal is exerted on the constrictor centre alone, I am unable to state. The nearest approach to a positive result was a fall followed by a rise at a certain stage of chloroform action.

The general antagonism of chloral and strychnine is shown in an interesting way in fig. 26. A small rabbit, under the influence of ether, gave curve A on excitation of the anterior crural nerve, the blood-pressure, which was at this

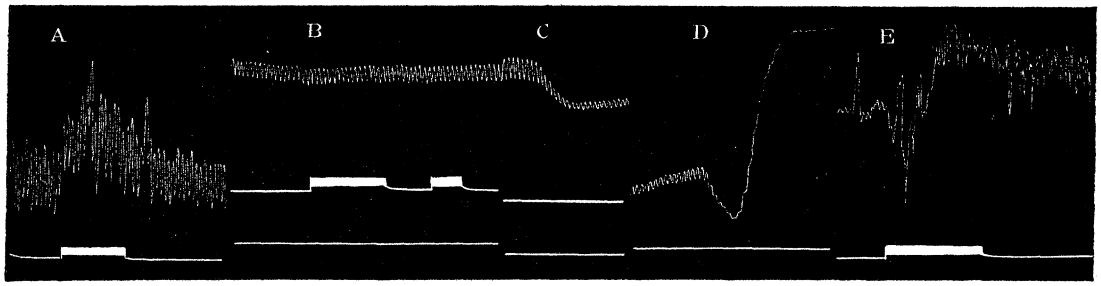

FIG. 26.—Antagonism of chloral and strychnine. A. Effect of excitation of ant. crural on blood-pressure, under ether. B. Same after chloral. C. Effect of first dose of strychnine. D. Effect of second dose. E. Excitation of ant. crural.

time 100 mm. Hg., rose to about 130 mm.; 0·7 gramme of chloral hydrate was then injected intravenously, the arterial pressure fell to 30 mm. and the reflexes were almost abolished (curve B). In curve C is seen the effect of 13 milligrammes of strychnine sulphate. Although this was the first dose, a *fall* of pressure results; that is, the alkaloid acts like a sensory nerve under

chloroform, on the constrictor centre, the normal excitation becoming inhibition. In curve D a second similar dose was given: the first effect was again a fall, the chloral was not yet fully antagonised, but, after a short time, this was effected and the alkaloid now produced its usual excitatory effect. Moreover, excitation of the anterior crural also had its ordinary result, a rise of pressure (curve E).

Asphyxial blood is capable of causing rise of pressure and peripheral vaso-constriction under a dose of chloroform which reverses the effect of exciting a sensory nerve. This fact proves that the action of chloroform is not exerted on the efferent neurone itself, at least not as regards its effect in converting excitation into inhibition.

When electrodes are placed on the floor of the fourth ventricle, over the situation of the so-called vaso-motor centre, it is found that, in the rabbit, chloroform converts the usual pressor effect into a depressor one. It might be thought that this result is at variance with the view here taken as to the action of this drug. It seems unlikely that direct electrical excitation of the efferent neurone should cause inhibition of it. On the other hand, it is much more probable that, by this means, afferent tracts to the centre are excited, rather than the centre itself. So that the experiment is merely a variant of excitation of ordinary sensory nerves.

It is remarkable that the chloroform reversal cannot be obtained in the cat. I have seen a slight rise followed by a fall of pressure, but this latter proved, on examination, to be due to slowing of the heart, although the vagi were cut. It was, presumably, due to the enfeebled heart not being able to work under the raised pressure. In fact, the heart seems to fail before a dose of the drug has been given sufficient to effect change of excitation into inhibition.

As is well known, administration of chloroform is followed by fall of arterial pressure; this is usually attributed to failure of the heart's action, and, no doubt, this is the main factor, but I have several times observed, in plethysmographic tracings of both intestine and limb in the initial stage before the pressure has fallen to any great extent, an unmistakable dilatation of the peripheral vessels. This comes on too early in the fall of pressure to be due to rise of venous pressure and it gives place to a passive diminution of volume as the blood-pressure continues its downward course. It is possible that this dilatation may be produced by direct action of the drug on the arterioles; it is more probable, I think, that it is of central origin and brought about in this way: afferent pressor stimuli are continually being received by the constrictor centre, and are, to some degree at all events, the cause of its normal state of tonic excitation. Under chloroform these stimuli cause inhibition of constrictor tone, and, therefore, dilatation of peripheral vessels.

In view of the special properties of the "dilator" animal, it is not surprising to find that, in this condition, chloroform, if in not too high a percentage in the air respired, sometimes causes a decided rise in arterial pressure, which may continue for several minutes. I can only suggest, in explanation, that in these cases the dilator centre was in tonic excitation before the administration of the drug, and that this excitation was either converted to inhibition or the centre paralysed by the latter, both of which would produce a rise by removing dilator impulses.

On the whole it must be admitted that the effect of chloroform on the vaso-motor centres has not been so clearly made out as that of strychnine. The reason for this is its extremely depressant action on all vital activity, so that it is very difficult to so adjust the dose as to obtain the maximal reversal effect with the minimal paralytic effect.

V. General Remarks.

It will, I think, facilitate the understanding of the results described in the previous pages if they are represented in the form of a diagram (fig. 27) on the lines of that of Sherrington.*

When this diagram is compared with that of Sherrington, it will be seen that I have used the name of "reciprocal innervation" in a somewhat extended sense, in that the state of affairs in the vascular reflexes is, in some respects, more complex than that in reflexes to voluntary muscles. The antagonistic impulses, instead of acting on separate muscles, must here be looked upon as affecting one and the same smooth muscle cell. There are also two distinct sets of afferent impulses, pressor and depressor, having opposite relations to the two centres, dilator and constrictor.

There is, indeed, as pointed out by Sherrington himself,† another aspect of reciprocal innervation as concerns the vascular system. The heart and the muscular coat of the blood-vessels may be regarded as antagonistic muscles. The depressor nerve being the afferent nerve from the heart and aorta, will be expected to inhibit the antagonistic muscle, the wall of the arterioles. I hope to investigate the reflexes from this point of view at an early date.

In the present state of knowledge as to what is the essential meaning of excitation and inhibition in the central nervous system, it would be premature to attempt a complete explanation of the phenomena described in the preceding pages. At the same time I think it may be useful to indicate

* 'Roy. Soc. Proc.,' vol. 76, B, p. 286, 1905.

† *Loc. cit.*, p. 289.

briefly a possible hypothesis which unites what I may call the colloid-adsorption theory of Macdonald and the "drainage" theories of von Uexküll and Macdougall with the synaptic membrane of Sherrington. The doubtful assumption made is the existence of membranes permeable to electrolytes in one direction only. As Overton has pointed out, as a physical structure such a membrane infringes the laws of thermo-dynamics, since it would, by

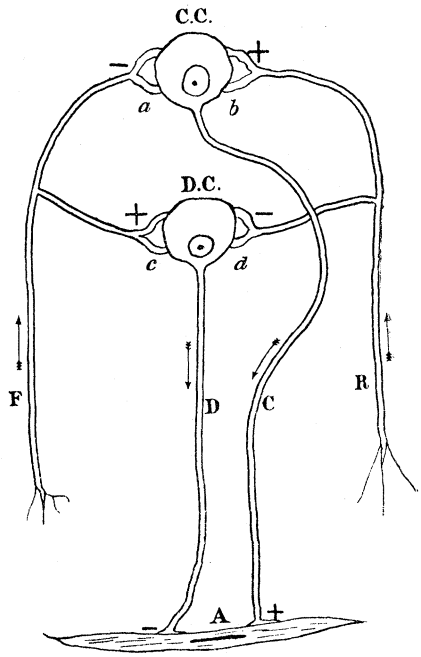

FIG. 27.—Diagram of relations of general vaso-motor reflexes. A. Muscle-cell of arteriole. D. Vaso-dilator nerve-fibre terminating on A, and inhibiting it. C. Vaso-constrictor fibre also ending on A, but exciting it. These fibres arise in the dilator centre (D.C.) and the constrictor centre (C.C.) respectively. F. Depressor afferent fibre, dividing into two branches (or collaterals), one of which (−) inhibits the constrictor centre, while the other (+) excites the dilator centre. R. Pressor fibre of sensory nerve, causing rise of arterial pressure by exciting C.C. and inhibiting D.C. *a*, *b*, *c*, *d*. The respective synapses of these branches with the efferent neurones. The probable intermediate neurones are, for the sake of simplicity, omitted.

creating potential differences, constitute a perpetual motion machine. I may venture to suggest that its existence may be ensured by the continuous supply of energy from the activity of cell-protoplasm. Macdonald has shown* that the colloids of the axis cylinder, when the nerve is injured, split off electrolytes, which were previously held in a "masked" state, or, as I prefer

* 'Roy. Soc. Proc.,' vol. 76, B, p. 348, 1905.

to call it, a state of adsorption. We are justified in supposing that the same change occurs in the state of normal excitation. If, under these conditions, a change takes place in the colloids of such a nature that diminution of surface occurs, coagulation for example, adsorbed electrolytes will necessarily be set free. Macdonald also assumes that the opposite process occurs in inhibition. Excitation, then, is associated with increase, inhibition with diminution, of electrolytes. Now in fig. 27 let us imagine that the synaptic membrane at *a* will allow ions to pass from the cell-body to the arborisation, but not in the reverse direction, while that at *c* allows ions to pass from the arborisation to the cell-body only. On arrival of a nerve-impulse, with its setting free of electrolytes, at *c*, these latter can pass freely into the dilator neurone D, causing excitation in it; the constrictor neurone C will not be excited, since the ions are unable to pass into it. Since ions have passed out of *c*, more will travel along the fibre to take their place, and since the membrane at *a* allows their passage from the cell-body of the constrictor neurone C to the fibre F, it is conceivable that such takes place, thus diminishing the concentration of electrolytes and producing inhibition in the constrictor neurone.

On this hypothesis the action of strychnine would be to make the membrane at *a* permeable to electrolytes in the same direction as *c*, so that excitation of both cells occurs.

This is the barest possible outline of a conceivable explanation of the phenomena. No doubt, much modification would be necessary. Moreover, I do not at present see how to account for the chloroform effect on these lines. Expressed shortly, the action of strychnine is to convert the minus signs at *a* and *d* into plus signs: that of chloroform is to convert the plus sign at *b*, and probably that at *c*, into a minus sign. According to the hypothesis sketched above, this statement seems to imply more than a mere summary of the experimental facts, as might appear at first sight.

Fig. 28 is a diagram of the probable relations in the Lovén reflexes.

There is a rather interesting point in connection with these reflexes. When an afferent nerve of a limb, *e.g.*, the median, is excited, vaso-constrictors to the kidney are excited; on the other hand, when the central end of a dorsal root of the kidney area is excited, these same constrictors are inhibited. Is the "final common path" in the two cases the same? Or are there two distinct sets of constrictors? I hope to be able to decide this question in the work on the Lovén reflexes, already in hand.

In respect to the action of strychnine, it will be remembered that it was found by Sherrington that inhibition was not converted into excitation in all cases of reciprocal innervation. Those muscles used to maintain the normal

posture of the body were those in the main affected. Now there is an obvious point of similarity between these muscles and the arterial wall, which consists in the circumstance that both are normally in a condition of tone. It is, as Professor Sherrington has suggested to me, a question worth

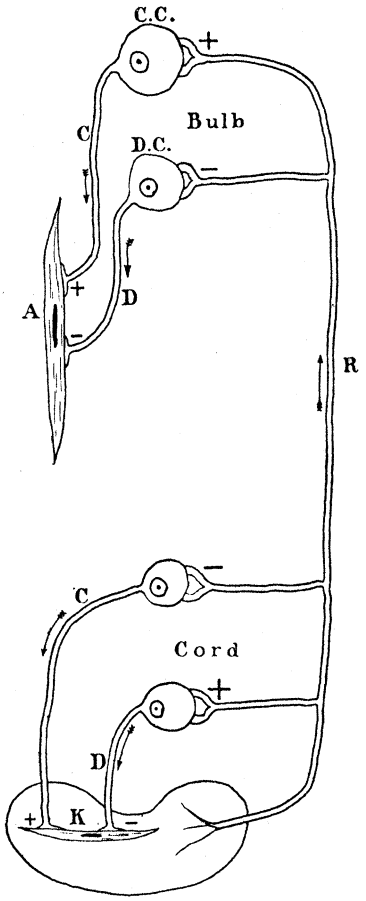

FIG. 28.—C and D. Constrictor and dilator efferent neurones. A. Arterial muscle-cell of body generally. K. Ditto of organ (*e.g.*, kidney) from which the afferent fibre R passes to the bulbar centres, giving off collaterals to the spinal centres. The connections of this fibre are such that it excites constrictor centres in the bulb and dilator centres in the cord, while its relations to the dilator centres in the bulb and the constrictor centres in the cord are inhibitory.

investigation whether there is any special connection between the vaso-motor centres and the labyrinth.

The statement is sometimes made that strychnine causes excitation of constrictors to the viscera and of dilators to the skin. This is not quite the correct way of expressing what happens on injection of the drug.

Constrictors and dilators indiscriminately are excited in all parts of the organism. But, since the skin is relatively more copiously supplied with dilators than the viscera are, it may happen that the net result is vaso-dilatation in the former and constriction in the latter. Moreover, since the volume of blood in the latter greatly exceeds that in the skin and neighbouring structures, the result on the general arterial pressure will be a rise, which itself will further increase the distension of the skin vessels.

During the course of this research I have carefully looked out for any indications of a normal opposition between the visceral and cutaneous circulations. None has been met with. Any reflex involving constriction in the one area was found to have the same effect in the other, and similarly with the dilator reflexes. I refer to the point here since such a state of affairs is still occasionally spoken of as if it had some foundation in fact; it would, obviously, if it existed, require treatment as a case of reciprocal innervation. It is scarcely necessary to repeat that an increase of volume in a limb, for example, in a pressor reflex, must not be taken as a proof of actual relaxation of arterioles; by preventing or diminishing the rise of general blood-pressure, it can be shown that their muscular walls are really in a state of contraction, which can be overcome by a sufficiently great internal pressure.

VI. Summary of Conclusions.

1. In depressor reflexes there is, along with inhibition of tone in the vaso-constrictor centres, an excitation of vaso-dilator centres. This has been shown in the cases of the sub-maxillary gland, the penis, the hind-limb, the external ear, and probably the tongue.

2. Correspondingly, in pressor reflexes, along with excitation of constrictors, there is, in appropriate conditions, inhibition of dilator tone. This is, however, more difficult to demonstrate.

3. Similarly, in the local, or Lovén, reflexes, there is also both excitation of dilators and inhibition of constrictors.

4. The action of strychnine is to convert the inhibitory phase of all vascular reflexes into an excitation, so that:—

5. The depressor nerve produces a rise of blood-pressure under full doses of the alkaloid. It does this by exciting the constrictor centre by the same mechanism which normally inhibits it.

6. In the "dilator" animal (see text) under strychnine, pressor reflexes become depressor, in that inhibition of dilators is converted into excitation.

7. Various parts (synapses) of the reflex arc are differently sensitive to the

alkaloid, the synapse of the press or fibres with the constrictor centre being the first to show paralysis as the dose is increased.

8. In the "dilator" animal strychnine causes a fall of blood-pressure on injection by exciting dilator centres. In the normal animal the first dose causes a rise and subsequent ones a fall of pressure, since the first dose, if not too small, after exciting the vaso-constrictor centre, paralyses the synapses concerned, so that the simultaneous excitation of the dilator centres can now make itself felt.

9. The excitation of constrictors produced by reversal of inhibition is more resistant to the alkaloid than that produced in the normal way.

10. Asphyxial blood does not act directly on the efferent constrictor neurones, since it has no action at a stage of strychnine poisoning at which the depressor still excites constriction, by reversal of inhibition.

11. Chloroform converts pressor into depressor reflexes (in the rabbit), by reversal of excitation of constrictors into inhibition.

12. This effect of chloroform is not exerted on the efferent neurones directly, but at some point considerably earlier in the reflex arc. This is shown by the fact that asphyxial blood causes rise of pressure when excitation of sensory nerves causes fall.

The expenses of this research were partially defrayed from the Government Grant administered by the Royal Society.

[*Note added March* 23, 1908.—Since the preceding paper was written, I have received from Professor Mislavsky, of Kasan, a number of tracings showing a dilatation of the tongue of the dog and cat on excitation of the central end of the vagus, after section of the cervical sympathetics above the superior cervical ganglia. In one case there was no obvious change in the blood-pressure, a fact which perhaps makes the reflex origin of the dilatation somewhat doubtful; in the other cases there was the usual fall. In all cases, as Professor Mislavsky informs me, the effect was abolished by section of the lingual nerves, so that there seems no doubt that it was due to excitation of vaso-dilator fibres. These experiments were performed by Professor Mislavsky in conjunction with his pupil, Mr. Fofanoff.

The results are of interest, in that they bring evidence of dilator-excitation in an organ on which my own experiments had been only partly successful.]