THE question of an enteric nervous mechanism capable of independent reflex activity has been under investigation since Nothnagel (1) and Luederitz (2) first noted that stimulation of the gut usually produces a contraction orad but not caudad. Luederitz also observed that this response could still be obtained after denervation and, therefore, considered it to be due to a local reflex which later was called the myenteric reflex by Cannon (3).

Although confirmed by Bayliss and Starling (4), partly also by Magnus (5) and Cannon (3, 6), recent investigators have cast doubt on the significance and even the existence of this reflex. In extensive studies on the rabbit, Alvarez (7, 8) could not find it. Ganter (9) and Rodin (10) and others failed to observe it in human subjects (cf. 7). Raiford and Mulinos (11, 12), on the other hand, demonstrated a reflex similar to the myenteric reflex in transplanted segments of the colon. They found that stroking the mucosa produced a contraction of the circular muscles above and of the longitudinal muscles below the stimulated region. Hukuhara (13) noted that pinching caused a stronger muscular response orad than caudad.

This question was reinvestigated using a variety of methods and preparations. The results obtained confirm the existence of an enteric reflex which involves a synaptic mechanism. It can be elicited by mild mechanical stimulation such as stroking the mucosa, or longitudinal stretching. These stimuli produced, on the oral side of the stimulated region, an augmentation of rhythmic activity or a prolonged powerful contraction with temporary cessation of rhythmic movements. This response does not progress along the intestine.

As will be shown below, the reflex response varies considerably under different conditions. The only constant characteristic of the reflex is its polarity. Therefore, in the following, all responses which show this property will be called myenteric reflex. The question whether the reflex also involves a descending inhibition, as claimed by some authors, will be discussed later.

In view of the simplicity of the experiments described below it may seem surprising that so much difficulty has been encountered in demonstrating the essential facts concerning enteric reflexes. The variability in the responses obtained is partly due to the use of abnormal, crude stimuli by many investigators. Confusion has also been introduced by the term peristalsis. The myenteric reflex comes into play in the transport of a bolus. It is erroneous, however, to assume that every wave of contraction in smooth muscle is caused by the reflex. Simple waves of contraction, such as those of the stomach and ureter, are due to muscular conduction, whereas peristalsis caused by a bolus is a much more complex phenomenon (14). It is unfortunate that the term peristalsis has been used to designate these two vastly different types of activity. The term reflex peristalsis, therefore, has been proposed for the peristaltic waves due to the myenteric reflex.

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METHODS

Anesthetized dogs (morphine, 3 mg/kg. subcutaneously and sodium barbital, 200 mg/kg. intraperitoneally), and rabbits (sodium pento-barbital intravenously) were used. Short lengths of intestine were exposed and covered with dry cotton except during observation. The room was kept at a temperature of 27° or higher and was often humidified. Electric stimuli were applied through platinum hand electrodes. Repetitive stimuli at a frequency of 20 to 50 shocks per second, supplied by a thyrotron stimulator discharging over a transformer, were used.

Action potentials were recorded by the technique described previously (22). Monophasic potentials were obtained by placing one lead on a small mass of tissue firmly tied off by a silk thread, the other lead on another region at the same level (16). The resulting injury diminished spontaneous motility in this region but did not prevent the passage of a peristaltic wave.

RESULTS

Normal Stimulus. In the dog's intestine, lateral distension, produced by spreading a hemostat introduced into the lumen, increases the strength of the rhythmic contractions on the oral side without any noticeable effect caudally. Usually, however, a stronger response is elicited by stroking the mucosa with a blunt instrument introduced through a small opening. Stroking the serous surface on the other hand, is ineffective. It may be concluded, therefore, that specific receptors for the myenteric reflex responding to mild mechanical stimulation are present in the mucosa.

The response to stroking probably is important for the initiation of reflex peristalsis by the introduction of a bolus. That distension is not necessary is indicated by the fact that a bolus so small that it does not distend the wall of the relaxed intestine can elicit peristalsis. Furthermore, stroking the mucosa in the region of a bolus often starts a peristaltic wave under conditions where the responsiveness of the intestine is low.

Curiously enough, in the rabbit's small intestine, stroking the mucosa never elicits a response. Lateral distension is effective only in rather sensitive preparations. However, longitudinal distension, gently performed by stretching a short piece of gut with the fingers, produces strong ascending contractions of the circular muscles without any effect on the aboral side (fig. 1). In the upper part of the small intestine, the response may extend orad for 5 to 10 centimeters and may last for half a minute, whereas farther down in the intestine often only a brief contraction or none at all is produced by the stimulus. The contractions are often rhythmic, differing from spontaneous activity only by the participation of the circular muscles, or they are single contractions lasting for as long as 20 seconds.

The differences in the character of the effective stimulus in the preparations studied are probably related to the different consistency of the intestinal contents under normal conditions and may be considered an adaptation to the prevailing type of mechanical stimulus.

That smooth muscle can also be stimulated directly by stretching has been shown by a study of action potentials in the ureter (17), but, since the response so elicited
has no polarity and consists of a single all-or-none conducted impulse, it evidently has no relation to the myenteric reflex.

_Effect of Electric Stimulation._ Luederitz (2) reported that electric stimulation produced chiefly an ascending contraction in the rabbit's intestine, but Alvarez _et al._ (7, 18) found the responses very variable, spreading, on the average of many observations, slightly farther caudad than orad.

In my own studies, the effects of electric stimulation varied in different parts of the intestine and under different conditions, but were reproducible. Strict polarity of the response was always observed in the proximal colon of the rabbit. Electric stimulation of a small region in this part of the intestine increased the activity of the haustra, increased the tonus of the circular muscles and often caused rhythmic contractions of the longitudinal muscles orally, never on the other side (fig. 2A).
In most parts of the rabbit's small intestine, electric stimulation can produce ascending and descending contractions. However, stimuli not more than 50 per cent above threshold always give strictly polar responses in all parts of the intestine (fig. 2B). Such weak stimuli are effective only after they have been applied for 5 to 10 seconds, showing the importance of summation in this reflex.

Weak electric and mechanical stimulation produces strong ascending and descending contractions during the period of hyperexcitability following the cessation of circulation. Similar nonpolar responses which are produced by stretching and are abolished by low concentrations of nicotine were obtained in isolated intestine by Fleisch (19).

Whether the descending response to electric stimulation, which normally has a higher threshold than the ascending contraction, is a part of the myenteric reflex or belongs to some other reflex mechanism cannot be decided at present. It is possible that the polarity of the reflex is only relative, stimulation causing a quantitatively different effect orally and aborally. These considerations are important for the question of anti-peristalsis which will be discussed later.

Muscular Response. The character of the response varies in different preparations and depends on the strength of stimulation. In the dog's small intestine, stroking always increases the strength of the spontaneous contractions without changing their frequency. This agrees with the observations on peristalsis which, likewise, usually is rhythmic (14).

Action potentials show a characteristic difference between duodenum and ileum. In the former, spikes are very prominent and have a high frequency, whereas, in the latter, the slow potentials (20–22) are very large. In the ileum of the rabbit the reflex responses always remain rhythmic, whereas in the duodenum the response to stretching may be sustained for 8 to 10 seconds (fig. 3).
Bayliss and Starling (4) and others (3, 13) observed that pinching the intestine usually produces a descending inhibition and that a wave of inhibition precedes peristaltic waves. Auer and Krueger (23) presented evidence for a wave of inhibition preceding both peristalsis and anti-peristalsis in the colon of the rabbit. They based their conclusion mainly on the observation that, if two peristaltic waves approach each other, one or the other stops. This, however, is not a constant phenomenon, because Alvarez (7) and I have observed strong and opposing contractions on both sides of a bolus. In my experiments, the colon usually was at complete rest, except for the region orad to the bolus, as indicated by the absence of action potentials. In the dog's small intestine, electric activity and motility, as far as it could be observed visually, were not diminished ahead of a peristaltic wave.

One may conclude from the literature on the subject that descending inhibition sometimes is associated with the myenteric reflex but that it is not a constant phenomenon. It is doubtful, therefore, whether it should be considered as a part of the myenteric reflex.

The observations by Youmans, Meek and Herrin (24) perhaps have an important bearing on this problem. These authors found that distension can cause inhibition of the denervated intestine extending beyond the stimulated region. Although this effect does not seem to have any polarity, it might, under appropriate conditions, mask a descending excitatory effect or cause inhibition without suppressing the strong ascending contractions. Bayliss and Starling themselves report that pinching sometimes caused ascending as well as descending inhibition which agrees with the conclusion that inhibition is not polar and is not an essential part of the myenteric reflex.

Coordination of Circular and Longitudinal Muscles. In reflex peristalsis the contractions on the caudal side of a bolus usually involve only the longitudinal muscles as indicated by the fact that they do not narrow the lumen, whereas the ascending contractions constrict the intestine and cause elongation, showing that the contraction of the circular muscles is predominating. In agreement with these observations Raiford and Mulinus (11, 12) found that stimulation of the colon of the dog caused contraction of the longitudinal muscles caudad, of the circular muscles orad. The studies of Auer and Krueger (23) on the colon of the rabbit also are essentially in agreement with these conclusions.

To explain the observations just described it is not necessary to assume a separate nervous control of the two muscle layers. Quite generally, during weak contractions, chiefly the longitudinal muscles are active, producing a shortening of the intestine, whereas strong contractions produce elongation, evidently due to the greater strength of the circular muscles. The relation between the two muscle layers, therefore, may be explained on the assumption that the circular muscles have a higher threshold than the longitudinal muscles. It is possible, also, that the nervous elements responsible for the myenteric reflex make connection preferentially with the circular muscles.

Mechanism of Conduction. The character of the response suggests that a nervous mechanism conducting chiefly in an oral direction is involved. That muscular conduction cannot account for the effect of stimulation is confirmed by the obser-
vation that the contractions often originate at some distance from the region stimulated. In the terminal ileum of the rabbit, strong contractions often first appear 2 to 3 mm. orad to the stimulating electrodes and only later spread to the electrodes. In the duodenum, the contractions produced by longitudinal stretching often start 5 to 10 cm. above the stimulated region (fig. 1B).

The principal question is the explanation of the polarity of the response. Rai-ford and Mulinos have proposed that nerve fibers are running from the mucosa orad directly to the muscle fibers, thus representing an axon reflex arc. Since the effect of local stimulation extends for several centimeters, these nerve fibers must be assumed to be very long. If they had terminations on muscle fibers over their entire length, electric stimulation would be expected to produce a response orad as well as caudad. As shown above, however, the responses generally spread caudad less than a millimeter. Therefore, on the assumption of an axon reflex, it must be assumed, furthermore, that each fiber has motor endings only at one certain distance from the sensory endings.

The polarity can be explained more readily by assuming a synaptic mechanism conducting preferentially in an oral direction. This possibility can be tested by the action of drugs. It is well-known that peristalsis of the intestine, in contrast to ordinary rhythmic activity, is abolished by the intravenous injection of small quantities of nicotine, an observation which has been considered as evidence for a synaptic mechanism (4, 25). However, the effect of the drug cannot be interpreted with certainty in such experiments because the possible effects of the drug on receptors, synapses and the muscle has not been evaluated.

In the present work, drugs were applied by placing narrow strips of cotton soaked in the solutions all around the intestine. Rabbits were used. Nicotine sulfate or pure nicotine in high concentrations, 1:1000 to 1:5000, produced strong ascending and descending contractions of the circular muscles. Following this response, which passed off in one to two minutes, the response to local stimulation did not spread beyond the nicotinized region (fig. 1, 2). In concentrations of 1:10,000 to 1:20,000, nicotine usually blocked the spread of the response without first producing a contraction. All of these effects were completely reversible.

Atropine in concentrations as low as 1:10,000 and tetraethylammonium chloride as low as 1:1,500 blocked conduction like nicotine. It was unexpected that adrenalin (1:50,000 or higher) also blocked conduction in many animals. However, the minimal effective concentration of these drugs, while constant in one animal, varied considerably in different animals. In the least sensitive rabbits, 14 of a group of 26 animals, adrenalin and tetraethylammonium chloride did not block completely at concentrations which were so high (1:10,000 and 1:500 resp.) that other effects of the drugs (vascular effects and local contractions) became prominent. This group was also less sensitive to the action of nicotine and atropine.

Acetylcholine at the lowest effective concentrations produced a weak local contraction, probably due to direct stimulation of the muscle. At slightly higher concentrations (about 1:2000 for the duodenum, 1:10,000 for the lower ileum) only an ascending contraction occurred. Still higher concentrations also gave a descending
response. These observations indicate that acetylcholine stimulates the muscle directly and indirectly through a nervous plexus.

Since none of the drugs mentioned, even in concentrations much higher than those used here, stimulate or block nerve fibers, it may be concluded that the reflex responses involve a synaptic mechanism. Furthermore, because the block is sharply limited and because generally the response to stimulation does not spread caudad noticeably, the neurons involved in the reflex must be assumed to be short.

**Summation and Fatigue.** The myenteric reflex has some of the characteristics of reflexes involving the central nervous system. Brief stimulation generally is ineffective. The weaker the stimuli the longer they have to be applied before a response appears. The importance of summation is strikingly illustrated by the responses to weak electric stimuli described above.

The reflex, furthermore, is subject to rapid and long-lasting fatigue. On continuous stimulation, the reflex generally subsides within 1 minute, often within 10 seconds. Following a strong response, stimulation is entirely ineffective for half a minute or longer.

The importance of summation and fatigue is also evident from observations on peristalsis (14). The introduction of a bolus into the small intestine of the dog usually does not initiate a peristaltic wave immediately. It first produces a gradual increase of rhythmic activity on the oral side. A peristaltic wave begins only when the contractions are strong enough to propel the bolus.

**COMMENTS**

The observations described here show that the myenteric reflex involves an enteric nervous plexus which conducts decrementally, chiefly in an oral direction. It consists of short neurons connected by synapses. Pharmacologically the synapses are similar to those of the autonomic nervous system, being blocked by nicotine and tetraethylammonium chloride and stimulated by acetylcholine. The blocking action of atropine and adrenalin is peculiar but Marrazzi (26, 27) has demonstrated a depressing action of these drugs on sympathetic ganglia.

The relationship of the plexus responsible for the myenteric reflex to the autonomic system is uncertain. It appears improbable, however, that the plexus consists merely of post-ganglionic parasympathetic neurons because vagal stimulation never sets off as powerful a response as can be elicited by appropriate stimulation of the intestine.

The polar character of the myenteric reflex explains why the peristaltic waves of the intestine generally travel only in an aboral direction. The reflex by itself, however, does not set up peristaltic waves as shown by the fact that the reflex response to local stimulation never progresses along the intestine and that such waves cannot be produced in the empty intestine. Their propagation is due to the continuous stimulation by the contents of the organ which reinforces the muscular activity on the oral side, particularly that of the circular muscles.

This type of peristalsis should not be confused with the peristaltic waves of the stomach and ureter. The waves of contraction of these organs are analogous to single impulses in cardiac muscle. They can be elicited by single electric shocks.
They are all-or-none responses and are conducted equally well in both directions. These and other observations on the effect of electric currents and on action potentials (15, 20, 21, 22, 28) agree with the assumption that conduction is purely muscular. The fact that, in contrast with true peristaltic waves, conduction is not blocked by high concentrations of cocaine and nicotine (28, 29) leads to the same conclusion.

Because the action potentials of the rhythmic contractions of the intestine are essentially like those of the ureter and the stomach, it is evident that the individual contractions in all of these organs involve muscular conduction. The chief difference lies in the fact that in the intestine single contractions are generally conducted only for short distances, a condition which is largely due to the independent initiation of activity in many parts of the organ. The peristaltic waves of the intestine can travel long distances but, as shown above, they are composed of a series of rhythmic contractions, each one travelling only a short distance.

Some investigators have occasionally observed anti-peristalsis. It can be seen frequently in the rectum of the rabbit (23). In my own studies it was often seen in this organ, but only when the intestine was depressed, for instance after several peristaltic waves were induced in succession. Peristalsis, then, was weak. A wave often came to a standstill and a new wave started in the opposite direction. This phenomenon indicates that the polarity of the enteric nervous system is not absolute. There is, in fact, some evidence indicating that impulses are conducted in this system also in a caudal direction and that the difference in the response to stimulation on both sides is purely quantitative. It is conceivable, therefore, that under certain conditions, for instance in fatigue, the effect on the caudal side predominates, thereby producing anti-peristalsis.

Polarity has not been demonstrated in other visceral smooth muscles. It is true that in the ureter and stomach the waves of contraction normally travel in a caudal direction. For the ureter, probably also for the stomach, this observation is explained by the fact that the upper end of the organ has the highest degree of automaticity, thereby acting as the pacemaker.

SUMMARY

Local stimulation of the intestine produces responses which spread considerably beyond the stimulated area. Under certain conditions the contraction is restricted to the oral side. Such polar responses, which are designated as the myenteric reflex, may consist merely of an increase in the strength of the rhythmic contractions or they may be more prolonged contractions, chiefly of the circular muscles. The most effective stimulus for the myenteric reflex is longitudinal stretching in the small intestine of the rabbit, stroking the mucosa in the small intestine of the dog. Abnormal stimuli such as electric stimuli or pinching often produce ascending and descending contractions. However, electric stimulation always produces a strictly polar response in the proximal colon of the rabbit, and in other parts of the intestine if the stimuli are close to threshold.

Nicotine in low concentrations applied locally prevents the spread of the response from the stimulated area. Local application of acetylcholine in minimal concentrations produces a polar response like that caused by appropriate mechanical or elec-
trical stimulation. It is concluded that a synaptic mechanism consisting of short neurons and conducting chiefly in an oral direction is involved in the myenteric reflex.

The results are in agreement with the conclusion that the spontaneous contractions of the intestine are myogenic but are ordinarily conducted only for a short distance. The myenteric reflex increases this activity on the oral side and thereby propels the contents of the intestine. The reflex response by itself is not propagated. The peristaltic waves depend on the continuous stimulation by the contents of the intestine.

REFERENCES