STUDIES ON THE INNERVATION OF SMOOTH MUSCLE. III. Splanchnic Effects on the Lower End of the Oesophagus and Stomach of the Cat.

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In the first article of this series (1, p. 258), it was stated that evidence in favour of an explanation advanced therein for inhibition of parts of the alimentary tract by the vagus had been obtained by stimulation of fibres coursing from the coeliac ganglion. Further investigation of the problem, however, has led to the conclusion that the splanchnic exercises its inhibitory action on the stomach by a method different from that employed by the vagus, though the results tend to support the conclusions reached for vagal inhibition. In the continuation of the investigation, the splanchnic major nerve, rather than fibres peripheral to the coeliac ganglion, has been subjected to faradisation. The method was modified thus, because Dr J. R. Pereira and the author (2) have found that the frequency of discharge from the cells of the superior cervical ganglion, and probably, therefore, from other peripheral nerve cells, is directly proportional to the frequency of impulses delivered to them from the preganglionic fibres.

Methods. The experimental method employed at Harvard has been described quite fully in a preceding paper (1), and the method at Cambridge was much the same. Shocks delivered by induction coils, whose primaries were supplied with iron cores, were used for stimulation. The primary current was supplied in all cases by a 2-volt accumulator, its intensity for the splanchnics, in the Cambridge experiments, being adjusted to ·09 ampère. In these experiments, moreover, the same inductorium, together with the new rotary interrupter described previously (2), was used exclusively for the splanchnics. At a secondary position of 8 cm., the shocks became detectable by the tongue. At 5 cm. they were weak; at 3 cm. they were moderately strong, and at 0 cm. they were slightly painful to the tongue, though they could be readily borne on it. In giving secondary positions in the following account of the results, the reference is to this inductorium. A rotary interrupter previously described (1) was employed also for the splanchnics at Harvard.

The method in which these interrupters were used, and the arrangements in the secondary circuits, did not differ from that described in the papers referred to. When both vagus and splanchnic were stimulated simultaneously, the series of cam wheels, *E*, of the Lucas interrupter, described by Adrian(3), served as contact breaker for the inductorium used in stimulating the vagus. The method in which this device was used has been described previously(2).

Platinum or silver electrodes were used in stimulation. The end of each wire, in the later experiments, was bent into a hook, the two hooks pointing in opposite directions, to prevent slipping off of the nerve. The electrodes were supplied usually with glass shields, though infrequently a rubber tube shield, similar to that described by Cannon(4), was employed. The latter type of shield was used almost exclusively in stimulating the fibre bundle peripheral to the coeliac ganglion. The glass shield was modified somewhat from that described by Sherrington(5), to eliminate the stopper at one end. Both ends of the shield were of a similar conical shape, the string connecting with the nerve being drawn out through the small opening and tied to the insulated leads to the electrodes. The total length of the glass shields varied from 2·5 to 3 cm.

In all experiments, the isolated vagus nerves, or at times the vago-sympathetic trunks, were cut in the neck. The splanchnic nerve was stimulated either above or below the diaphragm. In the former case, the sympathetic chain was isolated for about 2 cm. above the origin of the nerve through an incision between two of the lowermost ribs. The chain was cut at the cephalic end of this isolated portion; the rami communicantes were cut caudal to the section, and the splanchnic was then isolated almost to its exit through the diaphragm. Occasionally a smaller nerve appeared to emerge from the chain a few mm. below the splanchnic major, and an attempt was made to draw it with the splanchnic between the electrodes. This was probably the first minor. Once the splanchnic major was apparently divided into two separate trunks. Frequently the continuation of the chain beyond the splanchnic was cut. For stimulation beneath the diaphragm, the nerve was isolated through the incision for removal of the corresponding adrenal gland. The diaphragm was separated from its attachment to the lateral body wall, and the splanchnic major was isolated up to its connection with the sympathetic chain. Several mm. of the chain cephalad of the origin of the nerve were isolated also and left attached to the splanchnic. The rami communicantes and the continuation of the chain caudad were cut, and the nerve was brought beneath the diaphragm. A preparation

3 cm. long could be made thus before the coeliac ganglion was reached. The adrenal gland on each side was usually removed through an incision about 1 cm. beneath the last rib. In this operation, the portion of peritoneum overlying the adrenal was removed also, this being the only opening made into the abdominal cavity. In four experiments, however, the adrenals were removed through a median line incision through the linea alba, the incision being closed with sutures or covered with flannel moist with Ringer solution. In these cases, the viscera were considered exposed, but the results did not differ from those obtained when the adrenals were removed from the back.

The splanchnic major was stimulated in 38 cats. In most cases, both splanchnic majors, and in a large proportion, both adrenal glands were removed before the termination of the experiments. In eleven of the later experiments, the animals were prepared at the outset by cutting the vagi and both splanchnic majors, and removing both adrenals. As a rule, the animals were anæsthetised at first with ether or chloroform, or a mixture of both, and a dose of 3·5 to 5·0 c.c. of saturated chloralose solution in Ringer (a concentration of somewhat less than 1 p.c. of the drug) was injected intravenously. Ether was used thereafter if required. Two of the animals, however, were anæsthetised with urethane, two with ether, and two were decerebrated. Artificial respiration was administered by tracheal insufflation. Arterial blood-pressure was taken with an ordinary mercury manometer. In a few experiments the anti-coagulant was concentrated sodium carbonate, but usually it was 4 p.c. sodium citrate. Special procedures will be described in connection with the results obtained.

Stimulation of fibres peripheral to the cœliac ganglion.

The observations on stimulation of fibres peripheral to the cœliac ganglion were relatively few in number. Only motor effects were produced on the lower end of the œsophagus, the vagi and splanchnics having been cut, but often this part of the canal was apparently unaffected. The motor reaction consisted of a more or less marked and well maintained tonic contraction, on which rhythmic contractions were superposed, and it usually disappeared gradually on cessation of stimulation. In the case of the stomach, however, both inhibition and contraction occurred, though the former was probably more common. The occurrence of contraction was apparently favoured by a relatively low frequency of stimulation. In the one experiment in which a simultaneous record of blood-pressure was taken, a frequency of 15 per second

(475 z units) caused relaxation, whereas 5 per second (475 z units), in an immediately following observation, caused contraction. The rise in blood-pressure corresponding to the inhibitory reaction, however, was 22 mm. of Hg higher than that for the motor effect.

In another experiment, stimulation with a frequency of 5 per second (370 z units) resulted in a brief initial dilatation followed by well-marked contraction. The latent period for the occurrence of the relaxation was about 3 or 4 seconds, and the maximum extent of the succeeding volume decrease in the balloon was about 10 c.c. Increasing the frequency from 5 to 10 and from 5 to 15 per second, in this period of stimulation, resulted in each case in a diminution in the extent of the contraction, the partial relaxation being less for the former change than for the latter. In an immediately succeeding period of stimulation at 40 per second (370 z units), the initial quick relaxation took place, but it was followed by only a very slight and transient contraction. The latter fell far short of reaching the tonus level preceding stimulation. A succeeding relaxation of the stomach then occurred, becoming progressively greater till cessation of stimulation. The relaxation thus finally produced was considerably greater than that resulting from the initial dilatation. On cessation of stimulation, slow recovery took place, the tonus gradually rising to a level almost the same as that preceding stimulation. A brief initial dilatation followed by a temporary motor effect was observed also on crushing the cœliac ganglion with forceps, and in one experiment, a similar reaction occurred on stimulating the fibres peripheral to the ganglion after removal of both adrenal glands.

In a, relatively, few instances, the more or less predominantly inhibitory reaction evoked by excitation of these fibres was followed by temporary contraction well above the level preceding stimulation. At times this motor after-effect occurred very abruptly and almost immediately after cessation of faradisation.

Effects of stimulation of the splanchnic major in relation to vascular changes.

The only definite effect of stimulation of the splanchnics on the lower end of the œsphagus, with adrenals removed or intact, was motor. The reaction was similar to that described for the fibres peripheral to the cœliac ganglion, and it is illustrated in Fig. 3. The prolongation of the effect, after cessation of stimulation, was often longer than that there shown. In the case of the stomach, however, both motor and inhibitory reactions occurred. The motor effect was obtained in 13 of the 38 experiments, in animals to which no chemicals other than the anæsthetics

and Parke-Davis' adrenalin had been administered. In two of these, in which especially strong contraction took place, however, some concentrated sodium carbonate solution, the anticoagulant, had passed into the circulation. The result of splanchnic stimulation in one of the latter experiments is shown in Fig. 2. Whether one or the other effect takes place does not depend primarily on the frequency and intensity of faradisation, but on the extent of the change in the calibre of the blood vessels in the stomach wall, and to some extent, on the condition of the animal.

In experiments on 12 cats, with both vagi and both splanchnics cut, and with both adrenals removed, relaxation occurred in a total of about 50 observations, but contraction took place in 6 of the animals in a total of 25 observations. Blood-pressure was taken in 11 of these experiments, the anticoagulant being 4 p.c. sodium citrate. The former effect was produced by frequencies ranging from 1·8 to 225 per second and intensities varying from strong to weak to the tongue, *i.e.*, with secondary positions varying from 0 to 6 cm. with the Cambridge coil (in one observation, the intensity was 370 z units). The motor reaction was produced by very much the same frequencies and intensities, the former ranging from 2·5 to 185 per second, and the latter from strong to weak to the tongue (secondary positions from 0 to 5 cm.). Wider ranges of frequency and intensity were not tried for the two effects, except that in a few instances it was observed that a position of 6 cm. was about threshold. No definite combination of frequency and intensity could be predicted to give either effect.

In 45 of the observations in which relaxation occurred, simultaneous records of the blood-pressure were taken, and it was observed that the extent of the inhibitory reaction, in successive observations, closely paralleled that of the rise in blood-pressure, as illustrated in Fig. 1. Without a rise in blood-pressure, inhibition did not occur. At times, during rather prolonged stimulation, the tonus of the stomach began to rise, but concurrently the blood-pressure fell. In the experiment from which the figure was taken, the superior mesenteric artery and the abdominal aorta were tied. In all other experiments in which the splanchnic was stimulated, these vessels were not tied, but the results were in accord with those shown in Fig. 1.

The following series of observations may be mentioned in this connection, the intensity of stimulation remaining constant throughout (secondary at 2 cm.), and the animal being prepared with both vagi and both splanchnics cut, and with both adrenals removed. Stimulation of

the left splanchnic, with a frequency of 5·5 per second, caused a rise in blood-pressure of about 25 mm. and a fairly well maintained contraction

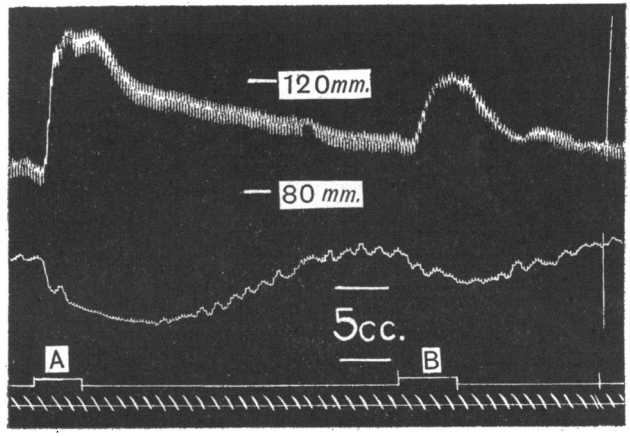

Fig. 1. Cat. Chloralose. Splanchnic majors and vagi cut. Adrenals removed. Superior mesenteric artery tied about 3 cm. distal to origin. Aorta tied between origin of renals and superior mesenteric. Viscera not exposed. Stimulation of right splanchnic. Shocks moderate to tongue (primary current = ·09 amp.; secondary at 3 cm.). Upper tracing, carotid blood-pressure; lower tracing, stomach. *A*: 80 interruptions per sec. *B*: 5·5 per sec. Time in 10 sec. intervals. In this and following figures the distance between the short horizontal lines near the stomach tracing represents the indicated volume change in the stomach balloon.

of the stomach, resulting in an expulsion of about 3·5 c.c. of air from its balloon. Quickly increasing the frequency to 185 caused a further rise in blood-pressure of about 10 mm., and simultaneously the stomach relaxed, allowing an entrance of about 6 c.c. of air. In an immediately succeeding observation, 11·5 per second produced a fairly well maintained rise in blood-pressure of about 35 mm., but a diphasic response of the stomach occurred. It first contracted, expelling about 3·5 c.c. of air, but in the course of about 15 seconds, relaxation began to take place, finally permitting an ingress of about 6 c.c. In the third observation of this series, 3·3 per second evoked a rise in blood-pressure of about 22 mm., which was accompanied by a maintained 1 c.c. contraction of the stomach, persisting throughout the period of 95 seconds of stimulation.

Though these observations indicate that the effect produced on the stomach depends on the degree of vaso-constriction in its walls, they might also be considered analogous to Wedensky inhibition. The apparent analogy is offset, however, by the following result obtained in

another experiment, the animal being prepared in the same way. A frequency of 11·5 (secondary at 2 cm.) caused a rise in blood-pressure of about 45 mm., and this was accompanied by a back flow of 2 c.c. of air. The blood-pressure began to fall gradually in the course of about 20 seconds and simultaneously the stomach tonus rose to its preceding value. The frequency was then increased to 185 per second. The blood-pressure continued to fall until it reached a fairly constant level about 20 mm. above that preceding stimulation, and concurrently contraction of the stomach took place, resulting in an expulsion of 7·5 c.c. of air.

The most pronounced contraction in response to splanchnic stimulation occurred in an experiment in which both vagi and both splanchnic majors had been cut, and both adrenals removed, the record being taken soon after preparation of the animal. The anticoagulant was sodium citrate. In 40 seconds of faradisation of the left nerve, at 4 per second and with a secondary position of 3 cm., 33 c.c. of air were expelled from the stomach balloon and the intragastric pressure rose considerably more than 11 cm. of water. This increase could not be accurately measured by the method employed. The effect was purely motor from the outset, the contraction rising very smoothly, and a period of about 4 minutes was required for the stomach to return to its preceding tonus level. A motor effect of such great magnitude has been practically maximal, in the author's experiments, for excitatory stimulation of the vagus. The corresponding rise in blood-pressure amounted to about 18 mm., and it was quite well maintained throughout the period of stimulation. The effect on the lower end of the œsophagus was strongly motor, the tonic factor being predominant.

The nearest approximation to this contraction occurred on stimulating the splanchnic of an animal with both adrenals intact, both splanchnic majors and both vagi having been cut. A small amount of the anticoagulant, concentrated Na_2CO_3 solution, had previously entered the circulation. A purely motor reaction developed, resulting in an expulsion of 27 c.c. from the balloon and an increase in intragastric pressure of considerably more than 9 cm. of water. The frequency in this observation was 160 per second, and the strength of the break shock was 370 z units. In this case the stimulation was without evident effect either on the blood-pressure or the lower end of the œsophagus. The reaction obtained is represented in Fig. 2.

In a number of experiments, the motor effect of the splanchnic became evident or well pronounced only under conditions in which it had lost, or almost lost, its ability to cause a rise in blood-pressure.

In one case, stimulation of the right splanchnic caused only relaxation of the stomach as long as a definite elevation in carotid pressure occurred.

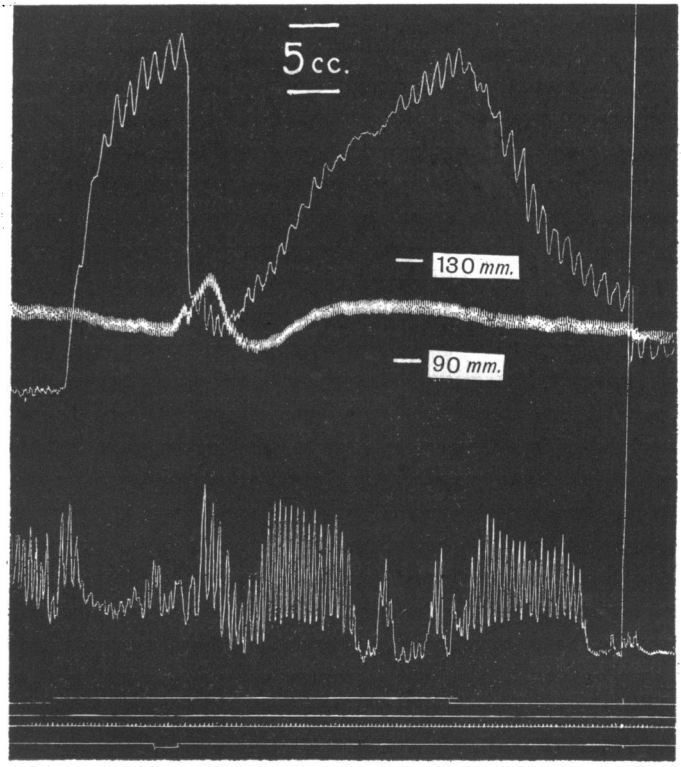

Fig. 2. Cat. Chloralose. Splanchnic majors and vagi cut; adrenals intact. Some concentrated sodium carbonate solution had previously entered the circulation. Upper tracing, stomach; middle, arterial blood-pressure; lower, lower end of œsophagus. Uppermost signal: stimulation of left splanchnic; 160 interruptions per sec.; strength of break shock, 370 z units. Lowest signal, injection of 2 c.c. of 1 : 100,000 Parke-Davis adrenalin (chloride) diluted with distilled water. Time in 5 sec. intervals.

As soon as this failed, however, the same intensity (secondary at 3 cm.) and frequency (2·5 per second) that had caused relaxation in a preceding observation, evoked well-marked contraction. In another experiment, contraction was produced by a frequency of 4·5 per second, the corresponding rise in blood-pressure being not more than 2 mm. Increasing the frequency to 23 per second resulted in a 4 mm. rise in blood-pressure and a pronounced diminution in the extent of the contraction. A similar

effect occurred, in the same period of stimulation, on a change from 4·5 to 72 per second, by throwing a switch in the primary circuit. The elevation in blood-pressure as a result of the frequency change was about 12 mm. The secondary position in this case was probably 3 cm.

In a preceding paragraph (p. 462) a diphasic response of the stomach to splanchnic stimulation was described. In this particular observation a transient contraction preceded relaxation, but such a reaction is very rare. It is more common to find that a more or less brief initial dilatation precedes contraction, but this type of response was observed in only 6 experiments, the vagi being cut in all. In each of 2 of these, the reaction occurred in only one observation. In the first, the left splanchnic major was cut and the left adrenal was removed, but the right splanchnic and adrenal were intact. Faradisation of the left splanchnic, with a frequency of 185 per second and a secondary position of 1·9 cm., produced an initial relaxation followed by contraction. A latent period of about 2 seconds preceded the dilatation. Its duration was about 5 seconds, and it resulted in an entrance of 2·5 c.c. of air into the balloon. Contraction then occurred, causing an expulsion of about 7 c.c. The stomach was not exposed to direct observation, and no record of blood-pressure was taken.

In the second experiment, both splanchnic majors had been cut, and both adrenals had been removed. The blood-pressure was very low and the heart beats were very weak, as indicated by the small extent of the corresponding oscillations of the mercury column. Under these conditions, stimulation of the left splanchnic resulted in a brief initial relaxation similar to that described in the preceding paragraph, the latent period being about five seconds. This was followed by contraction. The latter continued to increase for about a minute after cessation of stimulation, resulting in an additional output of air of about 6 c.c. The output during stimulation was about the same. This was the most pronounced motor after-action of which the author has either record or recollection from about 225 observations on stimulation of the splanchnic majors. As a rule, the beginning of relaxation from contraction coincides well with cessation of stimulation. The rise in carotid pressure, during the occurrence of the initial dilatation and the transition into contraction, was quite steady in this observation, and there was no indication of diminution in its extent for about 40 seconds of the total of 60 seconds of stimulation. It is improbable, however, that the carotid pressure, under such poor circulatory conditions, would have followed a quick

constriction of the stomach vessels corresponding to the brief initial relaxation.

In the other four experiments, this diphasic reaction was more constant in its occurrence, and the initial relaxation and the succeeding contraction, as a rule, were much more pronounced. The latent period for the occurrence of the relaxation in all observations was brief, usually amounting to about 5 seconds, as illustrated in Fig. 3. In one experiment,

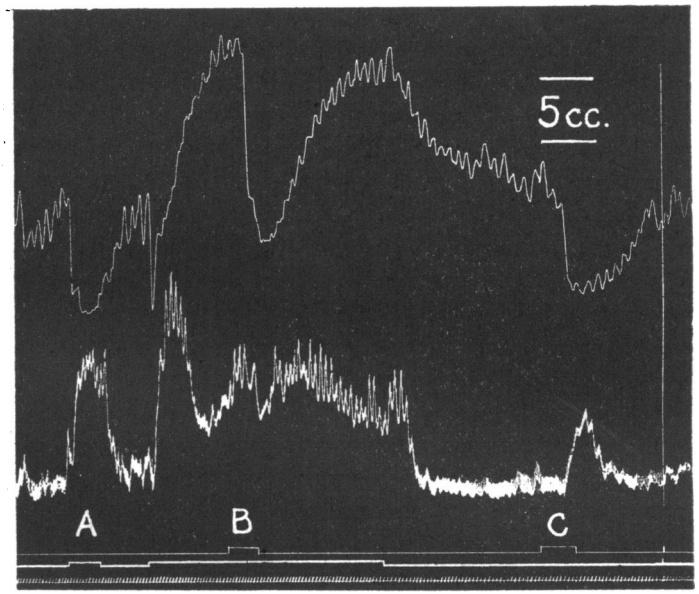

Fig. 3. Cat. Chloralose. Splanchnic majors and vagi cut; adrenals intact. Viscera exposed in moist chamber. Upper tracing: stomach. Lower tracing: lower end of œsophagus and cardia, balloon extending a few mm. below cardia. *A*: stimulation of right splanchnic; 40 interruptions per sec.; strength of break shocks, 145 z units. *B*: middle signal, stimulation of right splanchnic; 40 interruptions per sec.; strength of break shocks, 370 z units; upper signal, injection of 2 c.c. 1 : 100,000 Parke-Davis adrenalin diluted with distilled water. *C*: injection of 2 c.c. 1 : 100,000 Parke-Davis adrenalin. Time in 5 sec. intervals.

the response changed soon after removal of the adrenals into pure dilatation, but in another, their excision was followed by a change to pure contraction. In the latter, the blood-pressure was recorded, and the change, which consisted before removal of the glands of a brief rise followed by a slight fall, coincided well chronologically with the dilatation of the stomach. In the course of several seconds, however, the blood-

pressure returned to the level preceding stimulation, and about the same time, pronounced contraction developed. This condition persisted till the end of faradisation. After excision of the adrenals, the blood-pressure change was still limited to the beginning of stimulation, but it was greatly reduced, amounting to a rise of only 2 or 3 mm., and the effect on the stomach was motor from the outset.

In the remaining two experiments, a definite relation was found to exist between the effect produced and the intensity of stimulation. Blood-pressure was taken in neither, but in one of them the viscera were exposed to direct observation in the moist chamber described in a preceding paper (1). The nerves in each case were stimulated with glass shielded electrodes. In the experiment in which the viscera were not exposed, both adrenals and the left splanchnic being intact, stimulation of the right splanchnic with a frequency of 40 per second and an intensity of 145 z units resulted in dilatation. This relaxation persisted during 40 seconds of stimulation, when a gradual regain of tonus began to take place. In the course of 50 seconds, the tonus had reached its preceding level despite the continued faradisation. Suddenly increasing the intensity to 370 z units, then, caused marked contraction without a preceding dilatation. The maximal extent of the dilatation in this period of faradisation was 5 c.c., and of the contraction 16 c.c. Later the left splanchnic was cut and stimulated, after removal of the right adrenal. Faradisation of this nerve with a frequency of 40 per second and an intensity of 145 z units likewise produced pronounced dilatation of the stomach, permitting an entrance of 15 c.c. of air into its balloon, and persisting throughout a period of stimulation 70 seconds long. Faradisation afterwards, with the same frequency, but with an intensity of 370 z units, resulted first in an initial relaxation, with a latent period of about 3 seconds. This dilatation permitted a back flow of 5 c.c. of air. It persisted only about 5 seconds, however, pronounced contraction beginning then to take place. The latter continued to develop till the end of stimulation, resulting in an expulsion of 27 c.c. of air, and an increase in intragastric pressure of considerably more than 9 cm. of water.

The results of stimulation of the left splanchnic were similar to those obtained in the experiment in which the stomach was watched directly. The tracings represented in Fig. 3, taken from this experiment, are typical of these reactions. Both splanchnic majors were cut, but both adrenals were intact, and the right splanchnic was stimulated in the thorax. An intensity of 265 z units and a frequency of 60 per second

had given repeatedly a reaction similar to that shown in Fig. 3, *B*, the injection of adrenalin during the motor response of the stomach having the same effect as that there shown. After taking the tracings given in the figure, moreover, observations *A* and *B* were repeated, with the exception of the adrenalin injection, with the same results. The position of the electrodes, in the course of the experiment, was not changed.

The vascular changes were of special interest when taken into consideration with the reactions of the stomach musculature. When persistent dilatation occurred, in response to 40 per second and 145 z units, the blood vessels constricted, resulting in pallor of the stomach wall, and peristaltic activity ceased. The bulging of the stomach was quite evident. The vaso-constriction persisted, furthermore, till cessation of stimulation, when the vessels began gradually to dilate to their preceding calibre. At the same time, contraction of the stomach and a return of peristalsis became evident. With the stronger stimulation, however, the vaso-constriction and the dilatation of the stomach were limited to the beginning of faradisation. This inhibitory effect was recovered from quickly, the entire body of the stomach entering into a gradually developing tonic constriction. Simultaneously the blood vessels dilated to the calibre preceding stimulation, and slowly moving peristaltic contractions appeared. With the further development of the motor effect, these peristaltic waves progressed more rapidly toward the pars pylorica. The contraction consisted chiefly of a definite circular constriction of the distended body of the stomach, gradual relaxation being evident, on cessation of stimulation, to the size preceding excitation of the nerve. Shortening in the longitudinal dimension was not ascertained, nor was it determined whether the motor reaction involved the pars pylorica. Peristalsis was evident in the pars pylorica, however, soon after relaxation of the blood vessels from the initial constriction, though during the vasoconstriction, rhythmic activity in this part of the stomach had ceased. Whether these different reactions might have been related also to frequency of stimulation was not determined.

These observations show conclusively that the contraction of the stomach by splanchnic action is not the result of mechanical compression produced by excitation of the diaphragm or other skeletal muscles or their nerves by spread of current. No observation, throughout the course of the investigation, was considered valid in which there was any evidence whatever of such spread. When the splanchnic is stimulated in the thorax, the diaphragm usually lies directly on the electrode shield. Direct observation of this part of the structure, through the incision in

the thoracic wall, shows that it remains quiescent while the stomach contracts (cp. (6)).

Since current spread is insufficient to excite the diaphragm or its intramuscular nerves in the conditions just mentioned, the presumption that the motor reaction might be the result of excitation of the vagus by such means is removed beyond the realm of probability. It is rendered still further unlikely when it is considered that the strongest contraction was obtained when the left splanchnic was stimulated beneath the diaphragm. The peripheral end of the glass electrode shield was at least 1 cm. from the un-isolated cœliac ganglion. The shield was separated from the stomach by the cephalic pole of the left kidney, and usually under such conditions a layer of intact peritoneum adds to the completeness of the separation. Yet the contraction evoked compared favourably in magnitude with the strongest produced by stimulation of the vagus trunk, in the author's experiments, under the most favourable conditions. The shocks used, moreover, were only moderately strong to the tongue, and by no means painful. Stimulation of the right splanchnic with glass shielded electrodes, was observed to cause contraction with stimuli weak to the tongue, and in this case the possibility of effective current spread was further reduced by the intervention of the liver. In addition, stimulation of the splanchnic in the thorax may cause pronounced contraction of the stomach when the lower end of the œsophagus is unaffected. This state of affairs is illustrated fairly well in Fig. 2. If vagus fibres to the stomach were excited by current spread, under these conditions, fibres to the lower end of the œsophagus would also be stimulated.

It may be mentioned, finally, that tying and exerting slight tension on the left splanchnic produced well-marked contraction of the stomach in one case, the vagi having been cut. The most pronounced contraction in response to mechanical stimulation, however, was obtained in the experiment which gave the strongest contraction to electrical stimulation (see p. 463). About 15 minutes after this observation, sliding the shielded electrodes several mm. along the splanchnic, toward the cœliac ganglion, had a motor effect causing the expulsion of 29 c.c. of air.

Effects of adrenin.

In about 40 observations in some 18 experiments, Parke-Davis' adrenalin chloride, diluted usually with distilled water, but infrequently with Ringer solution, was injected intravenously in doses varying from 1 c.c. of 1 : 100,000 to $\frac{3}{4}$ c.c. of 1 : 1000. The result quite uniformly was relaxation of the stomach, often with complete cessation of peristalsis, and contraction of the lower end of the œsophagus, the extent of the reaction being proportional to the amount injected. In some cases, however, the latter structure was apparently not affected. From direct inspection by the moist chamber method (1), the impression was gained that the vaso-constriction produced in the stomach by the drug was not so great, with the smaller doses especially, as that which could be obtained by splanchnic stimulation. These reactions occurred whether the splanchnics were cut or intact, or whether the adrenals were removed or in place. Inhibition of the stomach occurred, furthermore, when it was contracted in response either to vagus or splanchnic stimulation.

The antagonistic action of the drug to the motor effects of the splanchnic is illustrated in Figs. 2 and 3, the signal for injection being on a few seconds too early and off a few seconds too late in each case. In these two examples, the adrenals were intact, but the reaction is similar after both these glands are removed, the vagi and splanchnic majors being cut.

The chloretone in the solution probably played no important part in these reactions for it was found that the dissolved Parke-Davis adrenalin powder, free from chloretone, had similar effects on the œsophagus and the spontaneously active stomach. For a particular experiment, 0·5 c.c. of ·02 N. HCl were added to 2 mg. of the powder, the mixture being allowed to stand about 24 hours. It was then diluted to 25 c.c. with distilled water, making a solution of about 1 : 12,000 adrenalin in about ·0004 N. HCl. Intravenous injection of 0·2 c.c. of this solution caused marked relaxation of the stomach and rise in blood-pressure, whereas 1 c.c. of ·0004 N. HCl was without definite effect on either. Then 75 c.c. of distilled water were added to the adrenalin solution, and 0·5 c.c. of this further dilution had the same effect, though less pronounced, as the larger dose. In this particular experiment, the lower end of the œsophagus failed to respond, but in another, 1 c.c. of 1 : 50,000 of the powder, prepared similarly in ·0002 N. HCl, produced a motor reaction.

Two experiments were exceptions. In one of them the lower end of the œsophagus was in a state of marked tonus and peristaltic activity, as indicated by the manometer method, and an injection of 2 c.c. of 1 : 100,000 of adrenalin chloride caused a loss of tonus and cessation of the contractions, which persisted for nearly a minute. A second dose of 1 c.c. of 1 : 100,000 had a similar effect of a duration of about 25 seconds. In each case, when activity began again, the tonus rose temporarily to a level decidedly above normal. In the second experiment, the cat had been anæsthetised with urethane, and the stomach was atonic and inactive, probably as a result of the action of the anæsthetic. Injections varying from 1 c.c. of 1 : 100,000 to ½ c.c. of 1 : 1000 dilutions having been made with distilled water, caused only weak tonic contractions. The

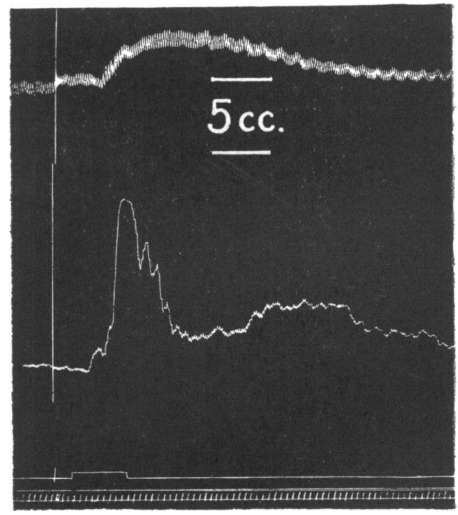

Fig. 4. Cat. Urethane. Vagi cut; splanchnics and adrenals intact; viscera not exposed. Upper tracing, stomach; lower, lower end of œsophagus. Injection of 5 c.c. Parke-Davis adrenalin chloride diluted 1 : 100,000 with distilled water. Signal for injection on a few seconds too early and off a few seconds too late. Time in 5 sec. intervals.

contraction was maximal for a dose of 5 c.c. of 1 : 100,000, amounting then to an output of only 3 c.c. of air. The reaction to this dose is represented in Fig. 4. Larger doses only prolonged the reaction. The effect on the lower end of the œsophagus was, as usual, pronounced contraction. In the same experiment, the stomach was thrown into strong contraction by stimulation of the left vagus, and 1 c.c. of 1 : 100,000 was then injected. Marked relaxation took place, though the level reached was somewhat higher than that preceding stimulation. Recovery took place in about 30 seconds, and the stomach began to contract in response to the continued vagus stimulation.

In some observations, the adrenal glands being intact, pronounced relaxation of the stomach, in response to splanchnic stimulation, did not take place till the secondary rise in blood-pressure occurred. Anrep(7) has shown this secondary rise to be the result of an output of adrenin, and inasmuch as it coincided well with the accentuation of the inhibitory reaction on the stomach, the latter was considered to have, in part at least, the same cause.

Parallelism between effects of splanchnic stimulation and anæmia on the stomach.

The close relation of splanchnic effects on the stomach to the changes in the calibre of its blood vessels described above (p. 460 et seq.), suggested that the inhibitory reaction might be the result of anæmia. To test this probability, the aorta was occluded cephalad of the level of the apex of the heart, and the effects on the spontaneous activity of the stomach and the contraction produced by vagus stimulation were recorded. They were found decidedly similar to the action of the splanchnic under these conditions. Five experiments were performed. In four, the vagi and splanchnic majors were cut, and the adrenals were removed. In the fifth, the vagi only were cut, the splanchnics and adrenals remaining intact, and the results of this experiment will be considered separately. In all cases in which the vagus was stimulated, the left was chosen, and its cardiac branches were cut to prevent any diminution in its effectiveness by simultaneous inhibition of the heart. The following description is taken entirely from tracings. The stomach was not watched directly.

Occlusion of the aorta has much the same effect on the stomach when spontaneously active and when contracted during vagus stimulation. Relaxation takes place at once and peristalsis ceases. On release of the aorta, there is a more or less rapid return to the condition preceding the occlusion, as illustrated in Fig. 5. In another experiment in which the

reaction of the spontaneously active stomach was recorded, the regain of tonus was more rapid than that shown in Fig. 5, and there was a

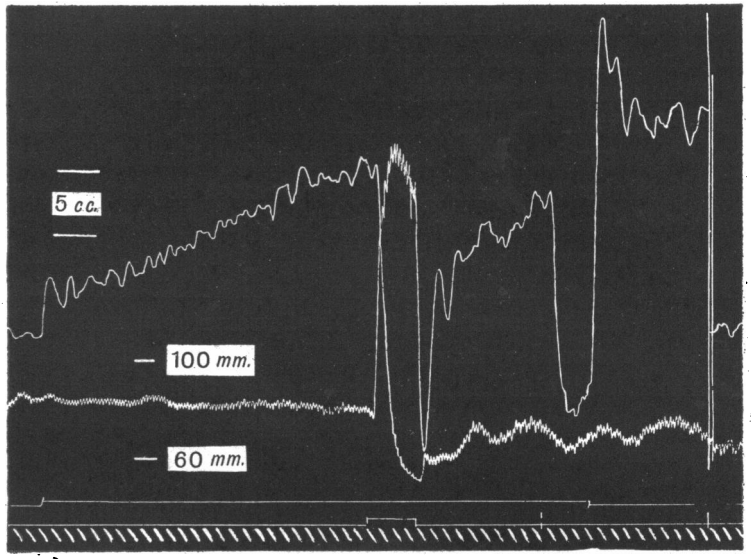

Fig. 5. Cat. Chloralose. Splanchnic majors, vagi, and cardiac branches of left vagus cut. Adrenals removed. Aorta clamped between origins of renal arteries. Viscera not exposed. Upper tracing, stomach; lower, carotid blood-pressure. Uppermost signal: stimulation of left vagus with shocks moderate to tongue; 1·03 interruptions per sec. to second upstroke in middle signal line, then quickly changed to 15·5 per sec. First signal on middle line: occlusion of thoracic aorta. Time in 10 sec. intervals.

tendency for the contraction to exceed temporarily the level preceding closure of the vessel. The longest period during which the blood flow was obstructed, in these two experiments, was about 60 seconds. In a third, however, in which the stomach was spontaneously quite inactive and atonic, closure of the aorta abolished the contraction in progress, in response to continued vagus stimulation, during a period of occlusion lasting 100 seconds. Longer closures were not tried.

Fig. 5 shows also the inhibitory effect of a relatively high frequency of vagus stimulation, in contrast to the excitatory effect of a lower frequency, without simultaneous inhibition of the heart (cp. (1)). No initial contraction preceded the relaxation. In a preceding observation, however, when the stomach was not contracted by excitation of the vagus, the same frequency and intensity of stimulation evoked a well-marked initial contraction, followed by inhibition. A strong motor

after-response followed the inhibition, similar to that represented in part in Fig. 5, and during this after-contraction, the aorta was occluded. The reaction was similar to that described in the preceding paragraph. The tonus on releasing the vessel, however, instead of rising only to the level preceding vagus stimulation, rose almost to the level of the after-contraction, *i.e.*, the motor after-response was resumed.

The inhibitory action of the splanchnic on the spontaneously active stomach has been considered in a preceding section and its inhibitory effect on the contraction produced by vagus stimulation is decidedly similar (Fig. 6). Concurrently with the rise in blood-pressure,

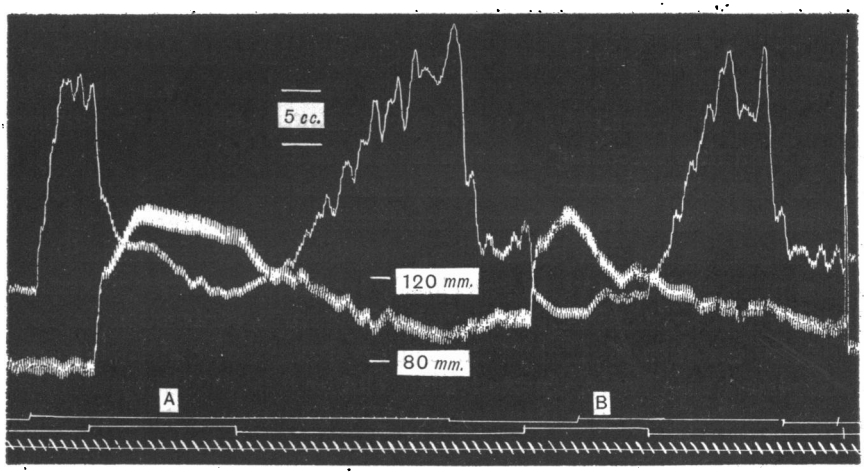

Fig. 6. Cat. Chloralose. Splanchnic majors, vagi, and cardiac branches of left vagus cut. Adrenals removed. Viscera not exposed. Upper tracing, stomach; lower, carotid blood-pressure. Uppermost signal line; stimulation of left vagus with shocks moderate to tongue; $7\frac{3}{4}$ interruptions per sec. Middle signal line: stimulation of left splanchnic with shocks moderately strong to tongue (secondary at 3 cm., primary current ·09 amp.); 60 interruptions per sec. Time in 10 sec. intervals.

the stomach relaxes, and if the spontaneous tonus before stimulation is pronounced, the relaxation proceeds to a level much below that preceding excitation of the vagus. On cessation of stimulation of the splanchnic, the rapidity of the development of the motor effect, in response to the continued stimulation of the vagus, corresponds well with the rate of fall in blood-pressure. This generalisation is made on the basis of five observations from two experiments. In an additional observation, the splanchnic was stimulated first and then the vagus. It is represented in Fig. 6, *B*. As long as splanchnic stimulation continued, the vagus

produced only a slight contraction. With the fall in blood-pressure, on cessation of splanchnic stimulation, however, the contraction developed more rapidly than in the corresponding part of observation *A*. Accordingly the fall in blood-pressure in the former case is extended over a shorter period of time.

In the experiment in which the splanchnics and adrenals were left intact, the effect of occlusion of the aorta on the contraction produced by vagus stimulation, in a single observation, was very much the same as that shown in Fig. 5. In this experiment, furthermore, the procedure was reversed. The aorta was occluded, and after the obstruction had been maintained about 30 seconds the vagus was stimulated. Only a slight trace of contraction was produced, resulting in an output of less than 1 c.c. of air. Stimulation was continued for 25 seconds, and about 20 seconds after its cessation, the aorta was released. The stomach contracted to a constant level in the course of 30 seconds, somewhat lower than that preceding deprivation of blood supply.

In these two observations, furthermore, there was evidence that occlusion of the aorta suppressed contraction of the lower end of the œsophagus. In the first observation, escape from vagal inhibition had taken place before the vessel was closed, but this procedure apparently brought about relaxation. After release of the aorta, contraction did not occur till cessation of stimulation. Then a strong motor after-response took place immediately. In the second, closure of the aorta apparently shortened decidedly the duration of the initial contraction, and the motor after-response was delayed in its appearance for some twenty seconds after release of the vessel. In the other experiments, closure of the aorta had apparently no effect on the activity of the lower end of the œsophagus, but it is possible, in these cases, that its blood supply was not greatly reduced.

Effect of sodium carbonate on the response to splanchnic stimulation.

It was stated in the section on the relation of splanchnic effects to vascular changes that a small amount of concentrated Na_2CO_3 solution, the anti-coagulant, had entered the circulation in two experiments, and that in these, stimulation of the splanchnic caused strong contraction of the stomach. In one of them, furthermore, there was no corresponding change in carotid pressure whatever (Fig. 2). It seemed probable, therefore, that Na_2CO_3, when injected into the circulation, might permit a reproduction of these effects. This probability has been put to test in only three experiments, but the results have been, for the

most part, positive. In all cases, the splanchnic majors and the vagi were cut.

In the most doubtful experiment, the adrenals were left intact, and the injection of 0·5 c.c. of 0·5 N. Na_2CO_3 apparently resulted in a change from inhibition to contraction during the primary rise in blood-pressure evoked by splanchnic stimulation. It did not abolish either phase of the blood-pressure change, however, and with the occurrence of the secondary rise, the stomach relaxed. Further injections gave indefinite results.

The other two experiments fulfilled expectation. In the animal, in which the adrenals were intact, the blood-pressure change in response to splanchnic stimulation was apparently completely abolished by injections totalling 5·8 c.c. of 0·1 N. Na_2CO_3, and at the same time, the reaction of the stomach became purely motor. This condition, however, was reached through stages of transition, the motor effect on the stomach appearing before complete disappearance of the rise in blood-pressure. The change brought about in the third experiment, after bilateral adrenalectomy, was similar to that produced in the second. In this case, moreover, initial dilatation of the stomach followed by contraction was obtained at times, after the injection, and the corresponding blood-pressure rise was transient and fairly well limited to the beginning of stimulation.

Discussion.

The parallelism between the extent of inhibition of the stomach by splanchnic stimulation and that of the corresponding constriction of its blood vessels indicates that the important factor in the production of the inhibitory reaction is vasoconstriction. The occurrence of a motor reaction of the stomach when the vasoconstriction is slight or entirely lacking, or when the vessels relax during stimulation, points to the same conclusion. It is supported further by the fact that anæmia affects the stomach in much the same way as splanchnic stimulation, both when the organ is spontaneously active and when it is thrown into contraction by stimulation of the vagus. The results of occlusion of the thoracic aorta on the stomach are in accord with those of Bastianelli(8) for the dog, and with those of most investigators who have studied the effect of anæmia on the intestine. Bastianelli, Mall(9), and Bayliss and Starling(10) have reviewed preceding literature.

It is quite certain that the inhibitory and motor effects of splanchnic stimulation on the stomach are not the result of differential excitation of inhibitory and excitatory nerve fibres. In 36 of the 38 experiments,

neither effect could be certainly produced by any combination of frequency or intensity. In two experiments, a definite relation between intensity and reaction did appear. The results in both were the same, however, and direct inspection in one of them showed that the inhibition was closely paralleled by vasoconstriction. The similar parallelism in the other experiments, in which evidence for the presence of specific inhibitory nerves could not be obtained, indicates that in these two cases also, inhibition was the result of vasoconstriction.

The occurrence of an initial vasoconstriction with relatively strong stimulation, whereas weaker shocks of the same frequency produced continued constriction, suggests that under the proper experimental conditions, a Wedensky effect may be obtained on the blood vessels innervated by the splanchnic. Whether a similar effect can be brought about by increasing the frequency of stimulation remains to be determined. The brevity of the latent period (cp. (7)) and the duration of the initial constriction, and of the accompanying dilatation of the stomach, indicates that it is not the result of an output of adrenin. The results obtained by Langley and Dickenson(11) on the vessels of the bucco-facial region of the dog, by stimulation of the cervical sympathetic, are of interest in this connection. Their clear description of the results should be consulted. In regard to intensity of stimulation at least, the dilatation is similar in its mode of production to Wedensky inhibition.

A number of cases of lack of parallelism between the action of adrenalin and that of the thoracico-lumbar autonomic nerves have been considered by Langley(12) and the papers cited contain references to related literature. The antagonistic action of this drug to the motor effect of the splanchnic on the cat's stomach may be added to the list.

The apparent effect of sodium carbonate, viz. prevention of splanchnic action on the blood vessels with the result that pure contraction is produced, the author intends to investigate further.

The tendency of the lower end of the œsophagus and stomach to return to a constant level of tonus (cp. also (1)), after having been inhibited or thrown into contraction by nervous action, indicates that their tonus is dependent on a constant state of excitation. If it were the result of the engagement of the two parts of a catch mechanism(13,14), these structures would be expected to remain indefinitely in the condition imposed upon them by the extrinsic nerves.

Summary and conclusions.

1. The extent of inhibition of the cat's stomach by stimulation of the splanchnic major nerve parallels the degree of vasoconstriction produced within its walls (Fig. 1). If the constriction of the vessels is slight, or entirely lacking, contraction of the stomach often occurs (Figs. 2 and 3).

2. The effect of splanchnic stimulation on the lower end of the œsophagus is uniformly motor, though frequently it is apparently lacking.

3. Variation in frequency and intensity of stimulation fails to reveal the presence of specific inhibitory fibres in the splanchnic major trunk, before or after removal of the adrenal glands.

4. Effects of stimulation of fibres peripheral to the cœliac ganglion are described.

5. The action of adrenalin on a stomach, which exhibits a definite degree of tonus, is inhibitory. In one experiment, in which the organ was atonic, a weak motor effect was the apparent result (Fig. 4). Injection of the drug also usually causes contraction of the lower end of the œsophagus (Figs. 3 and 4), but often it is without effect. In one experiment, in which the tonus and rhythmic activity were pronounced, however, brief inhibition occurred.

6. When the stomach is contracted in response to stimulation of the splanchnic major (Figs. 2 and 3), or of the vagus, adrenalin injection causes pronounced relaxation. An antagonistic action of the drug to the motor effect of these two nerves is thus demonstrated.

7. The inhibitory action of the splanchnic on the stomach, either when spontaneously active or when contracted during vagus stimulation (Fig. 6), is similar to that of anæmia produced by occlusion of the thoracic aorta under these conditions (Fig. 5).

8. A few observations indicate that the injection of sodium carbonate into the blood stream results in a disappearance of vasoconstriction in response to stimulation of the splanchnic major, and that simultaneously the effect of the nerve on the stomach becomes purely motor (cp. Fig. 2).

9. On the basis of this evidence, it is suggested that the chief factor in the production of inhibition of the cat's stomach, by stimulation of the splanchnic major nerve, is vasoconstriction.

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