THE EFFECT OF VARIOUS POISONS UPON THE RESPONSE TO NERVOUS STIMULI CHIEFLY IN RELATION TO THE BLADDER.

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CONTENTS.

IN the course of some experiments upon the antagonistic action of curari and nicotine upon peripheral nerve cells I found that both of these poisons modified the effect of stimulating the sacral vesico-motor fibres in a peculiar way. A preliminary account of some of the results was published in the *Proceedings of the Physiological Society*[1]. I have

[1] July 9, 1910. This *Journal*, vol. XL. p. xlii.

repeated and extended the observations and give an account of them in the following pages.

Anæsthetics. The experiments were made on cats. Chloroform was first given and then A.C.E. mixture by a tracheal tube. The subsequent procedure varied, usually 25 p.c. urethane was injected either subcutaneously or into a vein; in a few cases paraldehyde (about 1·5 c.c. per kilo body-weight) was injected into the œsophagus and the œsophagus tied. Unless maximal amounts of urethane or paraldehyde were given, A.C.E. was administered at regular intervals throughout the experiment. In some cases urethane was injected slowly into the peripheral end of the carotid artery; drugs injected in this way appear to be largely taken up by the central nervous system and to have a less weakening effect upon the heart. In a few cases the animal was beheaded after giving chloroform[1] and no further anæsthetic was used. I have not found any certain difference in the results with the different methods.

Dissection. The sacral nerves are best exposed by cutting open the vertebral column from below upwards, starting from the last sacral vertebræ. When the cord is exposed up to the end of the 6th lumbar vertebra, a hook at the end of a string is passed into the vertebral canal and the string fastened round the cross-bar of a stand so as to raise the body; this serves the double purpose of lessening bleeding from veins, and of taking pressure off the bladder. The cord can be raised from the vertebral canal by the dura mater, and the sacral nerves brought to view. The cauda equina below the 3rd sacral can then be cut, or the spinal cord at the 6th lumbar vertebra, in the latter case a small piece of sponge is placed in vertebral canal above the cut. In either case the pairs of spinal nerves (right and left) can be readily tied together above the spinal ganglia. The 1st, 2nd and 3rd spinal nerves are thus tied, cut centrally of the thread, and lifted up to free them to their point of exit from the vertebræ.

When in addition the hypogastric nerves are to be cut or stimulated, they are best exposed from the side; an incision is made at the edge of the lumbar muscles, just in front of the leg, and all vessels ligatured.

The pelvic visceral nerve (nervus erigens) can be dissected out from the ventral side with little or no exposure of the bladder, the upper part of the pelvic symphysis being removed. The removal of the upper part of the symphysis allows also a catheter to be passed into the bladder and tied in the urethra without exposing the bladder.

[1] For the method see Sherrington. This *Journal*, XXXVIII. p. 375. 1909.

Apparatus. The apparatus used in recording the contraction of the bladder is shown in Fig. 1. A metal catheter having holes at and near the end, so that the fluid can readily pass in and out of the bladder, is connected with the lower aperture of the bulb *B*, and the burette *Bur.*, on the connecting tube is a side tube *T*. The upper aperture of the bulb is connected with the lower aperture of a piston recorder, a side tube *T'* being on the connection. The piston has in its centre a hook to which a thread is fastened; the thread passes over a

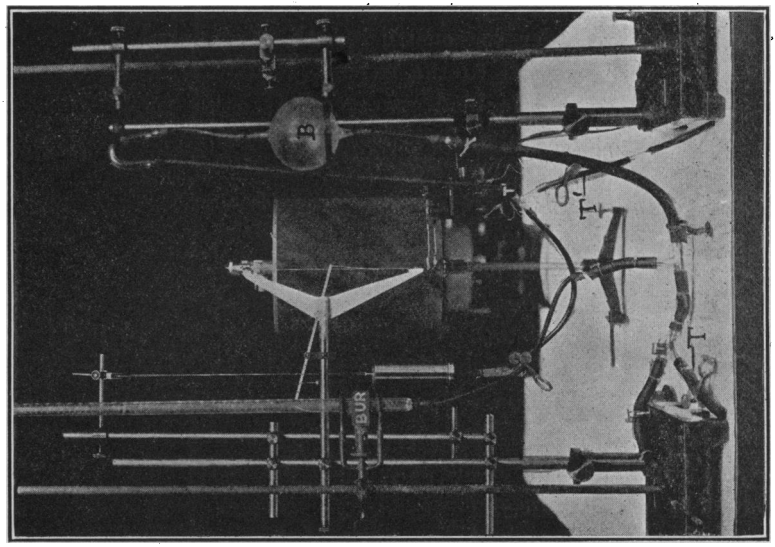


Fig. 1.

wheel and is hooked to one arm of a Lucas writing lever. A weight of a few grams is placed on the lever and adjusted so that when the tube *T'* is open the piston slowly falls, and when the piston is forced up, the thread passing to the lever is kept taut. Thus when the bladder contracts fluid is driven into the bulb, the air expelled from the bulb drives up the piston, and this causes a rise in the marking point of the lever. The method is a modification of that used by Elliott and other observers. The modifications consist in the piston recorder and in the writing lever.

The piston recorder[1] is fashioned on the plan of Hürthle's piston recorder for blood-pressure. Its internal volume is about 140 c.c.

[1] It was made for me by the Cambridge Scientific Instrument Co.

The Lucas lever has the great advantage that the writing point moves in a line which departs but little from the vertical. With slow movements, such as that of the bladder, the determination of the time relations of the curves of contraction obtained with an ordinary lever which describes an arc of a circle, is a very troublesome matter. With a Lucas lever the time relations are obvious within a limit of error which with the rate of drum movement of my experiments is 1 to 3 secs. For my purpose it was necessary to have some simple relation between the excursion of the lever, and the passage of a definite quantity of fluid from the bladder. Accordingly I had the lever and piston recorder so constructed that a rise of 1 cm. of the writing point corresponded to the expulsion of 2·1, 4·2, 6·3, 8·4 and 10·5 c.c.[1] of fluid from the bladder ascending as the hook from the piston was placed in the 1st, 2nd, 3rd, 4th or 5th hole of the lever. Above and below a certain point the lever does not write quite satisfactorily: these points are stopped; the lever was constructed so that the full excursion from stop to stop was 10 c.c., *i.e.* it corresponded to 21, 42, 63, 84, or 105 c.c. of fluid from the bladder.

Method of experimenting. Before an experiment, the tube T' is left open, the level of the piston recorder is arranged so that the piston touches or nearly touches the bottom of the cylinder when the writing lever rests on the lower stop. The hook from the piston is connected with the hole of the lever appropriate for the kind of experiment. This is the 5th and 4th from the axle, when the sacral nerves are to be stimulated, or nicotine injected.

In starting an experiment the neck of the bulb is placed at a definite height (as 8 cm.) above the level of the catheter; all the parts of the apparatus which are to contain fluid are warmed by running warm salt solution through them and the tubes are filled up to a mark on the neck of the bulb. The bladder is then emptied, the urine added to the warm salt solution used to refill it, the tube is connected with the catheter, a given quantity, *e.g.* 40 c.c., of fluid allowed to run into the bulb. The burette tube being clamped, the clamps on the bulb tube and the catheter tubes are removed. The whole or part of the fluid runs into the bladder; if the bulb empties, the catheter tube is clamped and a small amount (5 to 10 c.c.) of fluid passed from burette to bulb. The catheter clamp is removed and the process, if necessary, repeated till the fluid stays at the mark on the neck of the bulb. The

[1] These were intended to be 2, 4, 6, 8, 10 c.c. respectively, but the holes in the lever were not bored quite accurately.

bulb may be slightly raised or lowered to facilitate this. The tube T' and the catheter tubes are clamped, a given quantity of fluid (10 or 20 c.c.) is run from the burette into the bulb, this raises the writing lever and allows for some relaxation of the bladder during the experiment. The drum is then set in motion and the catheter tube is unclamped.

The volume of the fluid in the bladder is thus known, and the volume at any moment can be approximately seen from the tracing. The record does not give an accurate record of volume since the temperature of the fluid in the bulb varies and in consequence the volume of the air above it. At the end of the experiment the bulb is raised till the level of the fluid stands at the starting point, the tube from the bulb is clamped, the fluid in the bladder is collected by means of the tube T, and this allows the amount of urine secreted during the experiment to be roughly determined. Obviously a definite quantity of fluid may be removed or added during an experiment as may seem desirable. When changing the magnification of the lever, the catheter tube is clamped.

By this method the bladder contracts under nearly isotonic conditions. It is to be noted that when the animal is placed on its back, as in stimulating the pelvic visceral nerve or its branches, the abdominal muscles press more or less strongly on the bladder and tend to prevent its expansion.

In nearly all the experiments the effect of nerve stimulation before and after administration of curari or nicotine and the effect of varying the duration and frequency of the stimuli were determined: thus most of the results spoken of in this Paper were obtained over and over again.

Explanation of the figures. The animals in the experiments from which figures are taken varied in weight from $2\frac{1}{4}$ to $2\frac{3}{4}$ kilos. The time is in all cases marked in 10 second intervals. The number of c.c. of fluid expelled from the bladder has been shown by drawing two lines on the original tracings and writing between these the number of c.c. corresponding to a rise of the lever, from one line to the other.

With a few exceptions, the resistance to outflow from the bladder has consisted of a column of salt solution 7·5 to 12 cm. in height. In the description of the figures the column of fluid is indicated by Pr. = – cm.

The volume of fluid in the bladder at the beginning of each tracing is approximately given (Bl. vol. = – c.c.).

Unless otherwise mentioned the sacral nerves were stimulated in pairs (*i.e.* right and left together), the alkaloids were injected into the

jugular or femoral vein, and the stimulus was a faradic current of a du Bois Reymond induction coil, the currents being just distinctly felt on the tip of the tongue (towards the end of an experiment the strength of the currents was sometimes increased).

The curves selected for illustration have been taken so far as practicable from the same experiments, so that the course of events in any one experiment can be better seen. They are as follows:—

Exp. A.	Figs.	2 i, 15, 16, 21, 23	Exp. E.	Figs.	5, 8
,, B.	,,	2 ii, 20	,, F.	,,	14, 24
,, C.	,,	3, 6, 26	,, G.	,,	18, 19, 27, 28
,, D.	,,	4, 10, 11, 12, 13, 22			

One or two accessory results observed in the course of the experiments may here be mentioned.

Stimulation by anæsthetics. A sudden increase in any anæsthetic tends to cause a weak, transient contraction of the bladder. In some cases this no doubt may be due to a reflex from the spinal cord, but the contraction occurs after section of the sacral nerves and after injection of large dose (25 to 35 mgrs.) of nicotine which would probably interrupt all impulses from the spinal cord. Towards the end of an experiment the circulation usually becomes feeble and the body temperature falls. In these conditions an increase in the amount of anæsthetic, previously effective, becomes ineffective. Thus if an animal is anæsthetised with A.C.E. mixture, and the corneal reflex just abolished, intra-venous injection of 1 to 3 c.c. of 25 p.c. urethane usually causes a transient contraction in the early stages of an experiment. And if it is anæsthetised with A.C.E. and urethane, and the A.C.E. is discontinued for a short period, the first administration of A.C.E. by a tracheal tube at a stage when there is no corneal reflex, causes a slow, rather brief contraction of the bladder. The effect may be obtained two or three times at short intervals, then further A.C.E. causes some relaxation, probably in consequence of the decreased blood flow. On injecting chloroform or A.C.E. into the jugular vein or into the trachea at the end of an experiment (in order to kill the animal), there was usually a moderate, transient contraction. The contraction is not due to asphyxial stimulation of the spinal cord, since it follows the injection too quickly, and since at the end of an experiment in which nicotine has been administered, death by stopping the respiration or by bleeding rarely causes contraction; the usual result of this is a slow slight relaxation. It was noticed by Elliott[1] that after degeneration of the inferior splanchnics (the pelvic nerves being cut at the time of the experiment), the administration of ether caused contraction of the bladder; he considered that the degeneration of the nerves had rendered it abnormally irritable.

Spontaneous rhythmic contractions. In most of my experiments the sacral nerves were cut; in these there were either no spontaneous contractions, or very slight ones. When the sacral nerves were not cut, or cut on one side only, or when one pelvic visceral nerve only was cut, there was some tendency for small contractions to occur but they did not occur constantly; stimulation of the sacral nerves at times caused them or increased them. Injection of pilocarpine, as is known, sets up rhythmic contractions; I have occasionally observed a similar effect after injection of urethane, and once after injection of 60 mgrs. of atropine, and constantly after exposure of the bladder; these

[1] Elliott. This *Journal*, xxxv. p. 413. 1907.

rhythmic contractions occurred in all experiments in which the nerves in the bladder itself were dissected; they were decreased or arrested in placing the hinder part of the body with the bladder in Ringer's solution at 39°—40° C. A few minutes after death slight rhythmic contractions are common as a preliminary to the final relaxation.

CHANGE CAUSED BY CURARI AND BY NICOTINE IN THE RESPONSE OF THE BLADDER TO ELECTRICAL STIMULATION OF THE SACRAL AUTONOMIC NERVES.

(*a*) *Normal effect of stimulating the sacral vesico-motor fibres.*

As shown by Anderson and myself[1] the origin of the vesico-motor fibres from the spinal cord varies with the origin of the somatic nerves. With an anterior arrangement of somatic nerves, the 1st sacral has vesico-motor fibres and it may have more than the 3rd sacral. This arrangement is not very common and usually the fibres are confined to the 2nd and 3rd sacral nerves. With a posterior arrangement, the

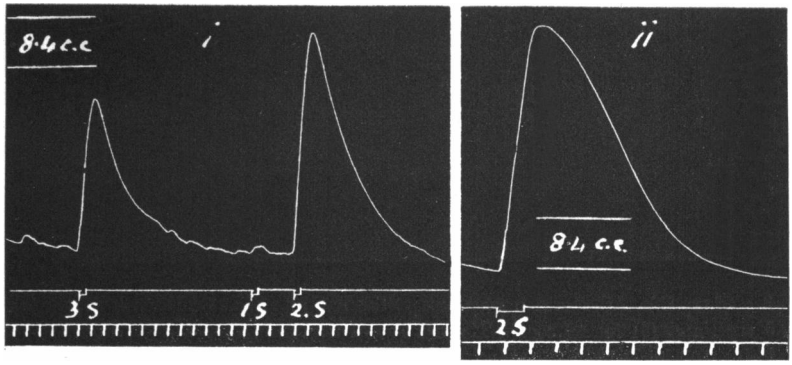


Fig. 2 i. (Exp. A.) Effect of stimulating the cut 1st, 2nd and 3rd sacral nerves (bilaterally) each for five secs. The slight rise with the 1st sacral was due to muscular contraction. Bl. vol. = 60 c.c. Pr. = 7·5 cm.

ii. (Exp. B.) All sacral nerves, and the hypogastrics cut. Stimulation of the 2nd sacral nerves for 10 secs. Bl. vol. = 65 c.c. Pr. = 8 cm.

3rd sacral may be more effective on the bladder than the 2nd. In one experiment in this series (posterior plexus), vesico-motor fibres were absent from the 2nd sacral nerve. In the majority of my experiments the 2nd sacral nerve was the most effective. The effect produced by stimulating the several nerves varies in degree only and not in kind (cp. Fig. 2 i).

[1] Langley and Anderson. This *Journal*, XIX. p. 81. 1895.

When the stimulation is brief, as 5 secs., the relaxation begins a few seconds after the contraction has ceased, so that with a slow moving drum the apex of the curve is sharp (cp. Fig. 2 i, also figures given by Sherrington. This *Journ.* XIII. Pl. 22. 1892). With a slightly longer stimulus as 10 to 15 secs. the curve may be as in Fig. 2 i, but there is a tendency to a less rapid relaxation at first, so that the upper part of the fall is convex to the rise instead of being concave as in Fig. 2 ii: in this case the hypogastric nerves were cut, but the form of the curve was much the same before the section.

Usually when the more effective nerves are stimulated for 20 to 30 seconds the bladder is emptied, and there is a tendency for the contraction to persist for a short time. I have only made a few

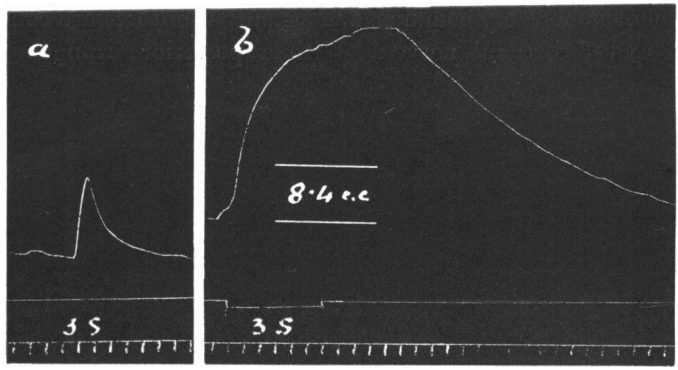


Fig. 3. (Exp. C.) All sacral nerves cut. Stimulation of the 3rd sacral nerves (*a*) for 5 secs. and (*b*) for 60 secs. The 3rd sacral nerves had relatively few vesico-motor fibres, the 1st sacral had rather more than the 3rd. Bl. vol. = 48 c.c. Pr. = 7·5 cm.

experiments with more prolonged stimulation; in these the persistence of the contraction varied, sometimes giving way during the stimulation, sometimes continuing after it; the result depending largely upon the height of the column of fluid the bladder had to support. There may, however, be prolonged contraction. I give an example in Fig. 3 from an experiment in which the 3rd sacral nerves (which had a much weaker effect than the 2nd) were stimulated.

Occasionally the relaxation is retarded by a slow contraction, giving a curve with a rounded top, which begins $\frac{1}{3}$ to $\frac{1}{2}$ way down the curve. A fairly marked form of this is shown in Fig. 4, and a less marked form in Fig. 6. The cause I have not determined. It might perhaps be due

to the fluid running back to the bladder having been cooled, but in that case, it would be expected to occur more frequently, and I am inclined to consider it a direct result of the stimulation.

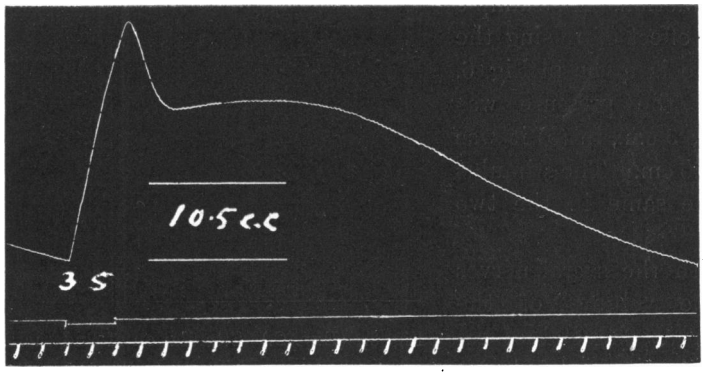


Fig. 4. (Exp. D.) All sacral nerves cut. Stimulation of 3rd sacral nerves for 20 secs. Bl. vol. = 80 c.c. Pr. = 13 cm.

In one case there were two such contractions, of larger dimensions (Fig. 5). In this experiment the 3rd sacral nerves were not cut on one side and the result may have been due to a reflex from the spinal cord. In other cases of unilateral stimulation I have not however found a similar effect.

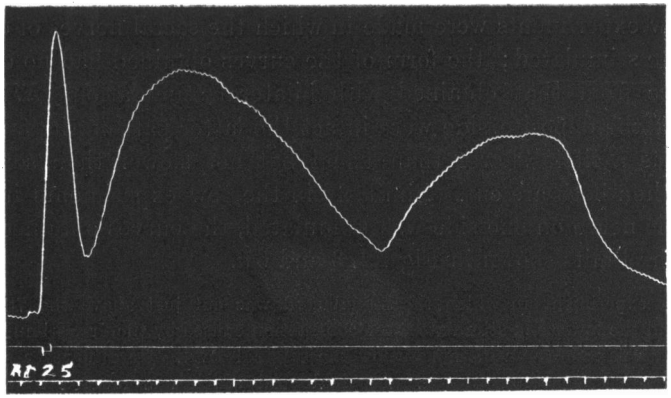


Fig. 5. (Exp. E.) Sacral nerves cut on one side only. Stimulation of right 2nd sacral for 5 secs. Pr. about 8 cm.

The preceding curves were all obtained with a pressure not exceeding 13 cm. of fluid. A high pressure of course increases the rate of relaxation and if the stimulus is brief lowers the height of contraction. An example of the effect of raising the pressure is given in Fig. 6. In (*a*) the pressure was 7·5 to 8·5 cm., in (*b*) it was 25 to 26 cm. The stimulus was the same in the two cases.

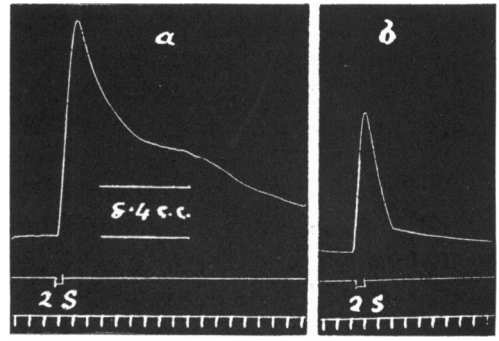


Fig. 6. (Exp. C.) Stimulation of 2nd sacrals for 5 secs. with different resistance to outflow from bladder. (*a*) Pr. = 7·5 cm. (*b*) Pr. = 25 cm. The slow fall at the end of the curve took place after the bulb was empty and the pressure low. Bl. vol. = 50 c.c.

With the sacral nerves cut the volume of the bladder at the end of relaxation was nearly always the same as that at the beginning of contraction, occasionally the increase of volume in relaxation was slightly greater than the decrease in contraction, but never sufficiently greater to give any satisfactory evidence of the presence of inhibitory fibres. Since the tone of the bladder after section of the sacral nerves is, as noticed by Elliott, slight, I tried in two experiments the effect of stimulating the sacral nerves after the tone of the bladder had been raised by pilocarpine; the curves were of the normal form.

A few experiments were made in which the sacral nerves of one side only were stimulated; the form of the curves obtained had no constant difference from that obtained with bilateral stimulation. When the nerves of the opposite side were intact the latter part of the fall in the curve was a little slower than usual but not slower than sometimes occurs when both are cut. Similarly in the few experiments in which the pelvic nerve on one side was stimulated, the curves obtained varied within the limits shown in Figs. 2, 3 and 6 *a*.

In one experiment in which the spinal cord was cut just above the 7th lumbar vertebra and the lower end stimulated, the contraction caused by the first stimulation was followed by relaxation considerably below the original level. Here however there may have been some tone from the sacral spinal cord which was lowered by the direct stimulation. The same result was obtained by the first stimulation in Exp. D. (Fig. 5 supra shows the second stimulation, in which as I have said the nerves were cut on one side only.)

The effect of stimulating the branches of the pelvic nerve will be considered later (p. 163).

The normal effect then of stimulating one pair of sacral nerves having vesico-motor fibres is a rapid contraction, which, if the stimulus is prolonged for 20 to 30 secs. and the fibres are many, leads to practically complete emptying of a bladder containing 50 to 80 c.c. The longer the stimulation (within certain limits) the slower the relaxation, *i.e.* the effect after the stimulus is of the same nature as that during it; and the curves give no satisfactory evidence of the presence of inhibitory fibres.

(*b*) *Effect of stimulating the sacral autonomic nerves after injection of curari.*

1·5 *to* 2 *c.c.* 1 *p.c. curari.* The minimal amount of curari which will produce a change in the effect of the sacral nerves on the bladder, I have not determined, but an amount barely more than sufficient to paralyse the motor nerves to the muscle has a marked effect. In Fig. 7 some curves are given from an experiment in which 2 c.c. of 1 p.c. curari were injected. On stimulating the 2nd sacral nerves a few minutes after the injection, the bladder began to contract in the normal manner, but instead of continuing until the bladder was emptied —as it had done before—it soon began to relax, and on ceasing to stimulate there was a second rather larger and more protracted contraction (Fig. 7 *a* 1). On repeating the stimulus before this contraction had disappeared but for a longer time the result was the same except that there was a very slow contraction during the latter part of the period of stimulation (Fig. 7 *a* 2).

The nerves were then stimulated at intervals of 5 to 10 minutes for an hour with a view of determining what modifications would occur during partial elimination of the curari. Some of the curves obtained are given in the figure, it will be seen that they undergo a number of changes. The strength of the contraction increases up to a maximum in *c*; the smaller contraction in *e* was due to the interval between it and the preceding contraction being too brief. The slow contraction during the latter part of the stimulus becomes in *c* a retardation of the relaxation, and it apparently disappears in *d*; this however may be partly due to the fact that a number of stimuli had previously been applied. The after-contraction decreases in abruptness and extent and other things being equal is greater with a longer duration of stimulation; the after-contraction in *d* and *e* is reminiscent

of the slow contraction which as I have said may occur normally (cp. Figs. 4 and 6). Throughout this, and another similar experiment, there was no indication of inhibition unless the quicker relaxation after the primary contraction is taken as such.

4 to 5 c.c. of 1 p.c. curari. After the larger dose of curari, there is an exaggeration of the change brought about by the smaller dose. The contraction immediately following the stimulus is brief and very slight and on cessation of the stimulus there is a much stronger and much more protracted after-contraction (cp. Fig. 8). If the stimulus is brief (2 to 5 secs.), the after-contraction more or less fuses with the initial one. If the stimulus lasts a little longer, the initial contraction is over before the stimulation ceases and the relaxation may pass into slight inhibition (cp. Fig. 8). The duration of the inhibition varies, but generally in the early stimulations a slow slight contraction begins in about 25 secs., *i.e.* there is some escape from inhibition.

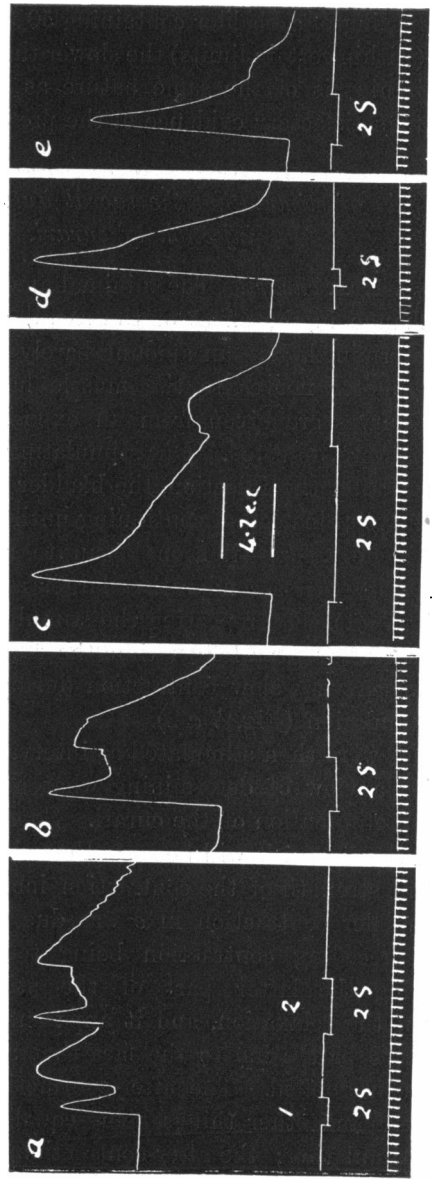


Fig. 7. Sacral nerves cut. 2 c.c. 1 p.c. curari injected. Stimulation of 2nd sacral nerves. The vol. of the bladder slowly increased throughout the Exp.; it was about 20 c.c. in (*a*). Pr. = 8 cm.
a. 3′ after injecting curari. Interval between *a* and *b*, 18′; *b* and *c*, 26′; *c* and *d*, 10′; *d* and *e*, 7′ (with a stimulation of 40″ between).

When the stimulus is repeated at any time before the relaxation from the after-contraction is complete, there is a brief slight initial contraction as with the first stimulus, but the following inhibition is much greater (cp. Fig. 8). Since the bladder has more tone there is of course more scope for inhibition. On cessation of the stimulus, there is again contraction; this may be less absolutely than the after-contraction produced by the first stimulus, but by summation it increases the quantity of fluid expelled from the bladder.

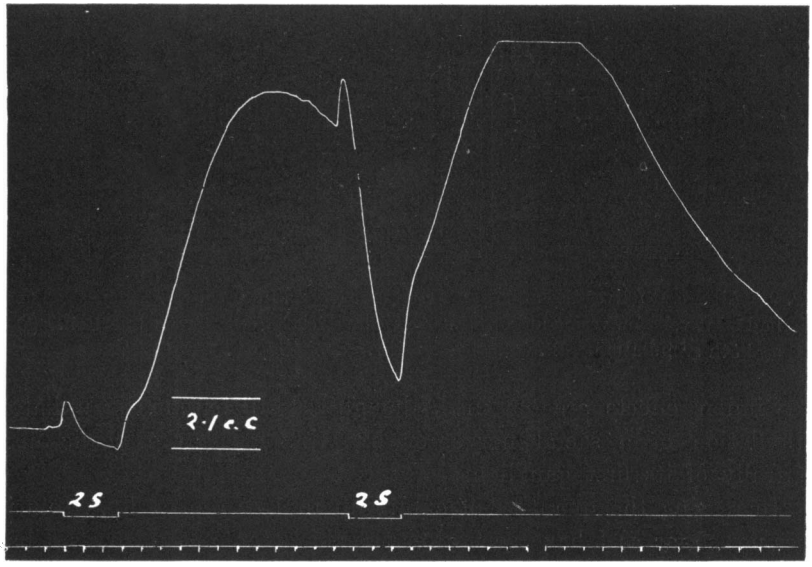


Fig. 8. (Exp. E.) Stimulation of the 2nd sacral nerves a few minutes after the injection of 5 c.c. of 1 p.c. curari. (After the tracing shown in Fig. 5, the sacral nerves were cut on both sides.) Pr. = about 8 cm.

On repeating a brief stimulus several times at intervals of two or three minutes, the initial contraction is little or not at all altered, but the after-contraction rapidly decreases (cp. Fig. 9). There may also be some decrease in the extent of the inhibition, this however depends chiefly upon the degree of tone at the time. On continued repetition of the stimulus the after-contraction becomes hardly stronger than the initial contraction. As mentioned above if the stimulus lasts for about 25 seconds, a slow contraction usually begins; if the stimulus is prolonged for a minute to a minute and a half, the slow contraction continues; it passes, on cessation of the stimulus, into the more rapid

after-contraction. The after-contraction is proportional to the duration of the stimulus up to a certain limit; in general the maximal after-contraction is produced by a stimulus lasting 20 to 25 secs. Some figures to illustrate the effect of varying the duration of the stimulus will be given below in describing the action of nicotine, which causes a similar change in response to that caused by curari.

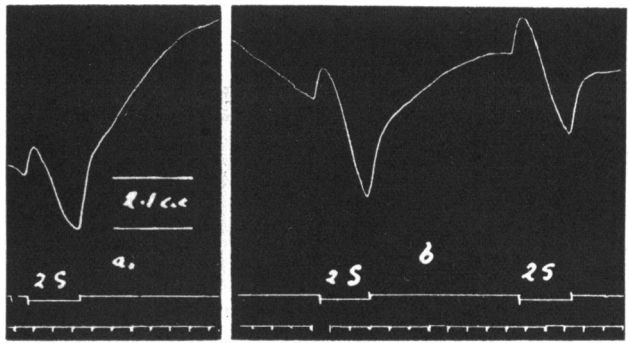


Fig. 9. All sacral nerves tied and cut; 5 c.c. 1 p.c. curari injected. The 2nd sacral nerves had relatively few vesico-motor fibres. (*a*) 2nd stimulation after the injection. (*b*) 4th and 5th stimulation. Bl. vol. = 65 c.c. Pr. = about 15 cm.

Similar effects are obtained, though less in extent, by unilateral stimulation of a sacral nerve, or by stimulating the pelvic nerve centrally of its first ganglion.

Increasing the quantity of curari up to 15 c.c. of a 1 p.c. solution does not so far as I have seen alter the character of the curves, I have however made a few experiments only with the larger doses. In view of the action of nicotine it is probable that a sufficient quantity would abolish the initial contraction.

(*c*) *Effect of stimulating the sacral autonomic nerves after the injection of nicotine.*

Nicotine, as is known, causes strong contraction of the bladder. Since this contraction may cause temporary fatigue, it is advisable to wait a few minutes after relaxation before stimulating the nerves. Some details of the action of nicotine will be given later (p. 147) in considering how the contraction it produces is affected by curari.

The amount of nicotine required to produce a given effect varies somewhat in different cats independently of their weight. In a few cases

I have found three or four times the usual amounts to be required. I am not certain however that this large difference was due to individual variation. I have in the great majority of cases used Merck's nicotine (extra pure), but the solutions have not all been made up from the same sample, and in some cases I have used nicotine not manufactured by Merck, or at any rate not having his label. In the following account I give the dose which I have usually found to produce a given effect, but lay no stress on the precise amount.

After intra-venous injection of 5 to 10 mgrs. of nicotine, the effects of nerve stimulation are similar to those already described for curari. Fig. 10 is from an experiment in which 5 mgrs. were sufficient to completely change the effect of stimulation. In this figure, the initial contraction means an expulsion of 3 c.c. from the bladder, the subsequent inhibition a passage of 6·8 c.c. into it, and the after-contraction the expulsion of 22 c.c.

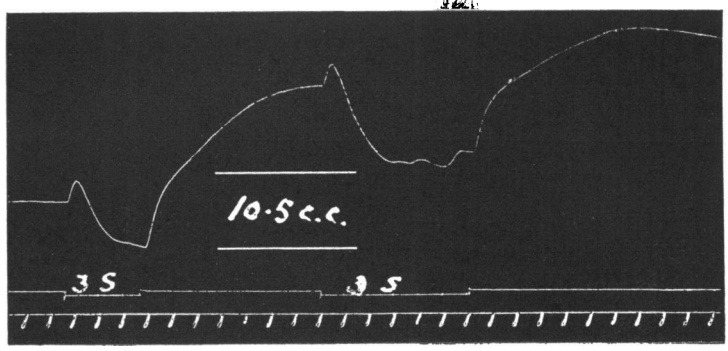


Fig. 10. (Exp. D.) (Cp. Fig. 4.) Stimulation of 3rd sacral nerves for 30 secs. and for 60 secs. a few mins. after injection of 5 mgrs. of nicotine. There was one stimulation just before these, so that the inhibition during the first stimulation in the figure is an inhibition of an after-contraction. Bl. vol. = 70 c.c. Pr. = 13 cm.

It will be noticed that in Figs. 8, 9, 10 the after-contraction consists of two parts, a quicker first part and a slower second part. So far as my experiments go, this distinction is only found when there is an initial contraction during stimulation, and then not constantly.

As I have already said in describing the action of curari, the form of the curve depends upon the frequency of the stimulation, and on the duration of the stimulus. Some examples may be given from the experiment from which Fig. 10 is taken, to show the kind of change caused by variation in these factors.

After the tracing of Fig. 10, one brief stimulus was given in 7 mins. and then the tracing of Fig. 11 obtained. It will be seen that the height of the initial contraction is as great with a stimulus of 2 secs. as with one of 20 secs., *i.e.* a very brief stimulus is sufficient to cause a maximal initial contraction. But with the brief stimulus, there is no inhibition, unless the slight check in the rise is taken to show a fleeting effect, with the longer stimulus there is marked inhibition. The course of the after-contraction is also different in the two cases, but the difference is chiefly if not wholly in the latter part of the contraction; the first quick part of the after-contraction in each case goes on at the same rate as the initial contraction, and in each case it is of practically

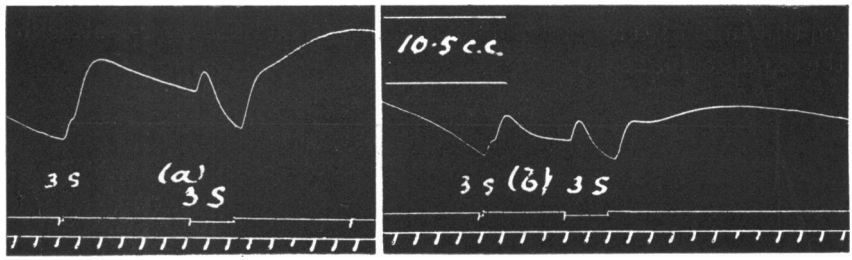


Fig. 11. (Exp. D) (see text). Between (*a*) and (*b*) there was an interval of three mins. Bl. vol. = 68 c.c. Pr. = 13 cm.

the same strength causing the expulsion of about 9 c.c. from the bladder; the second, slower, part of the after-contraction takes a different course with brief and with more prolonged stimuli; with the brief stimulus it continues for a few seconds and then slowly declines, with the more prolonged stimulus the contraction continues for more than a minute. Thus as between stimuli of 2 secs. and of 20 secs. the more prolonged stimulus caused a more prolonged second part in the after-contraction. At the time of taking these tracings there was some fatigue, since there had been some previous stimuli. The less the fatigue the more nearly the rate of the second after-contraction (using this term for convenience for the second part of the after-contraction) approaches the rate of the first after-contraction and of the initial contraction. At a short interval ($2\frac{1}{2}$ mins.) after the tracing of Fig. 11 *a*, the 3rd sacrals were again stimulated for 2 and for 20 secs. The curves are shown in Fig. 11 *b*. Here the effect of fatigue is marked, the first after-contraction being somewhat less and the second one much less.

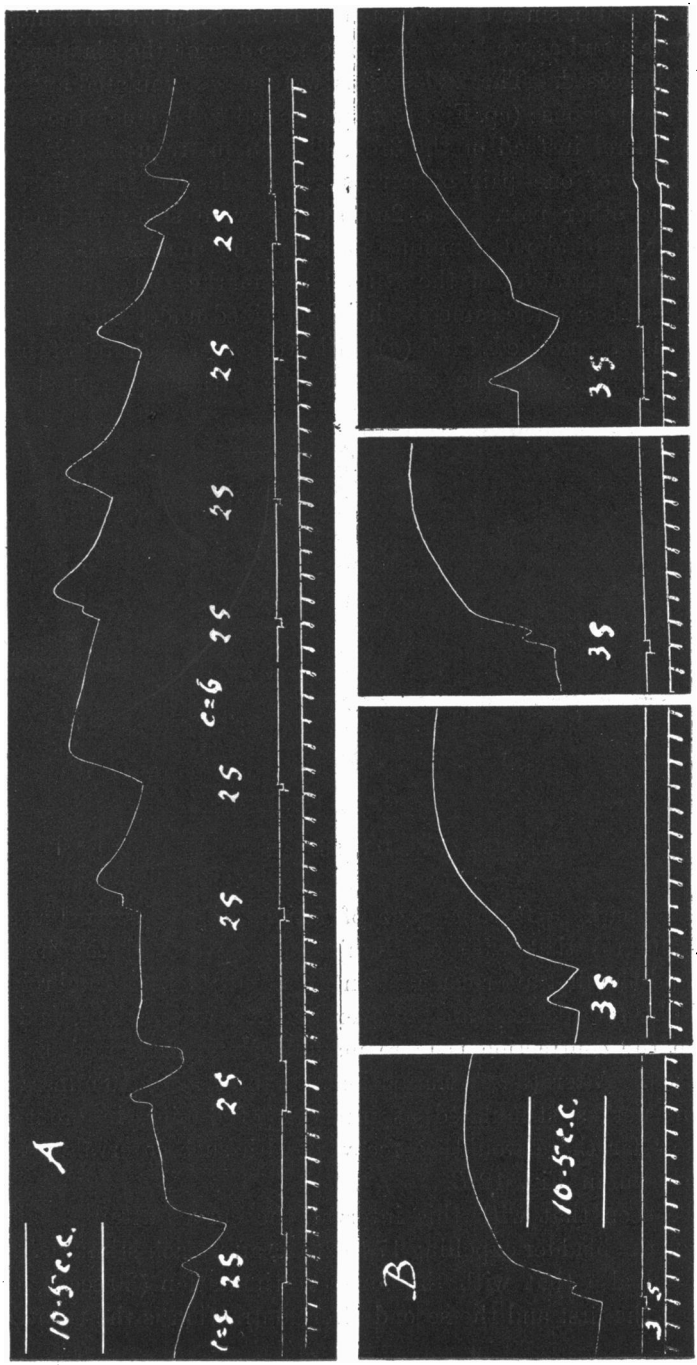


Fig. 12. (Exp. D.) The 3rd sacral nerves had been frequently stimulated after the injection of 5 mgrs. of nicotine, and fatigue produced.
A. Stimulation of the 2nd sacral nerves. The first four stimuli were with the sec. coil at 8 (shocks distinctly felt on the tongue, but not strong) and the last four with the second coil at 6 (shocks rather strong to tongue). Bl. vol. = 77 c.c. Pr. = 13 cm.
B. (See text.) Stimulation of 3rd sacral nerves at intervals of 6 minutes. Bl. vol. = 84. Pr. = 13 cm.

So far the stimuli, since the injection of nicotine, had been confined to the 3rd sacrals and as we have seen the response of the bladder had been greatly decreased. The 2nd sacrals were now stimulated and the reduction in the response (cp. Fig. 12 *a*) was found to be much the same as if the 2nd sacral instead of the 3rd had been in frequent action so that stimulation of one pair of nerves greatly lessens the effect of stimulating the other pair. The 2nd sacrals were stimulated eight times at intervals of about a minute for a varying number of seconds (Fig. 12 *A*). The duration of the stimuli are marked on the tracing. The general results are the same as those described under Fig. 11. In addition it will be noticed that (*a*) with the later stimuli of brief duration the increase of tone caused by the earlier stimuli slowly

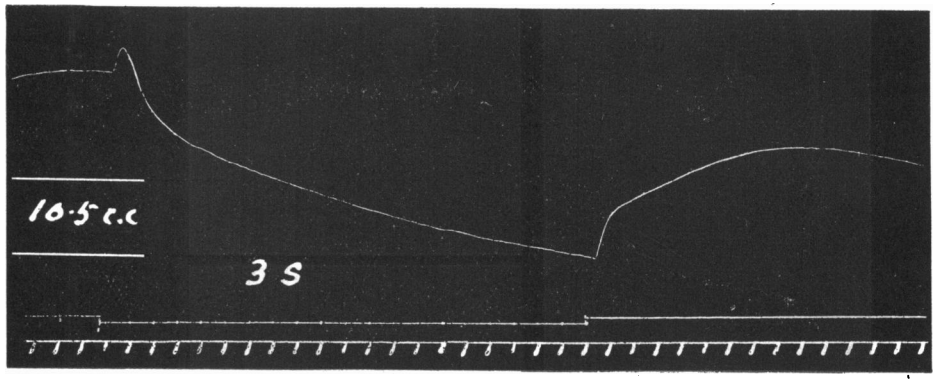


Fig. 13. (Exp. D.) See text.

decreases, this marks a further stage of fatigue of the second after-contraction, and (*b*) that with a stimulus of one second the initial contraction and the first after-contraction apparently form an unbroken curve; a slight retardation can however be seen with a lens, and is obvious when the contraction is more magnified and the speed of the drum increased. After these stimulations an interval of 10 mins. was left, and the nerves stimulated at intervals of 6 mins. in order to determine how far there would be recovery with such intervals. The results are shown in Fig. 12 *B*.

It will be seen that with this interval, the curves attain a fairly constant level, the bladder expelling 17 to 20 c.c. after each stimulus. It will be noticed also that with the longest stimulation (30 secs.), the break between the first and the second after-contraction is the greatest.

The duration of the inhibition may be very prolonged; its duration is favoured by repeated stimulation and by the stimulus being applied during an after-contraction. Thus in the Exp. quoted above, a quarter of an hour after the tracing of Fig. 12 *B* was taken, the three sacrals were stimulated and an after-contraction obtained causing the expulsion of about 30 c.c. of fluid from the bladder; at the top of the curve the nerves were again stimulated and this time for more than three minutes. There was inhibition during the whole time (cp. Fig. 13), followed by moderate contraction on ceasing to stimulate.

When a large quantity of nicotine is given (15 to 30 mgrs.), stimulation of the sacral nerves no longer causes an initial contraction, or if it does, the contraction is slight, and only occurs now and then in the experiment. (See Fig. 14 *b* and Fig. 16.) In place of the contraction there is slight primary inhibition. Fig. 14 *a* is an example of the absence of initial contraction. The after-contraction is no longer, so far as I have seen, divisible into two parts. (Cp. Figs. 14, 16, 18, 20, 21.)

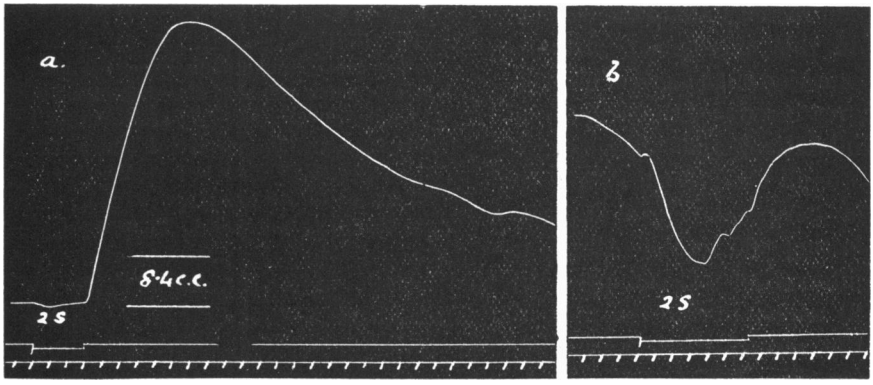


Fig. 14. (Exp. F.) 2nd and 3rd sacral nerves tied and cut, (*a*) 1st stimulation of the 2nd sacrals after injection of 15 mgrs. of nicotine, (*b*) 6th stimulus. Bl. vol.=about 65 c.c. Pr.=9 cm.

In the experiment from which Fig. 14 is taken, stimulation of the sacral nerves for 30 secs. before nicotine was injected had caused the expulsion of 63·5 c.c. of fluid from the bladder and had nearly emptied it. As shown in Fig. 14 *a*, similar stimulation after the injection of 15 mgrs. of nicotine caused no expulsion of fluid during the stimulation but caused 43 c.c. to be expelled after it had ceased. In this case there was very slight escape from the primary inhibition. In a later stimulation lasting 60 seconds, escape occurred (Fig. 14 *b*).

The degree of escape from inhibition whilst the stimulus continues varies greatly in different cases. Usually it is less in the later stimulations than in the earlier ones, and less with 30 or more mgrs. of nicotine than with 15 mgrs. Fig. 15 gives a marked instance of escape from inhibition after 15 mgrs. of nicotine. During the latter part of the stimulation the bladder expelled about 23 c.c. It will be noticed that the after-contraction was small, it was less than a half of that caused by the previous 5 secs. stimulus, this was no doubt due in part at any rate to the contracted state of the bladder. In this experiment, a second injection of 15 mgrs. of nicotine greatly reduced the escape from inhibition, and after several stimuli there was a mere trace of escape during a stimulus lasting 60 secs. After an interval of five minutes the 2nd sacrals were stimulated twice for $2\frac{1}{2}$ mins.; during the first stimulation there was slight escape, during the second there was inhibition throughout, though it was slight (cp. Fig. 16).

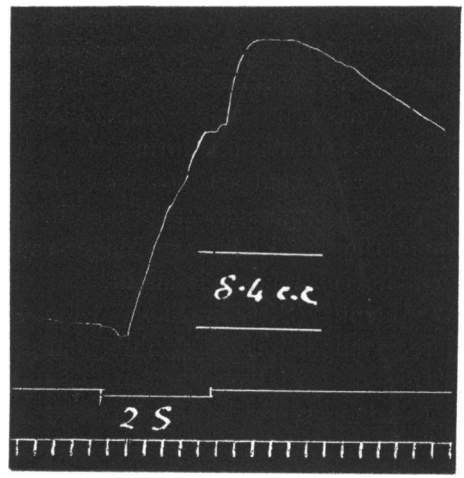


Fig. 15. (Exp. A, cp. Fig. 1.) All sacral nerves cut. Third stimulation of the 2nd sacrals a few minutes after injection of 15 mgrs. of nicotine. The after-contraction from the previous stimuli (one of 5, the other of 15 secs.) had caused about 33 c.c. out of 70 c.c. of the contents of the bladder to be expelled. Pr. = 7·5 cm.

Further the escape is, in general at any rate, greater when there is very little tone in the bladder than when the tone is considerable. This is shown in Fig. 16. A more striking instance is given in Fig. 18 *a*. Here when there was very little tone, stimulation for 20 secs. caused expulsion of 22 c.c. of fluid from the bladder, nearly all in the last 10 secs.; when the tone had been increased by an after-contraction a stimulus of equal strength caused relaxation only, apart from a trivial initial contraction.

I have said in speaking of the effect of small doses of nicotine that stimulation of one pair of sacral nerves if frequently repeated greatly decreases the effect of the other pair or pairs. I have only made

incidental observations with regard to this, but the fatigue in some cases is certainly only partial. Thus in the experiment from which Fig. 16 is taken, the 3rd sacral nerves, which had not been stimulated for 50 mins. caused much greater inhibition and greater after-contraction than the 2nd sacral nerves though the latter had more vesico-motor fibres (cp. Fig. 2 i).

In one experiment there was an indication that a nerve having few vesico-motor fibres (1st S.) may cause inhibition at an earlier stage of nicotine poisoning than a nerve having many vesico-motor fibres (2nd S.).

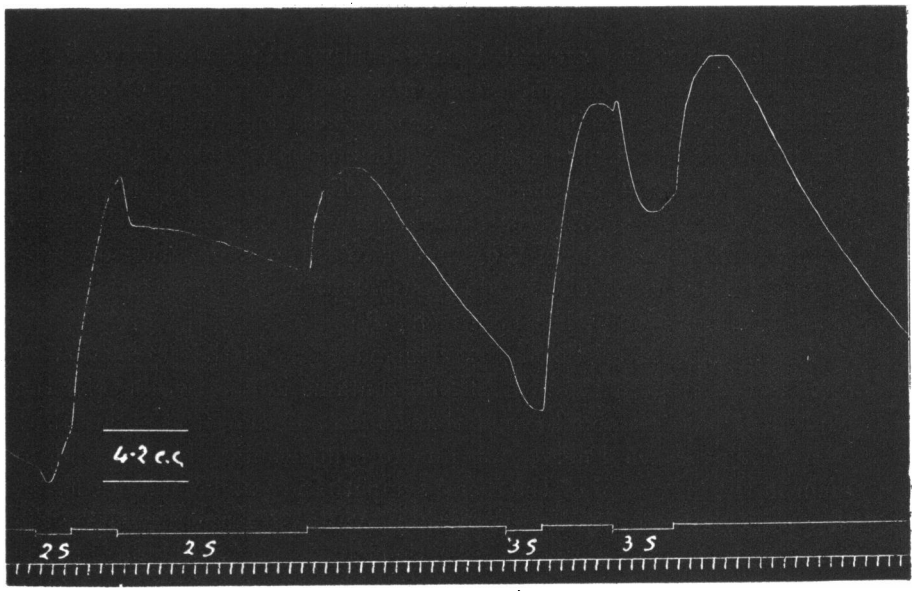


Fig. 16. (Exp. A.) Stimulation of 2nd and of 3rd sacrals after 30 mgrs. of nicotine, see text. Bl. vol. = about 55 to 60 c.c. Pr. = 7·5 cm.

Up to a certain limit of the duration of the stimulus the after-contraction increases in extent, as it does when a smaller dose of nicotine has been given. The maximum after-contraction is commonly obtained in 20 to 30 secs. With more protracted stimulation (1 to 2 mins.) the after-contraction has sometimes seemed to diminish, but this point I have not yet worked out.

Although it was unlikely that the after-contraction was caused by polarisation currents set up in the nerve at the point of stimulation, I thought it better to determine this by experiment. The 2nd sacrals

were stimulated and inhibition produced, during the inhibition the nerves were cut peripherally of the electrodes; an after-contraction of normal form ensued on the section.

There is a wide range of strength of stimulation within which the effect is increased by increasing the strength of the stimulus.

Large doses of nicotine (up to 75 mgrs.) do not abolish the inhibition or the after-contraction though they diminish them.

ORIGIN FROM THE SPINAL CORD OF THE NERVE FIBRES PRODUCING THE CHANGED RESPONSE.

In the preceding account I have assumed that the nerve fibres which cause inhibition and after-contraction after curari or nicotine arise from the sacral spinal cord. The direct evidence that this assumption is correct is of course afforded by stimulation of roots of the nerves. It is easy to obtain 2–3 cm. of the roots of the 2nd sacral nerve, and these give the same effect as stimulation of the trunk of the nerve. Moreover the fibres run in the anterior roots, for stimulation of these have again the same effect, whilst stimulation of the posterior roots (one experiment only) has no effect.

Since a characteristic of the changed effect is the production of inhibition, and since the sympathetic contains inhibitory fibres for the bladder, it was desirable to show that no part of the effect obtained by stimulating the sacral nerves was due to sympathetic fibres running to them in the grey rami of the sacral sympathetic ganglia. Evidence on this point has already been given by Anderson and myself[1]. We found that stimulating the sympathetic chain just below the 6th lumbar ganglion usually had no effect on the bladder but occasionally caused a trivial contraction, and so far as could be seen by the eye, no other effect, the slight contraction when obtained we considered to be due to fibres running by the aortic plexus to the pelvic plexus. Since it was possible that the sympathetic effect would only be brought out by curari I have taken a tracing of the bladder movements in the usual way and have stimulated the peripheral part of the sympathetic after cutting it below the 6th lumbar ganglion, before and after injection of curari[2]. Neither

[1] Langley and Anderson. This *Journal*, XIX. p. 135. 1895.

[2] It may be recalled that the sacral sympathetic ganglia do send post-ganglionic fibres (pilo-motor and vaso-motor) to the sacral nerves, and that these are stimulated by stimulating the sacral nerves a short distance from the spinal ganglia; the sympathetic fibres accompany all the branches of the sacral nerve except the pelvic nerve. The

before nor after was any distinct effect obtained; occasionally there was apparently a trivial contraction (expulsion of about ½ c.c. of fluid), but even this may have been due to other causes than the nerve stimulation.

THE TISSUE IN WHICH THE CHANGE OF RESPONSE OCCURS.

When stimulating the sacral autonomic fibres, the stimulus affects nerve fibres, nerve cells, and the unstriated muscle of the bladder. Since neither curari nor nicotine in small amount has been found to have any appreciable action on nerve fibres, we may put these out of account as being concerned in the changed response of the bladder. We have then to consider whether the change in normal effect occurs in the nerve cells or in the unstriated muscle of the bladder.

(*a*) *Effect of curari on the contraction caused by nicotine.*

It has been shown in all the cases investigated that nicotine has an action on peripheral nerve cells. In nearly all cases its primary action is a brief stimulation. This can be shown as regards the bladder by applying nicotine locally to one or more of the ganglia of the pelvic plexus, or to the inferior mesenteric ganglia. After the stimulation there follows, in the cat and some other animals, a paralysing action, in so far that there is more or less complete abolition of the normal effect of stimulating the pre-ganglionic fibres. As regards the bladder it was found by Anderson and myself[1] after injection of nicotine that stimulation of the pelvic nerve had no effect or only a slight one, that stimulation of the branches just past the 1st ganglion had a slight effect, and that local contraction, to the eye not greatly less than maximal, could be obtained by stimulating one or other of the branches close to the bladder. As has been shown in the preceding pages the abolition of the motor effect of the pre-ganglionic fibres only holds for the actual period of stimulation, and this only with some reservations. Our observations however showed that the absence of contraction during stimulation was due to an action of nicotine on the nerve cells and not to an action on the bladder itself. To this question I shall return in a later section (p. 163).

sympathetic fibres which should run in the pelvic nerve, run in the hypogastric nerve. The more primitive form occurs in the frog (cp. Langley and Orbeli, this *Journal*, XLI. p. 469. 1910), in this animal the sympathetic vesico-motor fibres run in the pelvic nerve; a hypogastric, of the type which is present in the mammal, is absent.

[1] Langley and Anderson. This *Journal*, XIX. p. 135. 1895.

Now we have seen above that curari modifies the effect of stimulating the pre-ganglionic fibres in much the same way as nicotine. We should then expect that this action of curari would also be due to a modification of the nerve cells. It has in fact been shown in certain cases that curari paralyses peripheral nerve cells in the same way as nicotine does[1]. One way of determining whether curari acts on the same part of the nerve cell as nicotine is to investigate how far one interferes with the action of the other. As a preliminary I may say a word or two on the action of nicotine and curari on the bladder.

Nicotine in any dose from half a milligram upwards causes contraction of the bladder. The minimal dose is no doubt much less than half a milligram, but I have not determined it, since it was of no importance for my main object. The contraction produced varies. Anything from a fourth to (practically) the whole contents of the bladder may be expelled. It is obvious that many conditions influence the volume of fluid expelled. I need only mention the rate of injection and the amount of nicotine. A slow injection tends to keep up the stimulus; a large amount tends to paralyse the nerve cells quickly; thus a small amount injected slowly may cause greater contraction than a larger amount injected rapidly. As with other stimulations by nicotine, contraction of the bladder may in certain conditions be obtained several times in succession.

The usual form of curve obtained by injecting nicotine after section of the sacral nerves is a simple rise and fall, the whole taking two to five minutes. The fall is usually somewhat quicker than when the sacral nerves are stimulated; this might be due either to the sympathetic inhibitory cells being stimulated or to a more abrupt cessation of the stimulation of the sacral motor cells. In one case, however, the relaxation took longer than five minutes; and in one case, for no obvious reason, the relaxation almost stopped when it had proceeded for about two-thirds of the rise caused by the contraction. A subsequent injection produced the normal result.

When no nerves are cut there is a tendency for the relaxation to go past the original level, this probably depends on the degree of tone in the sacral centres. In one case this greater relaxation was observed when nicotine was injected after section of the spinal cord in the 6th lumbar segment.

[1] Langley and Dickinson. This *Journal*, xi. p. 517. 1890. Langley and Anderson. *Ibid.* xix. p. 319. 1895.

In other conditions other forms of curve were obtained :

a. More or less complete relaxation followed by slow contraction not disappearing for ten or more minutes. The most marked case was in a young cat not full grown ; the third lumbar segment of the cord was excised and the sacral nerves cut ; the bladder volume under a pressure of 10 cm. salt-solution was only 20 c.c. ; 30 mgrs. of nicotine caused a small rise and fall followed in about a minute by a protracted contraction which nearly emptied the bladder. Slow contraction as an after-effect also occurred in an Exp. in which both hypogastric and sacral nerves were cut, and in an Exp. in which one pelvic nerve was cut and the bladder immersed in warm Ringer's fluid, in the latter case the slow contraction began before complete relaxation from the primary nicotine contraction.

b. Contraction with little or no relaxation. In one case, in which the nicotine (10 mgrs.) was injected into the peripheral end of the carotid artery, the bladder contracted nearly completely, and there was slight relaxation only. In another case, a half-grown cat, most of the ganglia were removed from one half of the bladder and the bladder immersed in Ringer's fluid. The bladder volume was only 19 c.c. with 10 cm. pressure ; 20 mgrs. of nicotine caused nearly complete contraction not followed by relaxation.

One cause of persistent after-contraction with nicotine may perhaps be an insufficient blood flow in the bladder.

Curari as noticed by Anderson and myself[1] causes on first injection a slight rise lasting for a minute or two. As a rule the rise is more prolonged with a small dose (1 to 2 c.c.) than with a large one (5 to 10 c.c.). It occurs after section of both sacral nerves and hypogastrics. It is possible that the contraction is due to a slight transient stimulation of the pelvic nerve cells, similar to, but much less than, that caused by nicotine[2]. Later doses of curari have either no effect or cause a slight transient relaxation. In two experiments curari was injected after the tone of the bladder had been increased by pilocarpine (5 mgrs.), in each case there was

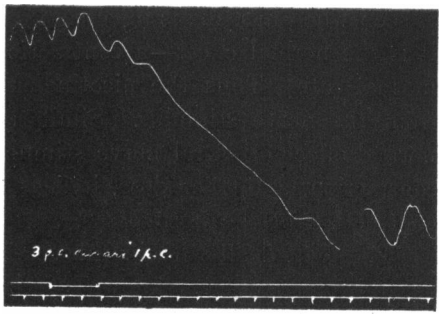


Fig. 17. Sympathetic nerves cut below 6th lumbar ganglion. 5 mgrs. of pilocarpine nitrate injected. The Figure shows the effect of injecting 3 c.c. of 1 p.c. curari.

In the other experiment, spoken of in the text, the sacral nerves were cut on one side only; the injection of 4 c.c. of 1 p.c. curari caused a more gradual fall (26 c.c.) followed by a gradual rise, the whole lasting 4 mins.

[1] This *Journal*, XIX. p. 82. 1895.

[2] The transient secretion from the salivary glands described by Cl. Bernard and others as caused by curari may also be due to stimulation of the nerve cells on the course of the chorda tympani. The statement of Czubalski (*Arch. f. d. ges. Physiol.* CXXXIII. p. 232. 1910) that curari causes no secretion after section of the chorda tympani does not agree with my experience, though it is true that secretion is sometimes absent.

a considerable but temporary relaxation and decrease of the rhythmic spontaneous contractions (cp. Fig. 17).

In Table I, I give an abstract of the results of some experiments on the effect of injecting nicotine after curari[1]. It will be seen that a sufficient dose of curari completely stops the effect of an amount of nicotine which otherwise would have caused strong contraction of the bladder, and that strong contraction can be obtained by giving a larger quantity of nicotine. Further it is fairly certain that a given quantity of curari stops the effect of a definite quantity of nicotine, when nicotine is given in excess of this quantity the contraction is proportional to the dose.

Thus there is a mutual antagonism of the same kind as that which I have shown to hold in the case of striated muscle[2].

We have seen that a large amount of curari does not prevent the sacral nerves from causing a slight initial contraction, that the contraction ceases during the stimulation and may pass into inhibition, and that after the stimulation there is again contraction. None of this is seen when nicotine is injected after curari; if it produces any effect, it is the normal effect—a contraction and relaxation of approximately normal rate. Thus the nicotine stimulus produces a different effect from the nerve stimulus. Similarly when nicotine has changed the normal effect of sacral nerve stimulation to slight inhibition and after-contraction, a further dose, if it is sufficient to have an effect, causes contraction of the normal type.

The facts dealt with in this section increase the probability, already great, from the facts known of the mode of action of nicotine and curari, that these poisons cause the changed response by an action on the nerve cells on the course of the sacral vesico-motor fibres.

Now just as nicotine and curari are types of alkaloids which have a

[1] The essential experiments given in this section were made in 1901 (though I have added some details since) in the course of a general inquiry into the antagonistic action of curari and nicotine on peripheral nerve cells. The experiments led incidentally to observations on the supra-renal extract and as these seemed to me more interesting, the original ones were put aside. On returning to them again I noticed the changed response of the bladder to sacral nerve stimulation, and this again has led to my deferring the completion of the original research. I may mention here that a sufficient dose of curari abolishes the effect of a small dose of nicotine (3 mgrs.) on all the peripheral nerve cells investigated except on some which cause a rise of blood-pressure, the effect on these was lessened only. The amount of curari required to stop the effect of a given dose of nicotine varies in different ganglia.

[2] *Proc. Physiol. Soc.* p. lxxi. 1909. (This *Journal*, XXXVIII.) This *Journal*, XXXIX. p. 249. 1909. *Proc. Physiol. Soc.* p. lix. 1910. (This *Journal*, XL.)

TABLE I. *Effect of intravenous injection of nicotine after curari.*

The time is given in minutes from the first injection of curari (0′). The contraction curve was a simple rise and fall unless otherwise mentioned.

Exp.	Nerves cut	Curari 1 p.c. injected	Nicotine injected	Effect of nicotine injection on bladder
1	Sacral nerves	0′—4 c.c., 7′—2 c.c., 10′—3 c.c.	29′— 1 mg.	No contraction, slight relaxation a little later.
2	,, ,,	0′—4 c.c., 13′—2·5 c.c.	18′— 2 mg.	No contraction, a little later a slow slight rise.
			26′—20 mg.	Contraction (10 to 12 c.c. expelled).
3	One pelvic nerve	0′—10 c.c.	27′— 3 mg.	No effect.
			58′—20 mg.	Contraction (15 c.c.) followed by inhibition.
			68′—30 mg.	Slight contraction.
4	Spinal cord at 7th lumbar segment	0′—2 c.c., 14′—2 c.c., 24′—2 c.c., 37′—5 c.c., 50′—5 c.c.	74′— 3 mg.	No effect.
			77′—30 mg.	Good contraction.
	In the following the effect of a smaller amount of curari was tried.			
5	Sacral nerves	0′—5 c.c.	16′— 1·5 mg.	Slight contraction, followed by inhibition.
			20′—20 mg.	Good contraction, relaxation slow.
6	,, ,,	0′—5 c.c.	12′— 3 mg.	Slight contraction.
			16′—20 mg.	Good contraction.
7	,, ,,	0′—5 c.c. (33′ 1 mg. pilocarpine)	43′— 2 mg.	Good contraction. (Here the longer interval allowed partial elimination of the curari.)
	In the following the conditions were varied.			
8	Sympathetic chain at 6th L. ganglion	0′—3 c.c., 14′—2 c.c., 27′—3 c.c., 43′—3 c.c.	60′— 3 mg.	(5 mg. of pilocarpine had been given before the curari.) Trace of contraction (1 c.c.) then great relaxation (40 c.c.).
9	Sacral nerves on one side	0′—4 c.c., 27′—4 c.c.	45′—20 mg.	(5 mg. of pilocarpine had been given before the curari; and the bladder was nearly fully contracted.) Slight contraction (3·7 c.c.).
10	Decapitated. Part of one pelvic nerve cut	0′—4 c.c.	13′—20 mg.	Large contraction, continues for about 5 mins.
			60′—20 mg.	Small contraction (8½ c.c.). (Bladder was partially contracted from response, and this slow contraction continued.)
11	Sacral nerves	0′—2 c.c., 16′—3 c.c., 28′—5 c.c., 35′—5 c.c.	52′—25 mg.	Good contraction.
			70′—50 mg.	Slight contraction.

specific action upon the structures in which pre-ganglionic fibres end, so pilocarpine and atropine are types of alkaloids which have a specific action on many of the structures in which post-ganglionic nerves end, it seemed then desirable to investigate whether pilocarpine and atropine would modify the change in the response of the bladder produced by curari or nicotine.

(*b*) *Effect of pilocarpine on the changed response.*

It is known that a small quantity of pilocarpine causes contraction of the bladder and that this continues as increased tone for a considerable time. The chief object of my experiments was to determine whether this tone is inhibited by stimulating the sacral nerves in a curarised or nicotinised animal in the same way as the tone of an after-contraction is inhibited.

The responsiveness of the bladder to pilocarpine (given as nitrate) varied considerably in my experiments. The amount injected was 1 to 5 mgrs., and in one case 10 mgrs. of the nitrate. The contraction may be quick or very slow, the maximum is kept up for 5–10 mins. and then slow relaxation sets in. Rhythmic contractions (1–3 c.c.) are caused.

In four experiments, 1 mgr. of pilocarpine nitrate was injected, in one the rise was rapid (see Fig. 19), in one it was slow, in two there was no contraction. There was copious secretion of saliva in all cases, the pupil contracted slightly in two only. The effect of pilocarpine upon the bladder appears to depend a good deal on the rapidity of the circulation in it.

During the tonic contraction, the volume of the bladder is more dependent on the resistance to outflow than I had expected; thus in one experiment with bladder volume 70–75 c.c. and pressure of 10 cm. of fluid, 5 mgrs. of pilocarpine caused a slow gradual contraction of the bladder which nearly emptied it, on raising the pressure to 15 cm. the bladder gradually filled; on lowering the pressure to 10 cm. it again gradually emptied.

The decreased volume of the bladder caused by pilocarpine naturally decreases the absolute quantity of fluid expelled by a given stimulus, thus in the experiment just referred to, stimulation of one 2nd sacral nerve for 15 secs. before pilocarpine was injected (bl. vol. 70–75 c.c.) caused 34·6 c.c. to be expelled, after 5 mgrs. of pilocarpine when the volume of the bladder had decreased by 26 c.c., the same stimulus applied again caused expulsion of only 21 c.c.

The broad features of the effect of curari and nicotine on the results of sacral nerve stimulation are not altered by pilocarpine, *i.e.* inhibition and after-contraction are still obtained, and with curari or nicotine below a certain amount, a small initial contraction also. Further the tone caused by pilocarpine can be inhibited in the same way as is the after-contraction; in order to show this, nicotine (or curari) is given, the sacral nerves stimulated, and whilst the after-contraction is near its maximum a second stimulus is sent in; when the after-contraction has completely disappeared, pilocarpine is injected and during the rise the sacral nerves are stimulated for a third time. The results of such an experiment are shown in Figs. 18 and 19.

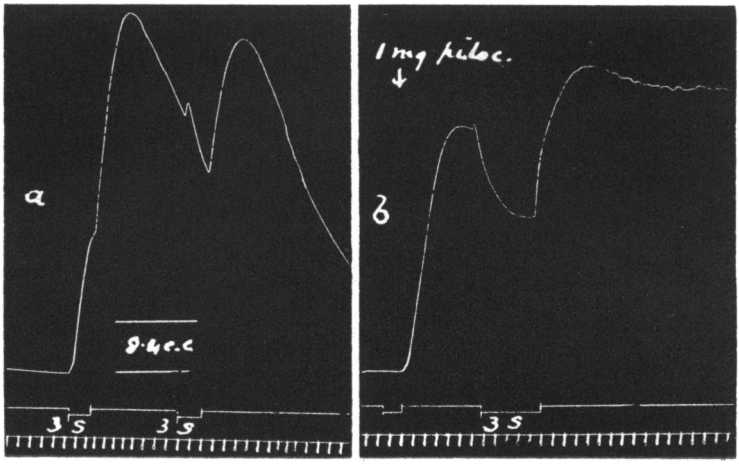


Fig. 18. (Exp. G.) Stimulation of sacral nerves after injection of nicotine and pilocarpine. Sacral nerves cut. Pr. = 10 cm.

0′—15 mgrs. nicotine injected.

4′—Bl. vol. about 65 c.c., 3rd sacral nerves stimulated for 20 secs. and the stimulus repeated during the after-contraction (see *a*), 48·7 c.c. expelled.

12′—Bl. vol. about 65 c.c. 1 mgr. of pilocarpine nitrate injected; when the bl. vol. was about 25 c.c., the 3rd sacral nerves were stimulated for 50 secs. (see *b*).

It will be seen that stimulation of the sacral nerves during the tonic contraction caused by pilocarpine caused good inhibition lasting (after a trifling initial contraction) for the whole period of stimulation (60 secs.), the fall corresponds to a passage of about 15 c.c. into the bladder. After subsequent injection of a larger amount of nicotine,

the bladder being nearly fully contracted, stimulation of the sacral nerves caused less relaxation, 6 to 7 c.c. only of fluid passing into the bladder. (Fig. 19.)

It may be noted that this experiment was exceptional in two respects. The injection of 15 mgrs. of nicotine did not prevent the first stimulation of the sacral nerves lasting 20 secs. from causing contraction, it only reduced it; before the injection of nicotine the stimulus had caused expulsion of about 55 c.c., after the nicotine it caused expulsion of about 22 c.c., though the after-contraction nearly made up the difference. Secondly the contraction with 1 mgr. of pilocarpine was much more rapid than in any other experiment, even in those in which when 5 mgrs. were injected.

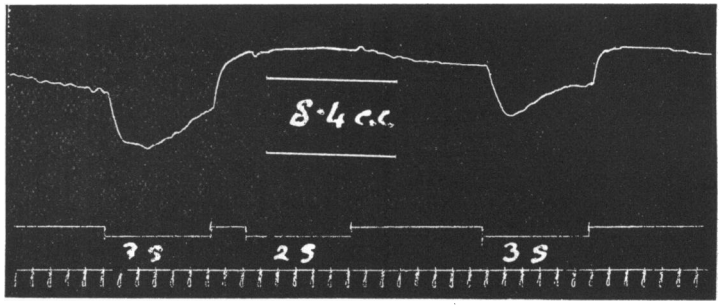


Fig. 19. (Exp. G.) Continuation of Exp. described in Fig. 18.
29′—Bl. vol. about 11 c.c.; 30 mgrs. of nicotine injected, about 8 c.c. expelled.
35′—Bl. vol. about 6 c.c. 3rd and 2nd sacral nerves stimulated (see Fig.), the 2nd sacrals had no effect.
During the 35 mins., there were no other stimuli than those mentioned.

In most of the other experiments—eight in all were made—both inhibition and after-contraction were much less striking than in this. There were great variations in the degree of inhibition, in the extent of escape from inhibition during the experiment, in the extent of the after-contraction, and in its duration. The conditions of the experiments were however in no two cases quite the same. But the general results were clear, namely that the changed response of the bladder to stimulation of the sacral nerves produced by curari or nicotine, is unaffected in its essential features by pilocarpine, and that the tone produced by pilocarpine can be inhibited.

(c) *The effect of atropine upon the changed response.*

It was shown by Anderson and myself[1] that in the normal state atropine in considerable amount (up to 50 mgrs. of the sulphate in the cat) does not paralyse the vesico-motor nerve fibres, but that it does cause a marked weakening of their effect. I have not determined the minimal effective amount, but 10 mgrs. is sufficient to cause a considerable decrease in the height of the contraction. Thus in one experiment in which the sacral nerves were stimulated, the results were as follows:

Nerve stimulated	Duration of stimulation in secs.	Number of c.c. expelled from bladder	
		Before 10 mgrs. of atropine sulphate	After 10 mgrs. of atropine sulphate
Both 2nd sacrals	15	54·6	36·8
,, ,, ,,	30	75·6	48·8
Both 3rd sacrals	15	25·2	19·0

A second injection of 10 mgrs. had no further effect. Bl. vol. = 80 c.c. Pr. = 13 cm.

The form of the curve is not obviously altered.

The contraction caused by pilocarpine is, as would be expected, rapidly abolished by atropine[2]. In my experiments atropine[3] caused a gradual decrease of the tone of the bladder when pilocarpine had not been given, and when both sacral and hypogastric nerves had been cut; usually its first effect was slight transient contraction.

A remarkable effect is produced by injecting atropine after nicotine. As we have seen, after a certain amount of nicotine has been injected, the sacral nerves cause inhibition during the period of their stimulation. Atropine almost instantaneously changes the primary effect. Instead of inhibition there is a slight contraction, followed by quick relaxation. The other features of the curve though they may be modified in extent are not usually altered in character; if there is a slow contraction during the latter part of the stimulation before atropine is given, there is a similar slow contraction after it has been given and this may begin before relaxation of the initial contraction is complete; this slow contraction is readily fatigued. The after-contraction is greatly reduced and if fatigue has been caused by repeated previous stimulations, there may be none. In Fig. 20 a typical result is shown.

[1] This *Journal*, XIX. p. 82. 1895.

[2] For earlier instances of abolition of pilocarpine effect by atropine, without paralysis of the motor nerves, see Dixon, this *Journal*, XXX. p. 122, 1904; and Cushny, *Ibid*, XLI. p. 234. 1910.

[3] In the rest of this Paper atropine is for brevity used for atropine sulphate.

The evidence of inhibition after the initial contraction varies in different conditions. When atropine has been allowed to produce its full dilating effect as in Fig. 20, the fall of the curve of the initial contraction does not go below the level at which the rise of the contraction started, and as I have said a second slow rise may begin before relaxation is complete. I have tried the effect of stimulating the sacral nerves during increased tone of the bladder brought about in three different ways. (*a*) During a strong after-contraction, atropine was injected, and the nerves stimulated before the after-contraction had passed off: an example is given in Fig. 21; it will be seen that there was slight, but only slight, signs of inhibition following the initial contraction. (*b*) After giving atropine, nicotine was injected, and the nerves stimulated before the contraction had passed off; in this case the inhibition was rather more marked (cp. Fig. 21*). (*c*) The nerves were stimulated during an after-contraction, in this case the

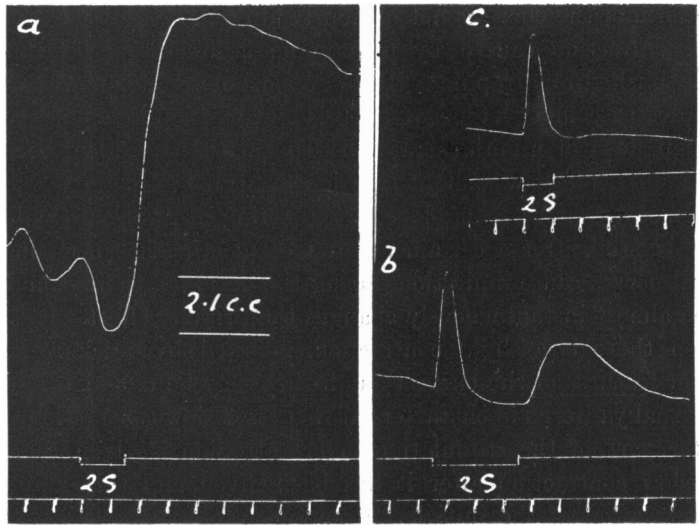


Fig. 20. (Exp. B.) Sacral and hypogastric nerves cut. 40 mgrs. nicotine injected in doses of 10, 10 and 20 mgrs. Pr.=7 cm.

a. Stimulation 2nd sacrals 15 secs.

10 mgrs. atropine sulp. injected. This was followed by a relaxation of the bladder, 1½ mins. after the injection the 2nd sacrals stimulated for 20 secs. gave a contraction like that in (*b*) but with less after-contraction.

b. Stimulation of 2nd sacrals for 30 secs. The relaxation of the bladder since the beginning of the stimulus (*a*) had led to the passage of 15 c.c. of fluid into it.

c. Stimulation of 2nd sacrals for 10 secs., a few minutes after (*b*).

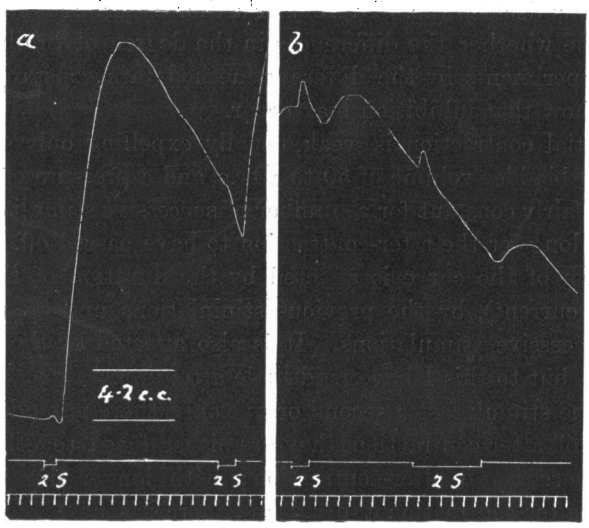


Fig. 21. (Exp. A.) Effect of atropine. 30 mgrs. of nicotine had been given about 50 mins. before (*a*) which shows the effect of two successive stimulations of the 2nd sacral nerves. Between (*a*) and (*b*) there is an interval of 2 mins. 20 secs. Five mgrs. of atropine sulphate were injected 70 secs. before (*b*). The effect of stimulating the 2nd sacrals for 15 and for 60 secs. is shown in (*b*).

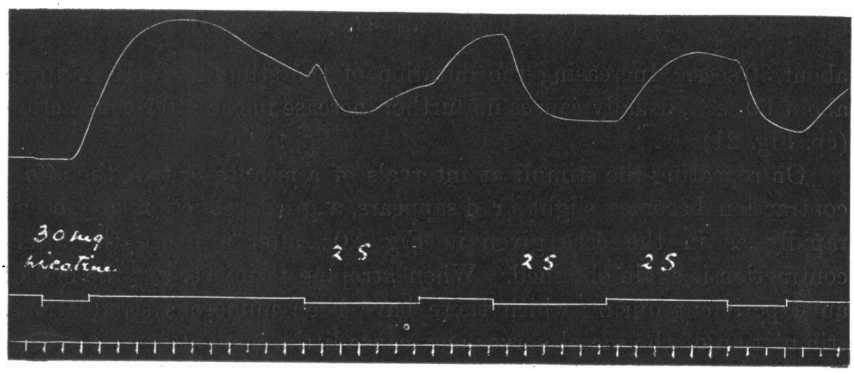


Fig. 21*. 40 mgrs. of nicotine and 45 mgrs. of atropine had been injected before the tracing given in the Figure was taken. 30 mgrs. of nicotine was then injected and the 2nd sacral nerves stimulated several times. The fall on the 3rd stimulation corresponds to a passage of 13 c.c. of fluid into the bladder. It will be noticed that the initial contraction decreased in the successive stimulations; after an interval, the initial contraction was of its original height.

inhibition was decided (cp. Fig. 21*). Further experiments are required to determine whether the differences in the degree of inhibition found in these experiments by the different methods are constant, but they suffice to show that inhibition may occur.

The initial contraction is weak, usually expelling only 4 to 6 c.c. of fluid with a bladder volume of 50 to 80 c.c. and a pressure of 8 to 10 cm. It remains fairly constant for a number of successive stimuli at intervals sufficiently long for the after-contraction to have passed off.

The form of the curve is affected by the duration of the stimulus (tetanising current), by the previous stimulations, and by the interval between successive stimulations. It is also affected by the strength of the current, but to this I have paid little attention.

When the stimuli last a second or two only, there is no distinction of initial and of after-contraction, they are either fused together or more probably there is no after-contraction; with longer duration of the stimuli the after-contraction appears and increases up to a duration of

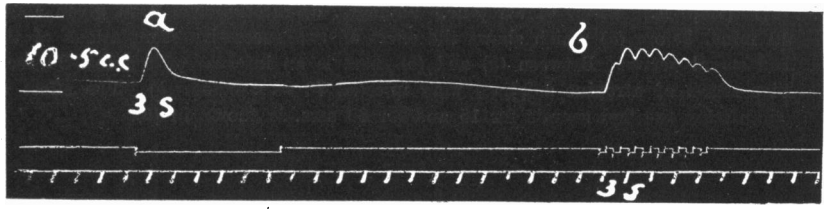


Fig. 22. (Exp. D.) Effect of atropine. See text.

about 30 secs. Increasing the duration of the stimulus further, up to about 60 secs., usually causes no further increase in the after-contraction (cp. Fig. 21).

On repeating the stimuli at intervals of a minute or two, the after-contraction becomes slight or disappears, a great reduction may occur rapidly as in the case given in Fig. 20; after a pause the after-contraction is again obtained. When atropine is injected at the end of an experiment during which there have been numerous stimulations, stimulation of the sacral nerves may cause little or no after-contraction. Thus in Exp. D (from which Figs. 4, 10, 11, 12, 13 of this Paper have been taken) 10 mgrs. of atropine were injected a few minutes after the tracing shown in Fig. 13. Stimulation of the sacral nerves then caused a slight initial contraction (4·7 c.c.) and a mere trace of after-contraction as shown in Fig. 22 *a*, and a little later it caused none. The conditions which conduce to the absence of the after-contraction on the first

stimulation subsequent to the injection of atropine are frequency of previous stimulation and a deficient circulation with lowering of body temperature leading to a reduction of irritability. Further the amount of atropine has some influence, thus when after-contraction is obtained subsequent to the injection of atropine, a large additional dose (30 mgrs.) may abolish it, without abolishing the initial contraction, possibly however this is an indirect effect due to weakening of the circulation.

I have said that with tetanising currents lasting a second or two only there is little or no after-contraction. When such currents are sent into the nerves at intervals of a few seconds, the first contractions are more or less summated according to the condition of irritability, the later ones are quicker and are not summated, still later ones become less in strength and duration so that relaxation occurs notwithstanding the continuation of the stimuli. In Fig. 23 *a* is shown the effect of stimulating for 5 secs. out of each 15 secs. for half a minute, in Fig. 23 *b* (taken a little later) the effect of stimulating for 2 secs. out of each 5 secs. for the same period. Fig. 22 *b* shows the effect of similar stimulation in a less irritable tissue.

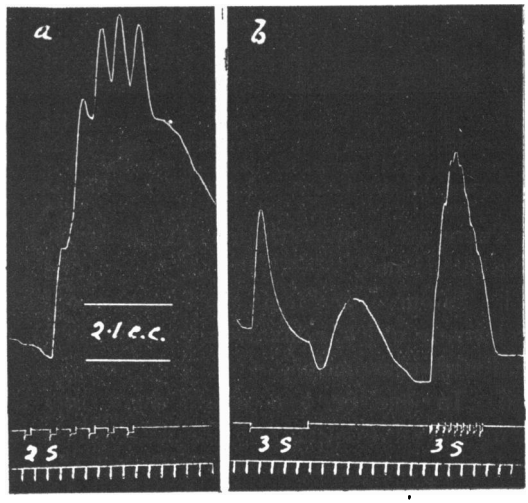


Fig. 23. (Exp. A.) Effect of successive brief stimuli after nicotine and atropine; see text. A short time before the tracings in the Fig. were taken 35 mgrs. of atropine sulphate were injected. In the previous hour 30 mgrs. of nicotine had been given in two doses.

After a further injection of 30 mgrs. of atropine there was still an initial contraction, but no after-contraction, and this persisted after a subsequent injection of 50 mgrs. of nicotine.

It may be noted that the latent period of the after-contraction varies from about 2 to 10 secs.

In the preceding experiments the pressure varied from 8 to 10 cm. salt-solution. I have only tried one experiment in which the pressure was varied. After injection of 10 mgrs. of atropine, stimulation of the

2nd sacral nerves, with a pressure of 17 cm. caused a slight contraction (about 4 c.c.) which was slow (as it usually is in fatigued conditions), and no after-contraction; the pressure was then lowered to 3·5 c.c., the fluid expelled was then greater (nearly 12 c.c.) and the relaxation (cp. Fig. 24) was very slow. No great stress however can be laid on a single observation.

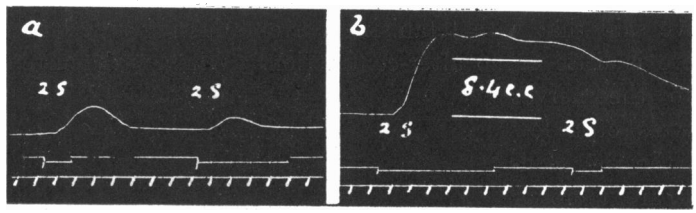


Fig. 24. (Exp. F.) Effect of internal pressure on the contraction obtained after nicotine and atropine (see text). Previous to the injection of atropine (10 mgrs.), and after injection of 45 mgrs. of nicotine, stimulation of the 2nd sacrals caused inhibition during the stimulation and expulsion of 27½ c.c. after it.

There are some variations in the forms of the curves which remain to be mentioned.

i. In one experiment the cessation of the stimulus was marked by a relatively quick relaxation (cp. Fig. 23 *b*), this was followed by the usual after-contraction.

ii. In one or two cases there was a slow slight contraction during the stimulation and immediate relaxation not greater than the previous contraction following it, and there was no after-contraction. An example is given in Fig. 25. Both contraction and relaxation were slight (about 2 c.c.). Related to this is probably the slowing of the contraction which occurs immediately after stimulation in the cases in which there is a slow contraction during the latter part of a stimulus.

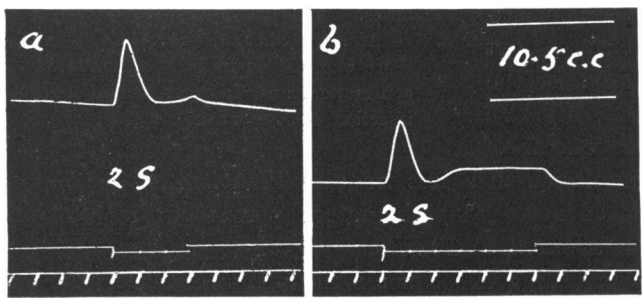


Fig. 25. Stimulation of 2nd sacral nerves after injection of 23 mgrs. of atropine sulphate and 15 mgrs. of nicotine.

iii. In one experiment large after-contraction was obtained. This was apparently conditioned by the nicotine paralysis being very imperfect. In this experiment all the drugs were injected into the peripheral end of the carotid artery and it is probable that a considerable portion was taken up by the central nervous system and did not pass into the general circulation. In fact in this animal 2 c.c. of pure chloroform injected into the carotid did not stop the heart in 8 mins. The point that concerns us here is that after injection of a large quantity of nicotine the 2nd sacral nerves stimulated for 10 secs. caused contraction in 2 to 3 secs. which was very nearly as rapid as the after-contraction, the whole contraction expelling 25 to 30 c.c. from the bladder. (Bl. vol. about 63 c.c. Pressure 15 cm.) The 1st sacral nerves which had relatively few vesico-motor fibres gave the usual effect (cp. Fig. 26 *a*). Ten mgrs. of atropine were then injected and the nerves again stimulated. The results are shown in Fig. 26 *b*, *c*. It will be seen that the 1st sacral nerves gave the usual result which occurs after atropine, so did the 2nd sacral nerves when stimulated for 5 secs., but when stimulated for 45 secs. there was a considerable after-contraction (14 to 15 c.c.).

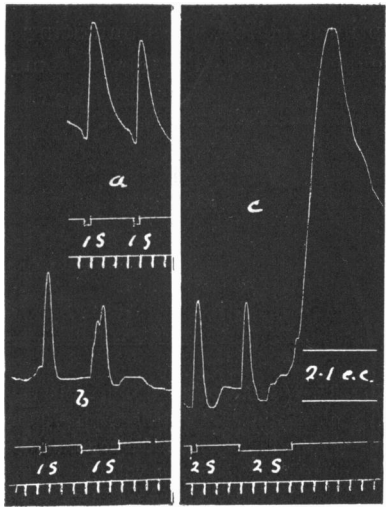


Fig. 26. (Exp. C.) Effect of atropine after nicotine; see text.

In this Exp., 10, 10, 20, and 30 mgrs. of nicotine were injected in 50 mins. The first injection caused a contraction of the bladder which nearly emptied it (bl. vol. = 55 c.c.), but the relaxation was very slow, not beginning till some minutes after the second injection. After the second injection, stimulation of the sacral nerves, the bladder still being contracted, caused a slight contraction and a slight after-contraction; when relaxation had occurred, the sacral nerves caused a good contraction on brief stimulation. The third injection caused slight contraction (14 c.c.); and the second sacrals stimulated for five secs. still caused expulsion of more than 20 c.c. The fourth injection caused little or no contraction of the bladder; the second sacrals stimulated for 10 secs. after a latent period with slight inhibition, caused expulsion of about 5 c.c. during the stimulation and of about 25 c.c. after it, the contractions being of nearly the same rate. After this atropine was injected, see text.

The conditions in which these variations occur obviously require further investigation.

I have made four experiments with a small amount of atropine ($\frac{1}{2}$, $\frac{1}{2}$, 1, and 1 mgr.) and it is clear I think from these that the main effects of atropine are caused by a very small dose. A reversal of the primary effect of stimulating the sacral nerves occurred in all the experiments. There was some slow contraction during the stimulus

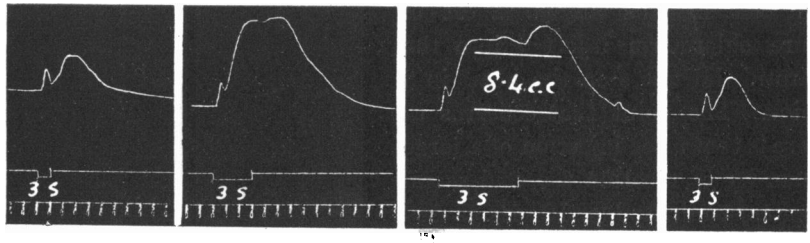


Fig. 27. (Exp. G.) Sacral nerves cut. The following injections had been made, 15 mgrs. of nicotine, 1 mgr. pilocarpine, 30 mgrs. of nicotine. 12 mins. before the first tracing in the Fig. 1 mgr. of atropine sulp. was injected, this caused large relaxation of the bladder, so that the vol. was 75 to 80 c.c. The Fig. shows the effect of stimulating the 3rd sacral nerves at five minute intervals. Pr. = 10 cm.

after the initial contraction, and in one case in which the stimuli were at intervals of 5 mins. the slow contraction was relatively large. The effect is shown in Fig. 27. It will be seen that the relaxation of the initial contraction is interrupted by a second contraction (about 10 c.c.) and that there is a slight slow after-contraction. In order to ascertain the effect of a larger quantity of atropine 10 mgrs. were then injected and the sacral nerves again stimulated. As will be seen from Fig. 28 there was only slight contraction during the stimulation and the after-contraction was only just perceptible.

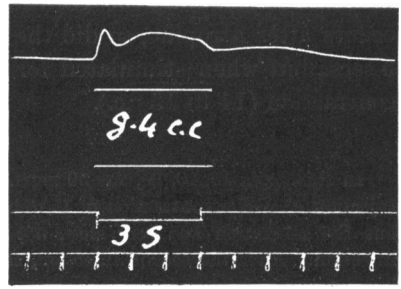


Fig. 28. (Exp. G.) The tracing is a continuation of that of Fig. 27, 10 mgrs. of atropine were injected and the 3rd sacral nerves again stimulated.

Atropine at whatever stage of an experiment it is given appears to have very little effect on the contraction caused by injecting 15 to 30 mgrs. of nicotine (cp. Fig. 21*).

(*d*) *Effect of poisons on the response given by the bladder to stimulation of portions of the vesical plexus.*

I have already mentioned (p. 147) the evidence there is that nicotine prevents the normal motor action of the sacral nerves by an action on the peripheral nerve cells and not by an action on the bladder. It seemed to me desirable to make a more complete investigation of this question by means of the graphic method, which might disclose some inhibitory effect, not obvious to the eye, and also by stimulating more purely post-ganglionic branches than exist outside the bladder itself.

Observations of this nature present more difficulty in the case of bulbar and sacral autonomic ganglia than they do in the case of sympathetic ganglia, for the former lie for the most part at the nodal points of a plexus in or on the organ. In investigations on the salivary glands this is of little importance, since tetanising currents applied to gland cells cause little or no secretion, and thus the electrodes may be placed on the peripheral parts of the plexus with little fear that the result is due to anything but nerve stimulation. But if the same method is applied to the nerve-plexus on a muscular organ, the direct effects of excitation will certainly obscure, and may completely hide the effects of excitation of the nerve fibres. Hence then in order to obtain satisfactory results from the plexus which lies on the bladder, one or more of the strands must be isolated. The isolation introduces some difficulties in procuring a successful result. It cannot be done without exposure of part of the bladder, and the part exposed is apt to pass into a state of more or less strong tone with rhythmic contractions. It interferes to a greater or less extent with the circulation in the bladder, this is less on isolating the peripheral portions of the plexus than in isolating the proximal portions. In general there is little difficulty in obtaining a strand consisting wholly, or almost wholly, of post-ganglionic fibres without rendering the bladder abnormal, but there is some difficulty in obtaining a proximal strand having an isolated ganglion on its course without interfering with the circulation. In Fig. 29, I give a sketch of the entering nerves[1], nerve-plexus and ganglia in a particular case. The smaller strands of the plexus and the smaller branches to the

[1] For the anatomy of the whole pelvic plexus see Langley and Anderson. This *Journal*, XIX. p. 374. 1896; XX. p. 378 *et seq.* 1896.

bladder are not drawn. Small ganglia sometimes occur more peripherally than in this case and no doubt additional groups of nerve cells would be visible under the microscope. Each branch of the pelvic nerve has an obvious ganglion on its course soon after it reaches the bladder, the ganglia are connected into a plexus; from the plexus, nerve strands of various size are given off, which usually at any rate do not anastomose in that part of their course which can be dissected, the largest run close to the line of the lateral ligament. It will be noticed that in this case a small branch from the hypogastric nerve accompanied the pelvic branches, it divided into two filaments both running dorsally, one to the neck of the bladder under the ureter; so far as they were traced they did not join the main ganglionic plexus.

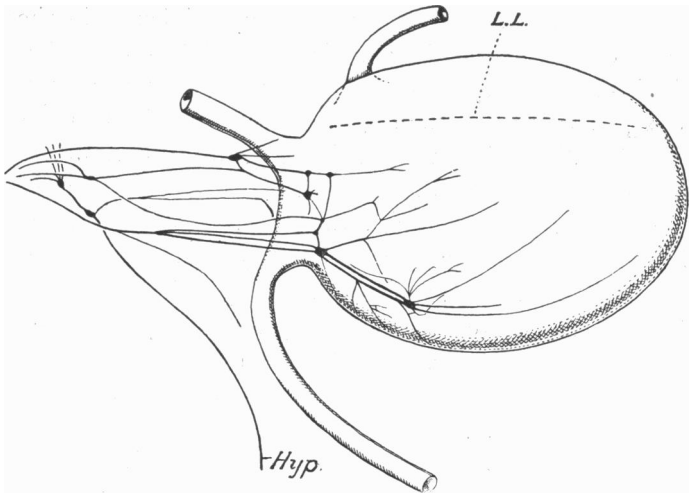


Fig. 29. Semi-diagrammatic sketch of the nerve plexus on the bladder.

In experimenting, one or more strands were tied and cut, the bladder being exposed as little as possible, then either the small cut in the abdominal wall was covered with warm moist flannel, or it was largely extended, and the posterior part of the animal placed in Ringer's fluid at 38°–40° C.

We may take first the effect of stimulating the pelvic nerves a little past the first ganglion of the plexus. Three experiments were made. In two curari only was injected; there was no certain difference in the effect of stimulation from that given by the pelvic nerve centrally of the ganglion. There was a primary small contraction, then relaxation with more or less inhibition, and after-contraction, *i.e.* if post-ganglionic fibres were present, they were too few to modify obviously the results

of pre-ganglionic stimulation. In the third experiment the curves gave evidence of the presence of both sacral and sympathetic post-ganglionic fibres. After the injection of curari, stimulation had the usual initial effect, but this was followed by more or less contraction (tone or rhythm) during the rest of the stimulation, *i.e.* some post-ganglionic sacral fibres were present. On ceasing to stimulate there was a slight after-contraction followed by prolonged inhibition. An example is given in Fig. 30.

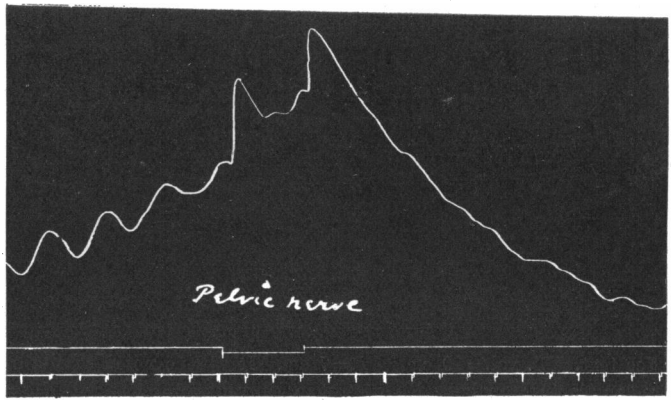


Fig. 30. Stimulation of pelvic plexus a little past the division of the pelvic nerve after injection of 10 c.c. of 1 p.c. curari. Tracing with Hürthle's piston recorder. Bl. vol. = 50 c.c. Pr. = 6 cm. The inhibition was not obvious before the injection of curari, but persisted after an additional 5 c.c. and after 50 mgrs. of nicotine, the initial contraction being diminished. The details of the curves varied considerably.

The inhibition had the characters of that produced by stimulation of the hypogastric nerves and was no doubt due to the inclusion in the nerves stimulated of some such hypogastric branch as that shown in Fig. 29. In one or two cases in which the stimulation was prolonged for 60 secs., there was no after-contraction, this apparently being overpowered by the inhibition which had then set in. The injection of nicotine only altered the curves by abolishing the initial contraction.

It has seemed to me that the posterior branches of the pelvic nerve which make their way to the bladder along the urethra, usually contain a few hypogastric fibres and a few post-ganglionic sacral fibres.

In investigating the more peripheral branches the procedure has varied somewhat. The most convenient way of dealing with the results will be to pick out the main features of some of the experiments.

I may first mention that when the bladder is exposed under warm Ringer's fluid, the stimulation of any small nerve branch can be seen to

cause strong local contraction. On stimulating adjoining post-ganglionic strands there is more or less overlapping of the contraction areas. The post-ganglionic fibres cause contraction for half-an-hour (and probably considerably longer) after death.

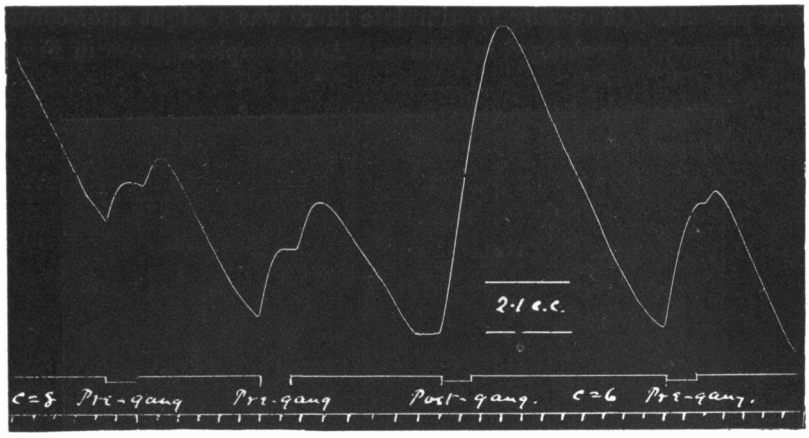


Fig. 31. See text. Bl. vol.=80 c.c. Pr.=7 cm. It will be noted that stimulation of the pre-ganglionic branches with a stronger current ($c=6$ instead of $c=8$) caused greater primary contraction and less after-contraction.

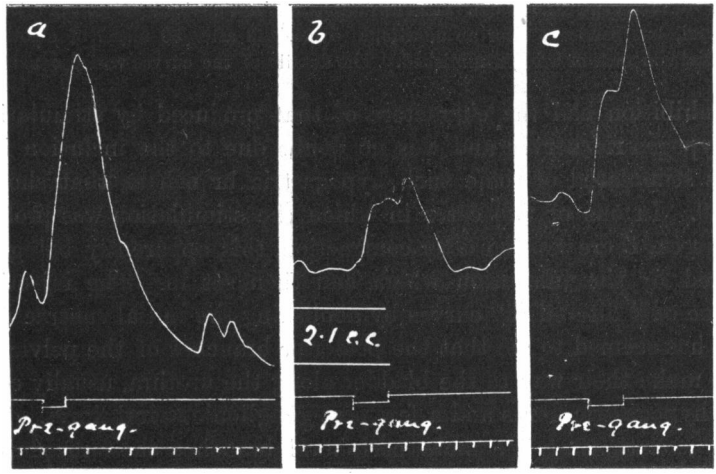


Fig. 32. Stimulation of two branches of the pelvic nerve outside the bladder *a* before, *b* and *c* after injection of curari and nicotine (see text). Pr.=7 cm. The latent period of the contractions was several secs. longer after injecting nicotine than before the injection.

(*a*) **Cat decapitated.** Stimulation of the 2nd and 3rd (anterior) pelvic branches 1½ cm. from the bladder for 5 to 10 secs. caused expulsion of 10–15 c.c. of fluid. Similar stimulation of a post-ganglionic branch in the bladder near the lateral ligament caused contraction of about the same extent. After injection of 5 c.c. 1 p.c. curari, stimulation of the pre-ganglionic branches of the pelvic nerve for 15 secs. with the same strength of current as before caused expulsion of only about 2 c.c. of fluid during the stimulation, and of about the same amount after it (Fig. 31), whilst stimulation of the post-ganglionic branch caused as strong a contraction as before; the rate of relaxation was a little faster. There was very little indication of the presence of inhibitory fibres in any of the curves obtained. In Fig. 31 the fall after the first stimulation of the pre-ganglionic fibres was only the continuation of the relaxation from an immediately preceding contraction caused by a stimulus applied to the post-ganglionic branch.

(*b*) This experiment was also made on a decapitated cat. Stimulation for 10 secs. of the 2nd and 3rd (anterior) branches of the pelvic nerve 1½ cm. from the bladder caused contraction (about 8½ c.c.) and slight after inhibition (Fig. 32 *a*). Stimulation of a small post-ganglionic branch medio-ventral of the lateral ligament caused a somewhat less contraction (Fig. 33 *a*). The injection of 2 c.c. 1 p.c. curari reduced the effect of the pre-ganglionic branches by about a half. After injection of an additional 2 c.c. of 1 p.c. curari, and of 20 mgrs. of nicotine, stimulation of the pre-ganglionic branches for 20 secs. with the same strength of stimulus caused a small contraction and a small after-contraction (Fig. 32 *b*). With a stronger stimulus, both contraction and after-contraction were greater (Fig. 32 *c*). Stimulation of the post-ganglionic branch had practically the same effect as before (Fig. 33 *b*). In this experiment there

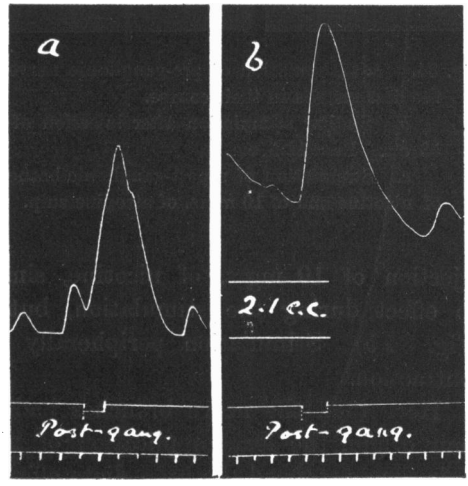


Fig. 33. Stimulation of a post-ganglionic nerve on the bladder, *a* before, *b* after injection of curari and nicotine. From the same Exp. as Fig. 32 (see text).

was always contraction during the stimulation of the branches outside the bladder, though the latent period was two or three seconds longer after nicotine had been injected. This may reasonably be attributed to the presence of a few post-ganglionic fibres.

(*c*) A.C.E. and paraldehyde used as anæsthetics. Second and third (anterior) branches of pelvic nerve tied and cut at their origin, dissected up to the bladder and for a short distance on it past the first group of ganglia (the lateral branches from the ganglia being cut), so that the nerves could be stimulated on either side of the ganglia.

Stimulation of the nerves at any part of their course caused a good contraction in a rather small area of the bladder, causing expulsion of about 7½ c.c.

The ganglia were then moistened with nicotine, which caused contraction (5 c.c.). Stimulation at the cut end caused a slight contraction (2½ c.c.) and a slight after-contraction (Fig. 34 *a*). After

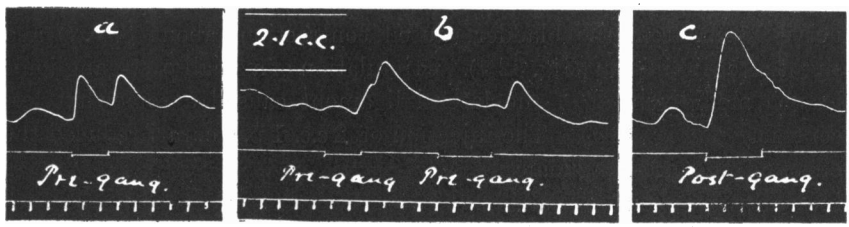


Fig. 34. *a*. Stimulation of pre-ganglionic nerves after local application of nicotine to the first ganglia in their course.

b. Similar stimulation after injection of 10 mgrs. of nicotine. Bl. vol. about 53 c.c. Pr. = 12·5 cm.

c. Stimulation of a post-ganglionic branch after injection of additional 5 mgrs. of nicotine and of 10 mgrs. of atropine sulp.

injection of 10 mgrs. of nicotine, similar stimulation had little or no effect during the stimulation, but still caused after-contraction (Fig. 34 *b*). Stimulation peripherally of the ganglia caused simple contraction.

Here then the nerve branches had no post-ganglionic fibres near their origin, the local application of nicotine to the first ganglia on their course stopped the immediate effect of most of the pre-ganglionic fibres and allowed after-contraction to appear; the injection of nicotine affected the more peripheral nerve cells, and stimulation then caused after-contraction only.

A small post-ganglionic branch was next dissected out, it caused a small contraction without after-contraction. The injection of 10 mgrs. of atropine produced no certain change in the effect of stimulating this but the relaxation was usually quicker; one of the curves obtained is given in Fig. 34 *c*.

(*d*) A.C.E. and urethane used as anæsthetics. Bladder exposed and lower part of animal in Ringer's fluid at 39°–40° C. After injection of 35 mgrs. of nicotine, stimulation of two branches of the pelvic nerve near their origin caused slight contraction only during the stimulation and contraction after it (Fig. 35 *a*). Stimulation of a post-ganglionic branch near the lateral ligament caused much the same contraction (Fig. 35 *b*) as it had caused before the nicotine was injected. After injection of 10 mgrs. of atropine it caused a similar though somewhat smaller contraction (Fig. 35 *c*).

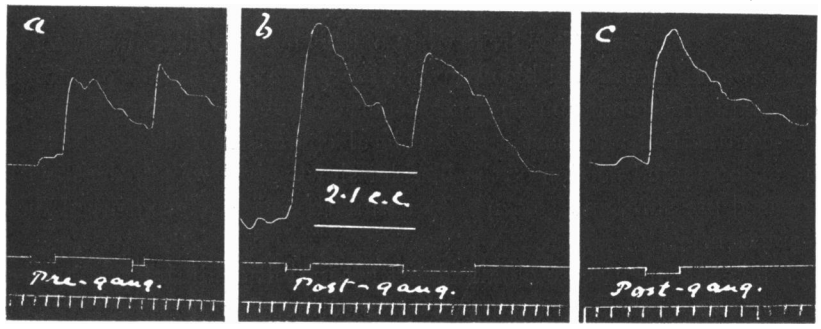


Fig. 35. *a*. Stimulation of two branches of the pelvic nerve near their origin after injection of 35 mgrs. nicotine. Bl. vol. = 40 c.c. Pr. = 8 cm.

b. Stimulation of a post-ganglionic branch after injection of 35 mgrs. of nicotine. Bl. vol. = 45 c.c.

c. Stimulation of post-ganglionic branch after injection of 35 mgrs. of nicotine and 10 mgrs. of atropine sulp. Bl. vol. = 53 c.c.

From these and other similar experiments the conclusions may be drawn that as long as there are nerve cells between the point at which a nerve branch is stimulated and the bladder, so long will after-contraction be obtained when curari or nicotine has been injected; that no after-contraction is obtained in any case by stimulating pure post-ganglionic fibres; that curari and nicotine do not alter the result of stimulating post-ganglionic fibres, and that atropine may weaken the result but does not alter its character.

The absence of after-contraction on stimulating post-ganglionic nerves cannot, I think, be reasonably attributed to an admixture of inhibitory sympathetic fibres. It is true that in all probability a few such fibres are commonly present, this was indicated in one or two experiments by a slight fall below the original level. It is true also that normally the inhibitory action of the hypogastric nerve continues after the end of the stimulus. But if the inhibitory effect was sufficient to stop the abrupt change occurring in an after-contraction it would be sufficient to cause a more rapid relaxation when this abrupt change was over, and this does not occur (cp. especially the curves of Figs. 32, 33). Moreover we have seen that on stimulating pre-ganglionic strands containing inhibitory fibres, the after-contraction is not suppressed (cp. Fig. 30).

The after-contraction is relatively less, and is relatively less prolonged on stimulating the branches of the pelvic nerve than on stimulating the pelvic nerve itself or the sacral nerves. The difference is, I think, due partly to a diminished irritability of the nerve cells consequent on exposure and diminished blood supply, for we have seen that on fatigue from frequent stimulation the sacral nerves give but a weak and brief after-contraction, and partly to the local character of the contraction. The uncontracted portion of the bladder slowly gives way to the slightly increased pressure, and so tends to annul the effect of continued local contraction.

I have not in any case obtained distinct inhibition during stimulation of a branch of the pelvic nerve after nicotine, this I attribute to the presence of a few post-ganglionic fibres in the branch. In the cases in which post-ganglionic fibres were few or absent (cp. Figs. 34, 35) I omitted to try the effect of a stimulus during an after-contraction.

Effect of induction currents of slow rhythm.

The effect of varying the rate of stimulation I have not systematically investigated. But I was led to make two experiments partly because shocks of slow rhythm have been used as a means of detecting vaso-dilator in the presence of vaso-motor fibres, and partly because of Keith Lucas' recent explanation of Wedensky inhibition, one main factor of which is that stimuli of certain frequency set up nervous impulses of sub-normal dimensions. One experiment I may briefly describe. A vibrating spring was placed in the primary circuit, graduated

so as to give 2½, 5, 10, or 20 double vibrations a second as required. Complete emptying of the bladder was obtained by stimulating the 2nd sacral nerve for 30 secs. with each rate of stimulus, the shocks being distinctly felt on the tongue but not strongly. The curves were of the normal form and there was no variation indicating inhibition. Complete tetanus of the muscles of the tail was not obtained with 20 D.V. a sec. until the muscles had been fatigued; with 5 D.V. the tail had a wide rhythmic swing (apparently much slower than the nominal rate of stimulation). Twenty milligrams of nicotine were then injected. All rates of stimulation caused inhibition followed by more or less contraction during the stimulation and on cessation of the stimulus by after-contraction. The duration and amount of the inhibition was apparently increased by increasing the rate of stimulation. Fig. 36 *a* shows the effect of 5 D.V. a sec.

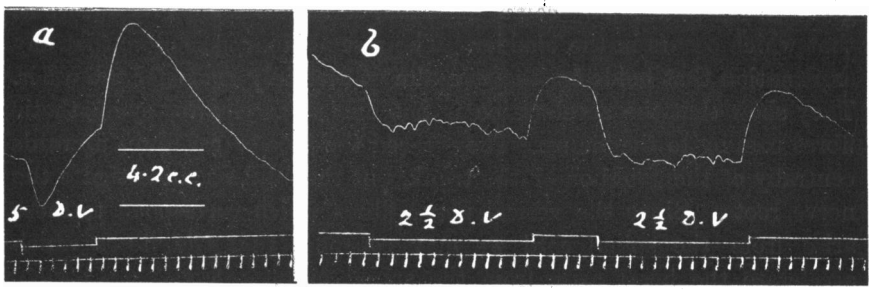


Fig. 36. Sacral nerves cut. Nicotine injected. Stimulation of the 2nd sacrals with induction shocks of slow rhythm. See text.

Thirty milligrams of nicotine were then injected. This decreased the escape from inhibition during stimulation and the height of the after-contraction. (Only the effect of 2½ D.V. a sec. was tried after the injection.) The effect of stimulating with 2½ D.V. a sec. is shown in Fig. 36 *b*. It will be seen that it caused during the stimulation initial inhibition followed by irregular small contractions, the irregularity may have been due to inequalities in the successive shocks.

Two milligrams of atropine were finally injected. After this, stimulation caused a very slight shallow contraction only (type of Fig. 24 *a*), followed by a similar after-contraction with the higher rate of stimulation. Tetanising currents had no greater effect.

Related phenomena in other tissues.

A number of observers[1] have found that stimulation of the vagus may cause acceleration of the heart instead of inhibition. The conditions in which the change has been found have varied, but Boehm[2] observed it in the cat at a certain stage of curari poisoning. It was generally considered to prove the presence of a few accelerator fibres, but after Gaskell had shown that sympathetic accelerator fibres pass to the vagus in the frog, there was reasonable doubt whether the vagus acceleration in the mammal might not be due to sympathetic fibres.

Dale, Laidlaw, and Symons[3] have recently shown that after injection of a small amount of curari or nicotine, stimulation of the vagus in the cat causes not only acceleration during the stimulation but also slowing of the heart after the stimulation. The change in action is, as they suggest from a comparison of their results with those given in my preliminary communication, of the same general nature as that which occurs in the bladder. The resemblance is so close that any explanation that holds for the one almost certainly holds for the other. They show that the acceleration is not due to accelerator sympathetic fibres passing to the vagus. They traced the accelerator fibres upwards centrally of the ganglion of the trunk, but they did not investigate the nerve roots. Since the vesical nerve fibres which correspond to these arise from the spinal cord we may conclude that the fibres which accelerate the heart arise from the spinal bulb.

Dale and his co-workers do not take a decided view as to the cause in the change of response, but they think the most probable theory is that accelerator fibres are present, the nerve cells on the course of these being less affected by curari and by nicotine than are the nerve cells on the course of the inhibitory fibres. They suppose that in the changed state of the inhibitory nerve cells, the inhibitory impulses are weaker but more prolonged and that the accelerator impulses are stronger but quickly cease on cessation of the stimulus. They discuss also the theory that the normally inhibitory fibres change their action when the post-ganglionic neurones are in a state of excitation, and by interference abolish the excitation. The objections they find to this are that the rate of heart beat may be greater at the end of one or more stimuli than before stimulation, and that the acceleration may be preceded by

[1] cp. Schiff. *Pflüger's Arch.* XVIII. p. 200. 1878.
[2] Boehm. *Arch. f. Exp. Path. u. Pharm.* IV. p. 351. 1875.
[3] This *Journal*, XLI. p. 1. 1910.

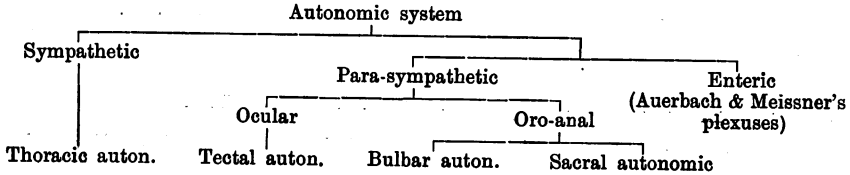
brief inhibition. The former reason seems to me inconclusive since the post-ganglionic neurone might be in a state of slight excitation before the stimulus is applied. I shall consider these and other hypotheses when discussing the results of this Paper.

Since both the inhibitory fibres for the heart and the sacral vesico-motor fibres belong to the oro-anal autonomic system[1] it was natural to look in the first place to the same system for other examples of changed response after administration of nicotine, and since in the bladder the after-effect is on the whole the most striking effect it was also natural to consider the cases in which a strong after-action is known to occur.

In the oro-anal system there are several instances of marked after-action. Stimulation of the sacral nerves in the rabbit[2] causes inhibition of the anal sphincter with or without an initial-contraction, and on ceasing to stimulate there is strong contraction. This however occurs normally. Stimulation of the vagus in the rabbit after curari and atropine have been administered causes inhibition of the cardiac sphincter of the stomach followed by strong contraction[3]. This may also occur normally. Both results have been taken as showing that the nerves contain a mixture of motor and inhibitory fibres, and pending further observations they support the similar hypothesis in explanation of the phenomena in the bladder and heart.

A strong after-action of a somewhat different character occurs in the salivary glands of the dog on stimulating the chorda tympani at a certain stage of nicotine poisoning[4]. There is a long latent period—with a stimulus lasting 15 to 20 seconds there may be no secretion—then the secretion begins, becomes fast, and goes on for several minutes after the stimulation has ceased. In the experiments on the effect of curari in the cat referred to above (footnote, p. 150), I occasionally observed a slight secretion of saliva, or a slight increase of secretion, on ceasing to stimulate the chorda tympani. Since this change in response

[1] I divide the autonomic nervous system as follows:



[2] Langley and Anderson. This *Journal*, XVIII. p. 88. 1895.
[3] Langley. This *Journal*, XXIII. p. 412. 1898.
[4] Langley. This *Journal*, XI. p. 147. 1890.

was produced by curari and nicotine I have made a few experiments to see whether, after the injection of nicotine, a protracted after-secretion is caused in the cat by stimulating the chorda tympani and whether the after-secretion which occurs in the dog would be decreased by renewed stimulation. In the cat, 1·5 to 2 c.c. of 1 p.c. curari did not appreciably alter the normal course of secretion on stimulating the chorda tympani, it only decreased the amount of saliva. A subsequent injection of 5 mgrs. of nicotine nearly paralysed the chorda tympani, but slight indications of an initial secretion, of an after-secretion, and of inhibition were obtained. The secretion was measured by noting the millimetres of flow in a narrow tube during each 10 secs. Two observations may be given, the first made a few minutes after the injection of nicotine, the second about 15 mins. later. During the secretion of the saliva corresponding to the numbers underlined, the chorda tympani was stimulated.

(1) 0.0.1.2.0.0.0.1.2.2.3.0.0.0.1.2.2.1.0.0.1.0.3.1.0.0.0.0.1.1.0.1.0.

(2) 0.0.3.3.2.1.2.3.5.9.3.3.2.5.9.8.10.4.6.5.5.9.10.7.7.6.5.6.4.4
(18 mm. in 3 mins. then ceases.)

The secretion was very slight (200 mm. = 1 c.c.), but possibly with rather less nicotine more marked effects may be obtained.

The injection of an additional 5 mgrs. of nicotine completely paralysed the secretory fibres of the chorda tympani. If inhibitory fibres are present, these need not necessarily be paralysed at the same time as the motor fibres. To test this a couple of drops of pilocarpine nitrate was forced into the duct and the chorda stimulated during the slow secretion caused by it. At first there was no effect during the secretion but an increase after it. This I think was probably due to increased blood flow the result of an after-effect of the vaso-dilator nerve cells.

(3) 6.5.4.5.5.6.6.8.10.12.12.15.11.11.12.12.13.12.13.12.12.11.11.10.
8.9.9.10.9.8.

Later the increase of flow was confined to the beginning of the period of stimulation.

(4) 2.7.5.2.3.3.2.2.2.2.7.2.1.2.1.2.2.2.4.1.1.1.1.1.2.

There was then no indication of inhibition of the pilocarpine secretion.

I have made also one experiment in the dog (11¾ kilos, morphia, A.C.E. and urethane). 5 c.c. of 1 p.c. curari greatly reduced the effect of

the chorda tympani, and the secretion slackened after about 20 secs. stimulation; on ceasing to stimulate, the secretion gradually stopped in the normal way. The injection of 30 mgrs. of nicotine completely paralysed the chorda tympani for a short time; there was then trifling recovery which remained about the same for an hour. The usual result was that the first stimulation (30 to 60 secs.) had no effect, the second and subsequent ones caused a very slight secretion greatest in the first 10 to 20 secs. and then fairly constant and going on for 3 to 5 minutes; once or twice only was there a slight increase on ceasing to stimulate. A drop or two of 1 p.c. pilocarpine was then injected into the duct, causing a moderate, steady flow of saliva from the gland. Stimulation of the chorda tympani had no inhibitory action on this flow, usually the only effect was a very trifling increase in the first 10 to 20 secs. of stimulation. It is clear that in this experiment the characteristics of the action of curari and nicotine on the heart and bladder were not produced in the salivary glands. Whether other results would be obtained in an earlier state of nicotine poisoning remains for further experiments to decide.

Further I have made two experiments on the sacral autonomic fibres of the rectum. One was by the graphic method, a balloon being placed in the rectum and connected with the apparatus described above for use with the bladder. The results were not the same as in the bladder though there were points of resemblance. After injection of nicotine brief stimulation had usually no effect, but on longer stimulation contraction occurred which generally lasted a considerable time. The latent period was usually 10 to 15 secs. Usually no after-contraction was obtained except when the duration of the stimuli was not much less than that of the latent period. Usually too, stimulation during a contraction did not cause inhibition; once or twice an initial fall in the curve and an after-contraction was obtained, but without further experiments no great stress can be laid on these results. It is to be noted that the second and third injection of nicotine caused relaxation (the effect of the first was not observed) indicating that the majority of the nerve cells were inhibitory. The nerves were not completely paralysed by 50 mgrs. of nicotine. The contraction after nicotine was apparently chiefly of the circular coat.

In the sympathetic system analogous results are very sparse. Dale, Laidlaw and Symons[1] describe a very slight similar effect on the cat's pupil after painting the superior cervical ganglion with nicotine,

[1] *op. cit. supra.*

and they suggest that the action of ergotoxine on the sympathetic described by Dale[1] resembles that of nicotine on the vagus. In a former Paper[2] I have mentioned that in the dog after the injection of nicotine, stimulation of pre-ganglionic pilomotor fibres causes erection of hairs only after a very long latent period, and that the hairs remain erect long after the stimulus has ceased. In the dog the paralysis of pre-ganglionic sympathetic nerve fibres by nicotine is very imperfect, and the occurrence of a long latent period and of a protracted after-action seems to me to be associated with such incomplete paralysis.

In the central nervous system a number of phenomena are known which present analogies with the changed response of the heart and bladder; these need not be described here, but it may be pointed out that the 'reflex rebound' described by Sherrington and others resembles in so many respects the after-contraction obtained in the bladder that it is difficult to believe that its causation is essentially different.

Summary of chief results and Remarks.

Curves have been taken of variations in the internal volume of the bladder by a method modified from those in previous use. Stimulation of the sacral nerves which contain vesico-motor fibres cause, as is known, strong contraction of the bladder. If the stimulus is brief, relaxation soon sets in; if the stimulus is prolonged, relaxation after the end of the stimulus sets in more slowly. After brief stimulation the relaxation is usually regular, slower towards the end and does not exceed the contraction, at times after partial relaxation there is a second slow contraction giving a curve with a more rounded top. No clear evidence of the presence of inhibitory fibres was obtained in the normal condition. The contraction is considerably weakened by atropine but the form of the curve is not markedly altered.

After injection of 1·5 to 2 c.c. of 1 p.c. curari the extent and duration of the contraction produced by the sacral nerves is diminished; the relaxation is however not complete during the stimulation (30 or more seconds) but gives way to more or less contraction, which increases when the stimulus ceases and then subsides relatively slowly.

After injection of 4 to 5 c.c. of 1 p.c. curari, the initial contraction is small, it passes off during the stimulus, and may be followed by slight inhibition, the after-contraction is relatively large. If the stimulation is kept up for more than 20 to 30 seconds there is usually during

[1] Dale. This *Journal*, xxxiv. p. 163. 1906.

[2] Langley. This *Journal*, xx. p. 243 (Footnote). 1896.

the early stimulations a slow contraction following the relaxation or inhibition; on ceasing to stimulate there is a relatively large after-contraction which only slowly passes off. Stimulation during the after-contraction causes as before a slight initial contraction and more or less marked inhibition; on ceasing to stimulate there is again after-contraction. The after-contraction may consist of a quicker small first part, and of a larger, slower and more prolonged second part; in fatigue the second part is much more reduced than the first part.

Similar effects are produced by a small dose of nicotine. A sufficient dose of nicotine abolishes the initial contraction, the other features of the curve being but little altered, except that there is rarely a distinction of two parts in the after-contraction. Thus the first effect of stimulating the sacral nerves is inhibition.

The after-contraction increases with increase in the duration of the stimulus up to about half-a-minute. Repeated stimulation, at intervals of a few minutes, greatly reduces the after-contraction. Stimulation of one pair of sacral nerves greatly reduces the effect of the others. The duration of the inhibition is favoured by repeated stimulation and to some extent by a state of after-contraction. Large amounts of nicotine reduce but do not abolish these effects. The effects can be produced by induction shocks of slow rhythm—3 to 5 a second.

The nerve fibres which cause the inhibition and after-contraction leave the spinal cord in the anterior roots of the sacral nerves.

Nicotine stimulates the peripheral nerve cells. A given amount of curari prevents the stimulating effect of a given amount of nicotine but not of a larger amount. There is then a mutual antagonism between the two poisons and both act on the peripheral nerve cells.

When the changed response has been produced and the tone of the bladder is increased by pilocarpine, stimulation of the sacral nerves causes partial inhibition of the tone.

When the changed response has been produced, the injection of a small amount of atropine changes it once more. On stimulating the sacral nerves there is an initial contraction in place of inhibition and the after-contraction is greatly reduced. The after-contraction appears to require a stimulus lasting more than 2–3 secs. to be produced, and it increases with the duration of the stimulus up to about half-a-minute to a minute. On repeated stimulation at intervals of a few minutes, the after-contraction but not the initial contraction disappears. On repeated brief stimulation at intervals of a few seconds, the contractions are at first summated, then get quicker and weaker, and the curve falls. A very small amount of atropine—($\frac{1}{2}$ a mgr.)—may

produce the change; a subsequent large amount (10 to 30 mgrs.) has some further effect, but it is relatively slight. Stimulation during an after-contraction causes inhibition when the initial contraction has passed off.

When curari or nicotine has been injected, stimulation of any branch of the pelvic plexus which has pre-ganglionic fibres causes after-contraction. Stimulation of a branch on the bladder which contains only post-ganglionic fibres causes a normal contraction with no after-contraction. The contraction caused by stimulating the post-ganglionic fibres may perhaps be reduced by atropine, but is not altered in form.

A slight similar change in response was obtained in the chorda tympani of the cat, but there was no inhibition of the secretion caused by pilocarpine.

The evidence given above is I think conclusive that curari and nicotine[1] produce their effects by an action on the peripheral nerve cells.

The action on the peripheral nerve cells may be of several kinds, it will be sufficient here to consider two.

(1) There is evidence that different nerve cells and even those in the same ganglion may be unequally paralysed by nicotine[2]. This gives a basis for the theory that both motor and inhibitory fibres are present and that nicotine paralyses the nerve cells on the course of the motor nerve fibres more than it does those on the course of the inhibitory nerve fibres. By inhibitory nerve fibres in the autonomic system I mean fibres which cause inhibition whether stimulated in their pre-ganglionic or in their post-ganglionic course.

But the theory of the presence of inhibitory nerve fibres—by itself at any rate—affords no satisfactory explanation of the phenomena.

On this theory the phenomena in the successive stages of nicotine poisoning are due to a progressive blocking of the motor nerve impulses in their passage through the nerve cells so that they are less and less able to overcome in the bladder the unaffected or but little affected inhibitory nerve impulses. In order to account for the phenomena two hypotheses are required, first that the inhibitory nerve impulses take considerably longer to produce their full effect than do the motor nerve impulses, for if they did not there would be no initial contraction, and secondly that when the stimulus ceases, the inhibitory impulses stop almost instantaneously, for after-contraction follows promptly at the

[1] In the following pages I shall as a rule speak of nicotine only since the phenomena produced by curari are essentially the same.

[2] Cp. Langley and Dickinson. This *Journal*, XI. p. 509. 1890.

end of the stimulus. If the inhibitory fibres acted in this way it is difficult to see that they would be anything but a hindrance to the normal working of the bladder unless indeed we suppose that there is coordination in the spinal cord so that inhibitory impulses are only discharged after the motor ones, and the reflex bladder contraction gives no evidence of this. A sudden cessation of inhibitory effect seems unlikely since when any of the autonomic inhibitory nerves are stimulated—chorda tympani, cardiac vagus, nervus erigens, splanchnic—the effect is more or less prolonged after the stimulus has ceased, in favourable circumstances this is also seen on stimulating the sympathetic inhibitory fibres to the bladder. Hence it seems to me more probable that the after-contraction is due to an outburst of new impulses from the nerve cells and not to a freedom of action of impulses already existing.

The smaller after-contraction which occurs when atropine has been given after nicotine might not unnaturally be referred to a paralysis of the post-ganglionic motor fibres on the analogy of certain other paralysing actions of atropine on fibres of the oro-anal system, but for the small quantity of atropine—$\frac{1}{2}$ a milligram—which may suffice, and for the fact that, so far as my experiments go, atropine does not much reduce the effect of electrical stimulation of the post-ganglionic nerves. The latter fact might be accounted for by the supposition that the impulses causing after-contraction are sub-normal in strength. It is conceivable that sub-normal stimuli would be greatly decreased in effect by a decrease of irritability of the end organ which would not reduce the effect of stronger impulses set up by electrical excitation. But if the 'all or none' theory applies to the stimulation of nerve fibres by nerve cells, the impulses could not be weaker than those set up by electrical excitation. It is possible theoretically that the relative weakness of the after-contraction should be caused by the impulses being fewer, for some of the motor cells may be completely paralysed when the paralysis of others is incomplete. If however the impulses, though passing by fewer post-ganglionic fibres, are normal in intensity, there seems no reason why so small a dose of atropine should have so great an effect on them.

Further, supposing that atropine given after nicotine does diminish the after-contraction by causing paresis of the post-ganglionic fibres, how are we to explain the fact that brief stimulation of the sacral nerves causes contraction (the initial contraction) although before atropine is given it causes none?

The foregoing considerations show I think that the theory of the

presence of inhibitory fibres is insufficient in itself to account for the phenomena, and they raise a doubt whether it is necessary to suppose that they are present at all.

(2) Another view which suggests itself for the action of nicotine and curari on nerve cells is that the properties of the nerve cells are altered so that they respond to normal impulses in an abnormal way (cp. Dale, Laidlaw and Symonds, *supra*, p. 172). It is obvious from the phenomena that fatigue dominates the situation. Repetition of stimuli causes changes with a rapidity entirely foreign to the normal behaviour of the bladder.

The initial contraction caused by stimulation of the sacral nerves after curari or a small dose of nicotine obviously resembles the initial contraction of striated muscle at a certain stage of curari and nicotine poisoning. The initial contraction after curari has I believe been long known; that after nicotine was described by Dickinson and myself[1], and both more recently have been further investigated by Hofmann[2]. Originally the phenomenon in muscle was considered to be due to the fatigue of the nerve ending. I have given reason to believe that the function attributed to the nerve endings are functions of a constituent of the cell in which they end. The constituent of the cell I have spoken of as the receptive substance, so that I attribute the short duration of the initial contraction to a fatigue of the receptive substance, the successive stimuli keeping down its irritability.

In fatigue the threshold of stimulation is increased, and the slow contraction which occurs at a certain stage of nicotine poisoning is probably the expression of two different effects of nerve stimulation, viz. on the one hand the decrease in irritability of the receptive substance, on the other of increase in the intensity of the stimulus, such as might be produced on Nernst's theory by a further accumulation of ions.

When, in consequence of the further action of nicotine, or of repeated stimulation, the irritability of the receptive substance is further reduced, there is no contraction during the stimulation.

The after-contraction presents greater difficulties. As I have said, I consider that this is due to an outburst of nerve impulses from the nerve cells after the stimulus has ceased. There are two cases (*a*) when there is an initial contraction, (*b*) when there is none.

(*a*) On the hypothesis given above, when there is an initial contraction, the irritability of the receptive substance is kept from

[1] Langley and Dickinson. This *Journal*, XI. p. 83. 1890.
[2] Hofmann. *Pflüger's Arch.* XLIII. p. 207. 1902.

rising by the successive stimuli. On cessation of the stimuli, the irritability can recover, and other stimuli will be enabled to act. But if the stimuli are of the same nature as those set up by electrical excitation of the nerve, they should have the same effect, viz. a brief initial contraction. The first part of the after-contraction looks in fact like the first part of the initial contraction, but instead of this passing off, there is a second larger and very protracted contraction.

(*b*) When there is no initial contraction, the irritability of the receptive substance is still further reduced, and it may be reduced to such an extent that it is not affected by the maximal change set up during nerve stimulation. In this case the receptive substance should remain unexcitable after the nerve stimulation has ceased, and we should not expect that any further stimuli should affect it. In fact on ceasing to stimulate there is a considerable after-contraction.

These considerations seem to show that the mechanism of normal stimulation by nerve excitation is different from that which occurs in an after-contraction, except perhaps as regards the first part of the after-contraction in the early stage of nicotine poisoning. On the theory that during nerve stimulation there is a passage of ions to a membrane in the cell, we might suppose that normally it is the passage of ions to the membrane which is the effective condition for stimulation, and that in the altered state of the receptive substance, it is the passage of ions from the membrane which is the effective condition, and this opens the question whether the substance acted on is the same in each case, or whether in one case the receptive substance and in the other the fundamental substance of the cell is acted on.

On the hypothesis that it is passage of ions from the membrane which conditions stimulation in an after-contraction, the inhibition of the after-contraction would naturally follow on renewed stimulation though the partial nature of the inhibition presents some difficulties[1].

But this hypothesis of the nature of the inhibition seems to demand that pilocarpine and atropine affect the nerve cells as well as the peripheral tissue and there is at present no independent evidence of this. It is possible that the question may be settled by applying pilocarpine and atropine locally to the nerve cells, but until it is settled I do not think any final conclusions can be drawn as to the cause of the various phenomena described in this Paper.

[1] The partial contraction suggests an anodic inhibition in the nerve cell like that which occurs in certain nicotinized striated muscles, but this explanation of the inhibition seems to be put out of court by the absence of kathodic effect during the first stimulation.