THE ACTIVITIES OF THE INTESTINAL MUCOSAL MOTOR MECHANISM

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Much has been written about the motor activities of the intestinal tract. A survey of the literature shows that with a few exceptions these writings have been based upon experiments and observations involving only the outer, the circular and longitudinal muscles of the intestine. Little attention has been given to the activities of the muscularis mucosae. Inasmuch as in all higher animals this musculature is well developed, it would seem necessary to assume that it manifests some sort of activity and contributes an essential rôle to the normal physiology of the small intestine.

At this point it is well to recall that some of the fibers of the muscularis mucosae extend into the villi, consequently mucosal motor activities in the intestine would imply movement of the mucosa as a whole, or in limited areas, and also movement of the individual villi.

A number of earlier workers have reported observations on movements of the intestinal mucosa. Lacauchie (1) observed a shortening of the villi after death. Gruby and Delafond (2) observed shortening, lengthening and lateral movement in the living animal. Brueke (3) was among the earlier students of the musculature of the villi and ascribed changes in shape and position in them to muscular contraction and relaxation. Exner (4) studied the reactions of the intestinal mucosa to mechanical stimulation and found it to respond sharply to such a procedure. Gunn and Underhill (5) recorded and studied the movements of the mucosa of the cat's small intestine, using strips from which the outer musculature had been removed. They were able to record a definite rhythmical movement. Hambleton (6) observed, by using a binocular microscope and watching lighted fields of intestinal mucosa in intact animals, shortening, lengthening and lateral movement of the villi.

The present study was undertaken for the purpose of inquiring more fully into the types and varieties of movement manifested by the mucosa.
of the dog's small intestine, and to investigate the nature of and the control of the mechanism involved.

METHODS AND MATERIAL. It is practically impossible to record movements of the intestinal mucosa, especially the individual villi in the intact animal, by mechanical means. One might think of photographic methods, a series of pictures showing the villi in different positions and shapes. Owing to the magnification required as well as the intensity of light, this method, at least in our experience, has proven next to valueless.

We have adapted the method of observing the field through an extension binocular microscope, using a magnification of 25 diameters, the field of observation lighted by a small arc light. The results are recorded as dictated by the observer, or in some instances the villi rhythm is recorded by means of a key and signal magnet.

With few exceptions dogs have been used. Cannon (7) has shown that the motor mechanism of the outer musculature of the intestine is relatively long-lived. Not so with the mucosal mechanism. It is extremely sensitive to circulatory changes, anemia in particular, to thermal changes, and to mechanical and chemical irritation. Our experience has been that the mechanism holds up better in dogs than in cats, rabbits and goats.

Ether depresses the irritability of the mucosal motor mechanism. For this reason we have partially decerebrated most of our animals. After preliminary ether anesthesia the parietal bone is rapidly drilled through, making the hole large enough to admit a Mall probe. The anterior half of the cerebrum is thus destroyed. The animal remains quiet without further ether, maintaining a normal respiration and blood pressure. Occasionally, if the brain injury has been extensive, respiration fails, accompanied by a fall in blood pressure. Although these latter animals may be kept alive for several hours by artificial respiration, it has been our experience that the mucosal motor mechanism seldom shows anything like normal activity.

After decerebration the abdomen is opened by a median longitudinal incision and a loop of the small intestine pulled up. An incision about 5 cm. long is made through the wall opposite the mesenteric attachment. The loop is then slipped through a slit in a small board and the edges of the gut are pinned out so as to present a flat mucosal field for observation. The board is held in position by a burette clamp attached to stand. The field is lighted by means of an arc lamp, the binocular adjusted, and the preparation is ready for observation.
PROCEDURE AND EXPERIMENTS. Mechanical stimulation. When the mucosal surface of the small intestine was touched or stroked with a probe or fine glass rod there appeared a depression or groove at the point of contact followed quickly by an anemia of greater or less intensity, depending apparently, within certain limits, upon the intensity of the stimulus. In case there was no further mechanical disturbance a normal appearance was resumed in from 30 seconds to 1 minute. With the field lighted and with magnification, in addition to seeing the almost disappearance of the blood from the villi capillaries, it was clear that two factors were involved in the formation of the pit or groove, the shortening of the individual villi, and a contraction seated apparently in the deeper portions of the muscularis mucosae.

The response to mechanical stimulation was sharpest in new preparations, then gradually diminished to a degree of sluggishness making the preparation useless for experimental purposes, or disappearing entirely. Thirty minutes represented about the average life of the mechanism under our working conditions. Drying and lowering the surface temperature were apparently factors involved, for the life of the preparation could be considerably prolonged by frequent irrigation with isotonic saline or dextrose at body temperature of the animal. That this change of condition was a local one is evidenced by the fact that, with the animal in good condition, a new preparation just a few inches from the old one manifested normal reactivity.

The irritability and activity of the intestinal mucosa were the greatest in the duodenum and upper third of the jejunum. The duodenum and jejunum usually manifested considerable spontaneous activity when the fields were first prepared, or in case the mucosa was quiet the response to various types of stimuli was very sharp. In the ileum one occasionally saw a few scattered villi in activity, more commonly not. Vigorous stimulation in the ileum brought on a fair grooving and ridging reaction but scarcely any reaction on the part of the individual villi.

A study of the progressive decrease in irritability to mechanical stimulation revealed the fact that the tops of the villi were the first points to diminish in irritability. When the gut was first opened and the top of a villus was touched with a fine glass rod it quickly retracted, became anemic and then lengthened. In many instances there was restlessness for a few seconds, a swaying movement, then it became quiet, or resumed its regular rhythm of what we might designate as spontaneous movement. If care was taken not to disturb the villus violently with the glass rod the reaction as a whole did not involve the neighboring
villi, but if the tip of the rod was applied in the neighborhood of the base of the villus or pushed deep into the mucosa, a characteristic anemic pit or groove appeared. As the preparation grew older the top of the villus gradually lost its sensitivity, the villus reacted more slowly and less completely, then manifested only a swaying movement, and finally gave no reaction at all. The deep mucosal reaction usually persisted after the individual villi ceased to respond.

The results of electrical stimulation were similar to those obtained by mechanical stimulation, the type, extent and duration of the reaction depending upon the strength of the stimulus applied.

**Thermal changes.** It is a general rule that the irritability of living tissue increases up to a certain limit with a rise in temperature, and diminishes with a fall. Our attention was first called to the marked sensitivity of the intestinal mucosal motor mechanism in an accidental way. During the course of an observation of a field manifesting active villi movement, one of the assistants opened the door leading into the laboratory. This created a strong draft of cold air. In an instant all movement ceased. The door was closed and movement was gradually resumed. On checking this point it was found that the same effect could be produced by blowing the breath over the field, or by fanning. The same fact was demonstrated by irrigation with isotonic saline or dextrose at different temperatures. In many instances a sluggish field was revived by irrigation at body temperature or slightly above. Likewise active fields were made sluggish or movement actually stopped by irrigation below body temperature. In determining this point care was taken to avoid variations in mechanical stimulation due to the flow of the fluid over the field.

**Local applications of irritants and drugs.** These experiments were carried out primarily to determine the reactivity of the mucosal motor mechanism to chemical stimulation. Cantharides, thymol, menthol, alcohol, peppermint oil, croton oil, colocynth and magnesium sulphate were used. One per cent cantharides in saline was used. The amount of cantharidin in such a preparation is small and its solubility slight. One drop placed on the tongue produced a slight tingling sensation. The tincture was avoided in order to eliminate the complicating effect of the alcohol. Both menthol and thymol are slightly soluble in water. Saturated solutions at 39°C. were used, and also small crystals were laid on the surface. Peppermint oil was used in the form of a saturated solution in saline. Croton oil was used in the form of an emulsion 10 drops in 100 cc. of saline to which had been added a few drops of a
solution of egg albumin. One per cent compound extract of colocynth
in saline was used. In this preparation several substances which are
irritating to the mucosa are present and the effect in all probability is a
complicated one. Magnesium sulphate was used in different strengths,
2.5 per cent, 3.5 per cent, and also crystals were placed on the surface.
Alcohol was used in strengths of 1 and 10 per cent.

All of the above named preparations augmented the activity of the
villi, although not to the same degree. Peppermint, menthol, mag-
nesium sulphate and the colocynth preparations were the most active.
Cantharides produced a restlessness, swaying movement, but did not to
any marked extent increase rhythmical movement. Croton oil was the
least effective. This might be expected, inasmuch as no provision was
made for the splitting of the oil, the action noted being due to the small
amount of free acid originally present. One per cent alcohol (ethyl) acted
as a mild irritant; 10 per cent alcohol was injurious and led to a rapid
loss of irritability of the villi.

There is no necessity for detailed protocols of these experiments.
There was no essential difference in the types of reaction produced. The
variations in results seemed to be due to the variations in the concentra-
tions of the active substances. With mild irritation the villi, if quiet at
the beginning, manifested only restlessness; if active, a slight increased
activity. More intense irritation led to vigorous activity on the part of
the villi. In some instances this might be designated as stormy. In
these cases the villi movement was more or less associated with a deeper
mucosal movement. Also with mild irritation one seldom noted any
change in the outer musculature, but with vigorous stimulation rhythm-
ical movement was set up, however coming on later than the increase
in mucosal activity.

In this connection should be mentioned a series of experiments on
irrigation of the musosa with hypotonic and hypertonic solutions of
sodium chloride and dextrose, and also irrigation with distilled water.
Hypertonic solutions of salt and dextrose produced a clear-cut shrinking
of the villi, hypotonic a swelling. Distilled water naturally represented
an extreme hypotonicity. The villi presented some evidence of injury,
but regained their normal appearance after some minutes. Two per cent
sodium chloride and 10 per cent dextrose were the limits used in the
hypertonic series. The sodium chloride was injurious, the dextrose
not. Very little difference could be noted in the effect on villi
movement of this concentration of dextrose and salt from that observed
with isotonic solutions. Distilled water also increased villi movement
but not so marked or so persistent as salt and dextrose.
During the study of the action of irritants, observations were made on the rate and rhythm of villi activity. A single villus was picked and watched for a given period of time and the interval elapsing between successive contractions recorded. In the most active fields the average time between successive contractions was about 3 seconds. In sluggish fields the time was so irregular that the term rhythm is scarcely applicable. In sluggish fields one very frequently saw a villus make two or three contractions at intervals of a few seconds, then rest for a minute or more and then repeat. It is difficult to say what represents a physiological rhythm. One never sees a regularity comparable to that seen in the heart or respiratory mechanism, or seldom even to that of the outer musculature of the intestine.

Small doses of pilocarpin, atropin, nicotine and barium, when applied locally, augmented the activity of the mucosa. Very large doses led to paralysis. The results were similar to those obtained on intravenous administration and will be more fully described under that heading. Pilocarpin when applied locally called forth an abundant secretion of mucus. Nicotine and barium were somewhat irritant. That this irritation was not an important factor is indicated by the fact that it is impossible to introduce enough of the drug intravenously to bring up the concentration to the point necessary for marked irritation on local application.

With the application of epinephrin the intestinal mucosa quickly became anemic. Immediately following this the villi retracted, then remained quiet for about 30 seconds on an average, then began to lengthen and shorten alternately. Usually after the elapse of several minutes the field had the same appearance as at the start. We have kept in mind the observations of various workers that the effect of epinephrin, especially with reference to the type of activity of the vascular system and the outer musculature of the gastro-intestinal system, is dependent upon the concentration of the drug used. We have applied locally concentrations from 1:100 up to 1:6,000,000. In no case where any reaction was noted have we found anything but augmentation of activity, differing only in intensity.

Work on the extrinsic nerves. It is a generally accepted fact that the motor activities of the small intestine depend primarily upon a local intrinsic mechanism. This has been shown in particular with reference to the work on the outer longitudinal and circular musculature. On the other hand, the various types of movement of the outer musculature may be modified either in the direction of augmentation or inhi-
bition by impulse from the central nervous system by way of the vagi and splanchnics.

A series of experiments was carried out to determine if the mucosal motor mechanism is similar in character in this respect. Stimulation of the peripheral ends of both vagi in the vast majority of animals used produced no effect upon the motor activities of the intestinal mucosa. In a few cases a stimulation of the peripheral ends of both vagi resulted in a retraction of the villi and a ridging of the mucosa, but no rhythmical movements were set up. Stimulation was done during quiescence and during activity of various grades and intensity. With the exceptions of the instances mentioned above, no change was wrought in the field under observation. It might be worthy of note that in a number of experiments the outer musculature of the intestine was connected with a recording apparatus and with but few exceptions responded to vagus stimulation with an increase in tonus, rhythmical movement, or both.

In this connection it was thought advisable to determine what effect, if any, decerebration might have. The mucosa was watched in a number of instances during the process. No effect was noticeable.

Attention was next turned to the splanchnics. Stimulation of the peripheral ends of the splanchnics called forth a vigorous reaction on the part of the whole mucosa, contraction of the villi in groups, and a ridging and pitting of the mucosa. No rhythmical movement was set up during stimulation. After cessation of stimulation rhythmical movement in some instances followed, in some not. The reaction was sharp, coming on shortly after the beginning of the stimulation with a tetanizing current. Single shocks were relatively ineffective, producing only a momentary restlessness. A second stimulation thrown in within from 10 to 30 seconds after the first produced no change. This refractory stage in point of duration bore some relation, within certain limits, to the strength of stimulus, the weaker the stimulus the shorter the refractory period.

The reaction of the intestinal mucosa to splanchnic stimulation was sharpest in the duodenum, good in the jejunum, and almost negative in the ileum. In some instances the line of demarcation appeared fairly sharp. In these cases fields were prepared at the ileo-jejunal junction. Stimulation of the splanchnic gave a clear-cut reaction in the upper half of the field and practically none in the lower half. For this work the splanchnics were picked up at the point of emergence from under the diaphragm (pre-ganglionic). Major and minor splanchnics on both sides were stimulated. The mesenteric fibers to the ileum (post-ganglionic) were also picked up and stimulated, the results being negative.
A few animals were used in which no reaction could be obtained through the splanchnic, although the villi presented a normal appearance, were reactive to mechanical stimulation and manifested spontaneous movement. It was thought that perhaps the vagus carried the motor fibers in these cases, but no evidence was found. Epinephrin in these cases was active with one exception. Stimulation of the vagi and splanchnics at the same time gave a typical splanchnic reaction.

Another series of experiments was carried out in which the splanchnics were cut aseptically and time allowed for degeneration. It had been observed in the crucial work that cutting of the splanchnics did not abolish movement of the villi. The nerves were cut in five animals. They were used 4 to 17 days after cutting. The fields of observation in all cases presented a normal appearance and a normal reactivity. Stimulation of the mesenteric fibers (post-ganglionic) provoked a reaction, as did also epinephrin. Stimulation of the vagi after splanchnic cutting gave no results differing from those previously described.

**INTRAVENOUS INJECTION OF DRUGS.** The drugs chosen were the same series as used in irrigation experiments: epinephrin, pilocarpin, atropin, nicotin and barium.

Reference has already been made to the use of epinephrin in relation to local application and to splanchnic work. It was assumed from the beginning that the effect of this drug upon the motor activity of the intestinal mucosa would be identical with that obtained with splanchnic stimulation. This assumption was borne out in a series of experiments in which the drug was used under a wide variety of conditions. The sharp contraction of the villi, the ridging of the mucosa, the refractory period and the gradual return to the previous state of activity were identical with the splanchnic picture. A number of instances was noted where the response to splanchnic stimulation was feeble before, and very sharp after epinephrin.

In the pilocarpin experiments, the dose was graduated so that the animal received about 0.5 mgm. per kilo body weight. The usual effect on the outer musculature, that of increased tonus and rhythmical contraction, was noted in practically every instance, also a fall in blood pressure and a decrease in heart rate. Synchronous with the decrease in circulation the intestinal mucosa became pale, then gradually recovered its normal appearance with the improvement in circulation. The mucosal motor reaction was very sharp. Synchronous with the reaction of the outer musculature the villi retracted, usually in groups, and the mucosa became grooved and ridged. Unlike the reaction with epineph-
rin, there was no clear-cut period of tonic quiescence but a somewhat rhythmical action of the mucosa and individual villi from the start of the reaction; this usually lasted for a few minutes, gradually diminishing in intensity, and leaving the villi in apparently less reactive condition than normal. Rapid covering of the surface with a thick tenacious and frequently whitish mucous was the rule after pilocarpin. This same phenomenon was commonly observed after nicotin; in fact, after any procedure which called forth a vigorous and sustained reaction, even in cases of repeated splanchnic stimulation or repeated epinephrin injection.

The next series of animals was used to determine primarily the effect of atropin. The dosage was graduated so that the animal received about 0.1 mgm. of atropin sulphate intravenously per kilo body weight. Larger and smaller doses were also used. After atropin the villi and submucosa manifested increased activity, but the reaction was not so sharp as with pilocarpin or epinephrin, a minute or two usually elapsing before the activity reached its maximum intensity. The reaction was also more in the direction of a rhythmical one. The outer gut wall was kept under observation during the atropin work. It clearly diminished its tonus and activity after pilocarpin, neither was pilocarpin as effective on the outer musculature after atropin as before. Two points of special interest were repeatedly observed. The effect of vagus stimulation on the intestine was not abolished by doses large enough to eliminate cardiac inhibition, nor was pilocarpin rendered ineffective on the mucosal activity by atropin, except after enormous doses.

Nicotin is a vigorous stimulant to the whole mucosal motor mechanism. The first series of nicotin experiments was carried out to determine the general effect upon the activity of the mucosa. The results were markedly uniform, a sharp contraction of the villi and grooving of the mucosa as a whole, followed usually, but not always, by a short period of quiescence, then rhythmical movement persisting for several minutes. Doses of 1.5 mgm. up to 10.0 mgm. were used, depending upon the size of the animal. A second dose gave the same type of response as the first, although not always so sharp. This took place after paralysis of the splanchnic ganglion, this based upon the fact that pre-ganglionic splanchnic stimulation gave no mucosal response. After the initial dose of nicotin the mucosa became covered with a thick whitish mucus. Repeated doses finally led to a complete loss of activity and reactivity, the paralysis being muscular, inasmuch as no reaction could be obtained with barium.
Correlation with the outer muscular mechanism. In the course of the experiments noted above we frequently observed vigorous movement of the villi and mucosa as a whole while at the same time the outer musculature of the gut remained quiet. At another time we have observed them both active at the same time. These observations in themselves speak against any close essential interdependence between the mucosa and the outer mechanism, at least so far as motor activity goes. In view of the fact that it is impossible to judge accurately changes in tonicity or to recognize any minute rhythmical movement by direct observation, we conducted a series of experiments where the changes in tonus as well as movement on both the longitudinal and circular muscles were recorded while the villi and mucosa were watched. We were also mindful of the fact that the normal physiological stimulus which sets off the various types of intestinal movements comes from inside of the intestinal canal; consequently attention was also given to any effect which might be produced on the activity of the outer muscles resulting from the mucosal stimulation.

The gut was prepared for mucosal observation as described in the beginning of the paper. In addition a slit was made near one end of the preparation running parallel with the circular muscle and extending almost to the mesenteric attachment. To the lateral edge a few centimeters from the slit a pin was attached to the gut wall which by means of a fine silk cord and a system of pulleys was made to connect with a muscle lever. The pulleys were so mounted that the pull was exerted parallel to the circular muscle. In the same manner a lever was attached to the edge of the slit made, and pull exerted in a direction parallel to the longitudinal muscle. While it is true that the contraction of one group of muscles also influences the position of the lever attached to the other, yet by proper choice of the point of attachment one can reduce this to a negligible amount. In any case there is no difficulty in recognizing the activity of the separate systems of muscles.

Records were taken of the effects of stimulation of the vagi and splanchnics, injection of epinephrin, pilocarpin, atropin, nicotin and barium, and of the application of peppermint oil, and mechanical stimulation of the mucosa.

It was during the course of these experiments that two dogs were found in which the villi contracted upon stimulation of the vagi. Both of these dogs were very reactive, also the outer musculature responded by both an increase in tonus and rhythmical movement, more marked in the circular than in the longitudinal muscle. The response of the outer
musculature to vagus stimulation in almost all of the animals studied
was in the same direction, that of increased tonus and rhythmical
movement. There was, however, a wide variation in details. In some
of these animals there was an initial period of relaxation followed by
contraction and in others no relaxation. In fact both of these phe-
nomena were repeatedly observed in the same animal, although so far
as could be determined the conditions were the same. There was also
considerable difference in the duration of the response. We were not
able to pick out and definitely associate any of the details with any
activity on the part of the mucosa.

This last statement also applies to the results of splanchnic stimulation.
With a few exceptions the splanchnic stimulation resulted in mucosal
activity. The effects on the outer musculature were not so constant,
both relaxation and contraction appearing, but relaxation predominat-
ing. A wide variation in detail was noted. In some instances both
muscles ran parallel courses, in others opposite. This was not due to a
mechanical defect or to a peculiarity of individual animals, because
these variations were observed in the same animal and in the same
preparation.

In the dog the reaction of the intestinal mucosa to stimulation
cannot be predicted on the basis of the reaction of the outer mus-
culature.

The injection of epinephrin revealed nothing new, the results being
essentially those of splanchnic stimulation.

Pilocarpin invariably produced an increased tonicity and frequently
rhythmmal movement on the part of both longitudinal and circular
muscles. On the whole the effect appeared more pronounced on the
circular muscle, especially with reference to rhythmical movement. In
connection with this it is to be noted that the villi as a rule exhibited
rhythmical movement after pilocarpin. At this point we often experi-
enced the phenomenon that although the outer musculature usually re-
atacted in orthodox fashion to a second or third dose of drug, the mucosal
mechanism seldom reacted the second time in a fashion at all comparable
to the first. The villi became covered with mucus and developed con-
siderable refractiveness to stimulation.

The effect of atropin on the outer musculature noted by us agrees with
those usually described, a clear-cut antagonism to pilocarpin without
complete stopping of rhythmical movement. The record often revealed
an increase in rhythmical movement, if given when the muscles were
somewhat relaxed. The mucosal mechanism responded by increased
activity, which however did not come on sharply, but was characterized by a gradual increase. Atropin was not effective after pilocarpin paralysis, but we frequently found pilocarpin active on the mucosal mechanism when stimulation of the vagus, after atropin had been administered, failed to yield any response.

The results with nicotin are rather bewildering. In a number of animals nicotin was ineffective on the outer musculature, although there was a marked vascular and respiratory reaction. In these cases the intestine responded sharply to vagus and splanchnic stimulation and to pilocarpin and epinephrin. The most common effect of nicotin was an increase in tonicity and activity of the outer musculature and a tonic contraction of the villi followed by rhythmical movement. There was, however, no sharp correlation, for we have observed a number of responses of the outer mechanism with none on the part of the inner, and also the reverse.

The effects of barium upon the circular and longitudinal muscles are constant, producing an increase in tonus and rhythmical activity in both, also a contraction of the villi. This might be expected inasmuch as barium acts directly upon the muscles. It was used throughout the work to determine the condition of the muscle in question. It was repeatedly demonstrated that the musculature of the mucosa ceases to respond to barium sooner than the outer musculature of the gut.

During the experiments on the coördination of the mucosal mechanism with the outer musculature, observations were made and recorded on the effect of mechanical and chemical stimulation of the mucosa on the activity of the outer musculature. The results were uniform. In case the outer musculature was relaxed, light mechanical stimulation of the mucosa gave no response, except the local mucosal reaction already described. In case the outer musculature exhibited considerable tonus, even light stroking of the mucosa resulted in quick relaxation more marked on the circular than on the longitudinal muscles. The relaxation persisted during the stroking. The relaxation was usually followed by a return to the normal state and in several instances by an increase in tonus and movement. In case the mucosal stimulation was vigorous, what might be termed punching the gut from the mucosal side, there was an initial loss of tonus quickly followed by an increase in tonus and rhythmical movement (figs. 1, 2, 3 and 4).

VITALITY OF THE MUCOSAL MOTOR MECHANISM. Cannon (7) has pointed out that the myenteric reflex mechanism is relatively long lived, standing up for a considerable time under varying degrees of anemia. It
has not been necessary for us to devise special experiments to determine this point in regard to the mucosal motor mechanism. The rapid collapse of the mechanism under experimental conditions has been to us a constant source of delay and mental irritation.

In planning the experiments on the effect of the drugs mentioned earlier in this paper it was thought that possibly it might be advantageous to employ strips pinned out and immersed in oxygenated isotonic solutions, inasmuch as under these conditions we would not be compelled to contend with radical vascular changes, or changes due to impulses from the central nervous system. This was a fruitless adventure, inasmuch

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**Fig. 1**

Upper curve carotid blood pressure. Middle curve, longitudinal muscle of jejunum. Lower curve, circular muscle of jejunum. 5. Stimulation of left splanchnic.

**Fig. 2**

Upper curve carotid blood pressure. Lower curve circular muscle of jejunum. 9. Light stroking of intestinal mucosa in region of lever attachment.

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as we never succeeded in getting any preparation to manifest more than a few feeble villi oscillations. Oxygenated Ringer's, Locke's and Tyrode's solutions were used. We used preparations in which less than a minute elapsed from the time of connection with the living animal and mounting in solution. The outer musculature manifested good activity in practically all cases.

Next a series of perfusion experiments was planned and carried out. Tyrode's fluid, to which had been added about one-third of a volume of defibrinated blood, was used. The pressure bottle was raised so that the pressure at the mouth of the perfusion cannula was approximately
that in the branches of the mesenteric arteries. The perfusion fluid was aerated by passing a stream of air through the fluid in the pressure bottle.

Fig. 3. Circular muscle of jejunum at levels about 2 cm. apart. At 73 the mucosa was vigorously stroked longitudinally past the three levels.

Fig. 4. Circular muscle of jejunum at levels about 2 cm. apart. At 83 stroking of the mucosa past the point of attachment. Taken from the same preparation as figure 3 but 10 mgm. of nicotin had been injected. Pre-ganglionic splanchnic stimulation not effective.
The fluid passed through a coil of glass tubes in a water bath near the preparation kept at such a temperature that it was delivered at the body temperature of the animal. Having learned from the suspended strip work that shutting off the circulation for only a short time renders the preparation useless, measures were adopted to mount the strip with as little delay and interruption of the circulation as possible. The anastomosis of vessels in the gut wall is good, so that a fair circulation is maintained in a segment a few inches long even though the main vessels supplying that segment be obstructed. A small cannula was inserted into the vessel as rapidly as possible and the perfusion started. The segment was then cut out and mounted while the perfusion was going on.

These preparations were much better than those merely mounted in oxygenated solution, but on the whole were far inferior to those in the intact animal. The villi and submucosa manifested considerable activity, but were relatively refractory to stimulation and short lived. The outer musculature on the other hand manifested vigorous activity, readily responding to drugs in an orthodox fashion and retaining its viability for a relatively long time. Epinephrin, pilocarpin, atropin, nicotine and barium were added to the perfusion fluid. The response of the mucosal mechanism in each case corresponded in type to that described under experiments on the intact animal. There is no occasion for going into details relative to these experiments for this reason, and there would be no justification for mention were it not for the fact that the results bore out our previous experience, that the mucosal mechanism is much more sensitive and breaks down under experimental conditions much sooner than the outer mechanism.

Another observation is worthy of note, that of the mucosal motor mechanism in shock. We have already mentioned the fact that villi activity was rarely seen when the animals were under a deep ether anesthesia. This observation led to decerebration as a routine measure. It was our object to decerebrate enough to keep the animal quiet but not to get back far enough to disturb the medulla. A number of our animals early, and a majority in the course of several hours, manifested some degree of shock. In addition to these factors the extensive and frequent handling of the abdominal viscera is a contributing factor in bringing on shock. We observed it frequently. The onset of shock was manifested very early in the intestinal mucosa. The villi became refractory to stimulation, appeared swollen and glistening, became covered with a thick clear mucus, and were congested. These signs appeared often before there was any marked and clear change in blood pressure and respiration.
DISCUSSION

The results of the experiments and observations recorded in the preceding pages of this paper present nothing new so far as the types of movement exhibited by the mucosa of the small intestine are concerned. Many of the details observed, however, are not generally mentioned in discussions of mucosal function, and to our knowledge have not found their way into the literature. The results of the work as a whole suggest more questions than answers. However, the results, when viewed in the proper light, point toward conclusions which serve to emphasize the motor element of the intestinal mucosa as a factor of possibly greater moment than is usually ascribed to it. They may also serve to throw light upon related questions, such as the enteric nervous mechanism, and the activities of the outer musculature of the small intestine.

The morphological basis for the intestinal mucosal motor activity is the muscularis mucosae, which is well developed in all higher animals. It is made up of a thick inner circular and a thinner outer longitudinal layer of muscle. This represents the most common arrangement in the dog, but there is considerable variation. In many cases the layers are of about equal thickness. Again there are frequent interruptions in the coats, the one or the other of the layers being very thin. Again the circular and longitudinal arrangement may not be so clear, the arrangement being retiform in character. From it there extend into the villi muscle strands, running in an axial direction and for the most part attached to the basement membrane of the sides and top of the villus. Trautmann (8) states that the muscular elements of the villi differ in various animals, being best developed in the dog and very poorly so in the cat. This may account, in part at least, for our failure to observe good movement of the villi in our cats. This muscular unit in the villi is innervated directly from Meissner’s plexus. Berkley (9) has demonstrated end plates in the main muscularis mucosae and has also followed the fibers to the muscular strands of the villi.

The movements of the villi present some points of interest. One might suppose that, upon shortening, the diameter of the villi would change. There are no circular muscles in the villi of the dog, consequently one would not expect any active ring-like contractions. We have never observed any distinct change in shape or size in the visible part of the villus associated with its activity. This might suggest that the retraction of the villus is not due to any shortening on the part of its body, but that it is merely pulled down from below. This is a difficult point to determine, but if it were the case one would expect regularly to
Fig. 4. An original drum record (no. 4) of the experiment of 5/26/21, showing the polyphasic thermocardiograms from a very slowly beating heart. For additional experimental data and analysis see table 1 and page 267. Time always three-second intervals.
see some disturbance in the neighboring villi. One commonly, on watching any particular villus, sees it simply slide down and disappear entirely from view without producing the slightest visible disturbance in any of its neighbors. Histological examination of the sections made from active and quiet fields after fixation with Flemming’s solution threw no light on the question. Another interesting feature of villi movement is that it is not regularly associated with general mucosal movement. Mucosal ridging, pitting, and group contractions of the villi are rarely seen except after application of some vigorous stimulant.

The application of the term rhythmical to the movement of the individual villi must be made with some qualifications. Rhythm implies regularity of occurrence. In very active fields any single villus usually executes its cycle at somewhat regular intervals, every two or three seconds, but as the field becomes more sluggish the interval becomes more variable and irregular. It often happens that a single villus will complete eight or ten cycles at rather regular intervals and then abruptly stop and remain quiet for many seconds. Another villus adjacent to it will maintain its movement without any variation or disturbance. When one views a large field he is reminded of the incoordinated contractions of the musculature of the heart in delirium cordis, and the temptation arises to apply in case of the villi activity the term delirium villi. This description holds in cases where the mucosa as a whole manifests rhythmical ridging and grooving as well as when quiet. It is suggested on this basis that the impulse which sets off the individual villus does not radiate from a given center but is more sharply localized.

The movement of the mucosa as a whole is more rhythmical than that of the individual villi. There is no progressive wave of movement in the mucosa. It is entirely local in character. So far as we know, Gunn and Underhill are the only observers who have succeeded in recording by mechanical means the movement of the mucosa. The conditions under which they accomplished their work were far from favorable, at least in light of our experience relative to the vitality of the mechanism, so that their results show probably only to a limited degree the possible activities of the mucosa. Their tracings show considerable rhythmicity, but show no evidence of progressive waves of activity, neither do they mention having observed any.

What manner of mechanism is necessary to account for the characteristics of the movements described? Is the stimulus which sets off the movement applied to the muscle through the nerve elements of Meissner’s plexus, or to the muscle directly?
It has been demonstrated that the rhythmical movements of the villi and the mucosa as a whole may be set up and augmented by both chemical and mechanical stimulation. In case of mechanical stimulation, if the stimulus is applied to the top of the villus, the reaction which follows does not involve any of the adjacent villi. In case the field is quiet at the time of stimulation, the reaction usually consists of a single contraction of the villus and return, but occasionally the movement persists through a larger number of cycles. In case the field is active, the reaction consists in, first, a quick contraction, then an acceleration of rhythm persisting for a short time. In case the stimulus is applied to the base of the villus, the reaction is in the nature of a group retraction, and in case of persistence of movement, which is more frequent than when the tip is stimulated, each separate villus establishes its own rhythm. In this instance there is no spreading, that is, the movement remains confined to the original site of action. The application of cocaine to the mucosa finally abolishes all activity and reactivity, but when this point is reached barium is also ineffective, indicating muscle paralysis.

The results with nicotine, pilocarpin and atropin also bear upon this point. The reaction to the initial dose of nicotine, about 0.5 mgm. per kilo body weight, consists of a sharp retraction of the villi in groups and a ridging and grooving of the mucosa as a whole. This is followed by a few seconds of tonic quiescence, then by rhythmical activity, persisting for some minutes. This dose is usually sufficient to block the effect of pre-ganglionic stimulation. The recovery state finds the mucosa slightly less reactive than normal, but still capable of normal type of response. A second dose provokes a response similar to the first, but less intense. If the nicotine is pushed to the point of disappearance of reactivity, barium is found ineffective again, pointing to muscular paralysis.

Pilocarpin provokes a reaction similar to nicotine, but appears to be more toxic to the mechanism. If a dose be given large enough to give a sharp circulatory reaction, but at the same time allowing prompt recovery, it invariably leaves the mucosa very refractory to stimulation. Barium again at this stage is ineffective.

The reaction to atropin is of a different character. Usually, 15 to 30 seconds elapse, often 1 minute, before there is any noticeable change. The activity of villi closely resembles the normal type seen on first opening the gut. Their activity gradually increases up to a maximum, then gradually diminishes, but the augmentation persists for some minutes.
Pilocarpin is active after atropin, but atropin is not active or is at least less so than normally, after pilocarpin has been given.

The isolated reaction in case of mechanical stimulation of a single villus, the scattered and incoordinated points of activity in a spontaneously active field, and the persistence of activity to the point of muscle paralysis, as evidenced by failure to react to barium, point strongly to a myogenic origin.

Impulses via the vagi nerves as a rule apparently do not reach the intestinal mucosal musculature, in the dog at least. This assertion is based upon the observations that stimulation or cutting both vagi, in the majority of dogs, does not modify the state of activity or reactivity of the mucosa. The splanchnics carry augmentor impulses. There is no evidence that impulses via the splanchnic directly excite rhythmic activity, the typical reaction being that of tonic contraction followed by some rhythmic movement, this latter coming on after the cessation of stimulation and never during the stimulation. The reactivity of any muscle depends in part upon its degree of tonus. The assumption in this case is that the splanchnic impulses modify the activity of the intestinal mucosa by producing a variation in tonus. So far as we know the distribution of the splanchnic is not essentially different in the ileum, except possibly in the last few inches, from that in the duodenum and jejunum. At least there is not enough difference to account for the differences in response between the duodenum and that of the ileum. The reason for this difference must be sought elsewhere.

Under physiological conditions the main factor which sets off activity of the outer musculature of the intestinal canal is mechanical stimulation by the food mass. Chemical stimulation by substances present in the canal and those absorbed, as well as by so-called peristaltic hormones, may also play a part. We have shown that both chemical and mechanical stimulation set the mucosal mechanism into activity. The question then arises: Is there any interrelation and coordination between the activities of the outer-musculature and the mucosa? That there is no essential interdependence is conclusively shown by the data already presented. One cannot predict the state of activity or reactivity of the mucosa by noting the state of the outer musculature. We have repeatedly observed excellent movement of the mucosa and villi during periods of quiescence of one or both of the outer layers of muscle and also during various stages and degrees of activity. Pinching the gut, thus setting up local contractions as well as advancing waves of contraction, does not set up any activity on the part of the mucosa unless the whole gut wall
is picked up and pinched. In this case there is a local reaction in the mucosa such as one sees when stimulating the mucosa directly with a probe or forceps.

Thus it is clear that a stimulus applied to the outer musculature does not affect the mucosa. Does a stimulus to the mucosa affect the outer muscles, and is the reaction of the mucosa in this case definitely coördinated with any phase of the outer muscular activity?

In case the outer musculature is quiet and relaxed, light mechanical stimulation of the mucosa sufficient to bring about a good reaction on the part of the villi and mucosa produces no immediate effect on the outer musculature. On continued stimulation one sometimes sees a slight increase in tonus and some rhythmical movement. In case the outer musculature is in tonus or manifesting rhythmical movement, stimulation of the mucosa brings on a relaxation. This relaxation persists for some time even though the stimulus be continued, but the outer muscle finally escapes from it. In case of vigorous stimulation there is at first a relaxation of the outer musculature followed by an increase in tonus and also by rhythmical activity similar to that seen on pinching the gut. The main effect seen on stimulation of the mucosa is a relaxation of the outer muscles followed by rapid recovery, which recovery is more rapid in case the stimulation is vigorous. This reaction can be demonstrated in case the outer musculature is thrown into a state of tonus and activity by vagus stimulation, by pilocarpin, and by nicotin, but not after barium. The application of peppermint oil to the surface provokes the same reaction. It is frequently seen on irrigation of the mucosal surface with isotonic dextrose.

What is the explanation of this reaction and its rôle? This throws open the whole question of the enteric motor mechanism. While the data thus far presented do not bear directly upon all phases of the question, yet a few hypotheses would seem to be in order.

It is a generally accepted fact that the motor activities of the outer musculature will go on after section of all extrinsic nerves. Our work shows th's also to be true for the mucosal motor activities. The mechanism in both cases is then inherent in the intestine itself. The main difference between the activities of the outer and the mucosal musculatures lies in the fact that the outer muscles in addition to local rhythmical contractions manifest also a progressive wave of contraction preceded by relaxation, true peristalsis, while the mucosal mechanism manifests only local activities.
Bayliss and Starling (10), Magnus (11) and Cannon (12) consider the peristaltic wave as a reflex dependent upon the plexus of Auerbach. Magnus found that Meissner's plexus takes no part in the so-called reflex. Gaskell is inclined to the view that the peristaltic wave is not a reflex, but is accounted for by the inherent properties of intestinal muscle and that the nervous elements are concerned merely in the regulation of tone.

On the basis of the view that the peristaltic wave is a reflex, it is necessary to assume that the stimulus is carried to the cells of Auerbach's plexus by afferent fibers, causing the cells to discharge impulses which go to the muscles producing contraction just behind the point of excitation and relaxation in front. Dogiel (13) has given evidence that the neurones of Auerbach's plexus have two axons with different terminations thus establishing a possible morphological basis for such a reaction. A survey of the literature would indicate that the reflex theory is the predominating view, as against the view expressed by Gaskell (14).

The tonus function of Auerbach's plexus is not denied by those who hold to the reflex theory; in fact, a reflex tonus mechanism seems necessary to account for the fact that after cutting of the vagi the gastrointestinal tract recovers in time to a large extent its normal tonus.

The peristaltic contractions are abolished by nicotin (15). This is not true for the movement of the mucosal musculature. If the behavior of the peristaltic mechanism to nicotin is an argument for a reflex origin, then it would seem that the mucosal activity is not the same type. This would mean then that Meissner's plexus does not play the role of a reflex nervous motor mechanism for the mucosal musculature.

The evidence brought forward in this paper would seem best interpreted in the light that Meissner's plexus relative to the mucosal musculature is a local reflex tonus mechanism. Recent work by Mueller (21) on the development of the vagus and splanchnic in the selachii indicate the presence of afferent fibers in the enteric plexuses of these forms. Accepting the conclusions of Langley (15) that the post-ganglionic fibers of the autonomic system end directly in the effector organ, and putting with it our observation that local stimulation of the mucosa has the same effect upon both the outer and mucosal muscles as splanchnic stimulation, the conclusions would be that Meissner's plexus is simply a local mechanism, splanchnic in function.

What then are the physiological relations of Auerbach's and Meissner's plexuses? It is generally conceded that Auerbach's plexus is vagal in origin. The fact that vagus stimulation in the majority of dogs as
well as local stimulation of the outer musculature of the intestine pro-
"vokes neither contraction nor relaxation in the mucosal musculature would
indicate that as a rule no afferent motor or inhibitory impulses pass from
Auerbach’s plexus to Meissner’s or directly to the muscularis mucosae.
Meissner’s plexus is splanchnic in origin (16). Taking the generally
conceded fact that impulses by way of the splanchnic produce relaxa-
tion of the outer musculature and our observation of tonic contraction
of the muscularis mucosae, we conclude that the splanchnic must carry
separate fibers to the outer and mucosal musculatures, or a single fiber
must divide, sending one branch to the outer, producing relaxation, and
one to the mucosal muscles, producing tonus.

The alternative would be that the splanchnic fibers terminate with
and distribute their impulses through the plexus of Meissner. To our
knowledge histologists have not furnished clear-cut proof for either
hypothesis.

The theory that no ganglionic cells lie in the path of the splanchnic
peripheral to the superior mesenteric ganglion is based mainly upon the
evidence that after nicotin paralysis of the superior mesenteric ganglion
stimulation peripheral to the ganglion provokes a reaction in the intes-
tinal musculature.

The answer to these questions hinges on the effect of nicotin on the
enteric ganglia. It is generally conceded that very large doses are
required to produce paralysis, much larger than for the autonomic gan-
glia. If nicotin does not paralyze the ganglia of Meissner’s plexus, and
our evidence indicates that it does not, then stimulation peripheral to
the superior mesenteric ganglion after its paralysis proves nothing as to
the termination of the splanchnics.

Magnus has maintained that Meissner’s plexus plays no part in the
myenteric reflex, but that it is dependent solely upon Auerbach’s plexus.
This conclusion is based upon the observation that the outer intestinal
musculature stripped away from the mucosal, consequently free from
Meissner’s plexus, manifests on proper stimulation the typical con-
traction behind and relaxation in front of the point of stimulation.
Granting this, may it not be true that in the intact intestine Meissner’s
plexus does play an important rôle in the motor activities of the intestine
during absorption and digestion? We are reminded of the work of Meek
(17), who found that on transection of the intestine the peristaltic wave
did not pass the point of cutting until the nerve elements had regen-
erated. Also Cannon (18) found that incisions around the stomach
down to the submucosa did not stop the wave. In the light of the data
presented on the reaction of the outer musculature to mucosal stimulation, and knowing that the mucosa is the normal physiological point of stimulation, it is suggested that impulses from the mucosa through Meissner's plexus may have a more important rôle than is usually thought. This does not belittle the importance of gut distension as a stimulus. Further work is now in progress relative to this question.

Our experience with nicotin in relation to the motor activity of the intestinal mucosa would indicate that there is no paralysis in Meissner’s plexus, else it is difficult to ascribe any function to it unless it be an afferent mechanism. Nicotin does not paralyze the posterior root ganglia. Our experience with Auerbach’s plexus is not large enough to make this statement relative to it, but we are mindful of the fact that the literature on this point is not completely harmonious. Langley himself, who is responsible for the most fruitful work on the autonomic system, using the nicotin procedure, suggests the necessity for further work.

It seems just as plausible, and explains our results better, to assume Meissner’s plexus as playing a double rôle, a terminal splanchnic mechanism, and a local reflex mechanism, tonus for the mucosal musculature and inhibitory for the outer. On this basis splanchnic and local stimulation of the mucosa should give identical results. Such is the case.

This necessitates the assumption of afferent elements in Meissner’s plexus, which is a mooted question. Gaskell and Langley maintain the absence of such elements. Dogiel (20) maintained cells of his type II to be afferent, and recently Mueller (21) published evidence for such elements in the stomach of selachii.

The differences in activity and reactivity of the mucosa between different levels of the small intestine are very striking. Most of the literature on the activity of the outer musculature makes no mention of the differences, the writers apparently not having noted any difference or attaching no significance to it. Macleod (22) and Lucciani (23) state that there is a difference in peristalsis between the upper and lower ends of the small intestine, peristaltic waves occurring less frequently in the ileum than in the duodenum and jejunum. Alvarez and his co-workers (24), (25) have studied the phenomenon rather extensively and account for it on the basis of a metabolic gradient. They have shown that the gradient curve for the outer musculature runs parallel with that of the intestinal mucosa. The comparatively slight motor activity and low degree of irritability manifested by the villi in the ileum may possibly be accounted for on this basis.
SUMMARY AND CONCLUSIONS

1. The intestinal villi manifest somewhat rhythmical movements, shortening, lengthening and lateral or swaying movement, both singly and in groups.

2. The mucosa as a whole exhibits movements which may be designated as ridging, grooving and pitting.

3. The movements of the individual villi may or may not be associated with movement of the mucosa as a whole.

4. The intestinal mucosal motor mechanism is set into activity by mechanical stimulation, by heat, irritants, and by epinephrin, pilocarpin, atropin, nicotin and barium.

5. The mechanism is very sensitive to anemia and is comparatively short lived.

6. Impulses by way of the vagi usually do not reach the mucosal musculature. The splanchnics carry tonus impulses to the mucosa.

7. Meissner's plexus is looked upon as a terminal splanchnic mechanism and a local reflex tonus mechanism.

8. There is no definite interdependence or correlation between the activities of the outer and mucosal motor mechanisms.

9. Impulses from the mucosa in case the outer musculature is in tonus bring about relaxation. It is suggested that this reaction may play a rôle not hitherto given prominence in considering motor activities of the intestine.

10. The reaction of the intestinal mucosa to stimulation is local in character and myogenic in origin.

11. The mucosal motor mechanism is most active and reactive in the duodenum and upper jejunum, less so in the lower jejunum and almost refractory in the ileum. The metabolic gradient of Alvarez is suggested as the basis for a possible explanation.

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