

## THE SYMPATHETIC INNERVATION OF THE STOMACH.

### III. The interaction of the vagus and sympathetic nerves.

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IN previous papers by McSwiney and Robson [1929 *a* and *b*; 1931], preparations of isolated strips of smooth muscle of the stomach and small intestine innervated by vagus and sympathetic nerves have been described. It was shown that the reaction of gastric muscle to stimulation of periarterial nerves depended on the type of stimulation employed. Stimulation of the nerves with a faradic current for short intervals or with frequencies of one to twelve break induction shocks per second usually caused contraction of the muscle: with twenty to fifty shocks per second relaxation was usually obtained. Evidence was put forward to show that the motor and inhibitor responses were due to stimulation of fibres conveyed in the periarterial sympathetic network.

Brown, McSwiney and Wadge [1930] have also demonstrated that contraction and relaxation of the stomach may be obtained in the spinal and decerebrate animal on stimulation of the thoracic sympathetic trunk. The effects on the stomach depended on the type of stimulation employed. Stimulation at a frequency of one per second caused contraction, while stimulation with a tetanizing current brought about relaxation.

Batelli [1896] and Oser [1892] have made qualitative observations on the relations between vagus and sympathetic stimulation in the intact stomach. They found that simultaneous stimulation of both vagus and splanchnic nerves reduced the effects of exciting the vagus. Oser observed that the vagus action first appeared. If, however, in place of simultaneous stimulation the splanchnics were stimulated so that inhibition was predominant, then a vagus effect was difficult to obtain. McCrea and McSwiney [1928] also noted that vagus responses are much diminished after splanchnic stimulation.

This paper deals with the effects of stimulation of the vagus and

periarterial nerves supplying isolated smooth muscle preparations, and demonstrates first the sympathetic response during vagus stimulation, and, secondly, the inhibitory action of the sympathetic on the vagus response.

#### METHOD.

The nerve muscle preparation was dissected from the cat, as previously described [McSwiney and Robson, 1931]. The preparation was placed in a bath of Ringer-Locke solution maintained at 37° C., bubbling and hydrogen-ion concentration being kept constant.

Records were made on smoked paper. A Lewis contact breaker and induction coil were used, and the rate of stimulation varied from one break shock in 2 seconds to fifty make and break shocks per second. The duration of the stimulus was regulated by an oil dash pot. The optimum intensity of stimulation was determined for each preparation at the commencement of the experiment.

#### EXPERIMENTAL RESULTS.

Preliminary experiments were undertaken to investigate the effect of sympathetic stimulation during a period of vagus excitation. It was found that, under certain conditions, reversal of the sympathetic response was recorded. This effect is demonstrated in the following experiment. Stimulation of the periarterial nerves, using a frequency of twelve break shocks per second, caused contraction. The vagus nerve was then stimulated to produce a sustained contraction. During the course of the sustained contraction, the periarterial nerves were stimulated, using the same frequency of stimuli as before. Under these conditions, reversal of the response was observed, as instead of the muscle contracting, marked relaxation occurred (Fig. 1). It is interesting to note the similarity between these results and the effects previously recorded by Brown and McSwiney [1926] and McSwiney and Brown [1926] with adrenaline.

It has previously been suggested that the inhibitor response depends on the tone of the muscle, but the relaxation obtained on stimulation of the periarterial nerves, which is demonstrated in Fig. 1, does not appear to be dependent on the length of the muscle. Stimulation of the periarterial nerves was first observed to cause a contraction. The vagus nerve was then stimulated to produce a sustained contraction. As excitation of the vagus was continued, the contraction gradually decreased through apparent fatigue, and the muscle relaxed to its original length. After the lever had reached a steady base line the

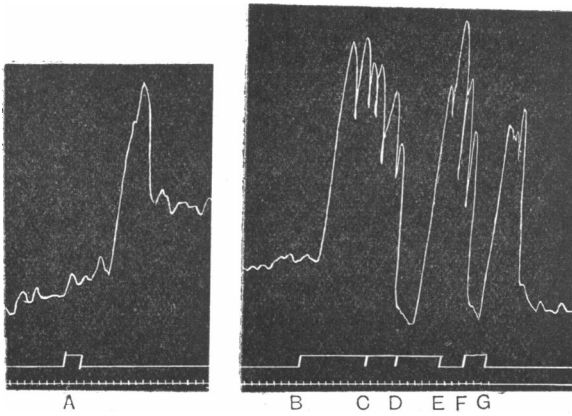


Fig. 1. Cat fundus. A, stimulation of periarterial nerves twelve shocks per sec. BE, faradic stimulation of vagus nerve. CD, stimulation of periarterial nerves twelve shocks per sec. FG, same as CD. Time intervals = 10 secs.

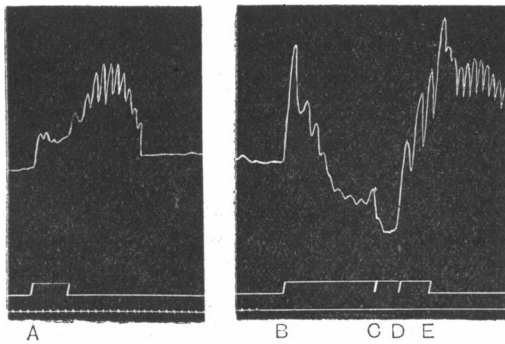


Fig. 2.

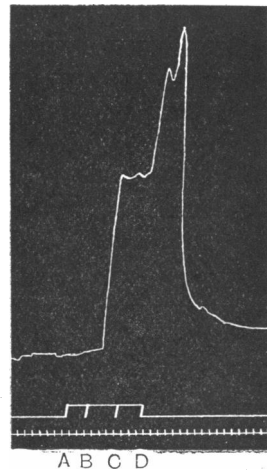


Fig. 3.

Fig. 2. Cat fundus. A, faradic stimulation of periarterial nerves. BE, stimulation of vagus nerves four shocks per sec. CD, faradic stimulation of periarterial nerves. Time intervals = 10 secs.

Fig. 3. Cat fundus. AC, faradic stimulation of periarterial nerves. BD, stimulation of vague nerves four shocks per sec. Time intervals = 10 secs.

periarterial nerves were stimulated, and relaxation was recorded: on cessation of periarterial nerve stimulation, the muscle again contracted (Fig. 2).

It would therefore appear that vagus stimulation may influence the response of the muscle to excitation of the periarterial nerves. This suggestion is confirmed in the following experiment, where the effect is strikingly shown. The periarterial nerves were stimulated using induction shocks too few in number to cause a contraction. (The frequency of stimuli used varied in different experiments: in fact with some preparations faradic stimulation was used.) On repeating the stimulation during the contraction following vagus stimulation, the periarterial stimulus became effective, and relaxation followed.

Experiments were then made to demonstrate the effect of stimulation of the periarterial nerves on the response of the muscle to vagus stimulation, and it was possible to show that excitation of the periarterial nerves inhibited the normal vagus response. The periarterial nerves were first stimulated. During periarterial stimulation the vagus nerve was also stimulated, and the muscle contracted. After a period of simultaneous stimulation the periarterial stimulation was cut off, vagus stimulation alone being maintained. On cessation of the periarterial stimulation an inhibitory effect was removed, as a further contraction of the muscle was recorded (Fig. 3).

In view of these findings, it was decided to determine quantitatively the effect of a short period of periarterial nerve stimulation on the response of the muscle to single break shocks applied to the vagus nerve. It has been previously shown that when the periarterial nerves are stimulated with a faradic current for short intervals (0.1 to several seconds), a contraction of the muscle ensues after a latent period of some 5 to 6 seconds. A single break induction shock applied to the vagus nerve supplying the same strip of muscle produces a contraction with a latent period of approximately 0.7 second. When the periarterial and vagus nerves were stimulated simultaneously, the break shock applied to the vagus falling at the end of the short period of faradic stimulation of the periarterial nerves, the vagus response was greatly decreased or totally inhibited. If the muscle responded to vagus stimulation, contraction was recorded after the usual period of 0.7 second. The muscle then relaxed, and contraction was again recorded after a latent period of some 5 seconds, the latent period of the sympathetic response (Fig. 4).

Attention was then directed to the investigation of the duration of the inhibitory effect produced by stimulation of the periarterial nerves.

The periarterial nerves were stimulated for a definite period with a constant frequency of stimuli, and the vagus nerve was excited with a single break shock in a series of experiments before, during, and after the period of periarterial stimulation. By recording the response of the muscle to vagus excitation it has been possible to estimate the duration of the inhibitory period. The results are expressed diagrammatically in Fig. 5. The abscissa represents the time, and the ordinate the height of the vagus response expressed as a percentage of the contraction obtained in the absence of any sympathetic effect. During the period of periarterial nerve stimulation the response to excitation of the vagus

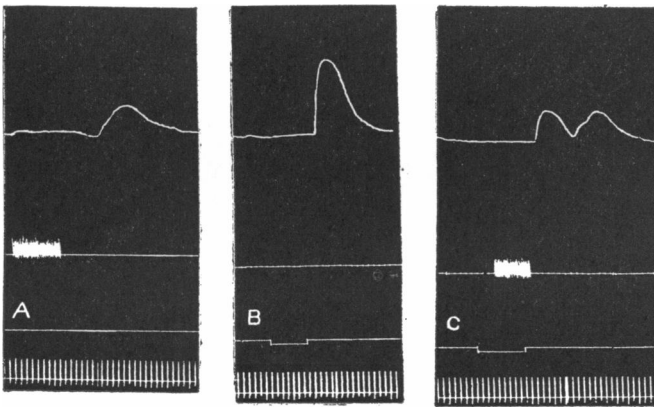


Fig. 4. Cat fundus. A, faradic stimulation of periarterial nerves for periods of 0.5 sec. B, stimulation of vagus nerve with single break shock. C, simultaneous stimulation of periarterial and vagus nerves. Upper signal marker displaced to left in A and C. Time intervals = 1 sec.

gradually decreased to a minimum. For a period following stimulation of the periarterial nerves the vagus response remained small or was absent. The inhibitory effect then decreased, and the contraction of the muscle gradually returned to its normal height.

These results demonstrate the average findings, but variations have been observed. In some experiments stimulation of the periarterial nerves at the rate of forty-five break induction shocks per second for a period of 0.2 second was sufficient to inhibit the vagus response for several seconds, while in other experiments stimulation at the same rate for several seconds did not completely inhibit the vagus response. It is of interest to note that if a single break shock applied to the vagus nerve at the end of a period of stimulation of the periarterial nerves was

ineffective, several stimuli in quick succession elicited a response. In the majority of experiments the vagus response regains its normal height within some 6 seconds after cessation of stimulation of the periarterial nerves. A vagus response may then summate with the contraction following stimulation of the periarterial nerves, producing a contraction greater than that caused by the stimulation of either nerve. In some experiments the inhibitory effect is more prolonged, and complete inhibition of the vagus response has been observed 14 seconds after cessation of a period of periarterial nerve stimulation lasting for 2 seconds.

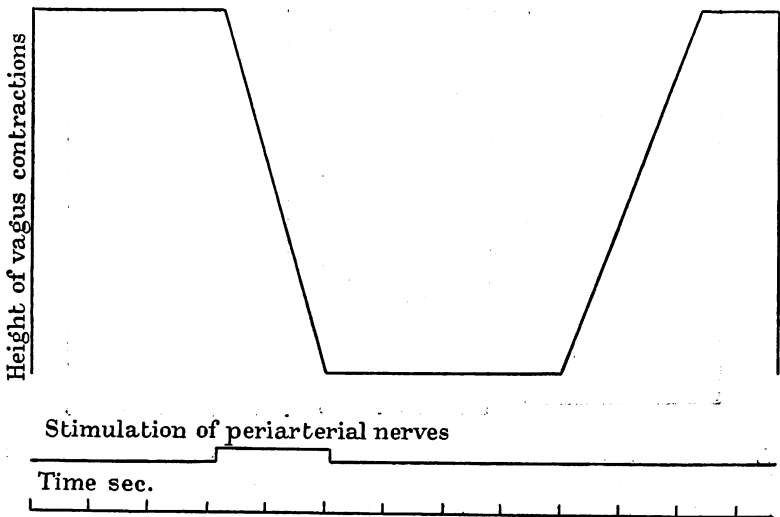


Fig. 5.

To obtain further information of the nature of the action, the effects of variation in the duration and frequency of stimulation of the periarterial nerves were investigated. The inhibitor effect on the vagus response of periarterial stimulation was found to increase as the frequency of stimulation increased. In one experiment, for example, the periarterial nerves were stimulated at the rate of one break shock a second: a single shock applied to the vagus at the end of the period of stimulation produced a response equivalent in height to some 60 p.c. of the normal vagus response. On increasing the rate of stimulation of the periarterial nerves to two break shocks a second, the vagus response was only 13 p.c. of the normal contraction, while, finally, with three break shocks a second, a single vagus excitation failed to elicit a response.

In another series of experiments the frequency of stimulation of the periarterial nerves was maintained constant, but the duration of stimulation was varied. The degree of inhibition of the vagus response increased as the duration of stimulation of the periarterial nerves was prolonged. On stimulation of the periarterial nerves at a rate of forty-five break shocks per second for a period of 0.34 second, the vagus response to a single break shock was only 58 p.c. of the normal response. With a period of stimulation of 0.47 second, the vagus response was decreased to 30 p.c., and finally after a period of 2 seconds a single break shock applied to the vagus nerve failed to elicit any response.

The increase in frequency and duration of periarterial nerve stimulation not only decreased the height of the vagus contraction, but also increased the period of effective inhibition. This effect is illustrated in the following experiment. The periarterial nerves were stimulated at the rate of six break shocks for a period of 2 seconds, and 4 seconds after cessation of the stimulation a single break shock produced a contraction 60 p.c. of the normal vagus response. On increasing the rate of stimulation of the periarterial nerves to forty-five shocks per second for 2 seconds, a single break shock applied 4 seconds later failed to elicit any response.

It would therefore appear that the sympathetic inhibitory phenomenon may be prolonged and increased in effectiveness as the number of stimuli per unit of time or total number of stimuli are increased. It must be concluded that the inhibitory effects may be summated.

#### DISCUSSION.

Experiments have been described in this paper which demonstrate that the contraction of smooth muscle following stimulation of the periarterial nerves may be reversed by stimulation of the vagus nerves. The reversal phenomena may be shown in three ways:

(a) Stimulation of periarterial nerves during the contraction produced by tetanization of the vagus nerve.

(b) Stimulation of periarterial nerves during vagus stimulation when the lever has returned to the previous base line through apparent fatigue of the muscle to vagus stimulation.

(c) Stimulation of the periarterial nerves which under ordinary conditions has no effect on the muscle may during vagus stimulation produce relaxation.

The time intervals in these experiments rule out the possibility of

interference phenomena of the Wedensky type. The length of the muscle does not appear to be of importance, as reversal may be obtained with the muscle at its resting length, as evidenced by the observations quoted under (b) and (c). It may be suggested that one set of muscle fibres are responsible for contraction and others for relaxation, and as no observations have been made on this point it is impossible to express any definite opinion.

The recent paper of Kuré, Ichiko and Ishikawa [1931] is of interest. These observers point out that the vagus supply to the stomach includes, besides parasympathetic fibres, a great number of sympathetic fibres. The greater splanchnic also contains besides the well-known inhibitory fibres many "spinal parasympathetic" excitatory fibres coming from the dorsal roots of the thoracic segments. The presence of two sets of fibres in the vagus nerve was previously accepted, but the existence of dorsal root fibres in the sympathetic distribution was not recognized and may clarify the problem. These authors suggest that the "spinal parasympathetic" fibres exercise an excitatory action on the stomach and intestine. The contraction recorded by Brown, McSwiney and Wadge [1930] and McSwiney and Robson [1931] may be due to stimulation of the so-called spinal parasympathetic fibres, and the effects produced by varying the strength and frequency of the stimulus could be explained on this hypothesis. Full discussion of the meaning of the results obtained by Kuré, Ichiko and Ishikawa must be left for the present, though indeed definite differences between the contractions obtained on stimulation of the vagus and periarterial nerves are described in this paper.

The interactions between the vagus and sympathetic nerves which are described in this paper can best be accounted for on the assumption of chemical changes occurring in the periphery. The experiments, in which the effect of stimulation of the periarterial nerves for a short period on the response to a constant vagus excitation has been determined, lend further support to this latter hypothesis. It has been shown that during the period of stimulation of the periarterial nerves, the vagus response gradually decreases. It remains at a minimum for a definite period and then slowly returns to its normal value. As a rule a full vagus response is again obtained after 4 to 6 seconds; but in some experiments it was delayed for a longer period, and in one experiment the full inhibitory effect of stimulation of the periarterial nerves was actually maintained for 14 seconds. These findings further emphasize the inadequacy of an explanation based purely on the assumption that



inhibition in the peripheral network is due to interference of conduction of nerve impulses.

On the assumption that some chemical substance (or substances) is built up at the periphery as a result of the stimulation of the nerves, it appears likely that the concentration of this substance, and hence the effectiveness of its action, could be increased by increasing the frequency or duration of stimulation. The experimental results are indeed in accordance with this conclusion. As criteria of the effectiveness of the inhibitory phenomenon, we have used (1) the reduction in height of the vagus response obtained at the end of the period of periarterial nerve stimulation, and (2) the period of time following the cessation of periarterial nerve stimulation during which the inhibition of the vagus response remains effective. If it be assumed that there takes place, during the period of stimulation of the periarterial nerves, the production of a definite concentration of some chemical substance at the periphery, then a more effective stimulation would result in an increase in the concentration of this substance at the end of the period of stimulation. This would result (1) in a more marked inhibition at the end of the period, and (2) in the maintenance of a concentration of the substance above a minimal level for a longer period. The experiments demonstrate these effects, as increase in the frequency or duration of stimulation of the periarterial nerves increases the effectiveness and duration of the inhibition of the vagus effect.

It therefore appears possible that each excitation may result in the formation of a definite amount of some chemical substance. Repeated stimulation would then result in a gradually increasing concentration, and the concentration caused by a period of stimulation would vary with the rate of stimulation and the period during which it was applied.

Summation phenomena may also be demonstrated on stimulation of the vagus nerve, for when a definite type of sympathetic stimulation has caused a complete inhibition of the response to a single break shock, the application of several rapid stimuli to the vagus is able to bring about contraction of the muscle. This is in agreement with previous experiments [McSwiney and Robson, 1929*b*], which showed that stimuli descending the vagus nerve may be summated at the periphery.

Dale and Gaddum [1930] review the literature and support the view that the vaso-dilator effects of parasympathetic nerves and the contracture of denervated muscle accompanying these actions are due to the peripheral liberation of acetyl choline. Finkleman [1930] states that the inhibitory nerves to plain muscle act by liberating

peripherally an inhibitory substance. Our results are in harmony with those of other observers and suggest a chemical theory, but we are unable at this stage to advance any evidence of specific chemical substances.

#### SUMMARY.

Preparations of smooth muscle obtained from the fundus of the stomach with a dual innervation of vagus and sympathetic nerves have been made. Experiments are described which demonstrate that the response of smooth muscle to stimulation of the periarterial nerves may be reversed by stimulation of the vagus nerves. Inhibition of the vagus response produced by stimulation of the periarterial nerves has also been demonstrated. The duration and factors regulating the inhibitory effect have been investigated. Evidence is advanced to show that the type of response resulting from nerve stimulation is determined by the liberation of chemical substances in the periphery.

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