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THE EFFECTS OF PRESSURE AND PHARMACOLOGICALLY ACTIVE SUBSTANCES ON GASTRIC PERISTALSIS IN A TRANSMURALLY STIMULATED RAT STOMACH–DUODENUM PREPARATION

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SUMMARY

1. A rat stomach–duodenum preparation in which pressures in the body and the antrum and flow through the pylorus could be recorded simultaneously has been used to study the effects of pressure and pharmacologically active substances on the peristalsis induced by transmural stimulation.

2. Vagal and transmural stimulation produced vigorous peristalsis and episodic flow. Simultaneous stimulation of the peri-arterial nerves abolished peristalsis and relaxed the pylorus.

3. After repeated stimulation the preparation lost tone and peristalsis failed. Peristalsis and tone could then be improved by lowering intragastric pressure. Vigorous peristalsis could be restored in an inactive preparation by eserine and more transiently by 5-HT.

4. Drugs which increased smooth muscle tone improved peristalsis and, under the conditions used, they reduced flow. Eserine was more active in this respect than acetylcholine or 5-HT.

5. Adrenaline and hyoscine abolished peristalsis and caused the stomach and the pylorus to relax.

6. The results suggest that the peristaltic activity of the antrum is more important than the tone of the pylorus itself in controlling gastric emptying.

INTRODUCTION

A preparation has been developed for studying *in vitro* gastric peristalsis, the function of the pylorus and the part they play in controlling gastric emptying (Armitage & Dean, 1962). The technique allows pressures in different parts of the stomach and flow through the pylorus to be measured

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simultaneously. In an earlier paper, in which this technique was used, we concluded that the pylorus does not act as a true sphincter but as an integral part of the antrum (Armitage & Dean, 1963). The effects of pressure and pharmacologically active substances on this preparation are now described.

METHODS

The apparatus is shown in Fig. 1. The stomach was attached to a two-limbed cannula and suspended in a bath of 140 ml. capacity containing Krebs's solution at 32° C, gassed with 95 % O_2 and 5 % CO_2. The composition of this was NaCl 6·9 g, KCl 0·35 g, $CaCl_2 \cdot 6H_2O$

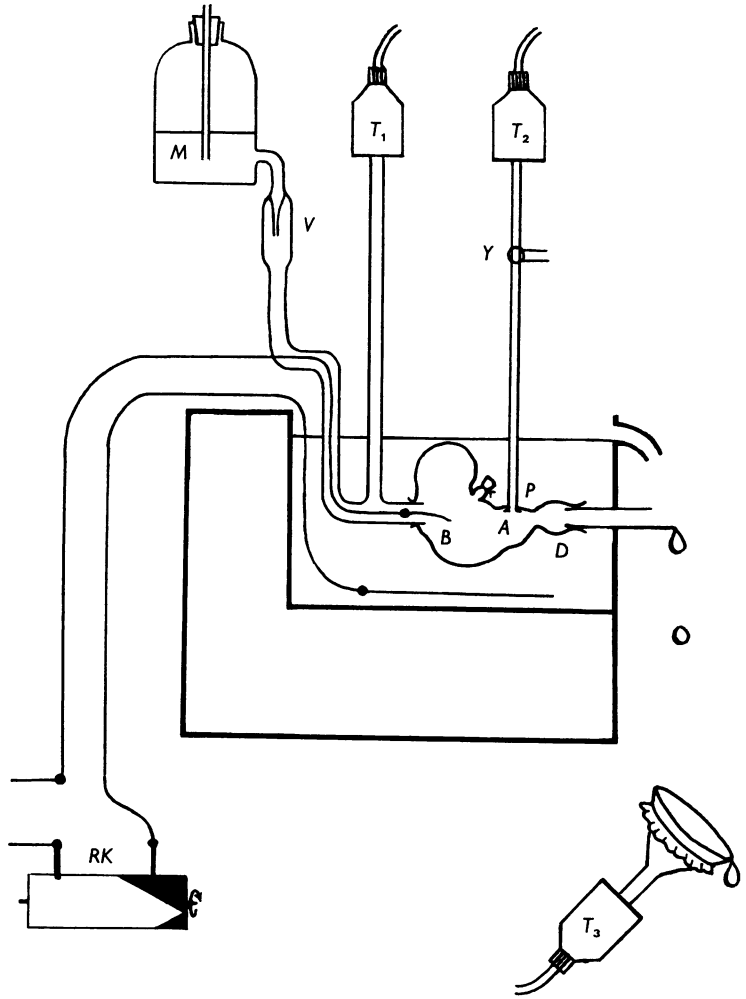

Fig. 1. The preparation and method of pressure recording. T_1, T_2, T_3, transducers; *M*, Marriotte bottle; *B*, body of stomach; *V*, valve; *A*, antrum; *Y*, three-way tap; *P*, pylorus; *RK*, rotary key for automatic intermittent stimulation of the stomach; *D*, duodenum.

0·55 g, KH_2PO_4 0·16 g, $MgSO_4.7H_2O$ 0·29 g, glucose 1 g, $NaHCO_3$ 2·1 g and distilled water to make up 1 l. The duodenum was tied to the cannula *D*. Pressure in the body of the stomach was measured by a transducer T_1 attached by an air-filled tube to one limb of the cannula and pressure in the antrum was measured by means of a second transducer T_2 attached to a narrow cannula by a tube filled with saline.

Blockage of the antral cannula by mucus produced during transmural stimulation was prevented by the slow injection of saline through the three-way tap *Y*. Any desired pressure could be applied to the stomach by raising or lowering the Marriotte bottle *M*. Fluid passing through the pylorus was measured by a device attached to a third transducer T_3 which recorded each drop as a transient rise in pressure.

The preparation could be stimulated transmurally by rectangular wave pulses using coaxial platinum electrodes (Paton, 1955) or by vagal stimulation. The vagi were dissected from the oesophagus from a point about 1 cm above the diaphragm and threaded through an electrode of the type described by Burn & Rand (1960). The peri-arterial sympathetic network was dissected out with the coeliac artery and was stimulated in the same way as the vagus. In most experiments 1 min or 3 min periods of stimulation were alternated with 1 min periods without stimulation using the rotary key RK.

Antrum–duodenum preparation. In some experiments the fundus and most of the body were excised and the two-limbed cannula was tied into the antrum at its junction with the body. No antral cannula was used in these experiments as antral pressure was recorded through the two-limbed cannula.

Assessment of tone. The tone of the preparation was assessed by photographing the stomach through a port-hole in the side of the bath. This was done after the period of stimulation so that peristalsis was not a complicating factor. The larger and more dilated the stomach at a given pressure, the lower was the tone.

Drugs. The drugs used were acetylcholine perchlorate, adrenaline bitartrate, noradrenaline bitartrate, 5-hydroxytryptamine creatinine sulphate, morphine sulphate, hyoscine hydrobromide, hexamethonium bromide, histamine acid phosphate and physostigmine sulphate. All drug concentrations have been expressed in terms of base.

RESULTS

Effect of pressure and transmural stimulation

When a pressure of up to 10 cm H_2O was applied to the stomach without electrical stimulation, the preparation was usually inert and dilated. In the exceptional cases where peristalsis occurred under these conditions it never persisted for more than a few minutes. There was no flow through the pylorus until the Marriotte bottle was raised to between 10 and 15 cm H_2O at which pressure the stomach was grossly dilated. Flow continued until the pressure was lowered to about half of that at which the pylorus had originally opened.

When the preparation was stimulated transmurally while under a low pressure (usually 5 cm H_2O) the pylorus opened and allowed fluid to flow into the duodenum. Peristalsis developed and the peak pressure in the antrum always exceeded that in the body except in the few experiments in which stimulation merely caused the whole stomach to contract. In these cases the pressures developed in the body and the antrum were the same. This behaviour was considered to be atypical and the experiment

was discontinued. Active peristalsis usually resulted when the rate of stimulation was 1–5 shocks/sec, the pulse width 1 msec and the voltage 50 V. The pressures developed under these conditions were usually submaximal. A reduction in either voltage or pulse width or an increase in the rate of stimulation reduced the response. In the experiments in which the vagus nerves were stimulated, the resulting peristalsis and flow were similar to those produced by transmural stimulation (Fig. 2) but less pronounced.

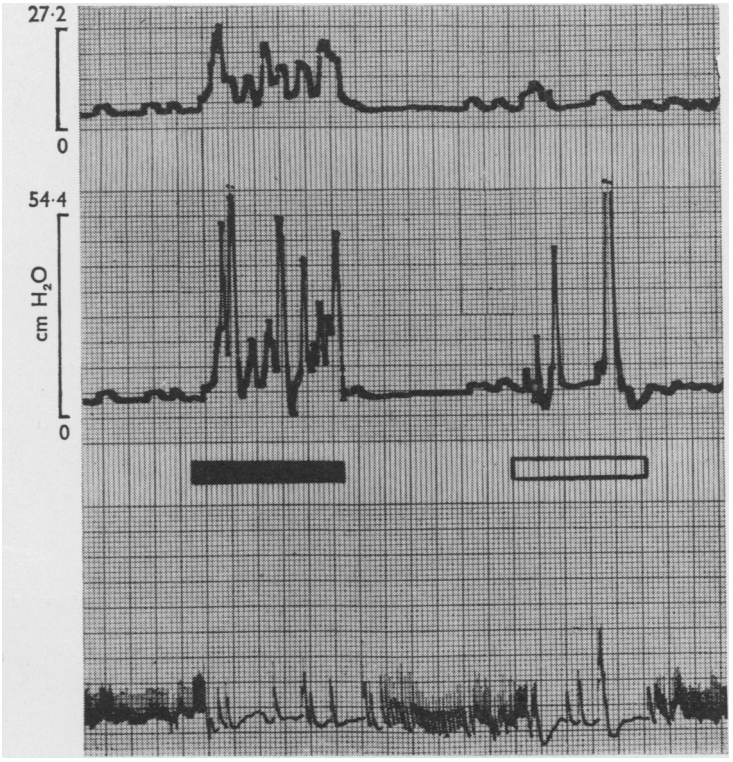

Fig. 2. Rat stomach–duodenum preparation, tracing of pressure and flow. Upper tracing: pressure in body of stomach; middle tracing: pressure in antrum; lower tracing: flow record (each vertical stroke corresponds to one drop). 2 min period of transmural stimulation indicated by black bar (5 shocks/sec, 1 msec, 50 V). Period of vagal stimulation indicated by non-shaded bar (5 shocks/sec, 0·1 msec, 10 V). Pressure calibration at left-hand side of tracing.

Sometimes intermittent stimulation continued to produce peristalsis for several hours. On other occasions the response to stimulation declined within 10–15 min, and the stomach became overdistended. The effect of varying the intragastric pressure was therefore investigated and was found to be related to the tone of the preparation. In a fresh preparation with

good tone, increasing the pressure from 5 to 7·5 cm H_2O improved peristalsis, but after a varying time the peristalsis became weaker and the stomach lost tone. Under these conditions peristalsis was dramatically improved by lowering the pressure (Fig. 3). In *A*, the preparation showed good peristalsis and episodic flow soon after being set up. In *B*, 7 min later, there was no peristalsis and the flow was almost continuous. The stomach was now greatly distended as shown by the photograph underneath the tracing. In *C*, 7 min later, after the Marriotte bottle was lowered to 2·5 cm,

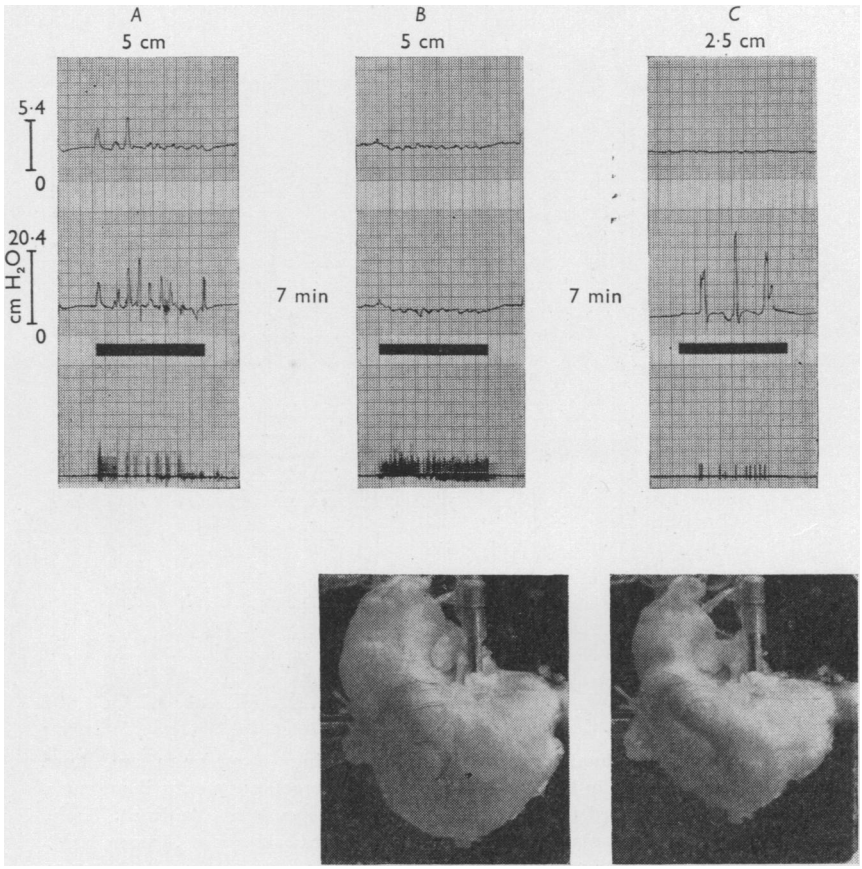

Fig. 3. Record as in Fig. 2. The photographs under sections *B* to *F* show the appearance of the stomach immediately after the period of stimulation. Peristalsis was poor when the tone was low as in *B* and *E*. When the intragastric pressure was lowered (*C* and *F*) tone increased and peristalsis improved. In this experiment tone was poorly maintained. The height in cm of the Marriotte bottle above the stomach is shown above each record and the time intervals between the various sections are shown between the records: *D* and *E* were in fact continuous records. 3 min periods of transmural stimulation indicated by black bars.

the peristalsis was vigorous, the flow was very much slower and the stomach smaller and more contracted. In *D*, 12 min later, after raising the pressure to 5 cm, good peristalsis was accompanied by episodic flow and the tone was still good, but during the next 3 min period of stimulation (*E*) the tone again became poor, there was no peristalsis and the flow was

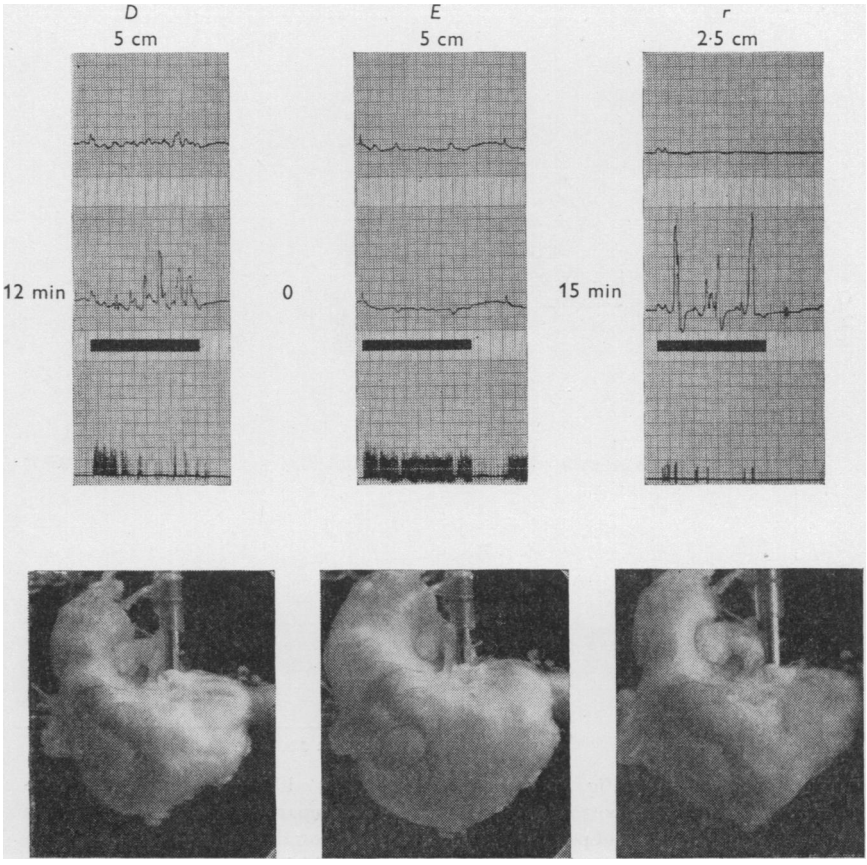

Fig. 3. For legend see opposite page.

almost continuous. Lowering the pressure again improved the performance after 15 min (*F*). This experiment showed that, when tone was good, increasing the pressure at first improved the peristalsis; but that, when tone was poor, improvement was obtained by lowering intragastric pressure. Similar observations were made on many occasions and it became standard practice to improve the performance of a failing preparation by lowering intragastric pressure.

Effect of drugs on the transmurally stimulated stomach

Acetylcholine (10^{-7} to 10^{-6} g/ml.) produced a slight increase in peristalsis and a small reduction in flow in each of six experiments. Eserine (3×10^{-8} g/ml.) always greatly increased peristaltic contractions and considerably reduced flow, even when the preparation was so fatigued that

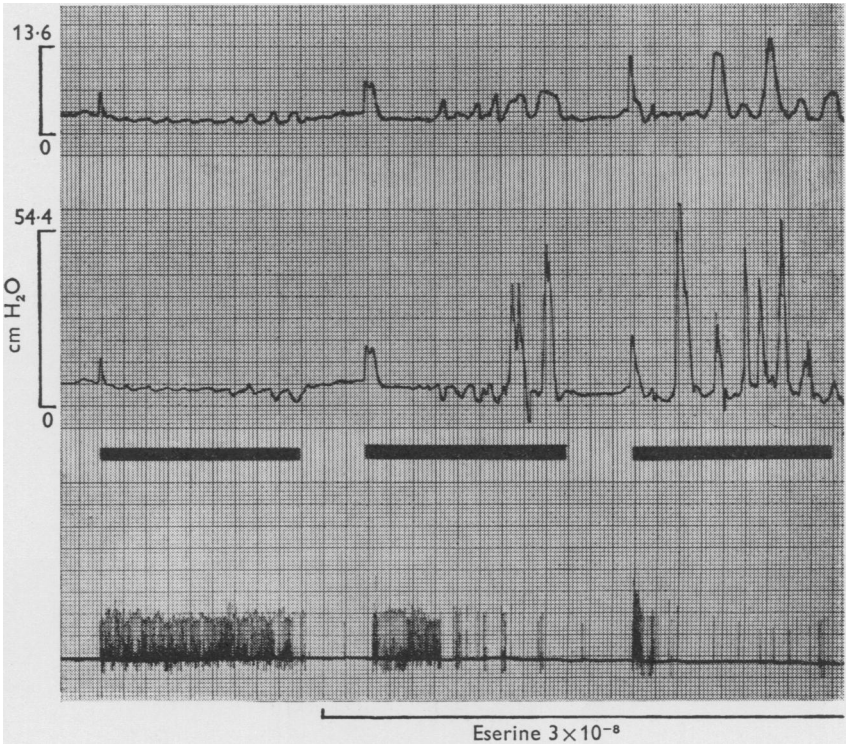

Fig. 4. Record as in Fig. 2. Eserine (3×10^{-8} g/ml.) added to the bath during the period shown at the bottom of the tracing. This preparation was a failing one as shown by the absence of peristalsis and continuous flow during the first stimulation period. Eserine rapidly restored normal activity which was maintained after removing the eserine. 3 min periods of transmural stimulation indicated by black bars (5 shocks/sec, 1 msec, 50 V).

pressure waves were small or non-existent and flow was continuous during transmural stimulation (Fig. 4).

Hexamethonium and hyoscine both abolished peristalsis. Hyoscine (10^{-7} g/ml.) abolished all contractile activity and produced rapid, continuous flow (Fig. 5). Although hexamethonium (up to 10^{-5} g/ml.) abolished co-ordinated peristalsis small rhythmic contractions persisted. Flow increased, but was still interrupted by the contractions. This effect

was observed in twelve experiments. In three experiments, however, peristalsis was not affected. Eserine (3×10^{-8} g/ml.) added to the bath in the presence of hexamethonium (up to 3×10^{-5} g/ml.) restored normal vigorous peristalsis in each of three experiments.

Adrenaline (10^{-8} g/ml.) and noradrenaline (3×10^{-8} g/ml.) abolished peristalsis and reduced the tone of the stomach. If the preparation

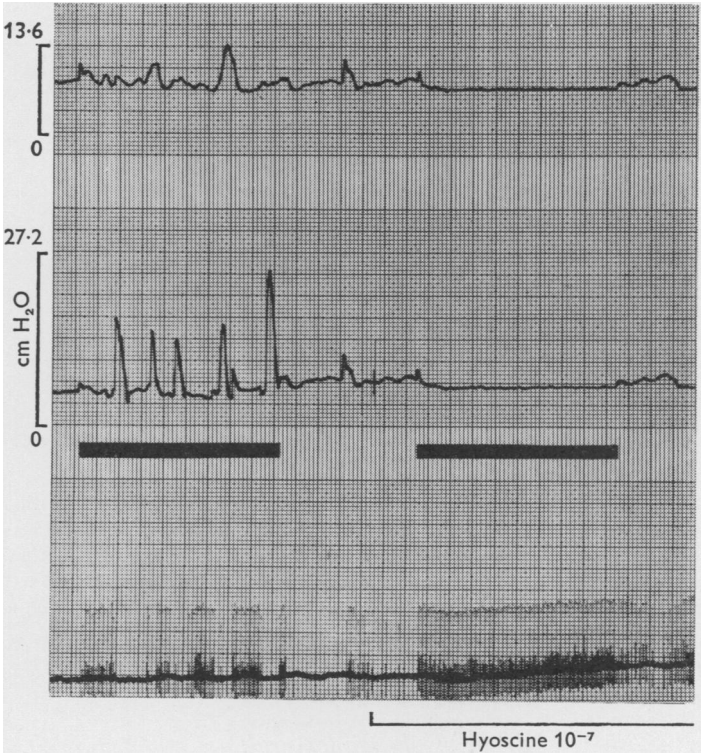

Fig. 5. Record as in Fig. 2. Hyoscine (10^{-7} g/ml.) added to the bath during the period shown at the bottom of the tracing. All peristaltic activity was abolished and flow became continuous. Persistent washing did not restore normal activity. 3 min periods of transmural stimulation indicated by black bars (2 shocks/sec, 1 msec, 50 V).

showed good flow because of a low threshold to pressure, the drugs increased flow but if the pressure was subthreshold (Fig. 6), flow through the pylorus stopped because peristalsis was abolished. Morphine (10^{-7} to 10^{-6} g/ml.) reduced peristalsis and flow was slightly increased. The effect of 5-HT was less constant. Out of forty-three experiments in which 5-HT (10^{-8} to 10^{-7} g/ml.) was added to the bath, it had no effect in thirteen and in nine of these it had been added when the preparation showed active

peristalsis. When the preparation had become less active, 5-HT in the bath produced a transient return of vigorous peristalsis in thirty experiments, one of which is illustrated in Fig. 7. Intraluminal administration of 5-HT (10^{-9} to 10^{-6} g/ml.) was less effective. In only six out of twelve experiments did it produce an increase in peristalsis. Histamine (10^{-8} to 10^{-6} g/ml.) had no effect on the preparation.

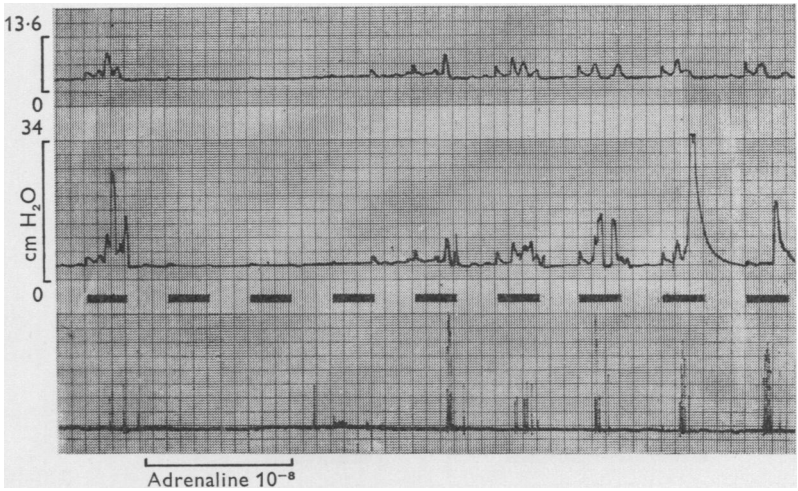

Fig. 6. Record as in Fig. 2. Adrenaline (10^{-8} g/ml.) added to the bath during the period shown abolished peristalsis. Flow was reduced in this experiment because the pressure gradient across the pylorus when the activity of the preparation was abolished was insufficient to overcome the high tone of the pylorus. Noradrenaline produced similar effects to adrenaline if added to the bath in approximately double the concentration. 1 min periods of stimulation indicated by black bars (2 shocks/sec, 1 msec, 50 V).

Effect of drugs on the transmurally stimulated antrum–duodenum preparation

Although more than half the stomach had been removed, this preparation showed rhythmic activity and episodic flow during transmural stimulation. It had been expected that flow would have been mainly affected by the tone of the pylorus but it was evident that the rhythmic activity of the antrum also exerted a considerable effect. A tracing of typical activity is shown in Fig. 8.

In two experiments adrenaline (3×10^{-8} and 10^{-7} g/ml.) increased flow and reduced antral activity (Fig. 8*a*). In a third experiment (Fig. 8*b*) in which there were only slight pressure variations in the antrum, adrenaline (10^{-8} g/ml.) increased flow, which persisted even in the absence of stimulation. This showed that the pylorus had relaxed. In two similar experi-

ments hexamethonium (up to 10^{-5} g/ml.) did not abolish contractile activity nor did it affect flow. Hyoscine (10^{-7} g/ml.), however, abolished all contractions and increased flow through the pylorus (three experiments). There was no evidence that morphine (up to 10^{-5} g/ml.) contracted the pylorus since flow was not diminished in any of three experiments. Acetylcholine (10^{-7} to 10^{-5} g/ml.) and eserine (3×10^{-8} g/ml.) both reduced flow.

Effect of stimulation of the peri-arterial nerves

Stimulation of the peri-arterial nerves at 5–20 shocks/sec, 1 m/sec and 10 V at the same time as transmural stimulation always abolished peristalsis and produced continuous flow (Fig. 9). Stimulation of the peri-arterial nerves alone had no effect.

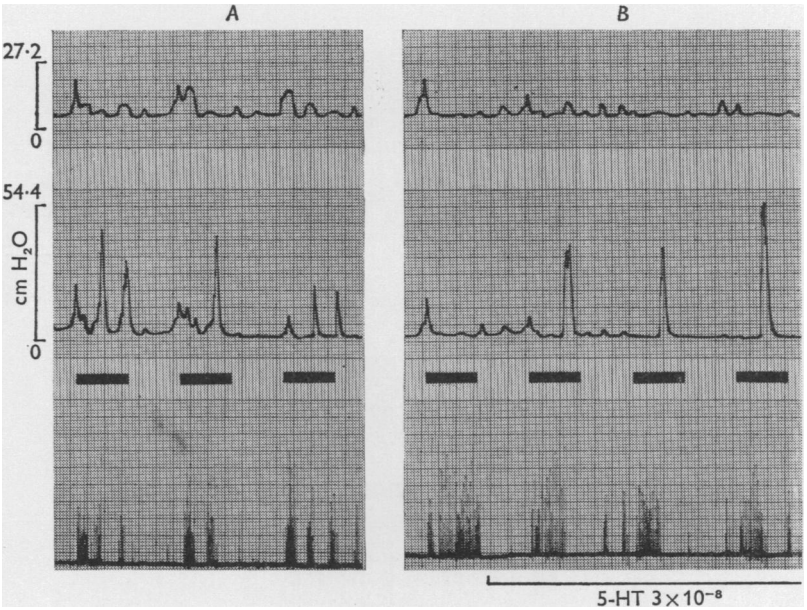

Fig. 7. Record as in Fig. 2. The time interval between *A* and *B* was 12 min. 5-HT (3×10^{-8} g/ml.) was added to the bath during the period shown. Activity in *A* is seen to be declining. In *B*, 5-HT partially restored antral activity and cut down flow. 1 min periods of transmural stimulation indicated by black bars (5 shocks/sec, 1 msec, 50 V).

DISCUSSION

The design of the apparatus, the choice of pressure-recording devices and the method by which peristalsis was induced and maintained have been discussed fully in an earlier paper (Armitage & Dean, 1962). The present experiments were concerned with the effects of pressure and of drugs on the stomach during active peristalsis. They therefore differed

from those of Paton & Vane (1963), who used an isolated pylorus-ligated stomach, in which general contractions and relaxations were measured rather than peristalsis. It is difficult to compare results since an electrical stimulus or a drug concentration which might produce or modify a single

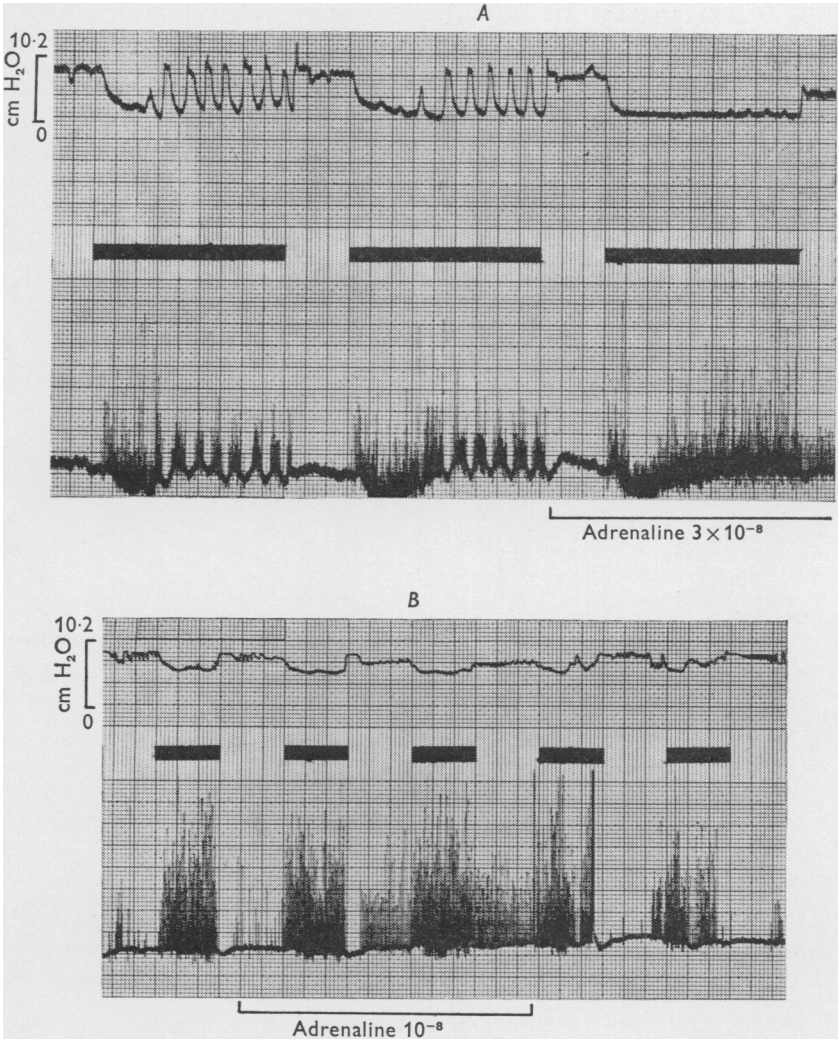

Fig. 8. Antrum–duodenum preparation. Upper tracing: pressure in antrum; lower tracing: flow record. Two different experiments shown in *A* and *B*. In a preparation with considerable activity (*A*), adrenaline (3×10^{-8} g/ml.) reduced antral activity and increased flow. In an experiment in which there were only slight pressure variations in the antrum (*B*), adrenaline (10^{-8} g/ml.) increased flow, which persisted in the absence of stimulation, showing that the pylorus was relaxed. Periods of stimulation indicated by black bars (2 shocks/sec, 1 msec, 50 V).

contraction in a pylorus-ligated stomach might not produce an observable response where co-ordinated peristalsis was concerned. For example, in the experiments of Paton & Vane (1963) 5-HT produced a marked rise of pressure mainly due to contraction of the fundus, but in our experiments, although the fundus became small and contracted in the presence of 5-HT, no sustained rise in intragastric pressure was recorded because the contents of the fundus were expelled through the pylorus.

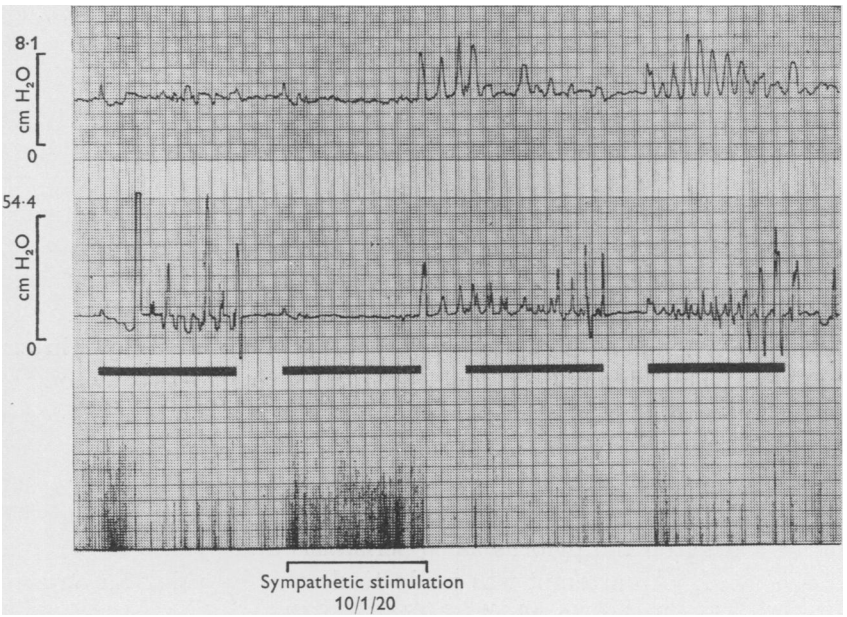

Fig. 9. Record as in Fig. 2. The first period of transmural stimulation (2 shocks/sec, 1 msec, 50 V) produced vigorous peristalsis and episodic flow. When the peri-arterial network was stimulated simultaneously (10 shocks/sec, 1 msec, 20 V) as shown at the bottom of the tracing, peristalsis was abolished and flow was continuous, showing that sympathetic stimulation opened the pylorus.

Paton & Vane (1963) showed that although transmural stimulation of the stomach excited nervous tissue there were several differences between transmural and vagal stimulation. We also found that the peristaltic response to transmural stimulation was larger than that to vagal stimulation and that the transmural response was only partially blocked by hexamethonium. Paton & Vane (1963) suggested that the transmural method of excitation activates some post-ganglionic fibres, the cell bodies of which are not innervated by the vagus. Nevertheless, transmural and vagal stimulation resulted in peristalsis of similar pattern. Most of our observations were made on the transmurally stimulated preparation.

Trendelenburg (1917) showed that the peristaltic reflex in isolated intestine easily became fatigued and failed if the intraluminal pressure was kept high for some time. The pattern of gastric peristalsis and flow were not indefinitely maintained at any particular pressure, so that our findings in rat stomach agree with this. In fresh preparations, however, an increase in the pressure was sometimes found to increase performance, though the effect was usually only transient. Peristalsis only improved if tone was maintained. It is clear that the peristaltic reflex can no longer be elicited when the stomach reaches a certain stage of distension. This may be of importance in clinical conditions such as ileus in which failure of peristalsis may be due in part to overdistension.

Contrary to expectation, vigorous peristalsis did not result in propulsion of more fluid. Flow through the pylorus was greatest when peristalsis was abolished and the pylorus relaxed, because the intragastric pressure was maintained by the Marriotte bottle. In an intact stomach containing normal food of high viscosity, abolition of peristalsis would remove the pressure gradient across the pylorus and the stomach would not empty even though the pylorus was relaxed. Drugs which raised muscle tone made peristalsis more vigorous but diminished flow through the pylorus. This diminution could have been due to two factors: (i) the periods during which the pylorus and antrum were contracted in each peristaltic wave were more prolonged; (ii) the tone of the pylorus itself was increased so that it never opened as widely as in the absence of the drug. In a whole-stomach preparation it is difficult to study the effect of a drug on the pylorus since peristalsis and pyloric tone cannot be dissociated. An attempt was made to do this by using an antrum–duodenum preparation in which the tone of the pylorus was relatively more important in affecting flow than in the whole-stomach preparation. Even in this preparation, stimulation produced flow which was usually episodic due to intermittent rhythmic contraction of the antrum and pylorus.

Adrenaline and noradrenaline showed typical activity in relaxing the stomach, including the pylorus, and abolishing peristalsis. There was no evidence in any of the experiments performed that adrenaline contracted the pylorus. Eserine produced a marked increase in peristalsis but the transport of fluid diminished. In the antrum–duodenum preparation the marked reduction in flow indicated that it had contracted the pylorus. Hyoscine had the opposite effect; it abolished peristalsis and increased flow. Hexamethonium had no effect on the tone of the pylorus.

When peristalsis was vigorous, 5-HT intraluminally or in the bath had no effect on it. This was surprising since Vane (1957) had shown that it caused a powerful contraction of the rat fundus strip, but in our pre-

paration, after the contents of the contracting fundus had been expelled through the pylorus, the pattern of peristalsis continued unchanged. When the peristalsis had failed after repeated stimulation, 5-HT produced a transient return of vigorous peristalsis with an improvement in the tone of the stomach. Intraluminal 5-HT was much less effective in the rat stomach than in the guinea-pig intestine (Bülbring & Lin, 1958; Bülbring & Crema, 1958) and this agrees with the findings of Paton & Vane (1963). It is possible that 5-HT plays little part in gastric peristalsis in the rat and that its action in restoring peristalsis in a failing preparation is due simply to improvement in the tone of the stomach in the same way that peristalsis can be improved by lowering intragastric pressure. The role of 5-HT has been investigated further by relating its output to intragastric pressure and peristalsis (Bennett, Bucknell & Dean, 1966).

The effect of morphine in blocking peristalsis is probably due to inhibition of the release of acetylcholine (Schaumann, 1957; Paton, 1957). There was no evidence from the antrum–duodenum preparation that morphine contracted the pylorus.

The rat is well known to be relatively insensitive to histamine and it was therefore not surprising that histamine did not modify the peristalsis induced by transmural stimulation.

Our results with peri-arterial stimulation agree closely with the findings of McSwiney & Robson (1931*b*) that the response of vagally stimulated stomach strips was inhibited by peri-arterial stimulation. We were never able to show motor effects of peri-arterial stimulation such as were observed by McSwiney & Robson (1931*a*) with muscle strips. Nor did our experiments on the whole stomach or the antrum–duodenum preparation provide any evidence for a motor effect of adrenaline on pyloric muscle. Adrenaline and noradrenaline have been shown to contract strips of pyloric muscle in the rabbit but not in the cat (Thomas, 1929), nor in the rat (Armitage & Dean, unpublished observations). It seems that in the rat as in the cat (Brown, McSwiney & Wadge, 1930) the sympathetic innervation of the pyloric antrum is predominantly or even purely inhibitory.

The high tone of the pylorus in the inert unstimulated rat stomach is an interesting finding not present in kitten and guinea-pig stomachs. The unstimulated rat pylorus could withstand intragastric pressures of 10–15 cm H_2O and this threshold could be decreased by hyoscine and by adrenaline in agreement with the findings of Harichaux & Thouvenot (1963). Yet transmural and vagal stimulation, instead of contracting the already tonic pylorus, relaxed it. Flow started as soon as transmural stimulation was applied, before there was any rise in antral pressure. Eserine and acetylcholine had the opposite effect. They raised stomach tone and

reduced flow. Possibly the vagal effect on the pylorus differs from that on the rest of the stomach and is due to stimulation of adrenergic neurones, some of which may be innervated by the vagus (Paton & Vane, 1963).

Clearly many factors affect gastric peristalsis, making investigations complex and results difficult to interpret. In our preparation variation in viscosity of gastric contents and in duodenal pressure have been eliminated. Our results suggest that the peristaltic activity of the antrum is more important than the tone of the pylorus itself in the control of gastric emptying.

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