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The Pacemaker Function of the Small Intestine

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THE PACEMAKER FUNCTION OF THE SMALL INTESTINE

by

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I certify that I have read this thesis and that in my opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

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INTRODUCTION

Contractions of the smooth muscle of the intestine induced by any means travel more readily in the aboral direction, except in pathological states and, normally, in a few short segments of the gut; the exceptions being the first part of the duodenum, the terminal ileum, and the mid-portion of the colon in some species. Even in these locations peristalsis travels preferentially in the aboral direction.

Doctor J. Earl Thomas in his publication, "The Gradient Theory Versus the Reflex Theory of Intestinal Peristalsis" (41), and Doctor Walter C. Alvarez in his book, "Introduction to Gastroenterology" (3), both express the belief that the most important attribute of the bowel is its polarity, that is, its ability to conduct better in one direction than the other. The purpose of this study is to add to the body of knowledge pertaining to the polarization of the bowel that currently exists today. Before discussing the most widely accepted theories that have been proposed in regard to the polarization of the bowel, it would be appropriate to describe first, the various movements exhibited in the bowel and second, to review the work which has precipitated these theories.

"The movements of the alimentary canal can be divided roughly into two types: those which serve principally to mix the contents of any given part of the tract, and those which primarily move the contents from one locus of activity to another." (25) These movements originate as a result of a series of complex contractions of the longitudinal and circular smooth muscle coats. "The contractions of the smooth muscle fibers are integrated by the intrinsic plexus, whose activity, however, is modified by the extrinsic parasympathetic and sympathetic innervation." (25)

In the classic work of Bayliss and Starling, (9) the 'law of the intestine' was formulated, which is as follows, "if cerebrospinal reflexes be excluded, excitation at any point of the gut excites contraction above and inhibition below." They believed this reaction was attributable to the myenteric plexus. Later Cannon (19) reported similar results and designated the reflex involved as the 'myenteric reflex'. Much controversy has originated from these observations with many holding to the opinion that the myenteric reflex can be elicited only under exceptional circunstances. Others feel that only the contraction phase can be demonstrated consistently or that such a reflex does not exist. That such a reflex does exist was brought out in some experiments of Thomas in 1956, in which he used the unanesthetized dog with a duodenal fistula.

The 'myenteric reflex' or the 'law of the intestine' is a response to local stimuli which occurs after extrinsic denervation but does not occur normally after the myenteric plexus is paralyzed by cocaine or nicotine.

The term peristalsis is generally used to describe a contraction phenomenon which is propogated in the aboral directinn. The contraction may or may not be preceded by a wave of inhibition. Any strong contraction in the intestine is bidirectional at its inception; however, the contraction which is directed orally is inhibited by some means, while the contraction which is directed aborally is, apparently, facilitated. This phenomenon will be discussed later in detail.

Another form of the peristaltic wave, which travels along the intestine without much pause and for longer distances, was described under the name

'Rollbewegungen' by Van Braam Houkgeest (45) in 1872 and called 'peristaltic rush' by Meltzer and Auer in 1907 (34).

Slow alterations in the muscular tone of the digestive tract have also been observed, which have been referred to as tonus rhythm. This is an adaptive function of the alimentary tract which serves to accomodate the capacity of the organs to the volume of their contents, however, since it occurs during fasting this is not its sole function.

Superimposed on the tonus rhythm are rhythmical contractions which have been very well described by a number of investigators, one of whom is quoted:

> "The dominant characteristic of the muscle of the small intestine is its rhythmicity which it manifests under appropriate conditions by alternating contractions and relaxations at a remarkably regular frequency. The rhythmic contractions may occur at regularly spaced intervals along a section of the intestine, dividing it into short segments (the "segmenting contractions" of Cannon 1902) or they may occur singly or in pairs or in a variety of other arrangements. The area involved in each contraction may be less than one cm. or several cms. long. The rhythmic nature of this activity reminded Ludwig (1861) of a pendulum, hence the name 'pendulum movements' often applied to these contractions." (10)

The frequency of these contractions varies with the species of animal and with different portions of the small intestine from which they are recorded. In 1896 Legros and Onimus (31) observed that the rhythmic contractions of the duodenum occur at a higher rate than those in the ileum. They sometimes found the contractions in the duodenum of the dog to be 18 per minute, but they were never more than 11 or 12 per minute near the cecum. They passed balloons through a gastric fistula and allowed them to travel down the intestine. Hess (28) in 1886 and Nothnagel (37) in 1884 used a similar technique and recorded that a gradient exists in the small intestine. Lüderitz (33) in 1890 described the differences in rabbit duodenum and the rest of the small intestine and colon. He gives the rhythm in rabbits as 19 to 22 in the duodenum and 12 to 18 in the rest of the small intestine and colon. In Luciani's Textbook of Physiology (1913) (32), the following statement is made, "both rate and force of the intestinal movements diminish regularly from duodenum to ileum." He gives the rhythm of the duodenum and jejunum of the rabbit as 14 to 23; that of the ileum as 12 to 18 per minute. In 1914 Alvarez (1) demonstrated, by placing excised segments of intestine in warm oxygenated Ringer's solution, the more rapid rhythm of duodenal segments than of those segments taken from the ileum. "Roughly expressed, he said, the rate varies inversely as the distance from the pylorus." (2) Douglas and Mann (24) in 1939 recorded rhythmic contractions from the small intestine of the unanesthetized dog using the following technique. Exteriorized loops in continuity with the rest of the gut were prepared at various levels in the small bowel of trained dogs and the occurence and rate of rhythmic contractions noted. The activity was recorded by a double-tambour air-displacement system, the receiving tambour being attached to the loop by an aluminium clip. Rhythmic contractions were found to be a rare form of movement in these preparations, occurring in about 2 per cent of all tracings. They recorded 18 contractions per minute in the upper jejunum and 12.5 contractions per minute in the terminal ileum.

The rhythmic contractions are fairly constant in rate in any one area of the small intestine; however, alight variations in frequency occur from day to day when recorded from a given area. Alvarez, Hosoi, Overgard and Ascanio (4) made a study on the effects of extrinsic denervarion on the small intestine of the rabbit. Rhey found that after vagal and splanchnic section, the rate of rhythmical contractions was less, in the jejunum and ileum, than in the normal animal. In the dog vagal and splanchnic section have no effect on the rate of rhythmic contractions as reported by Castleton (20) and Douglas and Mann. (24) When an exteriorized loop of bowel was completely isolated from the mesentery and derived its blood supply from the subcutaneous vessels, the rate decreased 25 per cent, but the gradient still persisted, (Castleton and Puestow) (38). Thomas and Kuntz (44) found that in dogs which had been given nicotine in doses sufficient to cause paralysis of the intrinsic nervous plexus, rhythmic contractions proceeded at the same rate and constancy as before nicotinization. All other movements which are believed to depend on the integrity of the nervous plexus were arrested. These findings plus work done on isolated, denervated intestinal segments suggest that rhythmic contractions are myogenic in origin. Plexus free, isolated segments of circular muscle show spontaneous rhythmic contractions. (27) The frequency of these contractions is not affected by the common neurotrophic drugs.

Rhythmic contractions may be induced locally by mechanical and chemical stimuli in an apparently inactive portion of the intestine; therefore the intestinal contents are doubtless adequate stimuli. The function of the rhythmic contractions is probably to agitate the intestinal contents thereby bringing the digesting material into intimate contact with the absorbing surface of the mucosa.

Although rhythmic contractions may be induced locally by proper stimulation, the frequency of contraction, locally, appears to be determined by some conducted process which is initiated at a higher level at a frequency corresponding to the frequency of the rhythmic contractions, and which is conducted in the aboral direction as a wave of excitation, (see Thomas, 1955). This supposition is based on the experiments of Douglas (23) in 1949 in which the jejunum was cut off from the duodenum after which the rate in the jejunum dropped from 18 to 12 per minute.

Electrical studies of the small intestine by a number of investigators lend to support to this supposition. Puestow (39) in 1933 recorded the rhythmical electropotentials in isolated intestinal transplants on the ventral abdominal wall and described two components, one a series of spike potentials and the other a smooth wave of relatively long duration. Berkson, Baldez and Alvarez (11) working together described similar results from studies on the intestine of anesthetized and pithed rabbits. Bozler (12-18) in 1939, 1941, 1945, 1946, 1947, 1949 and Ambache (7) in 1947 demonstrated these two characteristic electropotential waves and agreed that the rapid oscillations were action potentials from the muscle of the gut wall, but the origin of the slow component remains a subject of controversy. Bozler, Berkson (10) in 1933 and Ambache investigated the electropotentials of the gut in vitro by placing electrodes on the surface of the muscle at various distances apart. Ambache and Berkson suggested that the slow wave might originate from the nerve net in the gut because it could be detected in the absence of recordable movement. Ambache concluded that the intestinal nerve net acts like a "pacemaker" for pendulum movements. Bozler disagreed with these investigators and suggested that both components of the electrical record were muscular in origin. The smooth, slow component, he stated, was always associated with muscular contraction but this contraction was difficult to observe because it was asynchronous. In 1949, referring to the two types of electropotential change, Bozler admitted "that the significance of this duality is not known".

In 1955 Milton, Smith and Armstrong (36) using concentric needle electrodes embedded in the duodenal wall in the intact animal confirmed the electrical changes in the duodenum observed in vitro by previous workers. They also found the frequency and amplitude of the slow wave were unchanged by drugs which increased, or by drugs which eliminated, visible movement from the duodenum. The drugs used were methantheline in doses of 0.25 to 7.0 mg./kg., hexamethonium bromide 2 to 4 mg./kg., atropine 0.045 mg./kg., adrenalin 0.06 mg./kg. and neostigmine 0.062 to .15 mg./kg. Drugs which eliminated visible movement from the intestine, at the same time abolished the rapid spike-like potentials from the electrical record. The finding by these investigators, that the slow wave always precedes the fast potentials when there is visible movement in the gut, suggests that it may be associated with the mechanism which co-ordinates and stimulates muscle contraction in the gut. In studying the regional differences in the slow wave which exist between the duodenum, and the jejunum and ileum, Armstrong, Milton and Smith (8) have found the frequency of the slow waves and the frequency of mechanical contractions, as recorded by Douglas, (23) to agree closely. The greatest frequency was found in the duodenum. They have found, too, that the duration of the slow wave is shorter in the duodenum and jejunum than in the ileum. In the same paper they reported the linear velocity of the slow wave to be the fastest in the duodenum and the slowest in the ileum. They, therefore, concluded that the slow repetitive electro-potential wave may arise in a mechanism which supplies a rhythmic and coordinated stimulus to the muscle of the duodenal wall, and so governs the frequency and linear velocity of duodenal contraction.

In later experiments Milton and Smith (35) have been able to locate a "pacemaking" area in the region of the bile duct. They performed their experiments on dogs with an exteriorized loop of duodenum in continuity with the rest of the gut. According to these investigators, their experiments show the existence of a mechanism in the upper duodenum close to the entrance of the bile ducts which normally maintains the frequency of the slow wave and consequently that of the rapid spike deflections of the electrical record and that of the mechanical contractions in the duodenum and upper jejunum. The frequency of the discharges from this area may be decreased by cold or increased by heat; they may be blocked by clamping the bowel or by ring infiltration of procaine. The area does not appear to be a localized node, for they were unable to influence the frequency of the slow wave by cooling small patches of the duodenum, or by infiltrating small areas with procaine. It was only when the full circumference of the bowel was affected that the frequency of the slow wave decreased in the exteriorized loop. Although this area normally predominates over the rest of the duodenum, its influence can be overidden by stimulation (for example by heat) of the duodenum elsewhere.

In 1958 Holaday, Volk and Mandell (29) using unipolar electrodes on exteriorized segments of bowel in chronic dog preparations and in anesthetized dogs, cats and rabbits at laparotomy, reported two dominant types of electrical activity. The first type consisted of brief, nonpropogated, spike-like negative potentials which occurred only immediately preceding and during contraction. It was concluded that they represent action potentials of contracting muscle fibers. The second type consisted of a recurring complex of slow potential changes, the configuration of which varied with the region and type of preparation. The form of the wave was not altered by anesthetics or by sympathomimetic or parasympathomimetic drugs, and was the same during mechanical activity and inactivity. The spike-like potentials occured only during the relatively positive phase of the slow complex. They concluded that the slow complex is a non-propogated cyclic alteration of the resting potential of the smooth muscle cells of the intestine which originates more or less synchronously in adjacent cells and is associated with a mechanism which renders the muscle alternately relatively excitable and absolutely refractory.

Daniel, Carlow, Wachter, Sutherland and Bogoch (21) working together, with dogs intestine exposed at laparotomy under anesthesia, reported in 1959 the typical slow waves and fast action potentials noted by others. They have found by studying the electrical activity at varying depths in the intestinal wall that the action potentials appeared to originate in or near the longitudinal muscle since their amplitude decreased markedly when recording from other depths. The amplitude of the slow waves was less markedly affected by variation in the depth of recording. These observations, they said, suggested independent mechanisms of origin of these two waves. They have found the rate of slow wave activity to be greatest in the duodenum and decreasing progressively with the lowest values in the terminal ileum. In their experiments influence of the duodenal pacemaker on the ileum was lacking. This was brought out in experiments in which electrodes were attached at various sites in the small intestine, control records were taken, and the duodenum was severed or tightly occluded just below the ampulla of Vater. The effects of this procedure on slow wave activity were studied. In almost all experiments there was some decrease in the duodenal slow wave rate; much less decrease, or none, in the jejunal rate; and very little change in the ileal rate.

In the most recent work on the electrical activity of the small intestine, Daniel, Honour and Bogoch (22) reported interesting findings on the electrical activity of the longitudinal muscle of the small intestine. Using microelectrodes on immobilized intestinal segments in vivo, they found the electrical activity to be characterized by periodic slow depolarizations of from -3 to -15 mv starting from potentials of -35 to -50 mv. The frequency of these slow depolarizations was found to be less in the ileum than in the jejunum and is diminished by reduction in body temperature. Action potential spikes arise from the larger slow depolarizations. These records are analogous to the slow waves recorded extracellularly. Daniel et al propose that these slow depolarizations are a coordinating mechanism for motility of the longitudinal muscle of the dog intestine.

Thus far much has been said concerning the nature of the rhythmic contractions and for reasons which will now become apparent. As was previously mentioned, "the most dominant characteristic of the small intestine is its rhythmicity", which, doubtless, is also the easiest to observe. It has also been observed

> "that rhythmic contractions may, while retaining their rhythmic character, recur at successively more aboral levels and appear to travel along the intestine as a wave of peristalsis. In other situations the rhythmic contractions remain localized while the 'tonus' of the muscle increases in a particular area; if the tonic contraction spreads in the aboral direction and fades out orally it becomes a peristaltic wave which progresses without interrupting the rhythmic contractions. The tonic contraction may be powerful enough to obscure the relaxation phase of the rhythmic cycle and appear to progress along the intestine as a smooth, progressive contraction." (43)

However, a rhythm still persists as was brought out in the electrical studies of peristalsis by Bozler. (21)

It is not known whether the conditions that cause rhythmic contractions on the one hand and peristaltic movements on the other, differ quantitatively or qualitatively. It is known, however, that both mechanical and chemical stimulation favor peristaltic movements while mild stimulation is effective in promoting rhythmic contractions. For the purposes of this study the most important fact concerning the rhythmic contractions and peristaltic movements is that when these contraction phenomena occur and are propogated they move preferentially in the aboral direction. In spite of repeated investigations no satisfactory explanation for this has yet been found.

The two most widely accepted theories for explaining forward conduction in the bowel are the gradient theory and the reflex theory. The reflex theory is based on the law of the intestine which was stated earlier as follows, "if cerebrospinal reflexes be excluded, excitation at any point of the gut excites contraction above, inhibition below." The majority of evidence, however, suggests that peristalsis is not always preceded by a wave of inhibition. This does not conform with the idea of Bayliss and Starling that peristalsis is a progressing series of myenteric reflexes. The available evidence indicates that polar conduction in the bowel is dependent on the integrity of the myenteric plexus, but there is nothing in the literature which explains forward conduction in the bowel. As was brought out by Thomas, one wonders why the contraction phase of the myenteric reflex is not conducted orally into muscle that is already in a state of excitation; but instead it is conducted into the inhibited muscle below the stimulated point. Evidently more information is needed regarding the precise mechanism within the plexus that determines forward conduction in the bowel.

The other theory, the gradient theory of Alvarez, (6) is based on observable metabolic differences in the duodenum and the rest of the gut. Alvarez and his pupils made a special study of the metabolic gradients in the small intestine. They found that certain biochemical and physiological properties are more highly developed in the upper end of the bowel as opposed to the lower end. Among these properties were rhythmicity, irritability, shortness of latent period, susceptibility to anoxia, rate of carbon dioxide production, susceptibility to certain drugs and catalase content. The easiest to observe of these differences is the gradient of rhythmicity which manifests itself as having the greatest rhythmicity in the duodenum and decreasing progressively down the bowel. Alvarez in 1948 stressed the importance of metabolic gradients in establishing forward conduction in the bowel and he considers that local temporary reversals in the bowel which are associated with alterations in irritability due to disease, may cause disturbance of function in the gut. Thomas pointed out that the gradients do not of themselves satisfactorily account for the direction of conduction of the peristaltic waves. He gives the following explanation:

> "if the gradient of irritability has any influence on conduction it should favor conduction in the direction of increasing irritability; this is opposite to the direction in which conduction actually occurs. Elsewhere, as in the heart, where both a gradient of irritability and unidirectional conductions are manifest, the direction of conduction is not determined by the gradient but by the site of origin of the stimulus; if the pacemaker shifts position, for example to the atrioventricular node in the heart, backward conduction readily occurs."

It is evident that both of these theories of themselves are unacceptable, but as was brought out by Thomas, the gradient theory would be acceptable if the presence of a pacemaker or pacemakers in the intestine could be established. These pacemakers need not be fixed in any one location, but merely areas of superior excitability which initiate impulses in a rhythmic fashion. The gradient would insure that the impulses were initiated at the upper end of a functional unit whether it be the whole bowel or just a segment. Subsequently, the impulses generated would be conducted in an aboral direction. Oral conduction in this instance would be impossible in that ascending impulses would die out in the refractory phase of the decending impulse. It has also been suggested by Thomas that these conducted impulses in the intestine increase the excitability over the area which they pass causing little or no muscular contraction. In this manner they would increase the effectiveness of local stimuli and contraction would result from the summation of local and conducted excitations. This concept is illustrated in Figure 1.

Some of the evidence for the existence of a pacemaker or pacemakers has been alluded to before; however, the following summary is presented. As early as 1899 Bayliss and Starling observed shallow waves which passed down the intestine at regular intervals which initiated rhythmic contractions in an area of local stimulation. In 1915 Keith (30), who discovered nodal tissue in the heart, found similar tissue in the intestine. He proposed that the nodal tissue in the heart and in the intestine is similar in that they both have the same development, and appear to have a similar function, that of influencing the regulation, tone and rhythm of the musculature. He found that the area of the duodenum just proximal to the entrance of the common bile duct and the jejuno-iliac area were rhythmical zones which control the activity of the associated segments, namely the duodenum, jejunum and ileum, respectively. These rhythmical zones were characterized by having an abundance of nodal tissue. According to Alvarez, no one has

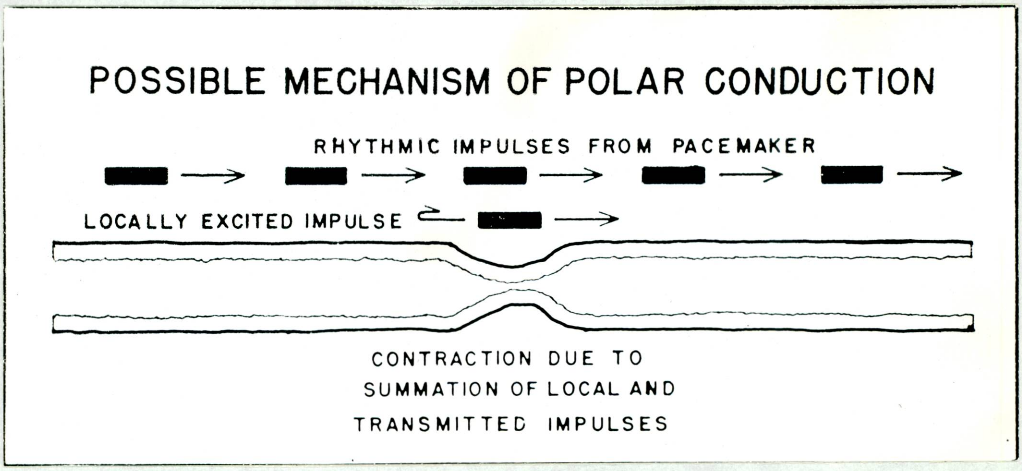

Figure 1 - Diagram illustrating a concept of the mechanism of polar conduction in the intestine. The rectangular blocks represent rhythmic stimuli (impulses) arising in a pacemaker and transmitted along the intestine in the direction of the arrows. A locally excited impulse would tend to travel in both directions but is blocked in the oral direction by the descending impulses. (from Thomas, Gradient Theory Versus Reflex Theory)

yet confirmed the anatomic findings of Keith. Douglas found that severing the duodenum from the jejunum caused a permanent decrease in the frequency of rhythmic contractions in the jejunum. This would seem to indicate that the frequency of contractions in the jejunum is normally dependent on conducted impulses from a higher level. Milton and Smith have located what they call a pacemaking area in the duodenum just proximal to the entrance of the common bile duct, which they say initiates slow waves that govern the rhythmicity of the duodenum and jejunum. They have found, by isolating the bile duct area by various means from the rest of the duodenum and upper jejunum, that the frequency of the slow wave activity, as was recorded in the duodenum and jejunum, was thereby affected. Additional evidence for the existence of a pacemaker is provided from the experiments which will be described in this paper.

PROCEDURE

Experiments were undertaken to study:

1. The gradient of rhythmicity in the small intestine of the unanesthetized dog.

2. The effect of applying heat or cold at various points in the intestine on the rhythmic contractions at various levels.

3. The relation of electrical activity of the intestine to the rhythmic contractions.

Five dogs weighing from 12 to 21 kilograms, prepared with duodenal fistulas as described by Thomas, Crider and Mogan (42) in 1934, were used in chronic experiments. The fistulas were placed at the level of the entrance of the pancreatic ducts in four of the dogs and at the level of the entrance of the bile duct in the fifth dog. The dogs were trained to stand on a table for a number of hours while data was recorded from the small intestine.

Using a method suggested by Thomas, rhythmic contractions were recorded from the small intestine by a small rubber balloon. (Figure 2) The rubber balloon was a modification of the Miller-Abbott balloon. It was, however, much smaller than a Miller-Abbott balloon, being approximately 1.5 cm. long.

It was found that balloons larger than this did not give as discrete recordings as balloons which were only 1.5 cm. long. The recording balloon was tied to flexible nylon tubing with an external diameter of 3 mm. Markers of string were tied around the tube at 10 cm. intervals so that the level of the small intestine at which the record was being taken could be determined and recorded. A Statham Physiological Pressure Transducer with a pressure range from 0 to 5 cm. Hg. was connected to the external end of the nylon tubing. Constant pen recordings were obtained by the use of a Grass Polygraph with the pressure transducer lead connected to a Low Level D. C. Preamplifier, Model 5P1A. In experiments in which mechanical and electrical activity were recorded simultaneously, an adaptation of the previously mentioned recording balloon was made. (Figure 3) The balloon was of the same length, (1.5 cm.), however, gold foil .002 of an inch thick was cut in 5 mm. strips and glued around the greatest circumference of the balloon. Fine enamelled copper wire, (no 31), was connected to the gold foil and another strip of gold foil was placed over the wire in such a way that that portion of the wire which was stripped of its enamel would not come in contact with the mucosa but only with the gold foil. Thus a circular electrode was formed. The lead from the gold foil electrode and the lead from the indifferent needle electrode, which was placed in the thigh, were connected to a Low Level D. C. Preamplifier with settings which provided a maximum frequency response to the incoming signal. The settings were as follows:

1/2 amplitude frequency ----- 60
input resistance ------------ 200,000 ohms
sensitivity ----------------- 2 mv/cm. deflection

The gradient of rhythmicity was studied by placing a small rubber balloon through a duodenal fistula into the small intestine. The balloon was carried down the intestine by peristalsis and the frequency of contractions at various levels as measured from the inside mouth of the

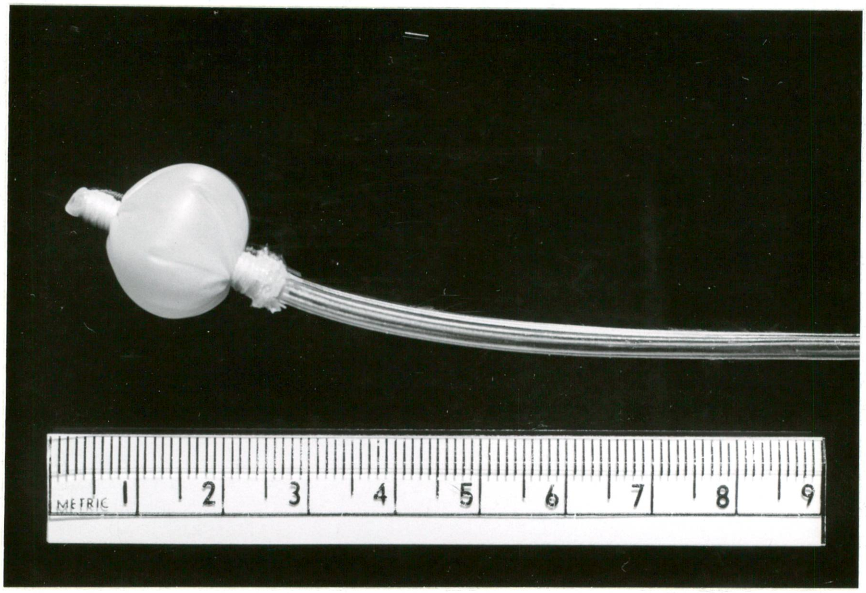

Figure 2 Recording balloon used to record rhythmic contractions.

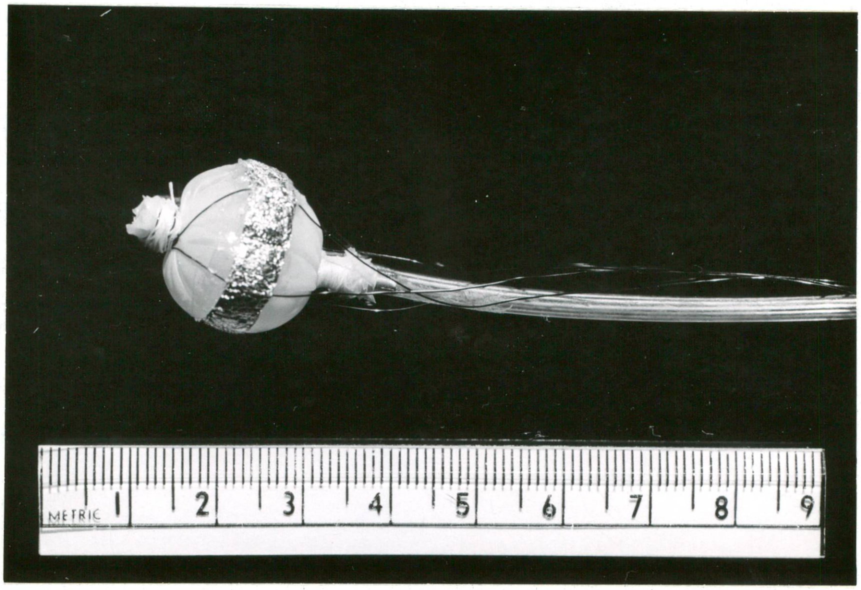

Figure 3 Balloon used to record combined mechanical and electrical activity.

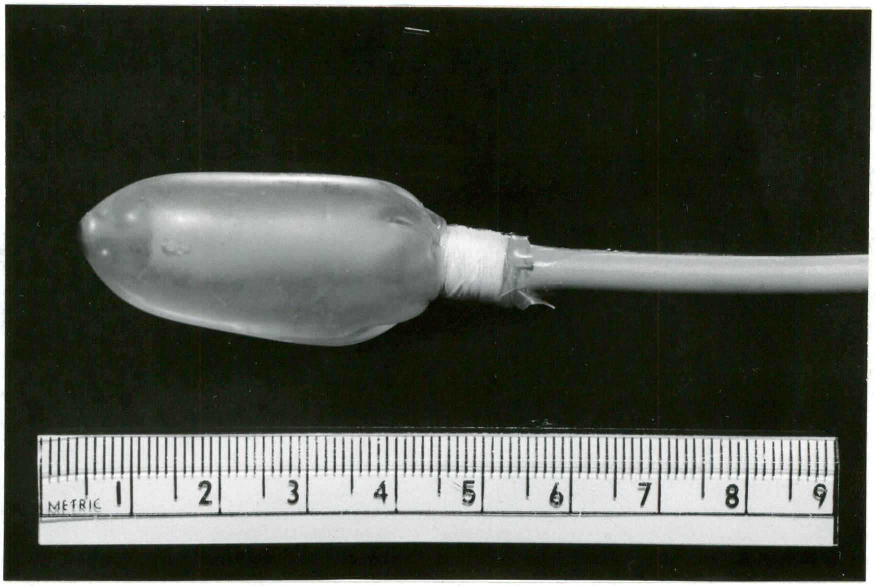

Figure 4 Balloon used to heat or cool segment of duodenum.

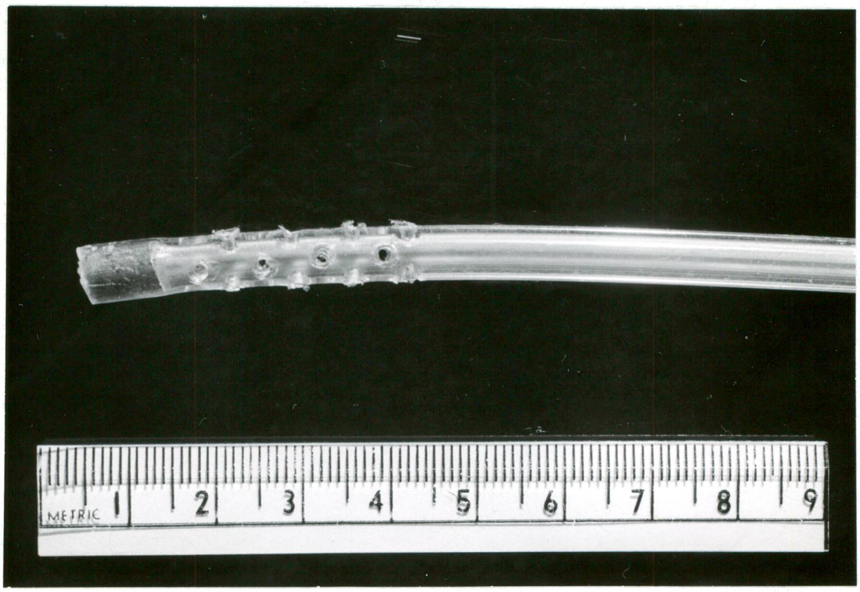

Figure 5 Tubing used to heat or cool segment of duodenum.

fistula-tube was recorded. Measurements of frequency were made at 10 cm. intervals.

The effects of heat and cold, applied just above or just below the level of the fistula, on the frequency of contractions recorded at 50, 100 and 150 cm., respectively, were studied. In order to heat or cool a small segment of the intact bowel, a modification of the Miller-Abbott tube was employed. (Figure 4) A balloon was made from a finger cot and tied to the tube so that when it was distended by water it was approximately 4 cm. in length. The water was circulated through the balloon fast enough so that a constant low temperature or moderately high temperature was maintained without causing over distension of the balloon. In experiments with cold water, the reservoir temperature was maintained at 4 degrees centigrade and the water coming from the balloon was approximately 10 degrees centigrade. In the experiments with hot water, the reservoir temperature was 45 degrees centigrade and the water coming from the balloon was approximately 40 degrees centigrade.

Another method of applying heat or cold to the intestine was employed in order to eliminate any possible effects of mechanical distension by the balloon and to determine the effects of heat or cold water applied to the bile duct area. This was accomplished by running water through a multi-perforated polyethylene tube with an external diameter of 6 mm. (Figure 5) In this manner hot or cold water was applied directly to the mucosal surface of the bowel. Later the same procedure was carried out with normal saline solution. It was necessary to use this particular procedure in heating or cooling the bile duct area, for it was difficult to keep a balloon in the segment of intestine just above the level of the fistula, due to the ever present peristaltic movements pushing the balloon out into the fistula. The peristaltic activity also obstructed the even flow of water through the tube, thereby causing the balloon to lose its effectiveness in cooling or heating the bowel.

Other experiments were carried out in order to eliminate any possible effects of mechanical distension on the frequency of contractions. Water at body temperature was applied to the small intestine by both of the methods previously described and the effects determined. There were no changes in the frequency of contraction recorded in these experiments.

Experiments were conducted to determine the effects of cold at a level above the point of application. The heat or cold was applied just below the fistula. One recording balloon was placed above the level of the fistula while a simultaneous record was taken at a level below the point of application.

In all of the experiments carried out with heat and cold applied to the bowel, simultaneous temperature recordings were taken before, during, and after the heat or cold application, at first a rectal thermometer was used; later constant temperature recordings were taken with a Honeywell Brown Electronik Constant Temperature Recorder which recorded once a minute the temperature at a thermocouple placed in the rectum.

The procedure followed in all of the experiments which dealt with the study of the effects of heat and cold was as follows. The recording balloon was passed through the fistula and allowed to drift down the intestine to the level at which the contractions were to be recorded. The balloon was then prevented from progressing further by taping the tubing to the animal's side. A control record was taken for at least five minutes before the heat or cold application during which the rectal temperature was observed and recorded. The balloon for applying cold or heat was inserted and was applied for five minutes after which it was removed and the temperature again observed and recorded. When the constant temperature recorder was used, the rectal temperature was recorded every minute before, during, and after the heat or cold application. The temperature recorded was continued until the rhythmic contractions returned to the control rate.

Combined simultaneous mechanical and electrical activity was recorded for the first time from the lumen of the dogs' small intestine. Previously Smith had recorded such combined activity in humans using an electrode-bearing Miller-Abbott balloon. Smith (40 made monopolar records from 2 of the 4 lead disk electrodes placed in discrete areas around the balloon. Later Holaday, Volk and Mandell (29) using a modification of Smith's balloon, recorded electrical activity from the human small intestine using one of the balloon electrodes as a unipolar electrode; an indifferent electrode was placed on the thigh or abdomen. In the experiments herein reported the indifferent electrode was placed in the thigh after a local anesthetic to the area. The records were taken from the duodenum 10 to 20 cm. from the level of the fistula.

RESULTS

The gradients of rhythmic contractions recorded from the small intestine of the five dogs are represented in Figures 6 through 10. These graphs were compiled in the following manner. Generally, 3 to 4 records of rhythmic contractions were obtained from each animal. The rhythmic contractions were recorded beginning with the duodenum, at the level of the fistula and ending with the ileum, 200 to 230 cm. from the fistula. For each record the average number of contractions per minute for each 10 cm. segment of intestine was calculated. The average rate observed in each 10 cm. of intestine was then calculated for all the other records from the same dog. Thus the average rate of contractions per minute for

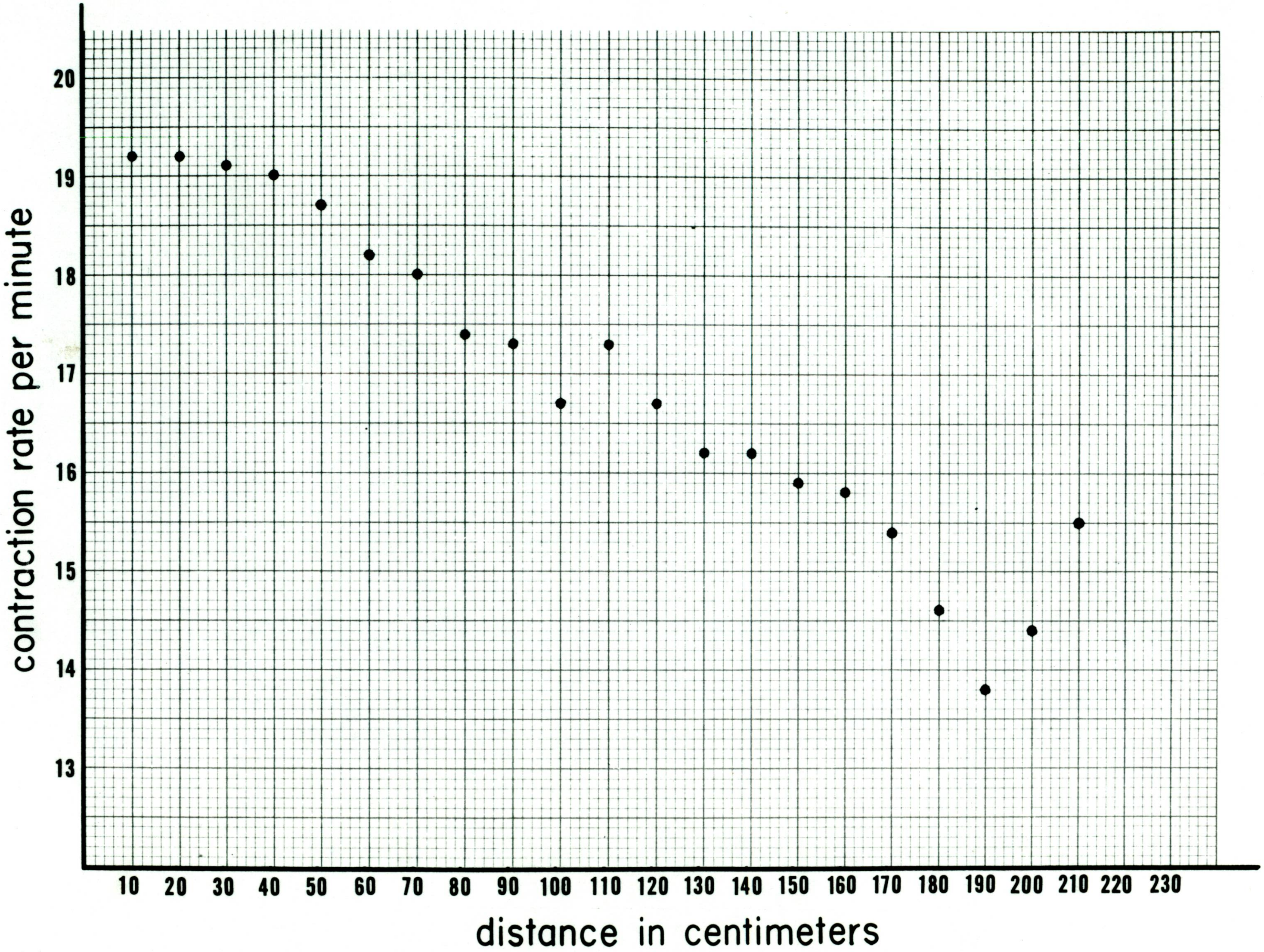

Figure 6 Gradient of rhythmicity in the small intestine of dog #1 (16 kg.)

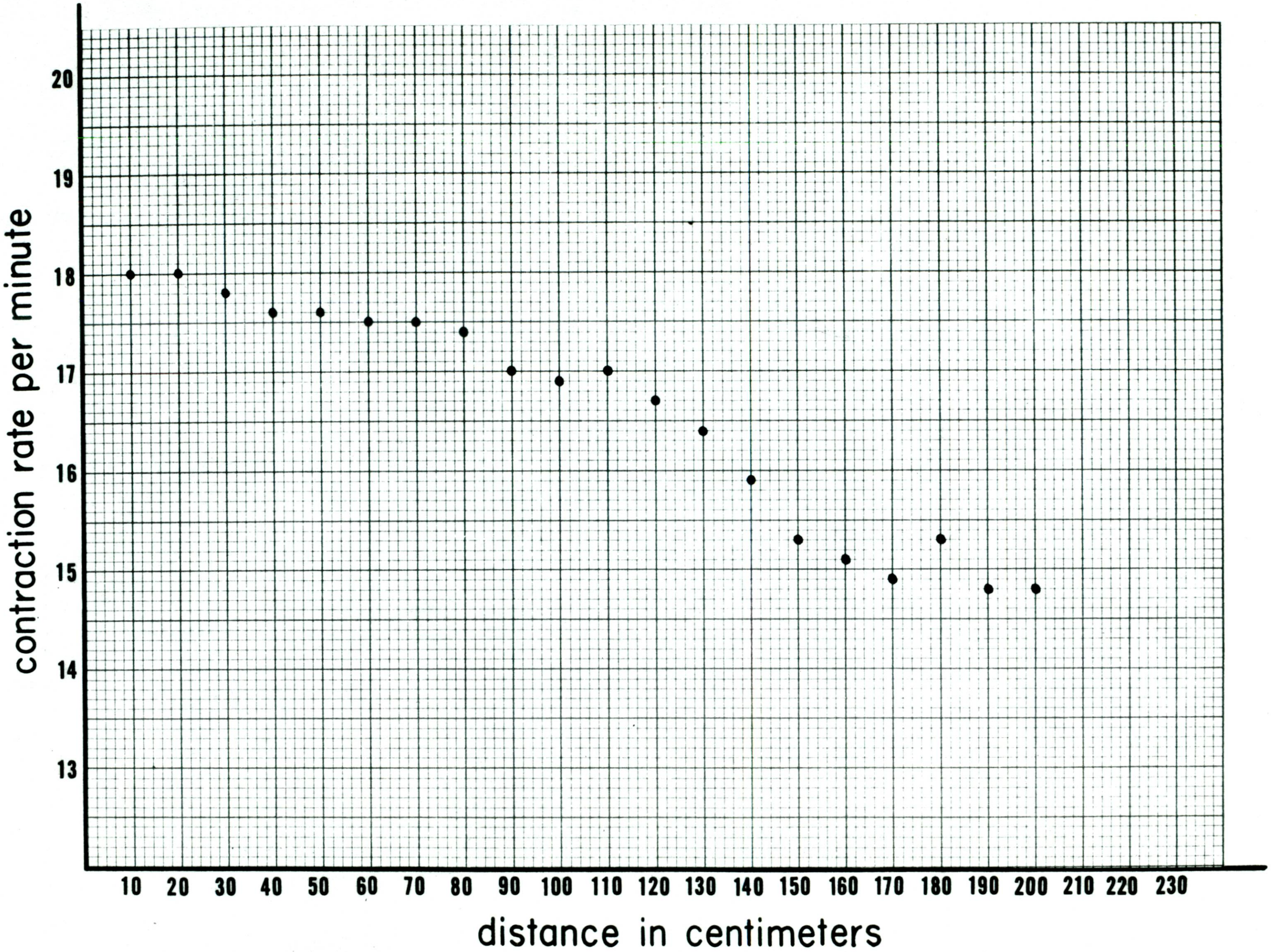

Figure 7 Gradient of rhythmicity in the small intestine of dog #2 (18 kg.)

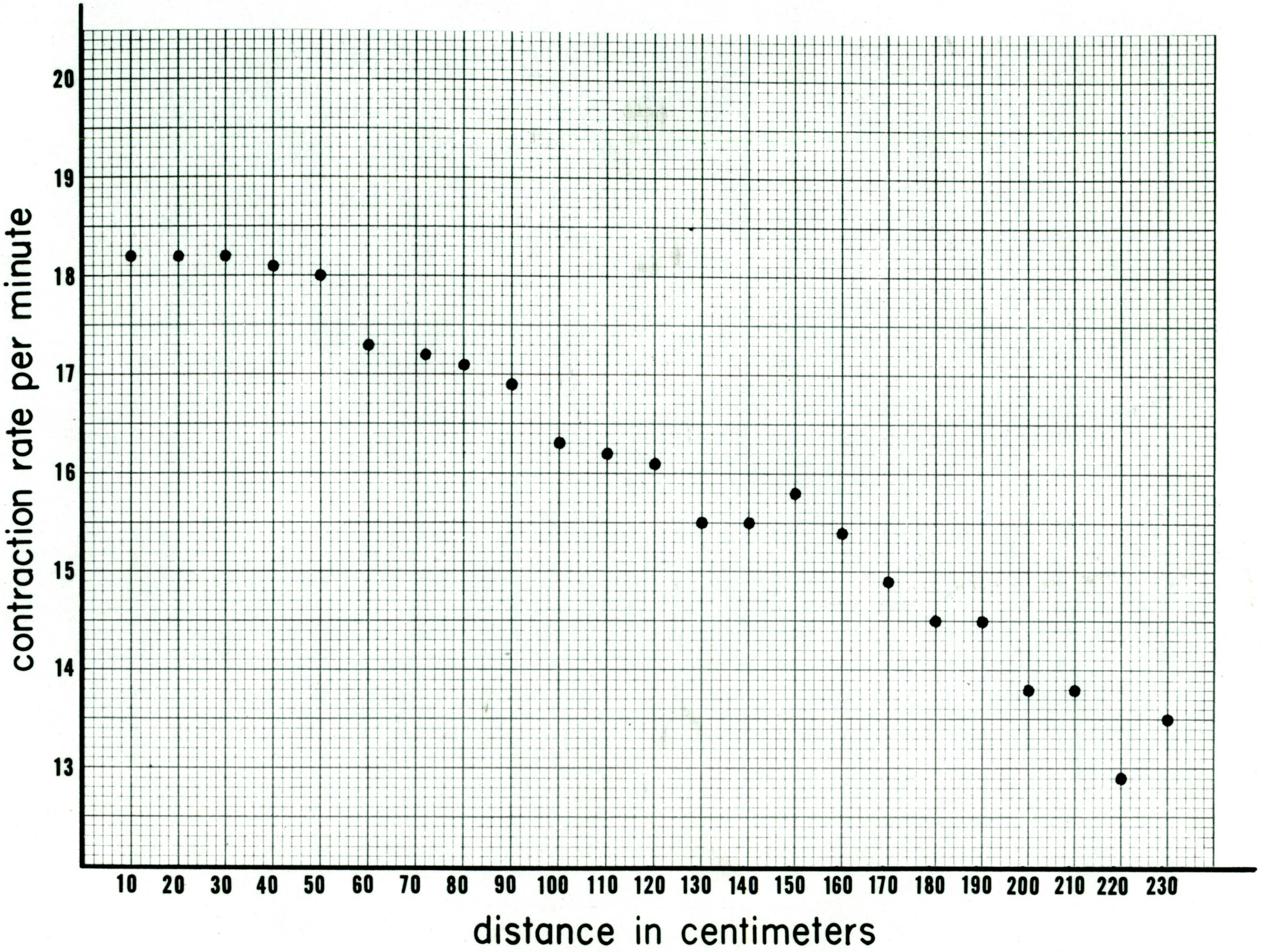

Figure 8 Gradient of rhythmicity in the small intestine of dog #3 (21 kg.)

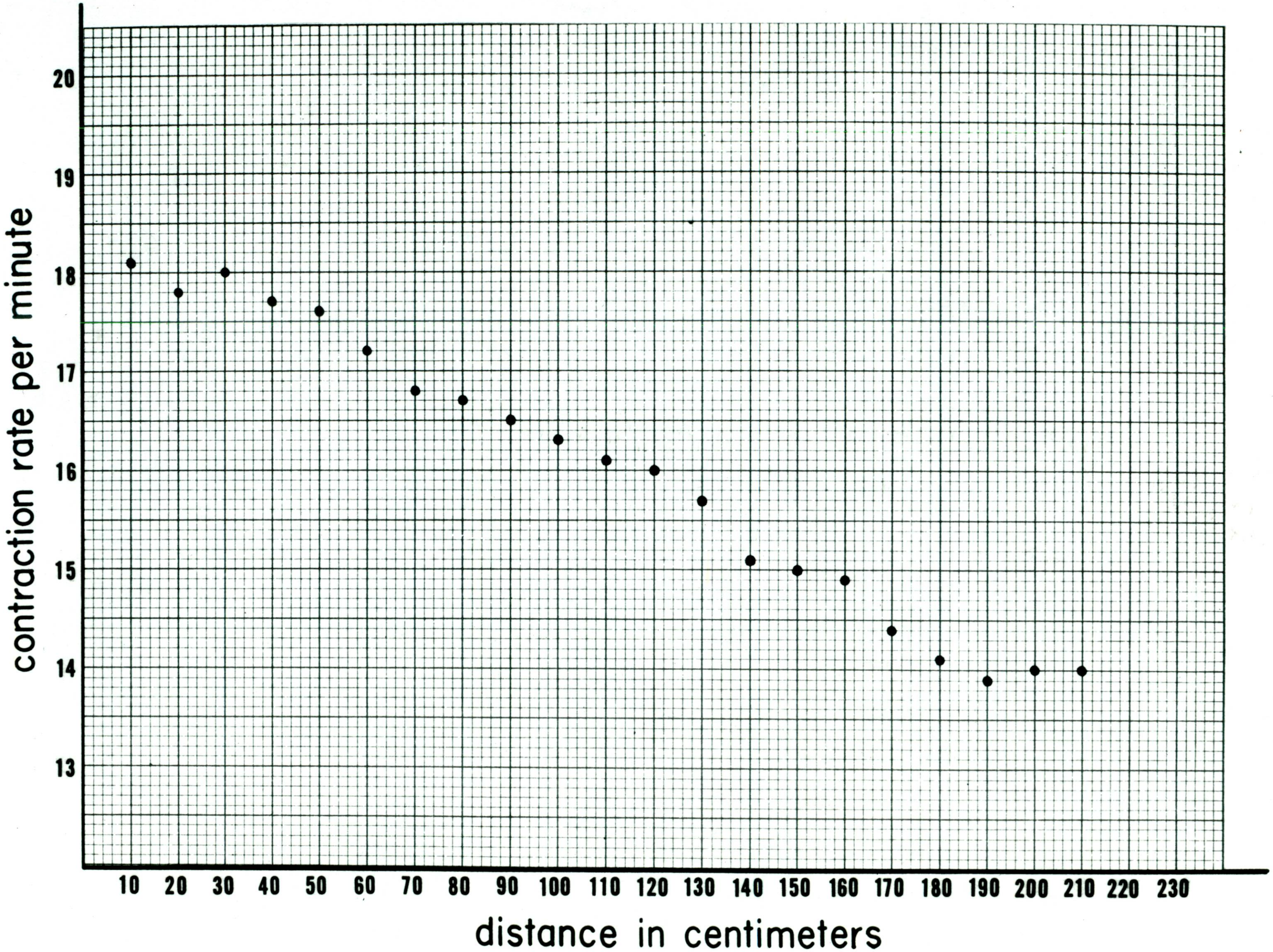

Figure 9 Gradient of rhythmicity in the small intestine of dog #4 (12 kg.)

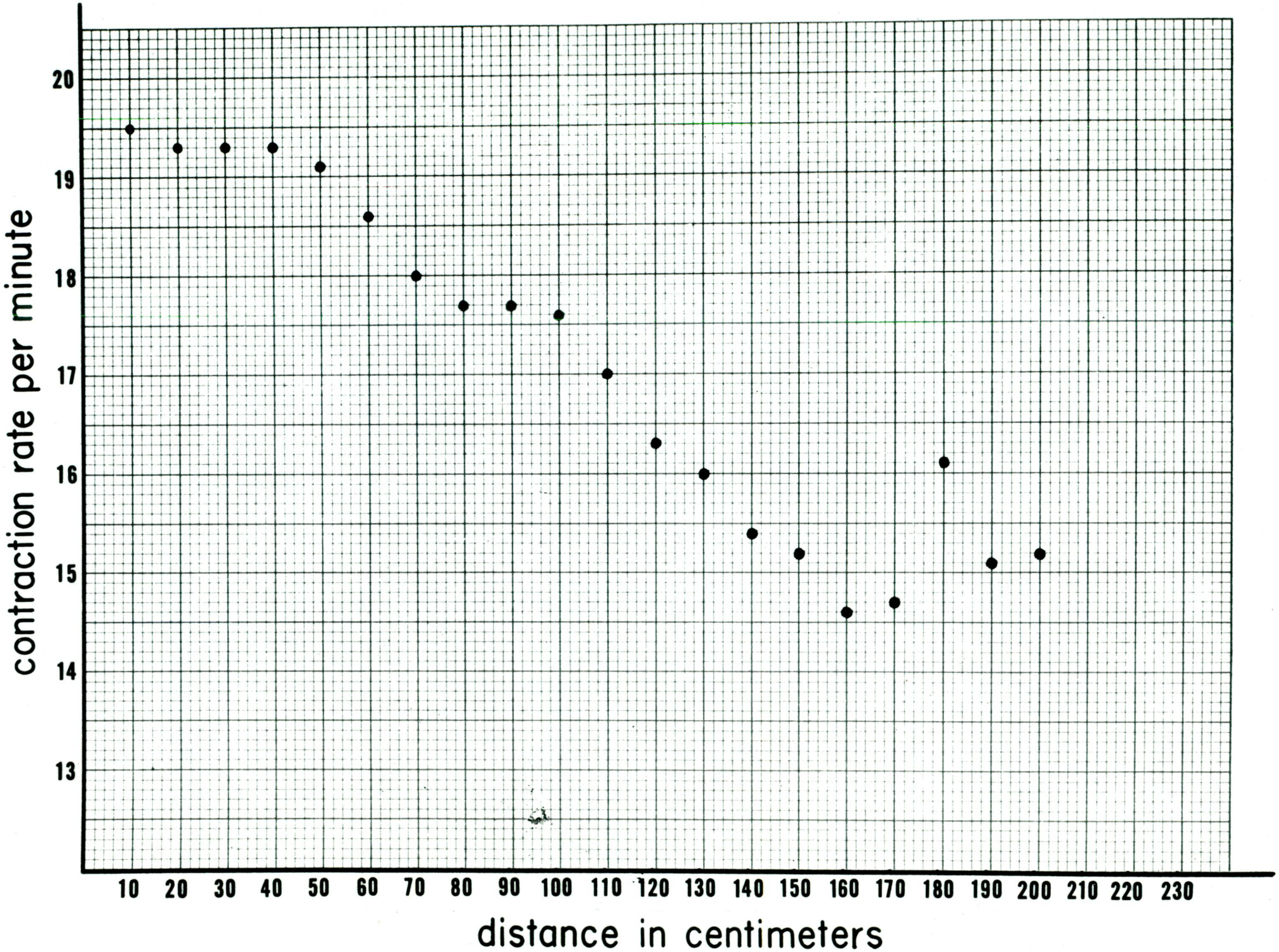

Figure 10 Gradient of rhythmicity in the small intestine of dog #5 (19 kg.)

a 10 cm segment of intestine was determined and the set of such numbers plotted on a graph represents the apparent gradient of rhythmicity in the small intestine.

The rhythmic contractions recorded in these experiments represented approximately 95 to 100 per cent of all of the activity recorded from the small intestine. The calculations are based on only those contractions which were discrete and easy to count. It is of interest to note that, at first, in experiments in which a recording balloon longer than 1.5 cm. was used, double contractions were encountered 80 to 100 cm. from the level of the fistula. Double contractions are asynchronous contractions of 2 segments surrounding the balloon; one area contracting when the other area is not contracting. The frequency of these contractions was considerably more than the frequency of contractions recorded with a balloon only 1.5 cm. long. The data collected from experiments in which a balloon longer than 1.5 cm. was used was not considered in the calculation of the gradient of rhythmicity.

The frequency of contractions was fairly constant for a given segment of intestine, showing little or no variations as recorded from day to day. It was shown in this experiment and in the experiments of Douglas and Mann, that the frequency of contractions in the small intestine are unaffected by fasting or feeding. Feeding, however, seems to effect the amplitude of contractions, the effect being an increase in the amplitude of the recorded contractions.

Peristalsis, which was very active in moving the recording balloon along the first 100 cm. of the intestine, was readily observable in all of the records. The rhythmic activity was generally superimposed on the peristaltic wave, but sometimes the peristaltic wave obscured the observable rhythmic activity. This was especially true in the upper duodenum.

At the beginning of a record, the recording balloon progressed along the intestine quite rapidly for the first 100 cm., after which it progressed more slowly. It took 2 to 3 times as long for the balloon to progress through the lower third of the small intestine as it took to move through the upper two-thirds. It usually required 4 to 8 hours for the balloon to travel 200 to 230 cm. from the fistula down to the terminal ileum. Many times the balloon would remain in one location for a long time without making any progress. In such instances, the dog was fed a little dry food; the dog not having had any food the day before, usually would respond quite well to this procedure. This was generally followed by an increase in peristaltic activity and subsequent progress of the recording balloon along the intestine. During this time secretions would abundantly pass through the fistula. It is of interest to note that the flow of secretions out of the fistula was most always concommitant with progress of the recording balloon. However, such was not the case if the balloon had been in the ileum for a long time.

It should be pointed out that the recording balloon in each experiment did not travel the total distance indicated on the five graphs; however, in every experiment the balloon traveled at least 180 cm. from the level of the fistula. In Dog #3, (Figure 8), the balloon traveled into the cecum as attested by the characteristic contractions recorded from this area. In the experiments performed on the other dogs in which the balloon was carried down the intestine 200 and 210 cm. from the level of the fistula, these characteristic contractions of the colon were not manifested. Instead, after the balloon had remained in this area for a long time, the contractions became quite irregular. They were unlike any of the other contractions recorded in the small intestine; however, some of these contractions had a rough similarity to those contractions obtained from the cecum. It was also noted that when the balloon was this far down the intestine, it remained in one location for hours without making any further progress.

Looking at the various graphs representing the gradients of rhythmicity recorded in each of the five dogs, one notices a stepwise declination in the frequency of contractions as the distance from the pylorus is increased. It can also be seen that in the terminal ileum there is an apparent reversal in the gradient. A possible explanation for these findings will be discussed later in detail.

The results of local cooling of the duodenum on the frequency of contractions recorded at 50, 100 and 150 cm. from the level of the fistula are summarized in Table 1. There are the results of 36 experiments performed on 5 dogs. The two previously described methods employed to locally cool a segment of the duodenum above and below the level of the fistula showed no difference in their effectiveness, as measured by the decrease in the frequency of contractions recorded at 50, 100 and 150 cm. Therefore, the results of the two methods employed were computed together.

The results of these experiments were calculated in the following manner. The average rate of contractions per minute during the control period was calculated from all of the experiments on the same dog in which the balloon was at the same level. Usually 2 or 3 experiments were performed on each dog in order to determine the effects of local cooling of the duodenum on the frequency of contractions recorded at each individual level. The lowest sustained contraction rates during local cooling were averaged in a similar manner. Only the lowest sustained values were used in calculating the averages because the effects of local cooling were not manifested immediately after cold application in every experiment.

TABLE 1

EFFECTS OF LOCAL COOLING OF THE DUODENUM

DOG	CONTRACTION RATE PER MINUTE								
	50 CM.			100 CM.			150 CM.		
	BEFORE	DURING	DIFFERENCE	BEFORE	DURING	DIFFERENCE	BEFORE	DURING	DIFFERENCE
#1	18.7	15.5	3.2	17.5	15.5	2.0	16.0	15.0	1.0
#2	18.2	14.7	3.5	17.1	14.2	2.9	15.5	13.7	1.8
#3	18.0	14.0	4.0	18.2	14.3	3.9			
#4	17.7	13.7	4.0	16.6	13.5	3.1	15.2	13.1	2.1
#5	18.5	15.5	3.0	16.8	15.4	1.4	16.0	14.2	1.8
MEAN			3.5			2.6			1.7
SE			.06			.14			.07
t			58.3			18.5			24.3
p			.001			.001			.001

The rates obtained for each experiment at any particular level for the same dog were averaged and the final value tabulated.

The effectiveness of local cooling of the duodenum was measured as the difference between the average frequency during the control period and the average of the lowest sustained frequency during cooling. The average difference for each level was calculated for each of the five dogs and these means averaged for each level for all five dogs. The mean values obtained at 50, 100 and 150 cm. from the level of the fistula are displayed graphically in Figure 11. It can be seen that the average decrease in the frequency of contractions at all three levels during local cooling is highly significant, (p equal less than .001). One can also observe from Figure 11 that the effectiveness of local cooling of the duodenum, as measured by the decrease in the frequency of contractions, proportionately decreases as the distance from the area of local cooling is increased.

It is of interest to note that the procedures normally involved in local cooling of the duodenum produced other interesting phenomena in addition to a decrease in the frequency of contractions in the intestine below the cooled area. It was observed that when the finger cot, which was attached to the Miller-Abbott tube, or the multi-perforated polyethylene tubing was placed into the duodenum, complete inhibition of rhythmic activity which was observed at all levels resulted. This inhibition lasted until the tubing was in place, usually 5 to 10 seconds, after which the frequency returned to the original rate. Complete inhibition probably resulted from mechanical trauma inflicted on the duodenum.

It was also noted that complete inhibition of rhythmic activity resulted when a thermometer or thermocouple was moved sufficiently to produce defacotory movements or, at least, activity of the anal sphincter.

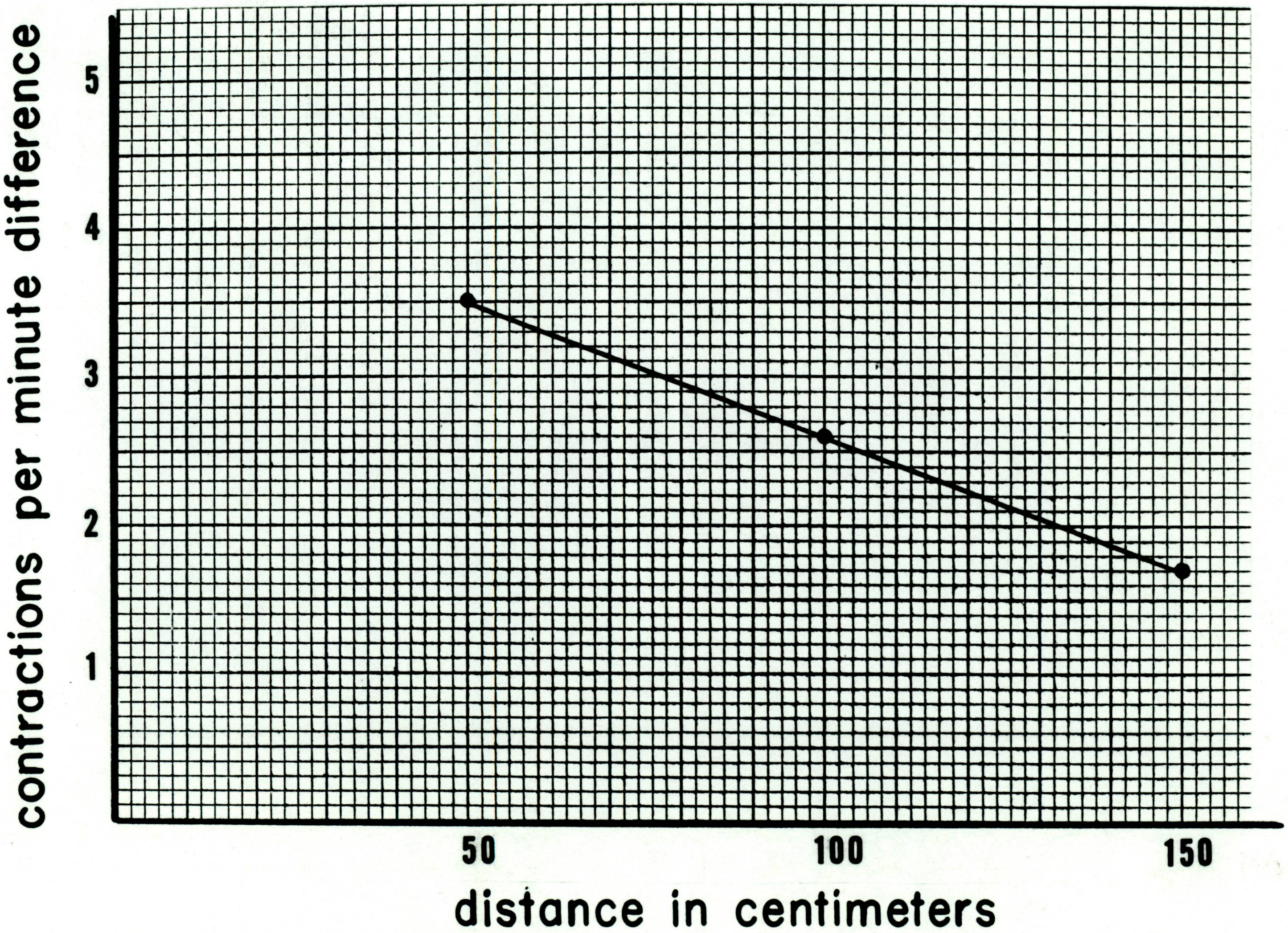

Figure 11 Effectiveness of local cooling of the duodenum on the frequency of contractions recorded at various levels.

This effect was previously noted by Youmans, Meek and Herrin in unanesthetized dogs.

When the Miller-Abbott tube or the multi-perforated tubing was in place and after having observed that the frequency remained constant, and the temperature observed and recorded, the cold water was circulated. The decrease in frequency was generally immediate at 50 cm. but at 100 and 150 cm. it appeared after a delay of about 1 to 2 minutes.

One could always predict when the local cooling of the duodenum had become effective, for the amplitude of the observed contractions would increase markedly. This increase in the amplitude of the observed contractions could have been due to the increase in the force of contractions of the smooth muscle surrounding the balloon or an increase in the area of contracting smooth muscle surrounding the balloon, which would tend to produce greater pressure in the balloon over a longer period of time.

When the Miller-Abbott tube or the multi-perforated tube was removed the frequency of contractions did not return immediately to the frequency observed during the control period. It was usually about 5 minutes before the frequency returned to the original rate at 50 cm. and approximately 10 minutes at 100 and 150 cm.

The rectal temperature during these experiments remained fairly constant, the maximum decrease observed during cooling was 0.2 of a degree centigrade. Sometimes there was an additional 0.1 of a degree decrease immediately after cooling. This decrease in rectal temperature apparently did not effect the contraction rate, for the frequency of contractions returned to the control frequency within 5 to 10 minutes after the removal of the cold, even though the temperature was 0.1 to 0.2 of a degree lower than that during the control period. In many of the experiments the rectal temperature remained the same before, during and after cold application of cold.

The experiments in which a recording balloon was placed above and below the point of cold application gave the following results. In every instance the frequency of contractions above the point of cold application remained the same while the frequency below dropped 3 to 4 beats per minute.

The application of hot water to the duodenum did not significantly alter the frequency of contractions below the level of heat application. In a few instances heat applied to the bile duct area increased thecontraction rate 1 beat per minute at 50 cm. Heat applied to the bile duct area never increased the frequency more than what was normally observed for a particular level. Milton and Smith working with unanesthetized dogs with duodenal loops, found that when they heated the bile duct area the frequency of the slow electrical waves increased 1 to 3 waves per minute, when recording from the caudal end of the loop. In looking at their graphs the original slow wave frequency before heating was found to be approximately 16 waves per minute, and the slow wave frequency during heating increased to 19 waves per minute. The latter frequency is approximately normal for this part of the intact intestine.

In the experiments in which combined mechanical and electrical activity was studied, 3 dominant types of combined activity were recorded. Figure 14 shows a record of vigorous mechanical activity with corresponding electrical recordings. No quantitative determinations were attempted for the electrical activity, due to the fact that the effects of shorting, resistance, etc. are indeterminate and one cannot ascertain how much of the apparent electrical activity was due to movement of the electrode with respect to the mucosal surface of the intestine.

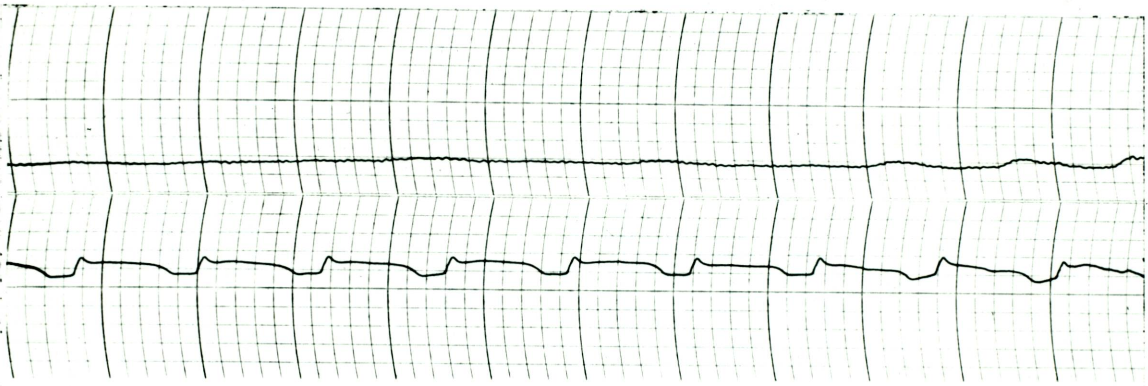

Figure 12 Tracings of combined mechanical (upper) and electrical activity. For description see text.

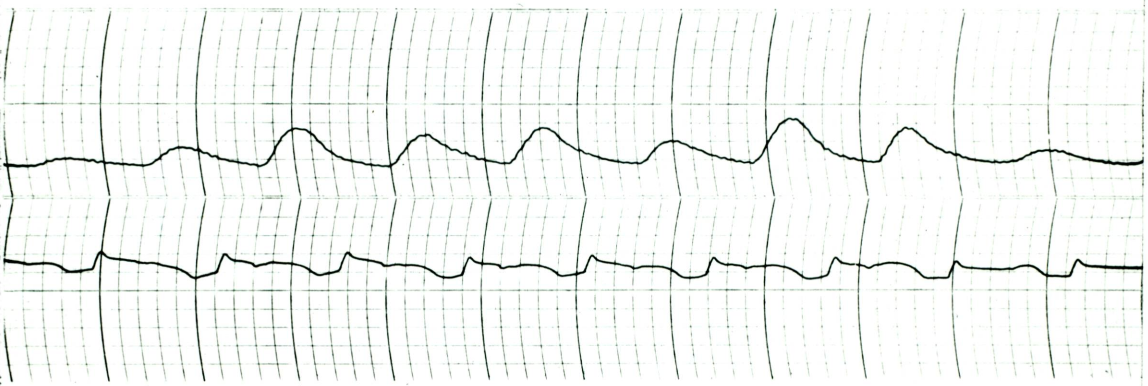

Figure 13 Tracings of combined mechanical (upper) and electrical activity. For description see text.

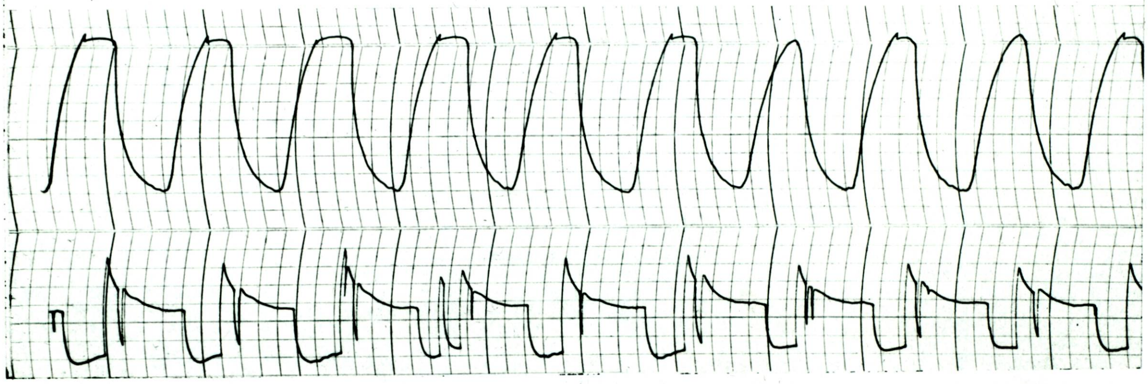

Figure 14 Tracings of combined mechanical (upper) and electrical activity. For description see text.

Figure 13 represents moderate mechanical activity with the typical slow waves similar to those recorded by numerous investigators using needle electrodes. One can observe the negative deflection during the positive phase of the slow wave, which some investigators have attributed to fused muscle action potentials.

Figure 12 shows apparently no mechanical activity while the typical slow waves continue. In this instance, the positive phase of the slow waves has no superimposed negative deflection. The upper tracing in Figure 12 represents apparently no activity with polygraph settings which provided maximum sensitivity to any pressure change in the intestine. The maximum sensitivity in this instance was provided by turning the gain as high as possible without having the pen go off the recording channel.

DISCUSSION

The existence of gradients of various sorts in the intestine has been proved and is not open to question. Generally speaking the functional activity involved in the gradient diminishes progressively with increase in the distance from the pylorus. The fact that a gradient in the rate of rhythmic contractions exists in the small intestine of the dog has been known for nearly 100 years; however, the significance of this gradient has been somewhat obscure. New evidence is presented in this thesis to clarify to some extent the significance of the gradient of rhythmicity in the small intestine of the unanesthetized dog. The evidance seems to indicate that in the dog the rate does not vary inversely in a linear fashion with the distance from the pylorus, but that in most instances the rate, as recorded in these five dogs, appears to vary in a stepwise fashion with the distance from the pylorus.

Several possible explanations for the gradient of rhythmicity in the small intestine in the unanesthetized dog may be given.

A. It may result from an unchangeable anatomic or chemical pecularity intimately built into the structure of the intestine.

B. It may be that a pacemaker mechanism in the duodenum sends impulses to all the smooth muscles at a uniform rate and that these respond at the maximum frequency of which they are capable, the frequency of each segment being limited by the inherent rhythmicity of that segment.

C. It may be that more than one pacemaker exists, for example one for each functional unit of intestine. These would be strategically situated along the intestine and function in the same manner as a duodenal pacemaker, but the influence of each would be limited to only a segment of intestine.

Upon observation of the graphs representing the gradient of rhythmicity, one notices a stepwise declination in the rhythmicity. This type of decrease would seem to favor the hypothesis that there may exist a series of strategically situated pacemakers along the intestine. However, this stepwise declination may also be due to the higher inherent functional capacity of some segments of smooth muscle to respond to the descending impulses of a single pacemaker located in the upper part of the gut.

One can also observe that in the terminal ileum the gradient does not seem to follow the general pattern of the rest of the small intestine in that there seems to be in most instances an actual reversal in the gradient as the distance from the pylorus is increased. Alvarez working with excised intestinal strips in oxygenated Ringer's solution found that strips of ileum with the ileocecal collar still attached contracted at a higher rate than those strips of ileum with the ileocecal collar removed. This may be a possible explanation for the reversal in the gradient of rhythmicity observed in this portion of the small intestine. Perhaps this may be one of the reasons why a balloon will remain in this portion of the intestine for hours without making any progress.

That a pacemaking mechanism exists in the upper part of the duodenum is brought out in the experiments of Douglas, Milton and Smith and in experiments reported in this thesis. Our findings, indicating that the duodenum controls the normal frequency of contractions of the jejunum, agree with the results of Douglas. Douglas found that when he sectioned and re-joined a section of duodenum 15 cm proximal to an exteriorized jejunal loop, the contractions in the jejunal loop decreased 3 to 5 per minute. He also noted the effects of procaine injected into the wall of the duodenum and recorded a mean fall of 3 contractions per minute in the jejunum. We have evidence that a duodenal pacemaker, besides influencing the normal frequency of the jejunum, also influences, to a lesser degree, the normal frequency of the ileum. Up until this time such evidence has not been found in the literature.

Daniel et al have presented what they thought was conclusive evidence to show that the influence of the duodenal pacemaker on the slow wave activity of the remainder of the small intestine is lacking. Their experiments were performed on the human, and on the dog small intestine exposed at laparotomy under anesthesia. Some of their experiments were designed to see if isolation of the duodenal pacemaker from distal segments of the intestine had any influence on the rate of slow waves in the jejunum and ileum. For example, in a number of experiments they attached electrodes at various sites in the small intestine, and after control records were taken, the duodenum was severed or tightly occluded just below the ampulla of Vater with a rubber tube 0.5 cm. in diameter. The effects of this procedure on slow wave rate in the jejunum and ileum were studied. Interestingly enough the animals which had low jejunal or ileal rates before this procedure showed little changes in the frequency of slow waves after the procedure. In some preliminary experiments with the unanesthetized dog with transplanted jejunal loops under the skin, we have recorded slow wave activity at 18.5 per minute. Records were taken with the use of monopolar needle electrodes recording simultaneously from two different areas of the jejunum approximately 5 cms. apart. When 2 per cent procaine was injected into the intestinal wall between the electrodes the slow wave frequency recorded at the oral electrode remained at 18.5 per minute, while the frequency at the caudal electrode dropped to 13 per minute. The evidence, therefore, seems to indicate that the slow wave frequency in the jejunum of the unanesthetized dog is normally dependent on descending impulses initiated from a higher level at a uniform rate. When the jejunum is cut off from this possible pacemaking area it will apparently assume an inherent rhythm characteristic of that portion of the intestine. The failure of Daniel et al to demonstrate a pacemaker may have been due to the fact that the slow wave frequency may be influenced by the various procedures employed in acute experiments involving the small intestine. It should be borne in mind that in working with the exposed small intestine of the anesthetized subject one must take into consideration the various inhibitory effects of the anesthetic, laparotomy, handling of the bowel, temperature, exposure to room air, dehydration, etc. Therefore, it is conceivable that the exposed duodenum, jejunum or ileum, being influenced by a number of inhibitory factors, would not be capable of responding maximally to the descending excitatory impulses of a pacemaker or it may be that the pacemaker itself is not actively functioning at its maximum capacity, so that it may initiate excitatory impulses at a lower uniform rate or it may be that the conducting mechanism responsible for transmission of impulses from the hypothetical pacemaker in the duodenum to the muscle in the jejunum is depressed or paralyzed. Perhaps it is the combined effect of these factors that produces the total response manifested in the exposed intestine of the anesthetized dog.

It is interesting to note that the frequency of contractions recorded from excised segments of rats' and rabbits' small intestine, as observed by a number of investigators, is not affected by the common neurotrophic drugs. Procaine, which is supposed to act predominantly on nervous tissue, will fail to effect the rhythmic contractions; however, as mentioned before, procaine when injected into the duodenal wall of the unanesthetized dog will cause a decrease in slow wave activity and contraction rate in the jejunum.

The experiments reported herein indicate that when the bile duct area or a lower segment of duodenum is cooled, the frequency of contractions recorded from the jejunum or ileum is decreased. Presumable, when a segment of duodenum is cooled the conducting mechanism in the wall of the intestine is affected, so that excitatory impulses from a pacemaking area to the remainder of the small intestine are interrupted. However, in experiments in which cold water or cold saline was applied to the bile duct area, the activity of the pacemaking mechanism might have been reduced, so that it initiated impulses at a slower uniform rate.

It is evident from some of the control experiments that this decrease in the frequency of contractions was not due to a reduction in total body temperature. The evidence from the control experiments is as follows: (1) the total body temperature in most instances only dropped 0.2 of a degree centigrade, and the drop in temperature did not correspond in time with a drop in the contraction rate; (2) after the cold was removed from the duodenum the contraction rate returned to the original frequency long before the body temperature returned to the original level; (3) when simultaneous recordings of the contraction rate were taken above and below the point of cold application, the point of cold application being just below the level of the fistula, the contraction rate above the point of cold application remained the same, while the contraction rate recorded at 50 cm. below the level of the fistula dropped 3 to 4 beats per minute. In some experiments there was no detectable change in body temperature but the decrease in frequency occurred as usual.

Some of the other control experiments indicate that this decrease in contraction rate recorded from the jejunum or ileum was not due to mechanical distension. The evidence is as follows: (1) water heated to body temperature and circulated through a finger cot placed in the duodenum did not affect the contraction rate recorded from jejunum or ileum; (2) cold saline or cold water applied directly to the bile duct area through a multi-perforated nylon tube produced the same results as cold water circulated through a finger cot in the duodenum. In a few experiments water heated to body temperature was forced into a finger cot inserted in the intestine in order to bring about distension of a segment of duodenum. In this instance there was no gradual decrease in contraction rate, but within a few seconds there was a complete cessation of all rhythmic activity. The frequency of contractions returned to the original rate after the water had been removed. This phenomenon was first studied by Youmans, Meek and Herrin and called the intestino-intestinal reflex by them. It is mediated chiefly through the extrinsic nerves of the bowel.

Evidence from the experiments reported in this thesis tends to point toward the possibility that the duodenal pacemaker influences the rhythmical activity of the jejunum and the ileum. However, the effectiveness of blocking the influence of the duodenal pacemaker from the rest of the small intestine by a cold block, as measured by the decrease in frequency recorded at 50, 100 and 150 cm., respectively, diminishes as the distance from the pylorus is increased, (Figure 11).

In a few preliminary experiments typical slow waves noted by others have been recorded in the presence and in the absence of apparent mechanical activity. Earlier investigators have shown that rapid action potentials and in some instances fused negative spikes occur during the positive phase of the slow wave. This relationship may result from facilitation of the occurrence of action potentials during the positive phase of the slow wave. As mentioned before it is generally believed that the action potentials and the fused negative spikes correspond with smooth muscle contractions, but the significance of the slow waves is obscure.

One can observe in Figures 12 through 14 that slow wave activity was recorded in the absence of apparent mechanical activity. These slow waves corresponded in frequency with the mechanical contractions when they were present. When mechanical activity was present a slight negative deflection and in some instances a very marked fused negative spike occurred during the positive phase of the slow wave. No attempt was made to quantitate the results obtained in these experiments.

It should be borne in mind that conclusions as to the occurrence of either mechanical or electrical activity in the absence of the other cannot be drawn unless sensitive measurement is made of both activities from precisely the same intestinal area. Thus far this has not yet been achieved.

SUMMARY AND CONCLUSIONS

The gradient of rhythmicity was studied in five dogs. It was observed from the results obtained that the frequency of rhythmic contractions decreases in a stepwise manner as the distance from the pylorus is increased. It was also noted that in some instances there was somewhat of a reversal of the gradient in the terminal ileum.

When local cooling was applied to the duodenum, above or below the level of the fistula, the frequency of contractions recorded at 50, 100 and 150 cm., respectively, was decreased. Possibly, the decrease in the frequency of contractions recorded at these levels may be due to the interruption of impulses initiated at a uniform rate from a duodenal pacemaker, which normally governs the frequency of contractions in the remainder of the small intestine. It was shown that the effectiveness of local cooling to the duodenum, as measured by the frequency of contractions recorded at 50, 100 and 150 cm., respectively, progressively decreases the greater the distance from the level of the fistula.

The effects of local heating applied to the duodenum in most instances gave no significant results. In a few experiments with a recording balloon at 50 cm., the frequency of contractions increased 1 beat per minute after applying heat to the bile duct area.

In a few preliminary experiments combined mechanical and electrical activity were recorded from the mucosal surface of the small intestine. The typical slow waves, recorded previously by a number of investigators using needle electrodes, were recorded using an electrode-bearing balloon. Slow waves were recorded in the absence of apparent mechanical activity. These slow waves corresponded in frequency with the mechanical contractions when they were present.

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COLLEGE OF MEDICAL EVANGELISTS

School of Graduate Studies

THE PACEMAKER FUNCTION OF THE SMALL INTESTINE

by

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New evidence is presented to clarify to some extent the significance of the gradient of rhythmicity in the small intestine of the unanesthetized dog. The gradient of rhythmicity was studied on five dogs prepared with duodenal fistulas. Rhythmic contractions were recorded from the small intestine by a small rubber balloon. The gradient of rhythmicity was found to decrease in a stepwise manner as the distance from the pylorus is increased. Roughly, the rhythmic contractions were found to be 18 to 19 per minute in the duodenum and 14 to 15 per minute in the ileum. In the terminal ileum there was somewhat of a reversal in the gradient of rhythmicity.

Additional evidence is presented to suggest that a duodenal pacemaker controls the normal frequency of contractions in the jejunum and in the ileum. The effects of hot and cold water, applied above or below the level of the fistula, on the frequency of contractions recorded at various levels were studied. The duodenum was locally heated or cooled either directly by applying water through multi-perforated tubing or indirectly by circulating water through a finger cot attached at the end of a Miller Abbott tube. During local cooling of the duodenum the average frequency of contractions recorded at 50, 100 and 150 cm. for all five dogs decreased 3.5, 2.6 and 1.7 beats per minute, respectively. The effects of local heating applied to the duodenum in most instances gave no significant results.

In a few preliminary experiments combined mechanical and electrical activity were recorded from the mucosal surface of the small intestine. The typical slow waves were recorded using an electrode-bearing balloon. Slow waves were recorded in the absence of apparent mechanical activity. These slow waves corresponded in frequency with the mechanical contractions when they were present.