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An improved method for studying the peristaltic reflex in the isolated colon

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Summary

1. A method is described for studying the peristaltic reflex in the guinea-pig or cat isolated colon, using a graded localized intraluminal stimulus consisting of a solid bolus.

2. The method gives an easy evaluation of propulsive activity and makes it possible to record simultaneously the segmental activity of the circular muscle in relation to the site of stimulation and the contractions and relaxations of the longitudinal muscle coat.

3. The velocity of propulsion, which is a reliable measure of propulsive activity, is dependent on the degree of distension and is easily affected by physical agents and nervous stimulation. A solid bolus is propelled only when there is simultaneous ascending contraction and descending inhibition of the circular musculature.

4. Since the peristaltic reflex could not be elicited from areas from which the mucosal and submucosal layers had been removed, these layers are essential for the triggering of the peristaltic reflex and for the propulsion of solid contents in the colon.

Introduction

The peristaltic reflex in the isolated intestine has been studied chiefly in the ileum by techniques similar to the original method described by Trendelenburg (1917) (for review see Kosterlitz & Lees, 1964). In the colon, propulsive activity was investigated *in situ* by Bayliss & Starling (1900), Elliott & Barclay-Smith (1904), Raiford & Mulinos (1934a, b), Auer & Krueger (1947), Bozler (1949b), Hukuhara & Miyake (1959) and in the isolated organ by Langley & Magnus (1905), Tyrode (1910), Currie & Henderson (1926), Lembeck (1958), Lee (1960), Hukuhara, Nakayama & Nanba (1961), Hukuhara & Neya (1968), and MacKenna & McKirdy (1969).

Generally, in the isolated intestine, the peristaltic reflex was elicited by distending the intestinal wall with fluid and the amount of ejected fluid was taken as the measure of the propulsive activity. A solid bolus was used as the stimulus by Bozler (1949b), Daniel, Wachter, Honour & Bogoch (1960) and Nakayama (1962) in the small intestine and by Bayliss & Starling (1900), Elliott & Barclay-Smith (1904), Langley & Magnus (1905), Tyrode (1910), Auer & Krueger (1947) and Bozler (1949b) in the colon.

There is no doubt that, for the greater part of the colon, distension with a solid bolus is the more physiological stimulus for the triggering of the peristaltic reflex.

Moreover, a localized stimulus permits a more detailed study of the behaviour of the intestinal segments adjacent to the site of stimulation, and of the time course of the responses of the muscular layers. To our knowledge no attempt has been made to evaluate quantitatively the propulsion of solid contents in the colon. In this paper a method is described for studying the peristaltic reflex in the isolated colon which permits the use of a localized graded intraluminal stimulus, the quantitative evaluation of the propulsive activity, the recording of the activity of the longitudinal and circular musculature at various levels and the stimulation of the parasympathetic and sympathetic outflows to the colon.

Methods

Guinea-pig isolated colon

Female guinea-pigs, weighing between 320 and 400 g, were anaesthetized with ether and laparotomized. The distal colon was exposed, leaving the vascular supply intact. The symphysis pubis was then split and the pelvic bones forcibly separated so that the pelvic nerves running in the mesocolon could be isolated. In order to maintain the nervous supply to the entire colon intact, care was taken to preserve the orally directed fibres. The entire distal colon, from the ampulla to a point 1 cm above the branching of the inferior mesenteric artery, was carefully isolated and gently removed together with the nerves and the artery. The total length of the removed colon ranged from 6·0 to 7·3 cm. The colon was transferred to a 100 ml organ bath containing Tyrode solution maintained at 35·5° C and bubbled with a mixture of 95% oxygen and 5% carbon dioxide, and mounted horizontally with the oral end tied to a fixed Perspex rod. The free aboral end was connected to a Basile L1 isotonic transducer exerting a tension of 2–2·5 g. For stimulation of the nervous supply of the colon, silver bipolar fluid electrodes were placed around the inferior mesenteric artery and pelvic nerves. For transmural stimulation two silver sheets (3 × 50 mm) were mounted in the bath in parallel, both facing the organ.

The reflex was elicited by distending a thin rubber balloon which had been pushed into the lumen through the fixed oral end of the colon (Fig. 1). The balloon, 5 mm long, was mounted at the end of a polythene tube (internal diameter 0·4 mm, external diameter 0·7 mm) and distended rapidly (5 s) with warm (36° C) water by means of a microsyringe. The injected volume ranged from 0·01 to 0·2 ml. When 0·01 and 0·2 ml of water were injected, the diameter of the balloon increased to 1·5 and 7 mm, respectively. Since the radial stretch of the intestinal wall is the adequate stimulus for triggering of the peristaltic reflex (Kosterlitz & Lees, 1964), we considered the volume injected into the balloon to be a measure of the localized distension. The balloon was initially placed at a distance of 8–10 mm from the oral end of the colon. After the balloon had been propelled by the intestine to the aboral end, it was emptied and drawn back to the oral end. For a record of the displacement of the bolus, the balloon was connected to an isotonic transducer exerting a tension of 200 mg. The mean velocity of propulsion (mm/s) was calculated by measuring the time required by the bolus to cover a known distance (usually 4–5 cm).

The size of the guinea-pig colon did not allow us to record the segmental activity of the circular musculature by means of force transducers applied to the surface of the colon, as was possible in the cat. In fact, we could not find a force transducer capable of recording the movements of the circular muscle without impairing propulsion at the same time. The behaviour of the circular musculature in the guinea-pig was therefore deduced from the changes in the diameter of the colon measured on photographic records taken during the peristaltic reflex or from the changes in the pressure in the balloon.

All the records were made on a Battaglia-Rangoni M-10 polygraph.

Cat isolated colon

Cats of either sex, weighing 2–3·5 kg, were used. Anaesthesia was induced with ether and maintained by a nitrous oxide-halothane mixture. During the operative procedure the animals were maintained on artificial respiration. The abdomen was opened along the midline and the entire colon exposed. The trunks of the common colonic artery, the inferior mesenteric artery, and the colonic vein were cannulated. The pelvic nerves were exposed on both sides as they arise from the sacral plexus and were cut as close to their origin as possible. After splitting the symphysis pubis, the entire colon from the ileocaecal valve to the ampulla, together with the adjoining mesocolon and the colonic branches of the pelvic nerves, was removed. After washing the lumen, the bowel was mounted horizontally (Fig. 1) in a 400 ml organ bath as described for the guinea-pig.

In the cat, the thickness of the wall did not permit proper nutrition of the organ from the surrounding medium and the reflex could be elicited for only a short period after mounting. The colon was therefore perfused through the cannulated arteries with oxygenated Tyrode solution containing polyvinylpyrrolidone (35 mg/ml) by means of a Sigmamotor finger-pump, at a rate ranging from 1·5 to 3 ml/min with a perfusion pressure of 65 to 80 mmHg (1 mmHg≡1·333 mbar). The fluid was drained through the cannulated vein. In perfused preparations, the propulsive activity was maintained for 4–5 h after mounting.

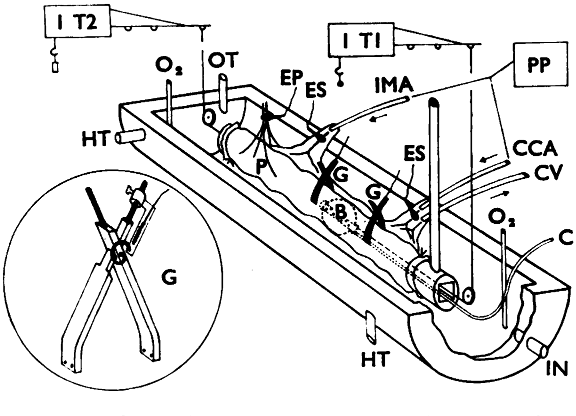

FIG. 1. Diagram of the experimental arrangement for studying the peristaltic reflex in the cat isolated colon. HT, Inflow and outflow tubes from hot water jacket; IN, inflow tube to organ bath; OT, outflow tube from organ bath; CCA, cannula inserted in the common colonic artery; IMA, cannula inserted in the inferior mesenteric artery; PP, peristaltic pump connected to the arteries; CV, cannula inserted in the colonic vein; ES, fluid electrodes around periarterial plexuses; EP, fluid electrode around pelvic nerves (P); B, intraluminal balloon; C, cannula for filling the balloon; I T1, isotonic transducer recording the displacement of the bolus; I T2, isotonic transducer recording longitudinal movements; G, force transducers recording the segmental activity of circular musculature.

The reflex was elicited as described for the guinea-pig. The balloon, 12 mm long, was filled through a polythene tube with warm water (36° C) over a period of 5 s. The injected volume ranged from 0·2 to 2·5 ml, corresponding to an increase in the diameter of the balloon of 6 to 18 mm. The displacement of the bolus was recorded as in the guinea-pig. The isotonic transducer used for the recording of longitudinal movements was loaded with 8–12 g. Three pairs of electrodes were placed around the pelvic nerves and the arteries. The two pelvic nerves were stimulated through the same electrode.

For the record of the movements of the circular musculature, two force transducers were applied (3·5–4 cm apart) to the serosal surface of the colon. Because isometric strain-gauges would have interfered with the inhibitory responses and impaired the propulsion, a type of auxotonic force transducer was used (Fig. 1G) which allowed the circular musculature to move freely. The strain-gauge assembly consisted of two Perspex arms (5 cm long, 0·5 cm wide, and 2·5 mm thick) joined together by a pin at a point 3·5 cm from the base ; the pin served as an axis around which the arms could pivot freely. One arm supported a 3 × 15 mm strip of phosphor-bronze sheet of 0·1 mm thickness, to which a strain-gauge (0·6/120 LB, 11K, HBM) was bound by means of adhesive (PR 9246/00, Philips). The other arm was connected to the central tip of a spiral watch spring (0·5 mm wide, 0·1 mm thick), placed around the axis ; the peripheral tip of the spring was 5 mm distant from the centre and pressed against the free end of the metal strip bearing the strain-gauge. The maximal mutual displacement of the two arms was 15 mm. The metal strip and the spring were arranged in such a way that the displacement resulted in a slight linear change in tension at the extremities, ranging from 0 mg, when separated maximally, to 300 mg, when in close opposition. The instrument was calibrated by fixing one arm and applying calibrated weights to the other arm tangentially, or by closing the two arms by a known distance. The arms of the strain-gauge assembly were tied to the serosa 8 to 10 mm apart to exert an initial tension of 150–200 mg.

Results

Pattern of the reflex

Guinea-pig

The first response of the colonic musculature to distension by the balloon was a phasic contraction of the longitudinal coat (Fig. 2). In preparations showing a high degree of tone or of spontaneous motility (18·4% of experiments) the contractor response of the longitudinal musculature was preceded by a relaxation or a cessation of motility (Fig. 3). During the phasic contraction of the longitudinal musculature, a contraction of the circular muscle started above the bolus and travelled in an oral-aboral direction leading to propulsion. During the entire period of propulsion there was a tonic and progressively increasing contraction of the longitudinal musculature.

The threshold distension necessary to elicit the peristaltic reflex varied between preparations. The mean threshold value (±S.E.) of distension was equivalent to $0{\cdot}049 \pm 0{\cdot}0028$ ml H_2O (seventy-five experiments) injected into the balloon. In each experiment the threshold volume remained constant during a 6–8 h period.

The propulsive activity, when evaluated as velocity of propulsion, did not follow the " all-or-none law ". In fact, in each preparation there was a relationship between the degree of distension and the velocity of propulsion (Fig. 4). The average distension, which caused maximal velocity of propulsion, corresponded to 0·11 ±0·0029 ml H_2O (eighty-two experiments) injected into the balloon. The mean velocity at threshold volume was 0·55±0·029 mm/s (seventy-five experiments), while the mean maximal velocity was 1·51 ±0·061 mm/s (eighty-two experiments).

The latency between the filling of the balloon and the beginning of the longitudinal response varied greatly between preparations. In each experiment, however, it was dependent on the degree of distension. At maximal velocity the mean duration of the latent period was 14·41 ±0·75 s (seventy-one experiments).

Some preparations (8% of experiments) were able to propel even the empty balloon, apparently without any distension of the wall. In very few preparations (5·7% of experiments) no degree of distension could elicit propulsion.

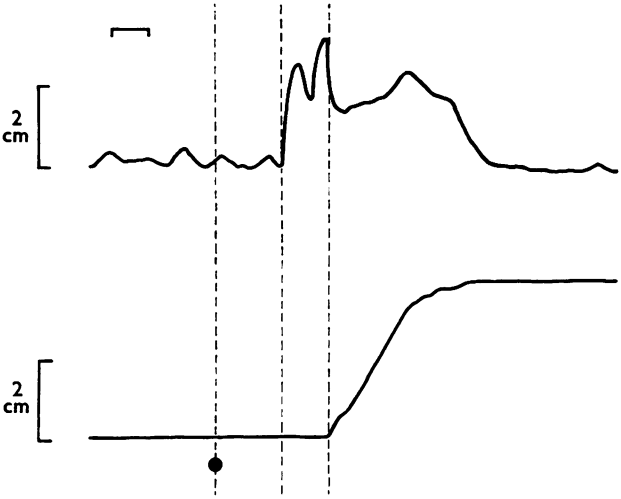

FIG. 2. Peristaltic reflex in the guinea-pig isolated distal colon. Upper tracing, record of longitudinal movements, shortening upwards; lower tracing, record of displacement of the bolus, aboral movement upwards. The mark (●) indicates distension of intraluminal balloon. Note the time lag and the biphasic contraction of longitudinal musculature in relation to the beginning of propulsion. Time mark: 10 s.

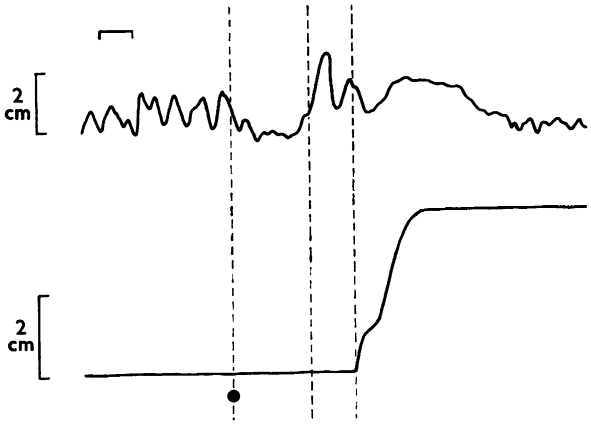

FIG. 3. Peristaltic reflex in the guinea-pig isolated distal colon. Tracings as in Fig. 2. The mark (●) indicates distension of intraluminal balloon. Note the relaxation of the longitudinal musculature before the contractile response. Time mark: 10 s.

Cat

As in the guinea-pig, the distension of the colonic wall caused first a contraction of the longitudinal musculature. The response of the circular musculature began after a latent period, the duration of which depended on the degree of distension; there was contraction above and relaxation below the bolus. Such a behaviour was clearly shown when the balloon was placed between the two strain-gauges which recorded the movements of the circular musculature (Fig. 5).

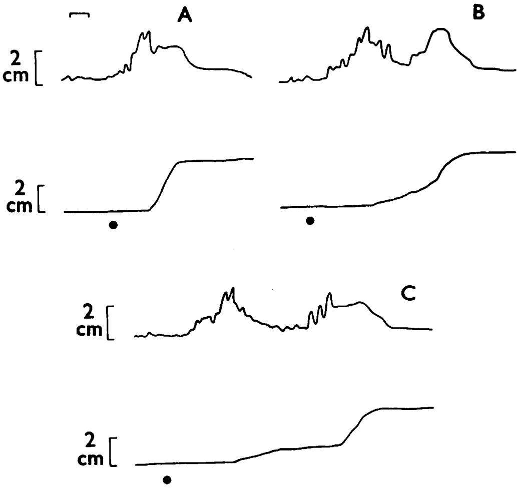

FIG. 4. Guinea-pig isolated distal colon. Peristaltic reflex elicited by various degrees of distension. Tracings as in Fig. 2. The marks (●) indicate distension of intraluminal balloon with volumes of 0·12 (A), 0·08 (B) and 0·04 (C) ml. Note the relationship between the degree of distension and the velocity of propulsion. Time mark: 10 s.

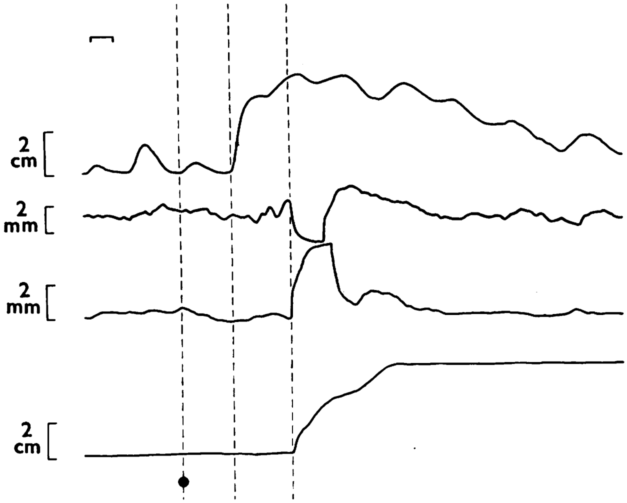

FIG. 5. Peristaltic reflex in the cat isolated colon. From top to bottom records of: longitudinal movements; movements of the circular musculature below the bolus; movements of the circular musculature above the bolus; oral-aboral displacement of the bolus. The mark (●) indicates distension of the intraluminal balloon placed between the two strain-gauges recording the activity of the circular musculature. Time mark: 10 s.

In a number of preparations (25% of experiments) propulsion through the entire colon, even at a distension causing maximal velocity, was accomplished in successive peristaltic waves with interposed periods of rest. In 12·5% of the experiments, no degree of filling of the balloon was able to elicit propulsion.

As in the guinea-pig, the threshold value of distension varied with preparations; the mean value was 0·67 ± 0·016 ml (thirty-five experiments). The velocity of propulsion also differed greatly between preparations. However, as with the guinea-pig, the velocity of propulsion increased when the degree of distension was increased. The average degree of distension that caused maximal velocity was 1·64 ± 0·068 ml (forty-two experiments). The mean velocity was 0·38 ± 0·057 mm/s (thirty-five experiments) at threshold volume and the mean maximal velocity was 1·08 ± 0·099 mm/s (forty-two experiments). The mean duration of the latent period between filling of the balloon and beginning of the longitudinal response was 17·38 ± 1·63 s (thirty-six experiments) at distensions that caused maximal velocity.

A few preparations (14·5% of experiments) were able to propel even the empty balloon.

Effects of temperature and of nervous stimulation

In the guinea-pig, lowering of the temperature of the bath progressively increased the latent period and the threshold of distension and it decreased the rate of propulsion and the degree of shortening of the longitudinal muscle. Between 21° and 25° C propulsion occurred without the phasic response of the longitudinal musculature. Below 21° C the bolus was no longer propelled. The relationship between maximal velocity and temperature is shown in Fig. 6.

In both the guinea-pig and the cat, stimulation of the pelvic nerves enhanced the propulsive activity. On the other hand, in both species stimulation of the periarterial nerves impaired the propulsive contraction. A different pattern of inhibi-

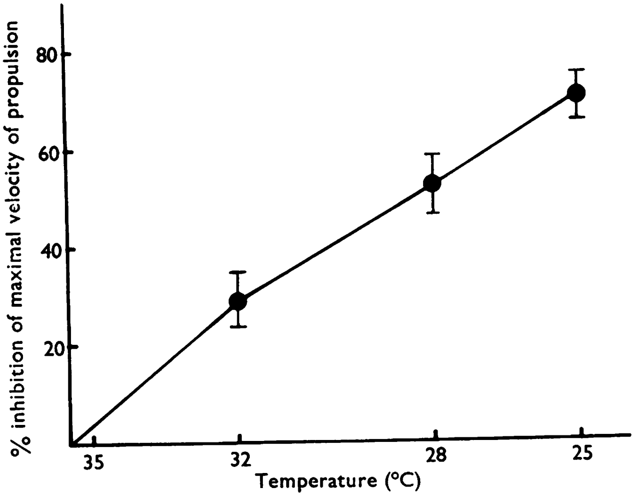

FIG. 6. Effect of lowering of the bath temperature on the propulsive activity of the guinea-pig isolated distal colon. Abscissa, temperature (°C); ordinate, inhibition of maximal velocity of propulsion (velocity at 35·3° C = 100). Each point represents the mean of seven experiments. Vertical lines indicate S.E. of mean.

tion was produced in the guinea-pig by transmural stimulation at frequencies higher than 10/s when propulsion was arrested due to contraction of the circular musculature both above and below the bolus.

Localized removal of the mucosal and submucosal layers

To carry out this procedure, the colon was turned inside out by slipping it over a glass rod, and a ring of mucosa of 0·5–0·8 mm length in the guinea-pig and of 15–20 mm length in the cat was then removed; in the guinea-pig it was scraped off with a scalpel and in the cat it was dissected out with the underlying submucosa. The colon was then returned to its normal position. In order to obtain a tract of sufficient length with intact mucosa both above and below the amucosal segment, the mucosa was removed from the central part of the colon. The experiments were carried out in eight guinea-pigs and five cats. At the end of the experiments the integrity of the underlying circular musculature was checked by histological examination.

When the balloon was inserted into the oral part of the colon, the propulsion ceased when the bolus reached the amucosal segment. In the aboral part of the colon, below the amucosal segment, the bolus was propelled normally (Fig. 7). It would appear that removal of the mucosal and submucosal layers impairs mainly the response of the circular musculature, because, when the empty balloon was placed in the segment deprived of the mucosa and then filled, the contraction of the longitudinal coat could still occur but there was no propulsion.

Discussion

The pattern of the reflex elicited by a solid bolus and recorded by the method described in this paper differs in some aspects from that obtained with methods usually employed in the ileum. For instance Lee (1960), using in the colon a method described for the ileum (Bülbring, Crema & Saxby, 1958), found the longitudinal contraction subsequent to distension to be rather irregular without a distinct " preparatory phase ". On the other hand, we could usually distinguish, both in the guinea-pig and the cat, a phasic contraction of the longitudinal coat which developed before the start of the propulsion. Moreover, Lee (1960) found that stimulation of the pelvic nerves arrested propulsive activity whereas in our experiments stimulation of these nerves increased the propulsion of a solid bolus.

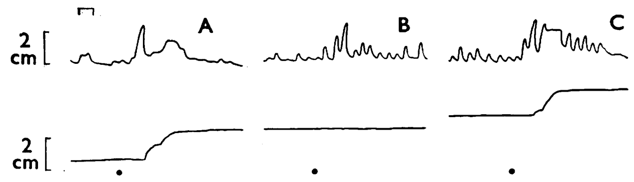

FIG. 7. Effect of localized removal of the mucosa on the peristaltic reflex in the guinea-pig isolated distal colon. Tracings as in Fig. 2. The marks (●) indicate distension of intraluminal balloon placed in the proximal normal segment (A), in the amucosal segment (B) and in the distal normal segment (C). Note that the propulsion stops as the bolus reaches the segment deprived of mucosa. The distension in the amucosal segment elicits contraction of longitudinal musculature but there is no propulsion. Time mark: 10 s.

There is no doubt that a diffuse stimulus, due to raising the hydrostatic pressure in the lumen, and a localized stimulus, due to a solid bolus, probably trigger the peristaltic reflex in different ways. We believe that the main advantages of our method are as follows: (1) The stimulus is similar to that occurring physiologically in the colon. (2) It is possible to elicit the reflex in different parts of one and the same preparation, and thus study the effects of localized changes, for example removal of the mucous membrane. (3) Since a solid bolus is propelled only when there is simultaneous ascending contraction and descending inhibition, the behaviour of the circular musculature in relation to the position of the bolus can be studied. It is therefore possible to investigate the effects of drugs and nervous stimulation on the mechanisms subserving propulsion. (4) It is possible to evaluate quantitatively the propulsive activity. The velocity of the movement of the bolus seems to be a valid parameter for the measurement of the efficacy of the peristaltic reflex. In fact, this parameter permits the continuous analysis of the efficiency of the intestinal segments that are recruited progressively. The velocity of propulsion seems to be very sensitive to nervous stimulation, physical agents and drugs.

The measurement of the velocity of propulsion of a solid bolus is not affected by changes in the capacity of the intestine produced by changes in the tone of the intestinal wall. On the other hand, a quantitative evaluation based on measurement of the amount of ejected fluid may be vitiated by changes in the capacity of the intestine. Moreover, while some of the fluid in the intestinal lumen may be ejected as a consequence of a non-propulsive contraction (MacKenna & McKirdy, 1969), any displacement of a solid bolus requires a well coordinated peristaltic wave. In addition to the velocity of propulsion, changes in threshold and latent period can be measured readily.

The experiments carried out on the effects of removal of the mucous membrane from a segment of colon are an example of the advantages of the new method. The role of the mucosa and submucosa in initiating the peristaltic reflex is still not clear. According to Bülbring, Lin & Schofield (1958) and Beleslin & Varagić (1958), destruction of the mucosa abolishes the peristaltic reflex in the ileum, while contrary results have been reported by Ginzel (1959a, b). Diament, Kosterlitz & McKenzie (1961) found that spontaneous shedding of the superficial layers of the mucosa during an experiment does not decrease the efficiency of the peristaltic reflex. In our opinion these discrepancies are due to the kind of stimulus employed and the difficulty found in removing the mucous membrane from the entire preparation. Our experiments, in which a localized piece of mucosa was removed, clearly show that the propulsion of the solid bolus ceases in the amucosal segment and then starts again in the contiguous normal segment. Since the reflex can be elicited by simply stroking the mucous membrane (Hukuhara & Miyake, 1959) and an empty balloon sometimes causes propulsion without any apparent distension of the wall (Bozler, 1949a and present experiments) it would seem that the receptors essential for the triggering of the peristaltic reflex are located either in the mucosal or in the submucosal layers of the colon.

The fact that the propulsion of a solid bolus is the result of differential and well coordinated contractions and relaxations of the circular musculature in relation to the site of stimulation is confirmed by the observation that transmural stimulation, in spite of an increase in the contraction above the bolus, prevents or arrests propulsion by a contraction of the circular musculature below the bolus. Thus the stoppage of propulsion of the bolus is not a consequence of an inhibition of the contractile mechanism but the result of an uncoordinated contraction of the circular muscle. Such inhibitory mechanism is different from that observed by Varagić & Kazic (1966) in the ileum, in which high frequency transmural stimulation inhibits the propulsion of fluid by impairing the contractile responses.

Since the individual variability of propulsive activity of the colon is less in the guinea-pig than in the cat, the former seems more suitable for the quantitative evaluation of the action of various agents on the peristaltic reflex. On the other hand, the segmental activity of the circular musculature of the cat colon is more easily recorded and this preparation is therefore particularly suitable for an analysis of the action of agents on the different components of the peristaltic reflex.

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