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FACILITATION AND INHIBITION IN THE SUPERIOR CERVICAL GANGLION.

By J. C. ECCLES.

(*From the Laboratory of Physiology, Oxford.*)

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It has already been pointed out that, since Langley's classical investigations, the sympathetic ganglion has been regarded merely as a relay station in the peripheral sympathetic pathway, each preganglionic fibre being in sole functional connection with a group of ganglion cells. In the previous paper this latter view was shown to be incorrect, for many ganglion cells are excited by each of two groups of preganglionic fibres. This overlapping distribution of preganglionic fibres on ganglion cells brings with it potentialities for coordination, each postganglionic neurone forming a final common path for the various preganglionic fibres in functional connection with it. This paper investigates these possibilities.

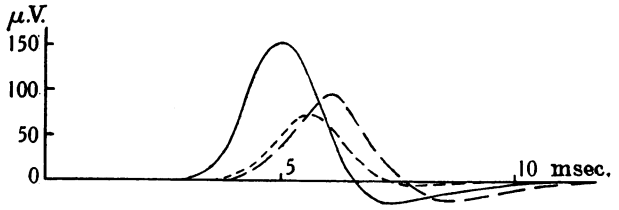
The method of experiment is similar to that described in the previous paper. In that paper it was shown that there are usually four distinct groups of ganglion cells, S_1, S_2, S_3 and S_4, each of which is supplied apparently exclusively by its own group of preganglionic fibres. The S_1 and S_2 groups, with which this paper is almost exclusively concerned, are the most constant and clearly separated of these groups, and are supplied by the preganglionic fibres of lowest threshold.

Facilitation.

A. *General considerations.*

Pl. I, fig. 1, shows a typical record which is obtained when two similar stimuli, each so weak as to be submaximal for the S_1 fibres, are applied at various intervals through the same electrodes on the preganglionic trunk. When the second stimulus is set up at a short interval after the first, it gives rise to an S_1 wave much larger than when alone and with a shorter latent period. As the interval lengthens these effects become less, and at a long interval (184 msec., observation 4) they have

almost disappeared. The shortening of the latent period is shown in faster records such as Text-fig. 1, where at an interval of 12·0 msec. it amounts to 0·45 msec. Otherwise in Text-fig. 1 the time course of the facilitated action potential is identical with the unfacilitated, so it appears likely that both responses are due to an almost synchronous discharge, for facilitation always tends to decrease asynchronism [Eccles, 1935]. At very short intervals, *e.g.* 3·8 msec. in Text-fig. 1, the latent period of the second response is lengthened, presumably on account of the relatively refractory state of the preganglionic pathway. The shortening of the latent period of the facilitated S_1 wave appears to be similar to that observed for the second of two maximal responses [Eccles, 1935].



Text-fig. 1. Enlarged drawing of action potentials evoked by a second stimulus at 3·8 and 12·0 msec. after a previous similar stimulus, the time of the second stimulus corresponding to zero on the time scale. --- Response to second volley alone. ———— Response to second volley 3·8 msec. after first. —— Response to second volley 12·0 msec. after first.

The increase in the S_1 wave also occurs when it is recorded postganglionically, so it must be due to an increase in the number of S_1 ganglion cells discharging impulses. This increased response cannot be caused by any alteration in excitability under the stimulating electrodes, for it also occurs when the second stimulus is applied through a different pair of electrodes from the first. It could not of course be due to a supernormal phase of excitability following the first volley, for the second stimulus alone excites all those fibres excited by the first, being set up as it is by a similar stimulus applied through the same electrodes. For this reason also the first and second volleys when alone would fire off the same ganglion cells, hence none of these additional ganglion cells which respond to the second volley at short intervals after the first is fired off by the first volley. This volley must therefore produce an excitatory condition of some ganglion cells without setting up the discharge of impulses, and as a result of this persisting excitement the second volley, previously subliminal for these ganglion cells, now produces a discharge of impulses from some of them. The similar time course

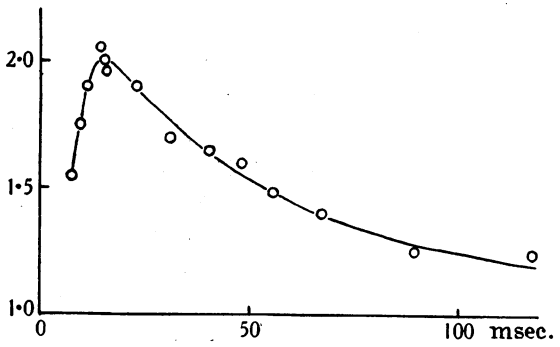
of the shortening of latent period indicates that it is produced by the same persisting excitement, and subsequent evidence confirms this identity.

The facilitation seems similar to that occurring with spinal reflexes [Eccles and Sherrington, 1930; 1931 *a*, *b*], so the persisting excitement may be regarded as an example of a central excitatory state (c.e.s.). Thus besides setting up a discharge of impulses from some ganglion cells, a submaximal preganglionic volley must also give rise to a subliminal fringe of excited ganglion cells—a condition paralleling that existing with spinal reflexes [Eccles and Sherrington, 1931 *b*]. Now by the above technique ganglion cells can only be demonstrated to belong to this subliminal fringe when a second similar volley produces additional excitement sufficient to set up a discharge. Such ganglion cells may be said to belong to the "effective subliminal fringe" in order to distinguish them from the ganglion cells which presumably are excited to lesser degrees of subliminality. The degree of S_1 facilitation at the optimal interval varies in different experiments, being in some experiments even more than 300 p.c. of the unfacilitated response (Pl. I, figs. 1 and 2), and in others as small as 30 p.c., but in none of our thirty-six experiments has facilitation been absent.

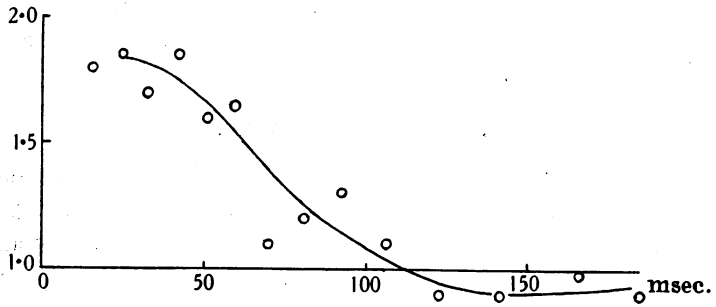
B. *The facilitation curve.*

The time course of the facilitation in series of observations such as those of Pl. I, figs. 1 and 2, may be represented as in Text-fig. 2 by plotting the relative height of the S_1 spike of the second volley against the stimulus interval. To some extent the increase of the S_1 spike is usually due to a decreased asynchronism as well as to the discharge of additional ganglion cells, but no appreciable error is thereby introduced into a facilitation curve such as that of Text-fig. 2, for these processes have identical time courses (section A). The decline in the facilitation curve for intervals beyond the maximum, which usually occurs at 10–15 msec., indicates the gradual subsidence of the c.e.s. in the ganglion cells of the subliminal fringe. Feldberg and Vartiainen [1934 *b*] suggest that the decline of the facilitation curve for intervals shorter than the maximum is due to the slow development of c.e.s., and in doing so apparently omit to take account of the relatively refractory state of the preganglionic fibres, which would probably persist as long as 15 msec. after the first stimulus. At shorter intervals the second stimulus would excite fewer fibres, and those impulses set up would be smaller in size,

especially in the fine terminal preganglionic branches, and hence probably less effective in exciting the ganglion cells—effects perhaps sufficient to explain the decline at these very short intervals [cf. Bremer, 1930; Eccles and Sherrington, 1930].



Text-fig. 2. The potential of each facilitated S_1 response to the second of two similar preganglionic stimuli (measured as a fraction of the second response alone) is plotted against the corresponding stimulus interval (abscissa).



Text-fig. 3. As in Text-fig. 2, but for S_2 responses, both stimuli being maximal and applied to the smaller of the annulus branches.

At relatively short intervals there is facilitation of the S_2 ganglion cells similar to that for S_1, and many S_2 facilitation curves have been constructed (Text-figs. 3 and 12), but at longer intervals inhibition gains the upper hand (section G), hence the actual period of facilitation is rarely more than 50 msec.

Facilitation of both S_1 and S_2 waves is also observed if two maximal stimuli are applied to one branch of the annulus Vieussens, especially if the smaller branch is chosen (Text-fig. 3). This facilitation shows that such a maximal volley gives rise to a subliminal fringe of excited ganglion cells exactly comparable with that produced by submaximal stimulation of

the whole preganglionic trunk, an effect which illustrates the similarity between submaximal preganglionic volleys set up either by submaximal stimulation of the whole preganglionic trunk or maximal stimulation of a part of it.

No attempt has been made to investigate possible facilitation with S_3 and S_4 ganglion cells.

C. *Facilitation between two volleys in different preganglionic fibres.*

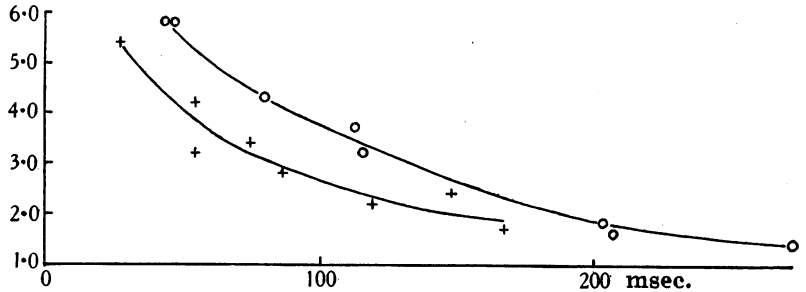
The complication introduced by the refractory period of the preganglionic pathway can be avoided by applying the first stimulus to one branch of the annulus Vieussens and the second to the other branch, but other complications are thereby introduced. It has already been seen [Eccles, 1935] that with S_1 preganglionic fibres there is often little overlap between the respective ganglion cell fields even with maximal stimuli, and, when these stimuli are submaximal, the chances of overlap become smaller. Moreover, when there is overlap, occlusion will occur with those ganglion cells which are excited to discharge impulses by each volley alone, *i.e.* with short stimulus intervals these ganglion cells will be prevented from responding to the second volley by the refractory period set up by their response to the first. As a consequence a decline in facilitation appears to occur at such short intervals. In four of our ten experiments the first complication has been avoided, facilitation of S_1 ganglion cells being obtained between volleys set up in different branches of the annulus, but in only one of these experiments has facilitation been maintained for intervals of a few milliseconds, there being presumably in this experiment a considerable overlap of the subliminal fringes of the two volleys with but little occlusion. However, the synaptic delay of the facilitated ganglion cells was then shortest at an interval of 4 msec., being no shorter than normal with simultaneous stimuli. This agrees with the results obtained for S_1 ganglion cells with interaction of two maximal volleys one in each branch of the annulus [Eccles, 1935, section J], and it will be considered in the general discussion of synaptic delay.

The S_2 facilitation between the two branches of the annulus is much greater than for S_1—a finding in agreement with results obtained with maximal stimulation, which indicated a greater overlap for the S_2 ganglionic fields. However, occlusion is a complicating factor in determining the true facilitation curve at short intervals, but, nevertheless, the

results indicate that facilitation is at a maximum when the stimuli to the two branches are simultaneous. The shortening of synpatic delay is then also maximal [cf. Eccles, 1935, section J].

D. *Facilitation after a maximal volley.*

If the first volley, instead of being the same size as the second, is maximal, there is still a facilitation of the response to the second volley (Pl. I, fig. 3), and the facilitation curve is not greatly altered in height or duration (cf. Text-fig. 4) except in the comparatively rare experiments in which there is a considerable inhibition of the S_1 ganglion cells (section G). Now the ganglion cells, which by facilitation are caused to respond to the second stimulus, must be amongst those which discharge



Text-fig. 4. The facilitation curve through the crosses is for equal submaximal stimuli as with Text-fig. 2. The curve through the circles shows the facilitation of a submaximal second response after a maximal first response.

impulses in response to the first maximal volley. This volley must therefore both excite ganglion cells to discharge impulses and produce a persisting c.e.s. on them. This also happens for S_2 ganglion cells, but with them inhibition rapidly removes the evidence of the persisting c.e.s. (sections J and L).

Now, when both preganglionic volleys are maximal, it has been shown in the previous paper (section I) that the response to the second volley is probably never increased by the preceding volley, *i.e.* under such conditions there is no demonstrable subliminal fringe. It may therefore be concluded that a single maximal preganglionic volley excites every ganglion cell to discharge an impulse. This conclusion is in agreement with that arrived at by Brown [1934] for the ganglion cells innervating the nictitating membrane. However, the c.e.s. set up by the first maximal volley is not without effect on the response to the second, for it undoubtedly is the

cause of the shortened synaptic delay [Eccles, 1935, section I] which has a time course similar to that of spatial facilitation (section B). This shortening of synaptic delay may be called temporal facilitation in order to distinguish it from the term spatial facilitation which may be applied to the spread of supraliminal excitation into the ganglion cells of the subliminal fringe.

Thus a maximal preganglionic volley not only excites every ganglion cell to discharge a single impulse, but it also sets up a persisting c.e.s. of the cells which

(*a*) enables a later submaximal volley to fire off more ganglion cells than it otherwise would have done (spatial facilitation of subliminal fringe);

(*b*) shortens the synaptic delay of those ganglion cells which are fired off by a later submaximal or maximal volley (temporal facilitation).

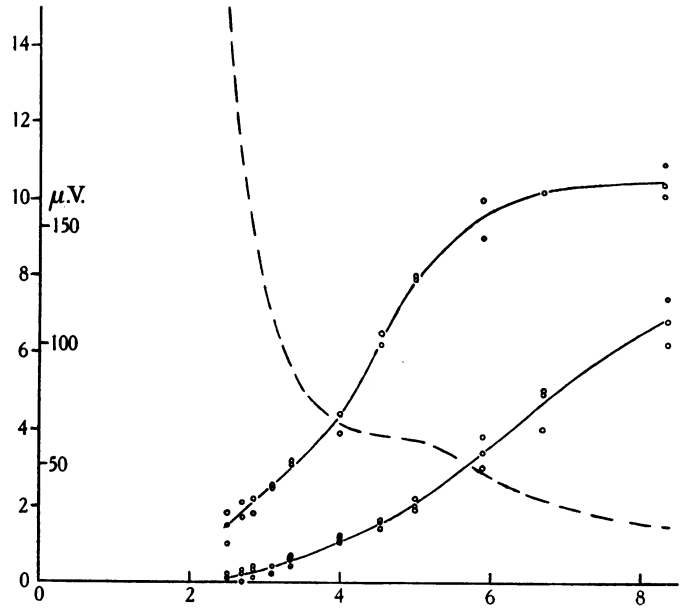
The absence of a subliminal fringe with a maximal volley shows that this volley must excite supraliminally all those ganglion cells which are included in the subliminal fringe of a submaximal volley. This must be brought about by the excitatory action on these ganglion cells of the additional preganglionic impulses set up by the maximal stimulus. The possibility cannot be excluded that some of these impulses alone are able to excite the ganglion cells to discharge impulses, *i.e.* are individually supraliminal, but it is more probable that the additional preganglionic impulses are individually subliminal, summation of the excitatory effects of several preganglionic impulses being essential for supraliminal excitation. Experiments with volleys in the same or different preganglionic fibres show that supraliminal excitation actually is thus produced by summation of the subliminal excitatory effects of successive impulses (sections A and C); but, while supporting the second explanation, such observations do not exclude the above first-mentioned possibility. Further discussion of this problem will be postponed until the evidence of the next section has been considered.

E. *Effects of alterations in the size of the facilitating volleys.*

(1) *Facilitating volleys equal in size.*

The degree of spatial facilitation between two submaximal volleys usually increases as the size of the volleys becomes smaller, *i.e.* the effective subliminal fringe bears an ever-increasing ratio to the supraliminally excited fraction. This is well shown in Text-fig. 5, but unfortunately it was impossible to measure the observations with stronger stimuli on account of the complicating effect of the large S_2 wave which such stimuli set up. However, it is clear that the facilitated response

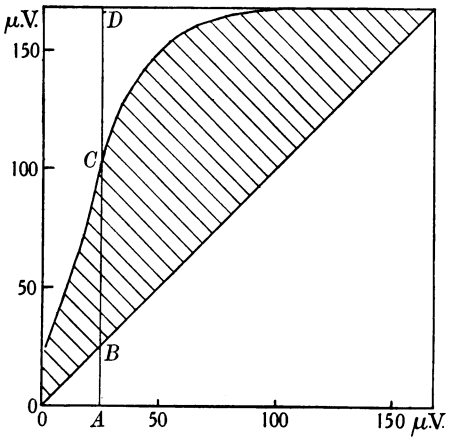
has practically reached a maximum with a stimulus strength as weak as 6·7, though the unfacilitated response is then less than half maximal, *i.e.* such a stimulus gives rise to an effective subliminal fringe which includes almost all those ganglion cells not excited supraliminally.



Text-fig. 5. For the lower curve through the circles the potentials of the S_1 spikes are plotted as ordinates against as abscissæ the corresponding strengths of the preganglionic stimuli in arbitrary units. The upper curve through the circles is similarly constructed, but the ordinates are the facilitated S_1 spike potentials evoked by a second stimulus at 16·5 msec. after a previous stimulus of identical strength. The broken line expresses the course of the relative facilitation, *i.e.* the ratio between the two curves, as the stimulus strength is varied.

In Text-fig. 6 the relation between the supraliminally excited fraction and the subliminal fringe is represented by plotting the facilitated responses against the corresponding unfacilitated responses. As a single preganglionic stimulus increases in strength, the ganglionic response evoked by it is indicated by the intercepts on an ordinate moved from the zero origin to the right, *e.g.* when the actual response AB has a potential of 25μV, the effective subliminal fringe for facilitation by a similar volley preceding it by 16·5 msec. corresponds to BC, a potential of 78μV, and CD represents the ineffective subliminal fringe and the fraction not excited at all. It has already been seen that with a maximal

preganglionic volley all the ganglion cells are supraliminally excited, there being no subliminal fringe. As the stimulus is weakened, Text-fig. 6 shows that all those ganglion cells not supraliminally excited are at first included in the effective subliminal fringe, but with further weakening some ganglion cells pass over to the upper area, presumably first into the ineffective subliminal fringe and later into the unexcited fraction. With still further weakening of the stimulus the subliminal fringe rapidly diminishes, but, nevertheless, always bears an increasing ratio to the



Text-fig. 6. For the curved line the potentials of the facilitated S_1 responses of Text-fig. 5 are plotted as ordinates against the potentials of the unfacilitated responses as abscissæ, the values being determined from the smoothed curves of Text-fig. 5. The shaded area represents the effective subliminal fringe, and the boundaries of the square are the limits imposed by the potential of the maximal S_1 response. Further explanation in text.

supraliminal fraction. This is better illustrated by Text-fig. 5, in which the broken line represents the relative facilitation at the various stimulus strengths.

The rapid increase in this ratio with further weakening of very weak stimuli suggests that still weaker stimuli would elicit a facilitated response though individually too weak to give rise to any detectable action potential. Pl. I, fig. 4, shows that this was actually realized in a later series of observations in this experiment, the individual responses being there undetectable (less than 1 μV), and the facilitated response as much as 28 μV at the shortest interval. In only one other experiment has this been observed, but in many experiments extrapolation of curves similar to Text-fig. 5 indicates that, with a sufficiently sensitive recording,

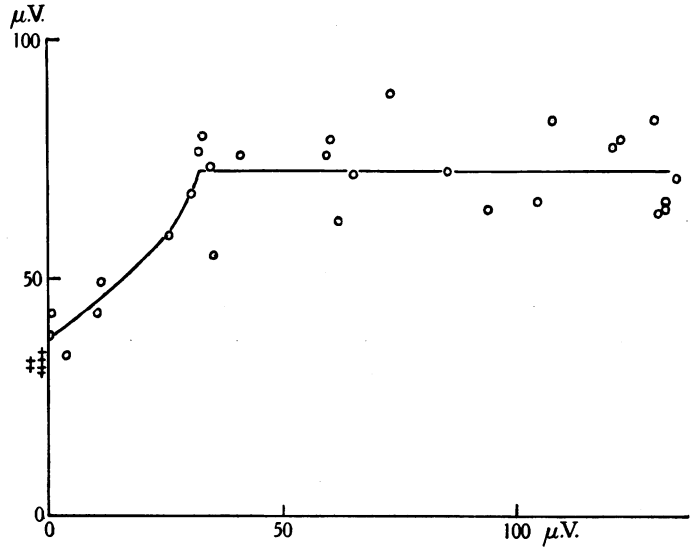
facilitation of subliminals would also be observed, *i.e.* either volley alone would only give rise to a subliminal fringe. Thus single impulses in the fibres so excited are unable to set up a discharge of impulses from any ganglion cells, and it may be assumed that such fibres are a fair sample of the whole S_1 group, for, being of lowest preganglionic threshold and therefore largest, they would be more likely individually to set up such a discharge than any other fibres of the S_1 group; hence it may be concluded that in such experiments a single impulse in a single preganglionic fibre never excites a discharge from ganglion cells. Summation either spatial or temporal is necessary for every discharge—a condition which has been found to exist for the spinal flexor reflex [Eccles and Sherrington, 1930].

In a few experiments weakening of the stimuli has not been accompanied by any significant change in the relative facilitation which has in such experiments always been small. It is possible that an increase would be observed with weaker stimuli and more sensitive recording, for even a just detectable spike of 1μV probably represents the combined discharges of at least 100 S_1 ganglion cells. However, it seems more probable that in those experiments single impulses in some preganglionic fibres are able to set up the discharge of single impulses from ganglion cells, summation being unnecessary.

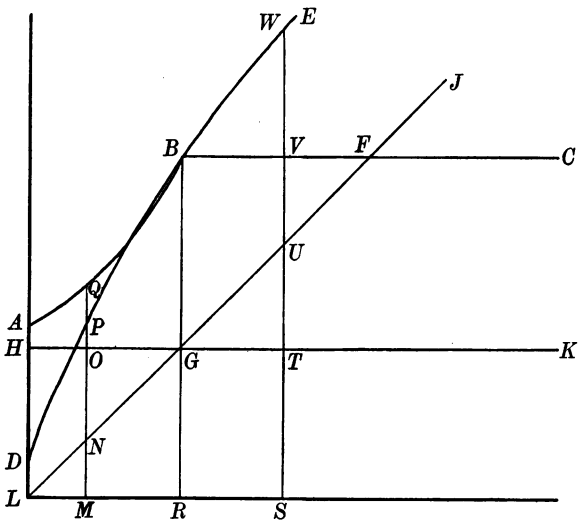
(2) *First volley varied, second of constant submaximal size.*

Pl. II, fig. 5, illustrates the effect of variations in the size of the first volley on the facilitation of a constant second volley at a fixed interval, 40 msec. after the first. As the size of the first volley increases up to that of the second the facilitated second response also increases (observations 7, 8 and 3), but further increase of the first volley does not appear to affect the facilitation (observations 4, 2 and 5). This is confirmed by the curve of Text-fig. 7 in which are plotted the whole series of observations of which those of Pl. II, fig. 5, form a part, the potentials of the facilitated and corresponding first reponses being respectively ordinates and abscissæ. It will be seen that, even when the first response is zero, facilitation of the response to the constant second volley demonstrates the presence of an effective subliminal fringe.

The sharp angle in the curve appears to coincide with the point at which the first response equals the response to the second volley alone, the potential being 32μV, and this has been characteristic of ten of our twelve series of observations (six separate experiments). In both of the exceptional series the second response was large. In one the angle



Text-fig. 7. A constant second preganglionic stimulus is applied at 40 msec. after a variable first stimulus, and the S_1 potentials of the first responses are plotted as ordinates against the S_1 potentials of the corresponding second responses. The crosses indicate the S_1 potentials of the responses evoked by the second stimulus alone, the average being about 32 μV.



Text-fig. 8. Full explanation in text.

appeared to occur when the first response was rather larger than the unfacilitated second response, and in the other the curve was so flat that no angle could be detected. Beyond the angle the facilitation in Text-fig. 7 is unaltered by further increase of the first volley, a result typical of most series of observations, though in two it has declined slightly and in two it has risen slightly.

Consideration of the conditions responsible for the shape of the curve of Text-fig. 7 will be made easier by reference to Text-fig. 8 in which this curve has been redrawn as the line *ABC*. When both volleys are equal *DBE* is the approximate curve for this experiment corresponding with that in Text-fig. 6, the stimulus interval being identical with that for the curve *ABC*. The actual experimental curve did not pass through *B*, presumably on account of a change in the preparation between the two series of observations. In order to simplify the following discussion this change was approximately allowed for by raising the experimental curve throughout by about 10 p.c. to form the curve *DE* which passed, as it should, through *B*. Now the line *HK* represents the height of the unfacilitated second response for the curve *ABC*, and *LJ* drawn from *L* at 45° represents the height of the unfacilitated second response for the curve *DBE* (cf. Text-fig. 6).

The facilitations produced by any first response may be determined in Text-fig. 8 by drawing the ordinate at the point corresponding to that response. For example *MNOPQ* represents such a line for a first response *LM*. With a second volley equal to the first, *MN* and *MP* are respectively the facilitated and unfacilitated second responses, *NP* being the effective subliminal fringe. On the other hand, with a constant second volley giving an unfacilitated response *MO*, the facilitated response is *MQ*, the effective subliminal fringe *OQ* being less than *NP*. Similarly for any other value of the first response less than *LR*, which equals *LH* the size of the constant second response, the effective subliminal fringe is less for facilitation of the response to the constant second volley than it is when the second volley equals the first. Now since both volleys are set up in the cervical sympathetic by stimuli applied through the same electrodes, the larger volley will always include all the preganglionic impulses of the smaller, and consequently the group of ganglion cells supraliminally excited by the larger volley will include not only all those ganglion cells in the supraliminal group of the smaller volley, but also many of the ganglion cells in the subliminal fringe of that volley, for presumably the supraliminal group is largely recruited from the fringe as the exciting volley is increased [cf. Sherrington, 1931]. The first

volley facilitating a larger second volley must therefore act at a disadvantage, for many of the ganglion cells which it almost excites supraliminally will be among those excited by the second volley alone, and so not available for the facilitation which would certainly occur with an equal-sized second volley; hence the smaller effective subliminal fringe under such conditions.

Now the response to the constant second volley *LH* is facilitated so as to include more ganglion cells than respond when the second volley equals the first, the curve *AQB* lying above *DPB* (the crossing of the curves before *B* is of course due to an error in their determination). This almost certainly indicates that with the larger second volley the effective subliminal fringe of the first volley extends over a larger field of ganglion cells than obtains for a second volley equal to the first, *i.e.* ganglion cells in the effective subliminal fringe under the former conditions are too weakly excited to be in the effective subliminal fringe when the second volley equals the first. This result suggests that many grades of subliminality exist, for with equal volleys each would contribute approximately half the threshold c.e.s. for those ganglion cells just within the effective subliminal fringe, while with a larger second volley ganglion cells on which the first volley sets up considerably less than half the threshold c.e.s. must be in the effective subliminal fringe on account of the larger contribution made by the second volley.

That different conditions obtain for first volleys larger than the constant second volley may be seen by considering the effect of a volley of strength *LS*, the conditions being determined from the line *STUVW*. As before *SU* and *SW* are respectively the facilitated and unfacilitated responses when the first and second volleys are equal, *UW* being the effective subliminal fringe, and *ST* and *SV* are the respective responses with a constant second volley, the facilitation *TV* being no greater than it is for a first response equal to *LR*. Now according to the above conclusion an increase in the first volley should be accompanied by an increased facilitation, for this volley would contribute considerably more than half the liminal c.e.s. to many of the ganglion cells which are excited to less than half by the constant second volley. Experiment has indicated that this increased facilitation has usually failed to appear for all strengths of the first volley greater than the second, the curve *BC* being approximately parallel to *HK*. Now conditions for first volleys stronger than *LR* differ from those where they are weaker not only by an intensification of the excitation of the more weakly excited ganglion cells, but

also by the supraliminal excitation of additional ganglion cells, which presumably would be largely recruited from the previous effective subliminal fringe. Thus the only probable explanation of the absence of an increased facilitation would seem to be that the resulting discharge of impulses by these ganglion cells diminished their c.e.s., an effect comparable with that inferred for motoneurones of the spinal cord [Eccles, 1931; Eccles and Sherrington, 1931 *c*; Eccles and Hoff, 1932]. Thus, when the first volley is made larger than the second, facilitation would increase on account of the recruitment of fresh ganglion cells into the effective subliminal fringe, but it would diminish on account of the defection of those ganglion cells recruited into the supraliminal group, an approximate balance being struck in most experiments, though a slight increase or decrease of facilitation could occur.

For a first response increasing from *LR* to *LS* in Text-fig. 8, *TU* represents the maximum defection that would thus occur, the effective subliminal fringe being then recruited by an identical amount from the previously ineffective subliminal fringe. It seems, however, unlikely that all the ganglion cells represented by *TU* would be recruited from the effective subliminal fringe *GB*. Moreover, even when ganglion cells discharge impulses, the surviving c.e.s. is often sufficient for effective facilitation of the response to a subsequent volley, as is shown by the facilitation after a maximal volley, which sets up a discharge from all ganglion cells (cf. section D and the observations to the right of Text-fig. 7). Presumably such ganglion cells are excited to a degree considerably above threshold. Thus the facilitated response would remain constant along the line *BC* although the recruitment of the subliminal fringe was insufficient to compensate for the defection of ganglion cells recruited from the supraliminal group along the line *GJ*.

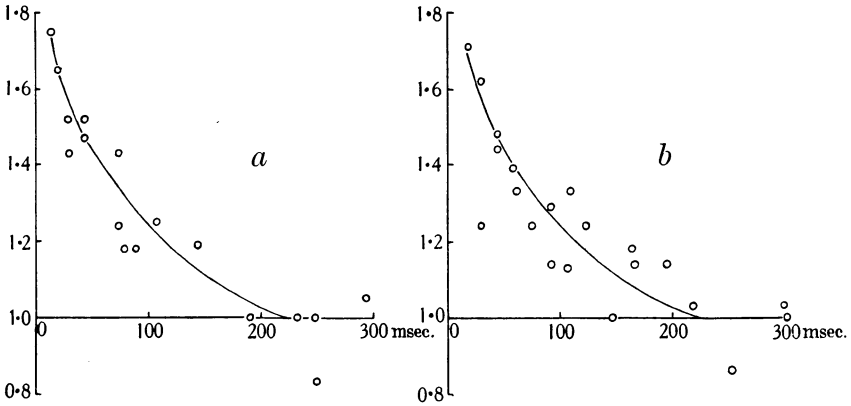
The complicating effect of inhibition has prevented this investigation for S_2 ganglion cells, and even with the S_1 group inhibition might play a part in modifying the curves, though it could not be an important factor in determining the angle *ABC*. It must be concluded that the only likely explanation of this seems to be the diminution of the c.e.s. of a ganglion cell when it discharges an impulse.

F. *The effect of various drugs on facilitation.*

Pl. II, fig. 6, shows a series of observations before and after painting the ganglion with a 0·01 p.c. solution of nicotine. There has been a complete removal of both spatial and temporal facilitation, though the trans-

mission of impulses through the ganglion is practically unaffected. A similar result is also invariably obtained on the intravenous injection of 0·4 mg. of nicotine per kg. A smaller dose of nicotine, *e.g.* 0·2 mg., diminishes the facilitation and shortens its duration. The effect of nicotine soon passes off, almost disappearing in 30 min. A subsequent dose of nicotine has an action similar to the first dose.

Besides abolishing facilitation the above doses of nicotine also increase the *S* waves set up by a submaximal volley, but do not affect the *S* waves of a maximal volley. It may therefore be concluded that, in the presence of minute amounts of nicotine, many ganglion cells are excited to discharge impulses by a submaximal preganglionic volley which previously



Text-fig. 9. Text-fig. 9 *a* is similar to Text-fig. 2, but in another experiment, while Text-fig. 9 *b* has been obtained immediately after an intravenous injection of 1·0 mg. eserine sulphate. The curve of Text-fig. 9 *a* has been drawn through the points of Text-fig. 9 *b*.

had only excited them subliminally, *i.e.* nicotine has increased the excitability of these ganglion cells or in other words it has lowered their threshold. It is probable that this action is produced by doses of nicotine too weak to cause the well-known effect of the discharge of impulses from the ganglion. Larger doses of nicotine, *e.g.* 1·0 mg. per kg., have the usual depressing effect on the excitability of the ganglion cells.

The effect of eserine on facilitation has been investigated both by painting eserine solutions of various strengths directly on the ganglion, and by injecting intravenously quantities varying from 0·05 to 1·0 mg. per kg. body weight. Text-fig. 9 is typical in showing an absence of effect on the time course of the facilitation curve. Occasionally with the largest doses a slight slowing of the facilitation curve was observed.

In doses of 0·1–1·0 mg. per kg. eserine increases the excitability of the ganglion cells, but to a less extent than nicotine. This was sometimes not observed with the largest intravenous doses, but even with them there was no depression of excitability as was produced by painting the ganglion with a 1 in 1000 solution of eserine. The increased excitability (potentiation) produced by small doses of eserine was observed by Feldberg and Vartiainen [1934 *a*] and attributed to the specific depressant action of eserine on the cholinesterase of the ganglion. They therefore regarded this potentiation as evidence supporting the hypothesis that acetyl choline functions as a transmitter at the synapses of the ganglion. It was pointed out[1] by the author that cholinesterase would not be likely to hydrolyse a significant quantity of acetylcholine during the short synaptic delay of S_1 ganglion cells, about 3 msec., and hence the potentiating effect of eserine would not be due to its depressant action on the cholinesterase, a non-specific increase in excitability of the ganglion cells being suggested as an alternative explanation. A substantially similar explanation has since been adopted by them [1934 *b*].

Painting the ganglion with solutions of strychnine as strong as 1 in 5000 has no appreciable effect on the facilitation curve, but a 0·1 p.c. solution has a depressing effect on the excitability of the ganglion [cf. Feldberg and Vartiainen, 1934 *b*].

Nembutal (40 mg. per kg. intraperitoneally) anæsthesia is without effect either on the facilitation curve or on the ganglionic action potential. Deep ether anæsthesia is similarly without effect.

Inhibition.

G. *Introduction.*

Pl. II, fig. 7, shows a series of postganglionic action potentials evoked by two preganglionic volleys at various intervals apart, the first being maximal for S_1 and S_2, the second submaximal for S_2. At the shortest interval (observation 1) the S_1 spike set up by the second volley shows some increase in size over the normal control, and at longer intervals it is not appreciably affected by the preceding volley. The S_2 spike however exhibits a very different behaviour, for though increased slightly in observation 1, it is greatly depressed at relatively long intervals. This depression reaches a maximum at about 200–300 msec. (observations 3 and 4), being less at longer intervals (observations 5 and 6). Thus many S_2 ganglion cells which discharged impulses in

[1] Discussion at meeting of the Physiological Society, Cambridge, May 12th, 1934.

response to the second volley alone must be prevented from doing so when it is preceded by the first volley. This first volley must produce a depression of the excitability of such ganglion cells, for in the preganglionic pathway there would be no interference between two volleys at such long intervals, and later evidence confirms this conclusion. This depression of excitability is not due to a refractory period of the ganglion cells following the discharge set up by the first volley, for observations at short intervals, *e.g.* observation 1, show that this depression only appears after recovery from the refractory period is almost or quite complete. The depression must be due to an inhibitory process similar to that described for spinal reflexes [Eccles and Sherrington, 1931 *d*] and called the central inhibitory state (c.i.s.).

As shown in Pl. II, fig. 7, the inhibition is almost entirely confined to the S_2 ganglion cells, though in some experiments a definite inhibition of the S_1 and S_3 cells is also present. These inhibitions, however, need not be separately treated, for in all respects they seem similar to the S_2 inhibition.

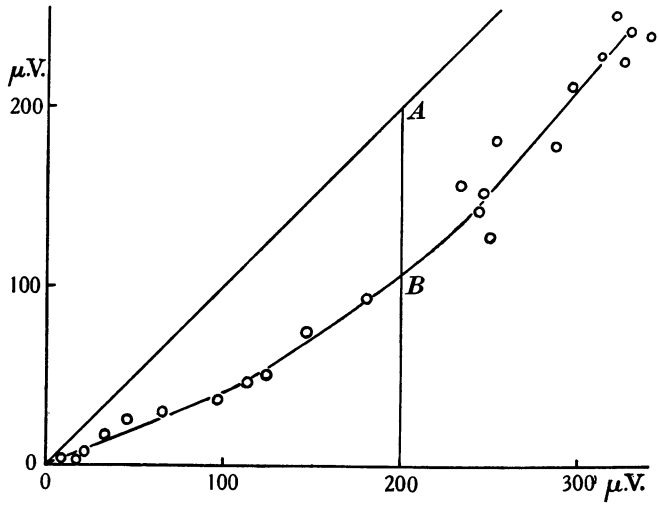
When the first volley is set up in one branch of the annulus Vieussens, the response to a later volley in the other branch also suffers an inhibition exactly comparable with that obtaining with both volleys either in the whole preganglionic trunk or in either of the branches of the annulus. This confirms the above conclusion that at such long intervals the successive volleys do not significantly interfere during their preganglionic course. Further, it shows that there is no selectivity in the distribution to the ganglion cells of the excitatory and inhibitory fibres of one branch of the annulus, *i.e.* the field of ganglion cells excited by one branch of the preganglionic trunk is not singled out for a selective inhibition or freedom from inhibition by the inhibitory fibres in that or the other branch.

H. *The effect of the size of the interacting volleys.*

Pl. II, fig. 8, shows part of a series of observations in which the size of the second volley was varied, both the first volley and the stimulus interval being kept constant. It will be seen that the relative inhibitory effect decreases as the second volley increases, but there is still a considerable inhibition of the response to a maximal volley. In Text-fig. 10 the S_2 potential of each inhibited response is plotted against that of the corresponding uninhibited second response for the whole series of observations. In order to avoid interference by the S_1 wave, the size of the S_2 wave is measured from its crest to the trough of its diphasic artefact.

Such measurements must give a fair approximation to the relative numbers of S_2 ganglion cells discharging impulses, for inhibition does not alter appreciably the temporal dispersion of the S_2 wave, though in some experiments there is a slight lengthening of synaptic delay.

As the uninhibited second response in Text-fig. 10 decreases from its maximal value, there is a slight increase of the absolute amount of inhibition (measured by the distance in the direction of the ordinates



Text-fig. 10. The S_2 potentials of responses to preganglionic stimuli of varying strengths are plotted as abscissae against as ordinates the corresponding potentials of the S_2 responses after partial inhibition by a maximal preganglionic stimulus applied 213 msec. previously. The amount of inhibition for any response is given on the corresponding ordinate by the intercept between the curve and the line drawn at 45° from the zero origin, *e.g.* an S_2 response of 200 μV is inhibited by the amount AB equal to about 93 μV.

between the curve and the line at 45° from the zero origin), and it is not until the uninhibited response becomes less than half maximal that the inhibition begins to decrease. In some experiments there is a much larger increase in inhibition as the uninhibited response decreases from maximal. This indicates that many ganglion cells whose responses to a small second volley are prevented by inhibition must discharge impulses in spite of this same inhibition when they are excited by a large second volley. In these ganglion cells the prevention of discharge by inhibition must depend on the intensity of their excitation, and this intensity of excitation must increase with the size of

the preganglionic volley, *i.e.* there must be a convergence of many preganglionic fibres on to those ganglion cells—confirming the conclusion already drawn. In the spinal flexor reflex the prevention of the reflex discharge of motoneurones by inhibition also depends on the intensity of their excitation [Eccles and Sherrington, 1931 *d*].

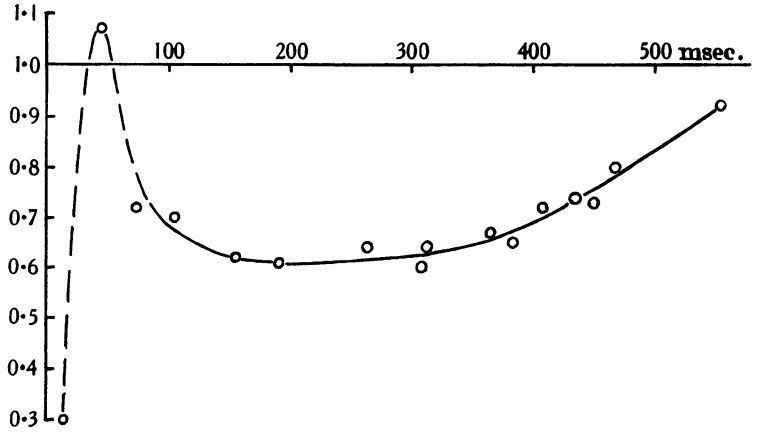
In Text-fig. 10 the points for very small responses lie about a straight line from the zero origin, *i.e.* the relative amount of inhibition is constant, even the smallest responses not being completely inhibited. This suggests that the effective action of the inhibition is confined to a fraction of the S_2 ganglion cells, *i.e.* there is a selectivity in the distribution of the inhibition corresponding to that described for the flexor motoneurones [Creed and Eccles, 1928; Eccles and Sherrington, 1931 *d*].

I. *Threshold of inhibitory fibres.*

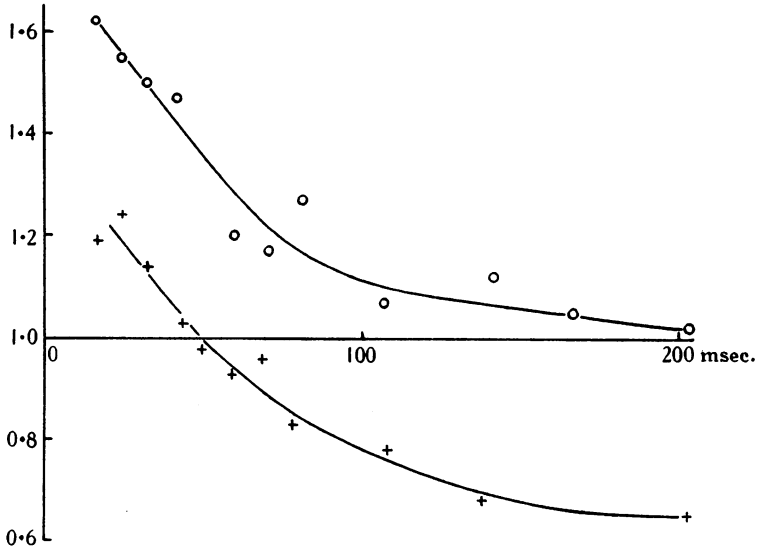
Pl. III, fig. 9, shows a series of postganglionic action potentials in which the strength of the first stimulus is varied, the size of the second volley and the stimulus interval being kept constant at conditions practically optimal for inhibition. As the strength of the first stimulus is weakened, the inhibition decreases, and with the weakest stimulus (observation 4) there is no inhibition. It will be seen that in Pl. III, fig. 9, there is a close correspondence between the thresholds of the inhibitory and excitatory S_2 fibres. This has also been observed in the other four experiments in which inhibitory thresholds have been investigated. When S_1 inhibitory fibres are present their threshold is lower than for S_2, but may not be so low as the S_1 excitatory threshold.

J. *Time course of the inhibition.*

Text-fig. 11 shows a typical inhibitory curve which has been constructed from the series of observations partly shown in Pl. II, fig. 7. Each point represents an observation, the intervals being abscissæ and the ordinates the inhibited responses expressed as fractions of the average normal response. A curve such as Text-fig. 11 must, however, not be taken to represent accurately the average time course of the c.i.s. of the ganglion cells. Just as with the facilitation curve and c.e.s. the time course is related statistically to this inhibitory curve and sufficiently well indicated by it for ordinary purposes. The inhibition reaches a maximum at about 200 msec. and has almost passed off at about 600 msec. It is



Text-fig. 11. A submaximal preganglionic stimulus is applied at various intervals after a maximal stimulus, and the S_2 potentials of the ganglionic responses (expressed as fractions of the S_2 potential for the second response alone) are plotted against the corresponding stimulus intervals.



Text-fig. 12. The line for the crosses shows an S_2 inhibitory curve constructed as with Text-fig. 11, and the line through the circles an S_1 facilitation curve constructed as with Text-fig. 2.

thus slower than the inhibitory curves expressing the time course of the inhibition of the spinal flexor reflex [Eccles and Sherrington, 1931 *d*]. At 45 msec. the second response is actually greater than normal, but at

12 msec. it is very small, an effect presumably due to the relatively refractory state set up in the ganglion cells by their response to the first volley. In some experiments the relatively refractory state of the ganglion cells overlaps with the later inhibitory effect.

However, at these short intervals facilitation is a complicating factor. When the second volley is small, a curve constructed as in Text-fig. 11 is often considerably above 1·0 at short intervals and only descends below this value, *i.e.* inhibition only becomes apparent, at intervals of 50 msec. or even longer (Text-fig. 12). The possibility must be considered that facilitation is still present when submerged below a preponderating inhibition, *e.g.* the descending part of the inhibitory curve in Text-fig. 11 may be largely if not entirely due to a passing off of this submerged facilitation, and not to a progressive increase in the inhibition. This possibility receives support from a comparison in the same experiment between the pure facilitation curves for S_1 and the inhibitory curves for S_2 (Text-fig. 12). It is seen that, if the facilitation of S_2 lasted as long as that for S_1, it would afford an explanation of the whole of this descending phase, provided that the time course of the c.e.s. was not interfered with by the co-existing c.i.s. Thus the possibility is envisaged that the c.e.s. and the c.i.s. of a ganglion cell have an independent existence and only interact through their opposing effects on the discharge of impulses by that cell (see section L).

K. *The interaction between the inhibitory and excitatory effects of two successive volleys.*

The interaction of the effects of two volleys is tested by a third volley, and it is best illustrated by observations in which the first and second volleys are large so as to produce a maximum inhibitory effect and the third volley is of such a size as to suffer a large inhibition. Probably the simplest conditions are provided by a series of observations in which the interval between the first and third volleys is kept constant at a value longer than the interval for maximum inhibition, *e.g.* at 200 msec., the position of the second volley being varied relative to them. Under such conditions the first volley has a purely inhibitory effect on the response to the third volley, for the interval is sufficiently long for complete disappearance of the c.e.s.

If the second volley is close to the first volley, *e.g.* within 50 msec., the inhibition of the third volley is greater than with either the first or second volleys alone. This occurs even when the first and second volleys have been set up by similar stimuli applied through the same electrodes

(Pl. III, fig. 10, cf. observations 1 and 4 with 2 and 3). There must therefore be a summation of the c.i.s. produced by successive impulses in the same inhibitory fibres, *i.e.* by successive impulses incident on the same inhibitory synapses. This summation of the c.i.s. of individual ganglion cells shows that different grades of c.i.s. may exist on a ganglion cell just as with a motoneurone [Eccles and Sherrington, 1931 *d*]. The increased inhibition produced by a larger inhibiting volley would be due to an increase in the c.i.s. of some ganglion cells from a latent to an effective intensity.

The combined inhibitory effect of two maximal volleys is always much less than the sum of the separate inhibitory effects. However, as shown in Table I, this apparent occlusion becomes less as the stimuli are

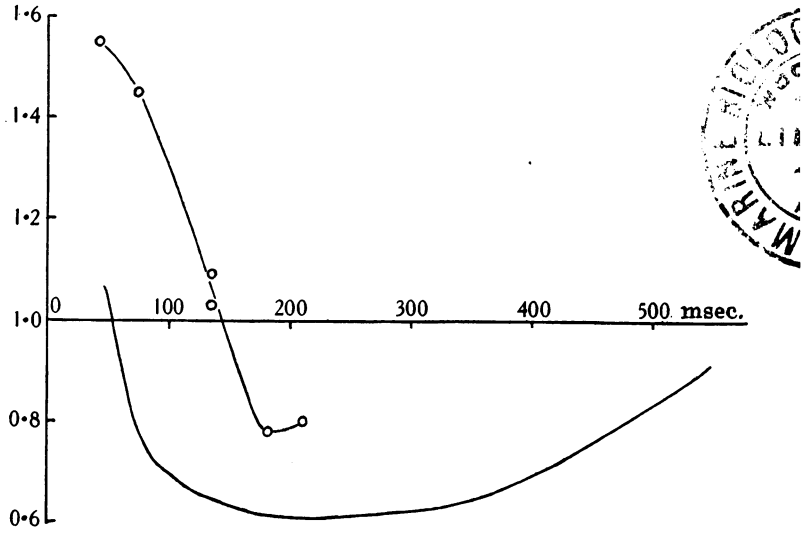
TABLE I. All amounts of inhibition are expressed as a fraction of the average response to the third stimulus alone, its strength being constant at 10·0 arbitrary units.

1	2	3	4
Strength of first and second stimuli in arbitrary units	Inhibition of third response by first volley only	Inhibition of third response by second volley only	Inhibition of third response by first and second volleys
33·3	0·39	0·36	0·50
	0·37	0·43	0·57
10·0	0·20	0·24	0·46
		0·23	0·41
7·7	0·18	0·16	0·39
	0·09	0·13	0·30
			0·33

weakened and may even pass over to a combined inhibitory effect greater than summation, the average value of column 4 being greater than the sum of columns 2 and 3 at a strength of 7·7. Such an increased inhibitory effect is well shown for S_1 (*sic*) inhibition in Pl. III, fig. 10, observations 1 and 4 being compared with 2 and 3. But in interpreting such results it must be remembered that the intensity of c.i.s. in any particular ganglion cell is not directly related to the amount of the inhibition so recorded, *i.e.* to the number of ganglion cells prevented from discharging by the inhibition. For example, the above results with maximal volleys do not prove that the second volley adds less c.i.s. to that produced by the first volley than is produced by it alone. Rather do they suggest that with maximal volleys further extension of the inhibition by summation is limited on account of the selectivity in the distribution of the inhibitory effect on the ganglion cells (cf. section H).

As the second volley is progressively moved nearer to the third volley, the combined inhibitory effect diminishes, and eventually it becomes less than the inhibitory effect of the first volley alone (cf. observations

3 and 5, Pl. III, fig. 10). The averaged results for the whole series of observations are shown in Text-fig. 13. Thus for intervals less than 150 msec. the second volley protects the response to the third volley from the inhibitory effect of the first volley. This happens when all three volleys are set up by stimuli applied through the same electrodes, or when any one of the volleys is set up in one branch of the annulus Vieussens and the other two in the other branch. It must therefore be due to an interaction of the effects of the volleys on the ganglion cells.



Text-fig. 13. The lower line is the inhibitory curve when the second volley alone precedes the third by various intervals (cf. Text-fig. 11). Each circle shows the average potential of the response to the third volley expressed as a fraction of the potential to that volley when preceded by the first alone, the abscissa being the interval between the second and third volleys. The interval between the first and third volleys was constant at 232 msec.

The two possible ways in which this interaction could occur will be considered later in the light of further evidence (section L). Thus either

(*a*) the excitatory impulses of the second volley remove some of that c.i.s. which was set up by the first volley and which inhibited the response to the third volley [cf. Eccles and Sherrington, 1931 *d*], or

(*b*) the excitatory impulses of the second volley produce c.e.s which, persisting until the time of the third volley, would facilitate the response to it with the result that some ganglion cells discharge impulses which otherwise would be inhibited by the first volley.

If a long interval, *e.g.* 400 msec., separates the first and third volleys, and if the second volley be introduced approximately midway between them, the inhibition by the combined first and second volleys is less than that produced by the second alone (compare observations 1 and 3 with 2 and 6, Pl. III, fig. 11). The first volley has in some way diminished the inhibitory effect of the second. This effect of the first volley may be observed even if it precedes the second by intervals as long as 500 msec. The effect of the excitatory impulses of the second volley does not therefore provide a complete explanation of the effect of the second volley on the inhibition produced by the first volley.

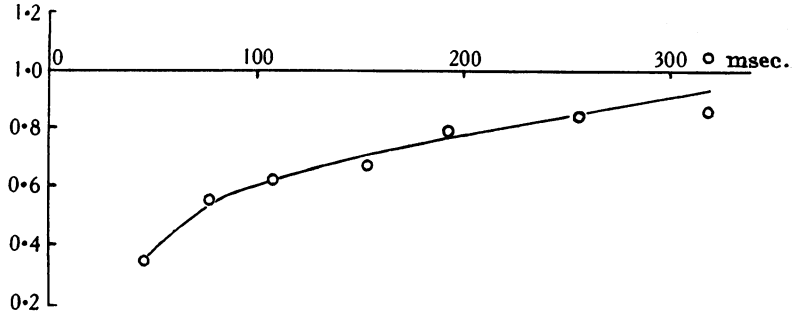
A similar conclusion is also suggested by Text-fig. 13. When the second volley alone precedes the third, its facilitating effect is much smaller and shorter in duration than when it protects the third from the inhibition of the first volley. Even if allowance be made for the occlusion of the inhibitory effect of the second volley, there is still an obvious discrepancy. Thus the first volley has increased the exciting effect of the second volley and diminished its inhibitory effect, actions which probably are attributable to the reaction of the ganglion cells to the continued inhibition produced by the first volley. Such a reaction of the ganglion cells would be analogous to the anelectrotonic and katelectrotonic states of nerve [cf. Erlanger and Blair, 1931]. However, the inhibitory effect of the first volley presumably acts more directly as well, for it prevents the second volley from setting up the discharge of some ganglion cells, and hence from section E an increased c.e.s. of these ganglion cells should be produced by the second volley.

L. *The action of drugs on inhibition.*

The effect of small doses of nicotine, *e.g.* painting the ganglion with 0·005 p.c., or injecting intravenously 0·2 mg. per kg. body weight, varies in different experiments. In some the inhibitory effect is diminished, and the inhibitory curve shortened in duration, but its general shape is unaltered. Most experiments lie between this type and the other extreme type in which a suitable dose of nicotine, while not greatly altering the total duration of the inhibitory curve, removes entirely all trace of the phase of increasing inhibition (Text-fig. 14). The maximum inhibition, which may be increased, now follows directly on from the refractory period, the decline of the inhibition commencing at the shortest intervals, but continuing at long intervals so as to coincide approximately with

the original inhibitory curve. Larger doses of nicotine shorten the duration of the inhibitory curve (Pl. III, fig. 12), and all inhibitory effect may pass off as soon as 100 msec. after a volley. Still larger doses of nicotine always remove all trace of inhibition.

Now the dose of nicotine which removes the phase of increasing S_2 inhibition also removes the S_1 facilitation and also any S_2 facilitation which may appear above the background inhibition (section B). It is therefore suggested that this dose of nicotine removes only the c.e.s. of the S_2 ganglion cells leaving the c.i.s. to run its course uncomplicated, as it normally is, by this c.e.s. This suggested absence of an effect of such doses of nicotine on the c.i.s. is supported by the relatively unchanged state of the last part of the inhibitory curve. As shown in Text-fig. 14

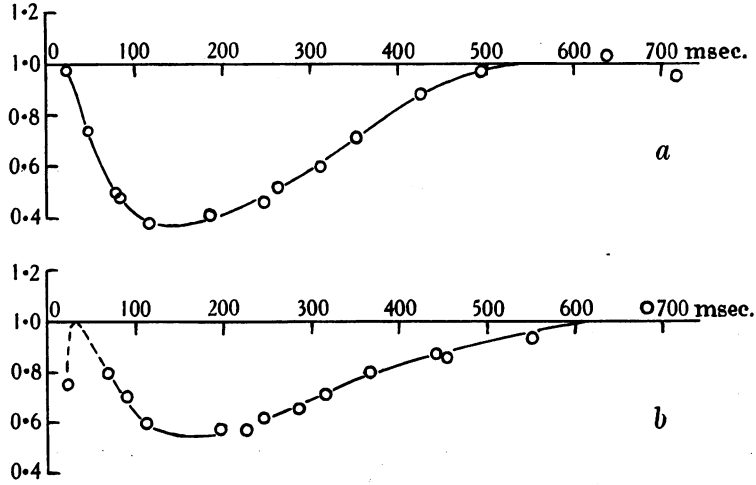


Text-fig. 14. Inhibitory curve as in Text-fig. 11, but in another experiment and approximately 10 min. after painting the ganglion with 1 in 5000 nicotine.

this c.i.s. would normally be at a maximum probably as soon as the end of the refractory period, a progressive decline ensuing from then onwards. The normally complicating c.e.s. (S_2) also would be maximal at a very short interval, and in most experiments then approximately balances the c.i.s.; but its decline is more rapid, hence the phase of increasing inhibition, the decline in the c.i.s. only becoming apparent when most of the c.e.s. has disappeared.

According to this explanation the different effects of nicotine in different experiments are due to differences in the relative sensitivities of c.e.s. and c.i.s. to its action. At one extreme experimental observations show that they are equally sensitive, and at the other c.i.s. is unaffected by a dose of nicotine totally removing the c.e.s. The explanation of the composite nature of the inhibitory curve also removes the difficulty that otherwise arises in explaining the production by a single volley of an inhibitory effect which increases for as long as 150 msec.,

for it now seems probable that the maximal inhibitory effect is exerted with no more delay than the maximal excitatory effect. Moreover, the explanation presupposes that the c.e.s. and c.i.s. of a ganglion cell exist independently of each other and only interact by their opposite effects on the discharge of impulses by that cell (cf. section J). It therefore conforms with the second explanation suggested in section K for the interaction of the excitatory and inhibitory effects of two successive volleys.



Text-fig. 15. *a*, Inhibitory curve as in Text-fig. 11, but in another experiment. *b*, Inhibitory curve a few minutes after Text-fig. 15 *a*, 0·75 mg. eserine suphate having been injected intravenously immediately after Text-fig. 15 *a*.

With the ipselateral spinal reflex the phase of increasing inhibition (lasting 40–90 msec. after a single volley) was regarded by Eccles and Sherrington [1931 *d*] as being due to a progressively increasing c.i.s., for it seemed too long to be explained as a diminishing c.e.s. However, it must be remembered that contralateral volleys were used for inhibition, and the above results suggest that the production of c.e.s. is greatly increased by a pre-existent inhibition. If the phase of increasing inhibition is due to the diminution of a complicating c.e.s., then the experiments on the interaction of excitatory and inhibitory volleys also need reinterpretation, for it was thought that c.e.s. could not persist sufficiently long (75 msec.) to explain the diminished inhibition produced by an interpolated excitatory volley. The direct interaction of c.e.s. and

c.i.s. may, therefore, be regarded as not proven, the experiments alternatively being explained, as with the ganglion cell, by the opposite effects on the neurones of the independently existing c.e.s. and c.i.s.

Text-fig. 15 shows that an intravenous injection of 0·3 mg. of eserine per kg. is without significant effect on the inhibitory curve, and similar results have been obtained in all such series of observations. Painting the ganglion with 1 in 5000 strychnine is also without effect on inhibition, as also is nembutal anæsthesia produced by injecting intraperitoneally 40 mg. nembutal per kg. body weight.

Discussion.

Histological investigation of the superior cervical ganglion shows that the fine terminal branches of the preganglionic fibres ramify in intimate relationship with the dendritic processes and the perikarya of the ganglion cells, there apparently being no continuity [de Castro, 1932; Heusner, 1935]. According to de Castro some of the preganglionic fibres end as small loops (boutons) similar to those occurring in the central nervous system, but it is doubtful if they are the usual form of ending [Heusner]. Moreover, degeneration of the preganglionic fibres does not produce any perceptible changes in the ganglion cells [Ranson and Billingsley, 1918; de Castro, 1932; Heusner, 1935], so the relation between the preganglionic fibres and the ganglion cells seems similar to that occurring at the bouton endings in the central nervous system [cf. Hoff, 1933]. Degeneration of the preganglionic trunk removes all the close meshwork of fibres which normally are in intimate relationship with the dendrites and perikarya of the ganglion cells, only the dendrites and postganglionic axons being left, hence it has been concluded that there are no internuncial neurones in the superior cervical ganglion [Ranson and Billingsley, 1918; Heusner, 1935], *i.e.* there is one synapse and one synapse only in every path through the ganglion.

The results obtained in a later paper confirm Bishop and Heinbecker [1932] and Brown [1934] in showing that antidromic impulses in the postganglionic fibres never pass into the preganglionic trunk. Irreversibility of conduction, which characterizes synapses, appears to occur between all preganglionic-postganglionic connections of the superior cervical ganglion. That a synapse occurs in every path through the ganglion is further shown by a delay, though short, being present in the transmission of all impulses (the synaptic delay).

Thus the physiological evidence is in agreement with the histological and in some respects it goes further, for it shows that several preganglionic fibres converge on to each ganglion cell, and that some of these fibres are inhibitory. Physiological investigation provides no direct proof of the existence of only one synapse in every pathway through the ganglion, but it indirectly supports this conclusion, for it reveals a directness of transmission through the ganglion. However, the ganglion must, nevertheless, be regarded as a co-ordinating centre as well as a transmitting and distributing station. It functions as an outlying part of the central nervous system, and the preganglionic fibres are the extended axons of internuncial neurones transmitting excitatory and inhibitory impulses to the ganglion cells, which themselves are the neurones of the final common path.

Though there is an overlapping distribution of these preganglionic fibres on the ganglion cells, the physiological evidence suggests that this does not occur beyond the confines of any particular group of cells, *e.g.* the S_1 preganglionic fibres and ganglion cells seem to constitute a system functionally distinct from the S_2 group [Eccles, 1935]. This also appears to happen with the inhibitory fibres, for in many experiments inhibition is absolutely confined to the S_2 ganglion cells. It has not been possible to determine if some of the terminals of a single preganglionic fibre are excitatory in function and others inhibitory. However, threshold determinations show that the fibres inhibitory for the S_2 ganglion cells could be excitatory for no ganglion cells other than those of this same group. It does not seem likely that such a wasteful antagonism would occur within one relatively homogeneous group, for Bishop and Heinbecker state that this group comprises the vaso-constrictor and the pilomotor fibres—two groups which functionally are closely related.

The overlapping distribution of the preganglionic fibres on the ganglion cells must result in some loss in the discriminative control which the central nervous system is potentially capable of exercising over the peripheral field of distribution of the postganglionic fibres. This loss probably has no physiological importance, for as pointed out by Cannon [1929] the sympathetic shows very little localization in its action.

The inhibitory impulses to the S_2 ganglion cells would have the effect of diminishing the normal discharge of vaso-constrictor impulses from these cells. It, therefore, seems probable that functionally these inhibitory impulses form part of the mechanism for inhibition of vaso-

constrictor tone, and for example are set up reflexly by centripetal impulses in the depressor and carotid sinus nerves.

Though exceptions appear to be provided by those ganglion cells which seem to be excited to discharge by single preganglionic impulses, the following general picture may be formed of the functioning of a ganglion cell under normal conditions in the body. It is subjected to a rhythmic bombardment of impulses along some or all of the preganglionic fibres incident on it. This rhythmic bombardment of each fibre will probably differ both in frequency and in phase from others, and some will be excitatory, others inhibitory. On account of the persisting excitatory and inhibitory states of the ganglion cell which are thus set up, this confused bombardment will become fused out to an undulating excitatory or inhibitory condition, and the ganglion cell will discharge an impulse down its axon, the postganglionic fibre, whenever the excitatory condition attains a certain intensity. The way in which impulses set up these excitatory and inhibitory states, c.e.s. and c.i.s., their nature, and their relation to the ganglion cell will be considered in later papers.

Summary.

Besides producing a discharge of impulses from some ganglion cells, a submaximal preganglionic volley sets up in both these and other ganglion cells an excitatory condition which increases the response to a subsequent submaximal volley (spatial facilitation of subliminal fringe) and shortens its synaptic delay (temporal facilitation). With S_1 ganglion cells this facilitating effect persists for about 150 msec., but with S_2 ganglion cells it is less in extent and duration presumably on account of the simultaneous presence of inhibition.

Facilitation is also observed after a maximal volley or between volleys in different groups of preganglionic fibres. Spatial facilitation usually undergoes a relative increase as the preganglionic volleys become smaller, and facilitated responses occur even when each volley alone is subliminal, indicating that a single preganglionic impulse fails to set up a discharge from any ganglion cells.

The facilitating effect of a variable first preganglionic volley on a constant second volley becomes greater as the first volley increases up to the size of the second, but is usually not altered by further increase of the first volley, a result suggesting that the c.e.s. of a ganglion cell is diminished when that ganglion cell discharges an impulse.

Facilitation is unaffected by eserine or anæsthetics, but is abolished

by doses of nicotine too small to affect the transmission of impulses through the ganglion.

In addition to this facilitating effect a preganglionic volley also has an inhibitory action largely confined to S_2 ganglion cells, which reaches its maximum in about 150 msec. and completely passes off at about 600 msec. Within limits this inhibition increases both absolutely and relatively as the second (inhibited) volley is made smaller, showing that the less the excitation of a ganglion cell the easier it is to inhibit. The preganglionic fibres inhibiting and exciting S_2 ganglion cells have identical thresholds.

Two inhibiting volleys at a short interval apart have a greater inhibitory effect than either one alone, though there is a considerable "occlusion" if the volleys are large. However, if the second volley is at a longer interval after the first, there is a diminution of the first's inhibitory effect for as long as 150 msec., an effect probably attributable to the reaction of the ganglion cells to the inhibition of the first volley, whereby the opposing excitation of the second volley is increased and prolonged and its inhibition decreased.

Doses of nicotine too small to prevent transmission of impulses may prevent an inhibitory effect from being produced. Still smaller doses of nicotine serve for analysis of the overlapping excitatory and inhibitory effects set up by a preganglionic volley, for the inhibitory effect then set up in the absence of complicating facilitation is at a maximum at least as soon as the end of the refractory period. This suggests that the normal phase of increasing inhibition is really due to the more rapid decrease of the opposing facilitation.

These excitatory and inhibitory states of ganglion cells resemble the corresponding states, c.e.s. and c.i.s., of the spinal cord, and show that the superior cervical ganglion must be regarded as a coordinating centre as well as a transmitting and distributing station.

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EXPLANATION OF PLATES I–III.

PLATE I.

Fig. 1. Action potentials of superior cervical ganglion (S_1 only) evoked by two similar submaximal stimuli applied to the cervical sympathetic at various intervals apart. Observations 3 and 7 show the response to the second stimulus alone. In this and all subsequent records 1 d.v. = 10 msec.

Fig. 2. As in Fig. 1 in another experiment. Observation 4 shows the response to the second stimulus alone.

Fig. 3. As in Fig. 1, but the first stimulus is maximal and the earthed lead has been moved from the ganglion to the postganglionic trunk. Observation 6 shows the response to the second stimulus alone. Each second stimulus is marked by an arrow.

Fig. 4. As in Fig. 1, but the stimuli are so weak that either alone fails to set up a detectable response, observation 4 showing this for the second stimulus. At the longest stimulus interval (observation 1) the second stimulus also evokes no response, but at the next shortest interval (observation 2) there is a small response, and this increases with further shortening of the interval. Each second stimulus is marked by an arrow.

PLATE II.

Fig. 5. Postganglionic action potentials evoked by two preganglionic stimuli at 40 msec. interval, the strength of the second being constant at 4·0 arbitrary units (observations 1 and 6 show the response to the second alone), and the first varied as follows: observation 2, 5·4; 3, 4·0; 4, 4·25; 5, 8·3; 7, 2·5; and 8, 2·8.

Fig. 6. A series of ganglionic action potentials similar to Pl. I, fig. 1, showing facilitation of the second response (compare observations 2 and 4 with observations 1 and 3). Observations 5–8 were obtained immediately after painting the ganglion with 0·01 p.c. nicotine.

Fig. 7. Postganglionic action potentials evoked by two preganglionic stimuli at various intervals, the second alone being submaximal for S_2 (observation 7). Inhibition of the S_2 spike is seen in all observations but the first. In this observation the S_1 and S_2 spikes are indicated by the corresponding numerals.

Fig. 8. As in Fig. 7, but the stimulus interval (213 msec.) and the first stimulus (50 arbitrary units) are constant, and the strength of the second stimulus is varied, being for observations 1 and 2, 12·5; for 3 and 4, 16·7; for 5 and 6, 33·3. Observations 1, 3 and 5 show the response to the second stimulus alone at the various strengths.

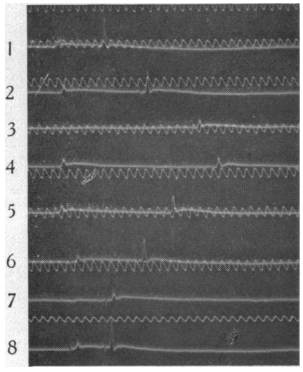
PLATE III.

Fig. 9. As in Fig. 7, but the stimulus interval (200 msec.) and the second stimulus (cf. observation 5) are constant, and the first stimulus is varied, its strength being for observation 1, 50; for 2, 20; for 3, 16·7; for 4, 12·5.

Fig. 10. Observations 1, 4 and 5 show postganglionic action potentials evoked by three preganglionic stimuli, observation 2 showing the second and third, observation 3 the first and third, and observation 6 the third alone. The first stimuli are maximal for S_2, the third submaximal. With observations 1 and 4 the first and second stimuli are at an interval of 14 msec., and with observation 5 at 152 msec.

Fig. 11. As in Fig. 10, but with longer intervals between the three stimuli.

Fig. 12. As in Fig. 7, but showing ganglionic action potentials after painting the ganglion with 0·02 p.c. nicotine which removes the stage of increasing inhibition.



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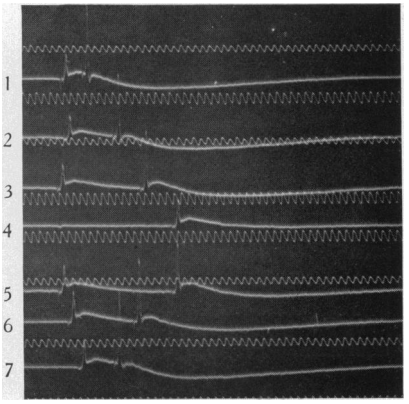

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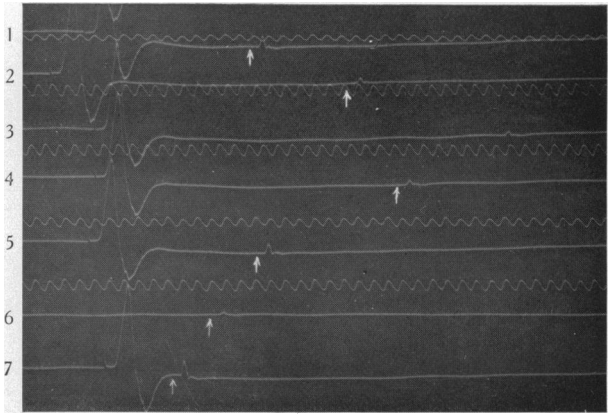

Fig. 3.

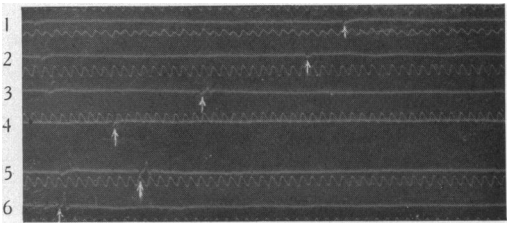

Fig. 4.

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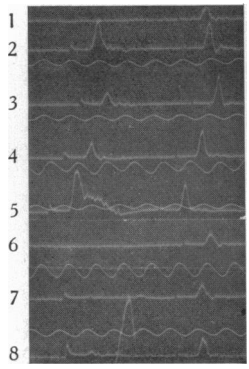
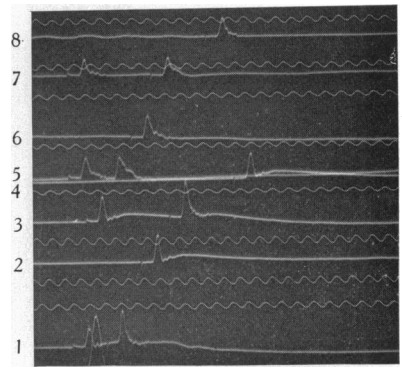


Fig. 5.



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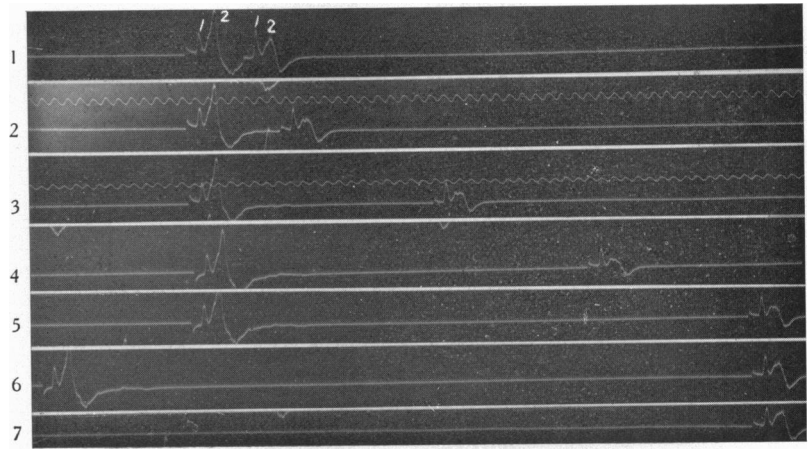


Fig. 7.

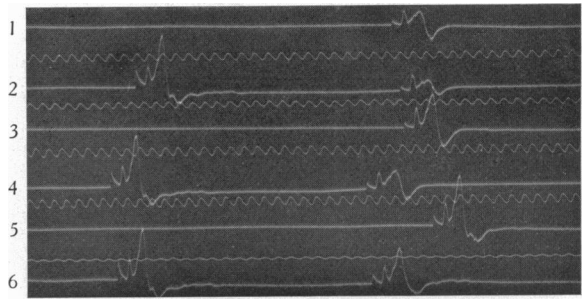
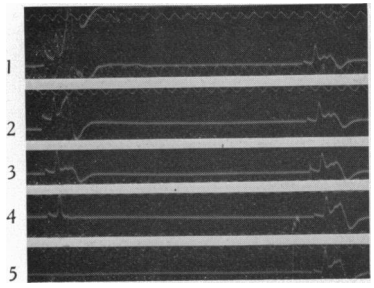


Fig. 8.



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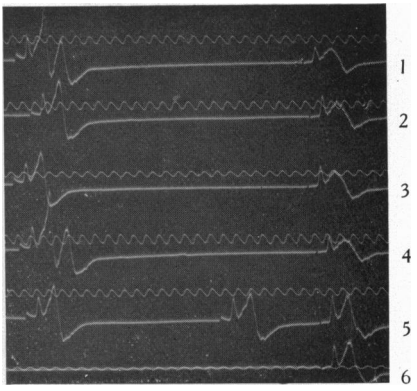

Fig. 10.

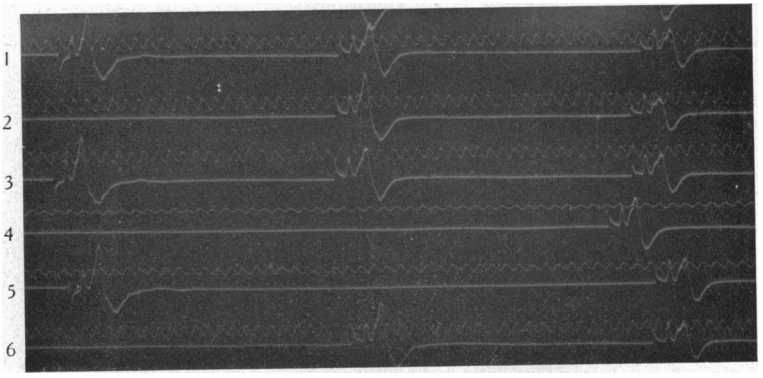

Fig. 11.

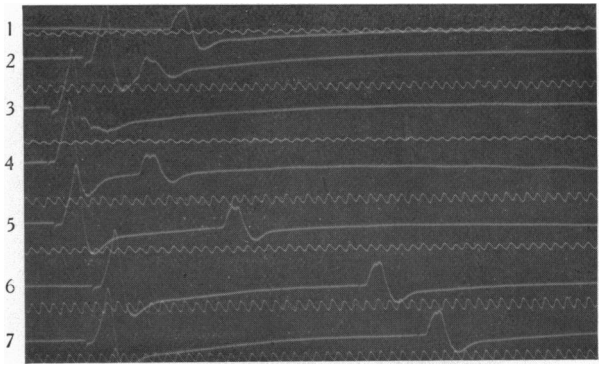

Fig. 12.