THE NERVOUS PATHWAYS OF INTESTINAL REFLEXES ASSOCIATED WITH NAUSEA AND VOMITING

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It has been shown (Gregory, 1946) that, when nausea and vomiting are produced in unanaesthetized dogs provided with Thiry-Vella loops of jejunum, there occur characteristic changes in intestinal tone and motility. The disappearance of these changes, following denervation of the mesenteric vascular pedicle of the loop, together with other evidence, indicates that the changes are of central reflex origin. In the experiments to be described, the efferent pathway of this reflex is shown to lie in the thoracic vagus, presumably passing thence, immediately below the diaphragm, through the upper abdominal autonomic plexuses to reach the gut in company with the nerves which arise from the autonomic plexuses. Besides the changes in tone and motility already described, nausea and vomiting also cause an increased flow of intestinal juice, which is of similar reflex origin, and for which the efferent pathway is the same.

METHODS

Six dogs provided with jejunal loops were used in these experiments; three had 2 Thiry-Vella loops each, one had 2 Thiry loops, one had 1 Thiry loop, and one had 1 Thiry-Vella loop. In preparing the Thiry loops, the cranial end of the segment of intestine was closed and the caudal end exteriorized, so that the direction of peristalsis was such as to empty the loop of its secretions. Although this choice of orientation ensures satisfactory drainage, it has the disadvantage that the balloon used for recording tone and motility is not easily kept in position. If it is intended to use such loops solely for recording motility, it is preferable to reverse the 'polarity' by closing the caudal end and exteriorizing the cranial end.

The operative preparation and method of recording tone and motility from the loops was the same as that described previously (Gregory, 1946). The flow of intestinal juice from the loops was measured by lightly covering the stomata with a weighed pad of cotton wool or square of surgical gauze backed with a piece of rubber dental dam. The complete pad weighed about 2 g. and was kept in place by means of a large pad of cotton wool and a cloth jacket worn by the animal during the experiment. These pads were changed every 15 min. and weighed immediately after removal; the increase in weight was taken to indicate the flow of juice from the loop during the preceding period. This method proved to be quite satisfactory for recording changes in the scanty flow of juice from these loops; its chief disadvantage seems to be that slight stimulation of the mucous membrane at the stomata is inevitable, and that the juice is not available for chemical examination.

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Thoracic vagotomy was performed through an incision between the 6th and 7th ribs on the left side. Using ether or cyclopropane-oxygen anaesthesia, with provision for artificial respiration, the thoracic cavity was opened and the oesophagus delivered to the surface of the wound. The two or three large vagal trunks present on its surface at this point were easily identified and a portion about 1 cm. long resected from each. The oesophagus was then released and the thorax closed in the usual way. This procedure is virtually bloodless, takes only a minute or two to perform, and is far more certain in its completeness than the alternative of division of all visible fibres on the abdominal oesophagus.

Nausea and vomiting were produced by the subcutaneous injection of minimal doses of apomorphine; as in the previous experiments, a dose of 0·02–0·10 mg./kg. body weight was found to be adequate.

<div align="center">RESULTS</div>

1. *Intestinal secretion during nausea and vomiting*

In the fasting dog, the flow of intestinal juice from unstimulated Thiry or Thiry-Vella loops of jejunum is very slow and probably continuous, with a tendency towards rhythmical fluctuations, the cause of which remains obscure (Boldyreff, 1928; Nasset, Pierce & Murlin, 1935). Different opinions are expressed in the literature as to whether the rate of flow of juice is increased by meals; in the present experiments no significant increase was observed when the dog was fed its daily ration of raw horse-flesh during experiments in which the flow of juice was recorded.

When nausea and vomiting were produced by the subcutaneous injection of apomorphine, there occurred a conspicuous increase in the rate of flow of intestinal juice (Fig. 1) which was limited in duration to the period of other discernible effects of the drug.

Fig. 1. The effect of nausea and vomiting on the flow of intestinal juice from a Thiry-Vella loop of jejunum. At *A* a dose of apomorphine produced nausea alone; at *B* a second dose produced nausea, retching and vomiting.

Attention was first drawn to the possibility of such a secretory response by an observation that during nausea and vomiting, juice dripped from the ends of the loops at an obviously greater rate than normal; and on several subsequent occasions the fact of an increased flow in these circumstances was verified by collecting the secretion in small glass cups fastened over the ends of the loops, but not in contact with them.

This method of collection was too difficult for routine use and it was soon discarded in favour of the much more convenient and accurate procedure of collection on weighed pads; but the preliminary experiments were of value in that they excluded a possibility which would otherwise have arisen, namely,
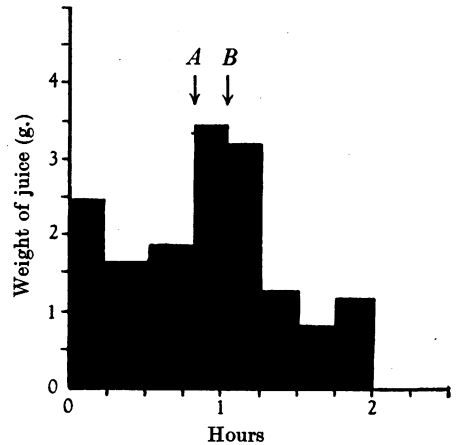
that the increased flow of juice recorded by the pad method was merely the result of mechanical stimulation of the ends of the loops by the pads during movements of retching and vomiting. Stronger evidence against such an interpretation of the increased rate of flow is however afforded by the fact that, in two experiments, the dose of apomorphine first injected proved inadequate to provoke retching and vomiting; nausea alone resulted, without the slightest sign of a retching movement, yet there was an obvious increase in the flow of juice from the loops (Fig. 1). This flow was in fact slightly greater than that during the succeeding period of the experiment, in which retching and vomiting, in addition to nausea, were produced by a second injection of the drug.

Occasional large irregularities in the secretion curves obtained during the earlier experiments were found to be due to the expulsion from the loops of yellow pasty material. The duplex quality of the intestinal juice in the dog is well known; it consists of a colourless watery fluid, with which is mixed discrete masses or plugs of a yellow material, termed 'mucus' by the older writers (Babkin, 1928), but apparently consisting of cellular debris, cast-off mucous membrane, lipides, etc., bound together by secreted mucus. Drainage of the watery component appeared to be regular, and no indication was obtained of any appreciable accumulation of it prior to collection during an experiment. Expulsion of the solid material was, however, relatively infrequent and irregular, and it occasionally occurred during the efforts of retching and vomiting, with consequent confusion of the results. Although this material undoubtedly constitutes in a sense a part of the intestinal secretions, no satisfactory means could be found of securing its regular collection; the procedure was, therefore, adopted of washing out the loops with warm saline just before an experiment, and then allowing the loops to drain for 15–20 min. before starting collection of the intestinal juice.

This routine did not alter the general nature of the results.

The effect of denervation. In two dogs (one with 2 Thiry loops and one with 2 Thiry-Vella loops) the vascular pedicle of one loop was denervated at a second operation.

For a day or two after denervation the loops secreted continuously and copiously (though in diminishing quantity) a watery fluid, faintly alkaline and often tinged with blood, in which there was no trace of the yellow material previously mentioned, and which was without the characteristic fishy odour of normal intestinal juice. At this stage, records of tone and motility taken by the balloon method showed that the intestine was in a highly irritable state. The muscle was in a state of spasm, so that the length of the loop was found to have diminished to about one-half to one-third of its length when originally prepared: partly because of this, partly owing to a concomitant increase in propulsive motility, the recording balloon was often expelled from the caudal end of the loop within a minute or so of its introduction into the cranial end. During the succeeding 4–7 days the spontaneous secretion and motility returned to their normal state, and the yellow pasty component of the juice and characteristic smell returned. After approximately 1–2 weeks the tone and motility of the loop, the secretory response to mechanical stimulation, and the rate of spontaneous secretion, was apparently normal.

Experiments on the flow of juice during nausea and vomiting were made about 4 weeks after denervation. The secretory response previously observed under these conditions was now absent from the denervated loop, whereas a definite increase still occurred in the untouched loop of the opposite side (Table 1). This result shows that the increased flow of juice, like the tone and

TABLE 1. Intestinal secretion in a dog with 2 Thiry loops of jejunum (one denervated) during nausea and vomiting produced by apomorphine

	Weights of juice collected from loops by pad method	
Time (min.)	Left (denervated)	Right (normal)
0–15	0·11 g.	0·19 g.
15–30	0·01	0·18
30–45*	0·20	0·30
45–60	0·09	0·82
60–75	−0·02†	0·10
75–90‡	0·04	0·13
90–105	0·05	0·48
105–120	0	0·12
120–135	−0·01†	0·18
135–150	0·07	0·16

* Apomorphine injected at 45 min.; produced nausea, retching and vomiting at 50 min.
† Pad lost weight.
‡ Apomorphine injected at 90 min.; produced nausea, retching and vomiting at 100 min.

motility changes previously described, is of nervous reflex origin. The question then arises as to the efferent pathway concerned; and this problem was investigated by studying the effects of dividing the vagi or splanchnic nerves at their entry into the abdomen.

2. The effect of vagal and splanchnic section on the secretory and motor responses associated with nausea and vomiting

A. *Splanchnic section.* Although there is evidence from acute experiments that the splanchnic nerves contain fibres which may normally have an inhibitory action on the secretion of pancreatic juice (Babkin, 1928; Harper & Vass, 1941), section of these nerves under similar conditions is said to produce little or no immediate effect upon the secretion or motility of the jejunum in cats (Brunton & Pye-Smith, 1875; Florey, Wright & Jennings, 1941); and it appears to be generally agreed from examination of unanaesthetized cats and dogs at a later stage after bilateral splanchnic section that the effects produced upon the motor functions of the digestive tract are not very pronounced. Thus, Cannon (1906) found no change in the motility of the stomach and intestines of unanaesthetized cats examined by X-rays after a radio-opaque meal; others have described some acceleration of the passage of similar material, or the production of mild but not persistent diarrhoea.

In two dogs, each provided with 2 Thiry-Vella loops, the splanchnic nerves on each side were found and divided through a midline incision under ether anaesthesia at an aseptic operation. Recovery from this operation was rapid

and uneventful and no discernible changes resulted in the general health and behaviour of the animals (one showed diarrhoea for a few days afterwards). No changes were observed in the tone and motility of the loops or in the rate of the spontaneous secretion when experiments were recommenced; measurements of propulsive motility were not made.

Records of tone, motility and secretion during nausea and vomiting were begun 5 days after the above operation and continued at least once weekly for several weeks afterwards. On every occasion the characteristic motor and secretory responses previously associated with nausea and vomiting were still as pronounced as before (Figs. 2, 3).

It seems clear from these results that the splanchnic nerves do not contain fibres which are concerned in the intestinal responses described.

B. *Vagal section.* In three dogs, one of which had been subjected some weeks previously to section of the splanchnic nerves, both vagi were divided in the thorax at an aseptic operation, and, after recovery, the effects of this procedure on intestinal motility and secretion ascertained.

During a period of several weeks' observation after the first occasion on which the vagotomized dogs were offered solid food, it was clear that section of the vagi had profoundly affected oesophageal and gastric motor functions; and the present findings are in complete accord with the description given by Meek & Herrin (1934) of the behaviour of their dogs after thoracic vagotomy, in their study of the effects of this on gastric emptying times. At first, when the animal ate its meals, several swallowing movements were made after each mouthful, as though the food had lodged in the pharynx or oesophagus; earlier portions of the meal were frequently regurgitated and re-eaten. Saliva and mucus accumulated in the lower end of the oesophagus between meals and were regurgitated at intervals. If retching and vomiting was produced by injection of apomorphine in a fasting animal, the vomitus often contained large lumps of undigested meat eaten the previous day. None of the dogs appeared to suffer more than slight discomfort during this period of interference with gastric emptying and digestion of solid food, and they did not appreciably lose weight. In addition to raw horse-flesh they were given to drink liberal quantities of a mixture of dried full-cream milk, soya flour, cod-liver oil and water, which was seldom vomited. After a week or two, the dogs all learned to eat solid food more slowly and in smaller portions; regurgitation of food and accumulations of saliva became infrequent and the dogs returned to their former excellent condition. At this stage, their appetite was noticed to have become much larger than before operation, and it continued so for months afterwards; this change was also noted by Meek & Herrin in their dogs, and attributed by them to loss of the feeling of satiety after a meal, due to division of gastric afferent fibres in the vagi.

They also observed as did Cannon (1906) in vagotomized cats that the initial difficulty in swallowing solid food was due to paralysis of the lower end of the oesophagus, as shown by fluoroscopic examination during the eating of a radio-opaque meal.

In the present work, records of intestinal tone, motility and secretion were started 7 days after operation and were continued once or twice a week for several weeks afterwards. The tone, motility and spontaneous secretion were not significantly different from before, but the changes associated with nausea and vomiting were now completely absent (Figs. 4, 5) and there was no sign of their reappearance when the last observations were made, about 7 weeks after vagotomy.
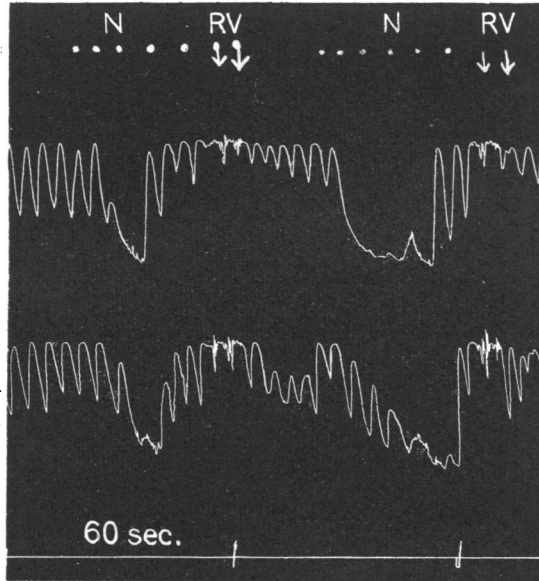
Fig. 2. The effect of nausea (N), retching (R), and vomiting (V) produced by apomorphine on intestinal tone and motility recorded in a dog with 2 Thiry-Vella loops of jejunum after section of the abdominal splanchnic nerves.
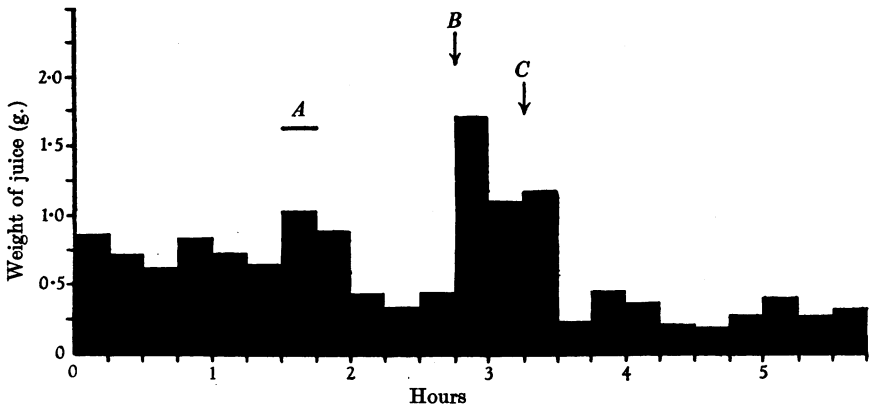

Fig. 3. The effect of nausea and vomiting on the flow of intestinal juice from a Thiry-Vella loop of jejunum after bilateral section of the splanchnic nerves in the abdomen. Nausea and vomiting were produced by injections of apomorphine at B and C; at A mechanical stimulation was provided by distension of the loop with the balloon used for recording tone and motility (pressure 15 cm. H₂O)

These findings appear to establish the vagi as the pathway for the fibres concerned in the changes in tone, motility and secretion of the intestinal loops
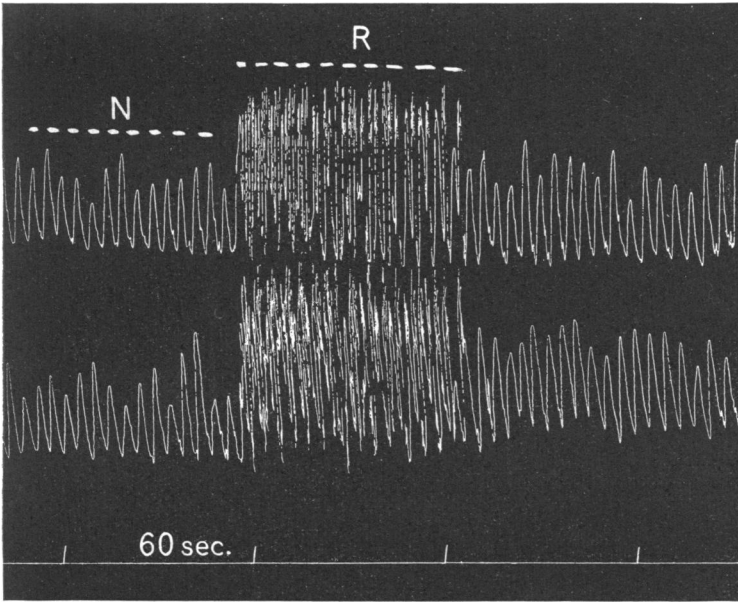

Fig. 4. The effect of nausea (*N*) and prolonged retching (*R*) produced by apomorphine on intestinal tone and motility recorded from a dog with 2 Thiry-Vella jejunal loops after thoracic vagotomy.
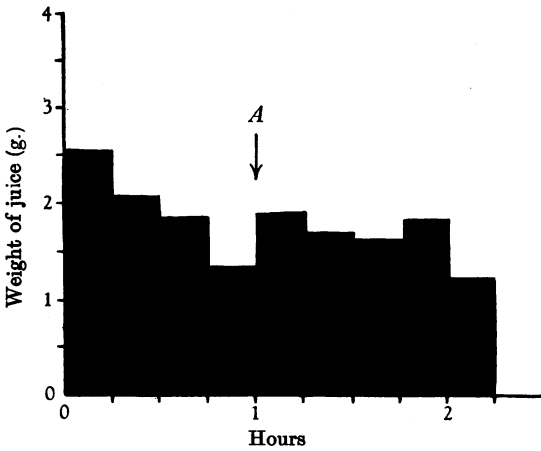

Fig. 5. The effect of nausea and vomiting produced by an injection of apomorphine at *A* on the flow of intestinal juice from a Thiry-Vella loop of jejunum after thoracic vagotomy.

during nausea and vomiting. No investigation was undertaken of the exact course of the vagal fibres from the thoracic vagal trunks to the intestinal loops;

but it is well established by the work of M'Crea (1924) and others (McSwiney, 1931) that immediately below the diaphragm the posterior vagal trunks send fibres to the coeliac ganglia. It seems highly probable that among these fibres are those concerned in the present responses, and that they run to the intestinal loops in company with the sympathetic fibres which form the main bulk of the mesenteric nerves.

It is perhaps noteworthy that in the one dog which underwent both vagotomy and splanch-nicotomy, no changes were observed in the spontaneous secretion or tone and motility of the loops, comparable with those produced by denervation of the mesenteric pedicle which are referred to previously in this paper. This fact appears to have been first noted in acute experiments on cats by Brunton & Pye-Smith (1875). In order to produce the 'paralytic secretion' of intestinal juice, it is necessary to damage or remove the abdominal autonomic ganglia (Brunton & Pye-Smith, 1875) or to denervate the vascular pedicle to a loop of intestine (Moreau, 1868) or to divide all the pre-ganglionic fibres to the abdominal ganglia (Wright, Jennings, Florey & Lium, 1940). These facts have led to the concept of the existence of a 'local centre' in the upper autonomic ganglia of the abdomen for the control of the secretion of the small intestine.

DISCUSSION

The exact nature of the intestinal movements which have been recorded in these and the previous experiments remains at present obscure. From the radiological observations of Gardiner (1928), Ingelfinger & Moss (1942) and of others on the occurrence of antiperistaltic activity in the duodenum of human subjects during nausea and vomiting, and from clinical experience that during protracted vomiting the contents of the lower parts of the digestive tract may ultimately appear in the vomitus, it appears highly probable that the intestinal activity concerned is propulsive in type and oralward in direction; the general sequence of changes recorded in these experiments by the balloon and water-manometer method, namely inhibition followed by spasm, are consistent with the occurrence of some type of peristalsis. Although the intestinal reflexes described in these experiments have been referred to as 'motor' and 'secre-tory' respectively, it is not intended to suggest by the use of these terms that the vagal fibres concerned are of two corresponding types. There is no evidence from the present work to suggest that such is the case, and histological investigations show that the extrinsic vagal fibres supplying the small intestine probably all end as pericellular arborizations around the Type II cells of Dogiel in the enteric plexus (Hill, 1927).

No precise information is as yet available regarding the characteristics of the motor response; but evidently the continuity of the intestinal muscle and enteric plexuses is not essential for its transmission, since it appears, in the present experiments, in loops disconnected from the rest of the gut.

SUMMARY

1. The production of nausea and vomiting in dogs provided with Thiry or Thiry-Vella loops of jejunum causes an increase in the secretion of intestinal juice.

2. This secretory response, and the changes in intestinal motility described in a previous paper, are unaltered by bilateral splanchnicotomy.

3. Both intestinal responses are abolished by thoracic vagotomy.

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