Old Herborn University Seminar Monograph 9:
Gastro-intestinal motility.
Editors: Peter J. Heidt, Volker Rusch, and Dirk van der Waaij.
Herborn Litterae, Herborn-Dill, Germany: 53-67 (1997).

SMALL INTESTINAL MOTILITY AND BACTERIA

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INTRODUCTION

There is a close interaction between small intestinal motility and small intestinal bacteria. Normal motility patterns have an important role in the regulation of the bacterial flora of the gut. This has been clearly demonstrated by the observation that small intestinal motility disorders may lead to bacterial colonisation of the jejunum (*Vantrappen* et al., 1977; *Scott* and *Cahall*, 1982). Conversely, there is good evidence that bacteria may contribute to the development of abnormal intestinal motility patterns, which in their turn may lead to the development of gastro-intestinal symptoms (*Mathias* et al., 1976; *Burns* et al., 1978; *Caenepeel* et al., 1989; *Husebye* et al., 1994a).

This review will briefly discuss: 1) Smooth muscle contractions and their myogenic control mechanisms; 2) The enteric nervous system; 3) Normal and abnormal motility patterns; 4) The interaction between small intestinal motility and small intestinal bacteria.

SMOOTH MUSCLE CONTRACTIONS AND THEIR MYOGENIC CONTROL MECHANISMS

The smooth muscle fibres of stomach and small intestine share with the myocardium two fundamental properties. Firstly, electrically and mechanically they function like a syncytium.

The intermediate junctions are the site of mechanical coupling. At these sites actin filaments, one of the basic contractile proteins, penetrate the dense bands of adjacent cell membranes where

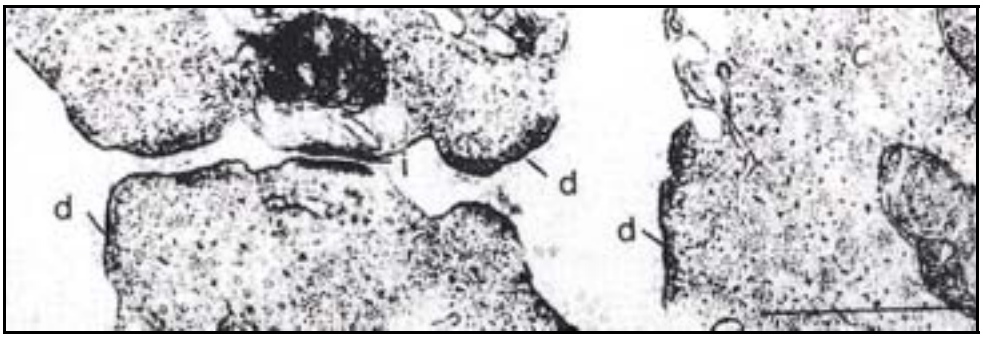

Figure 1: Intermediate junction between two smooth muscle cells: transverse section of guinea-pig *Taenia coli*. Bar: 1 mm; d: dense bands; i: intermediate junction. (From: *Gabella*, 1979).

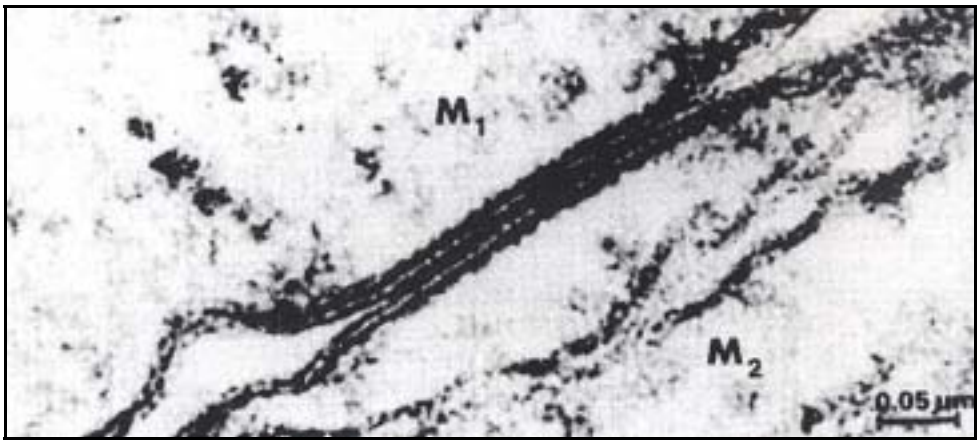

Figure 2: Gap junction between two smooth muscle cells grown in tissue culture. Magnification 155.000x.

they form a symmetrical structure that provides a direct link between the contractile units of two adjacent cells (Figure 1).

An other specialized cell membrane structure, the nexus or gap junction, is considered to be the site of electrical coupling between cells. At these junctions adjacent cells come into close proximity with only a 2-3 nm gap between them. They act as low resistance pathways for spread of electrical activity from one cell to the other (Figure 2).

The second property gastro-intestinal smooth muscles share with the myocardium is that of spontaneous rhythmic depolarisation. The resting membrane potential of 40-50 mV shows rhythmic decreases of 3-15 mV, thus giving rise to the so called slow waves.

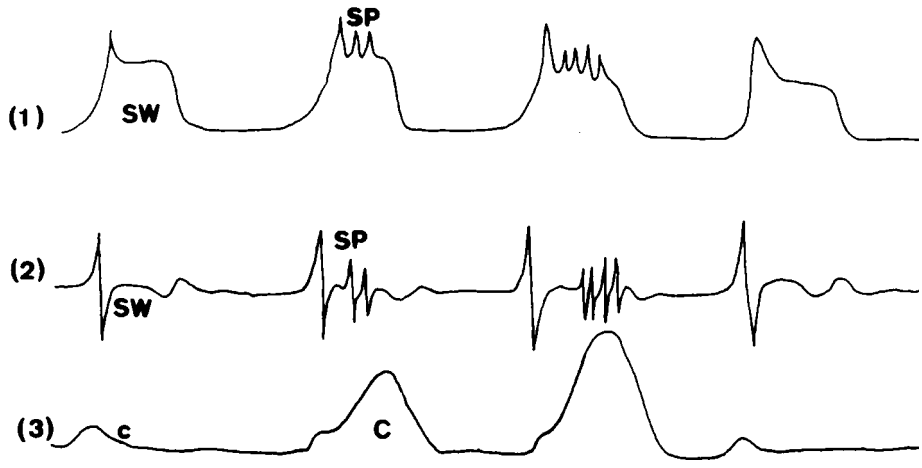

Figure 3: Schematic representation of slow waves, spikes and associated contractions. 1: intracellular recording showing slow waves (SW) with or without spikes (SP); 2: extracellular recording of the same phenomena; 3: manometric recording of contractions (C) induced by the electrical changes.

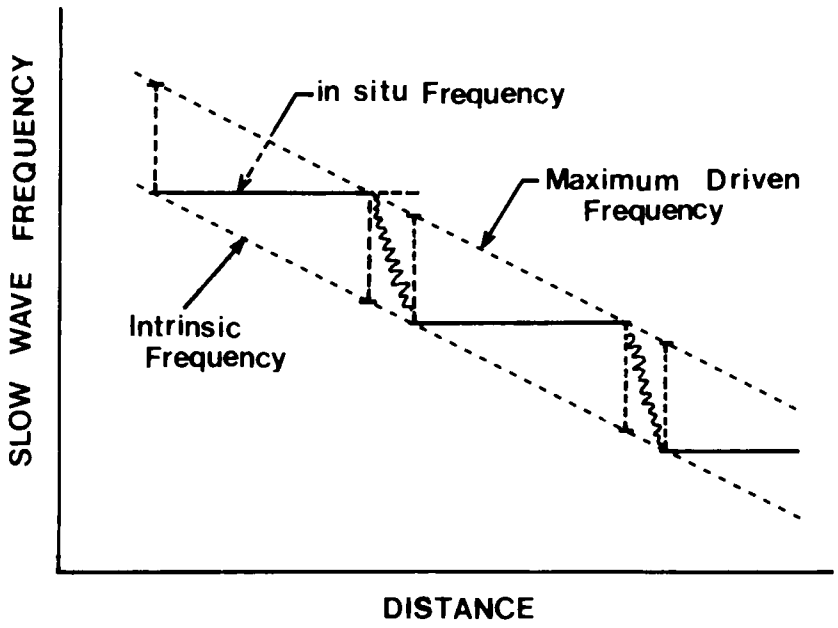

Figure 4: Schematic representation of slow wave frequency gradient in upper small intestine.

Slow waves are omnipresent (occur without interruption) but do not by themselves produce notable contractions. Contractions only develop when action potentials ("spikes") are superimposed on the plateau phase of the slow wave (Figure 3). The upper trace of Figure 3 represents an intracellular recording of electrical activity in small intestinal smooth muscle cells; the middle trace is an extracellular recording of the same phenomenon, and the lower trace shows the pressure changes produced by contractions. The strength of the contraction is related to the number of spikes.

There is an important difference between myocardial cells and intestinal smooth muscle cells. In the myocardium each depolarisation is associated with a contraction. The slow wave depolarisations of the small intestine only facilitate the contractions. As the contraction-inducing spikes only occur during a limited part of the slow wave cycle, slow waves control when and where contractions can occur.

The syncytial arrangement of smooth muscle cells and their spontaneous rhythmic depolarisations result in another resemblance between gastrointestinal smooth muscle and myocardium: the pacemaker activity.

The intrinsic rhythm of the slow waves decreases in man from 11-12/min in the duodenum to ± 8/min in the ileum. This is the so called slow wave frequency gradient. The decrease is not continuous but stepwise, giving rise to frequency plateaux. In the human small intestine the highest frequency plateau extends from the proximal duodenum to about 15-30 cm below the angle of Treitz. From there on the plateaux are shorter and more variable (*Coremans*, 1987; Figure 4).

The smooth muscle cells of the proximal duodenum have the highest intrinsic frequency and, therefore, act as a pacemaker for the more distal parts: the slow wave frequency of these more distal parts are pulled up to the fre-

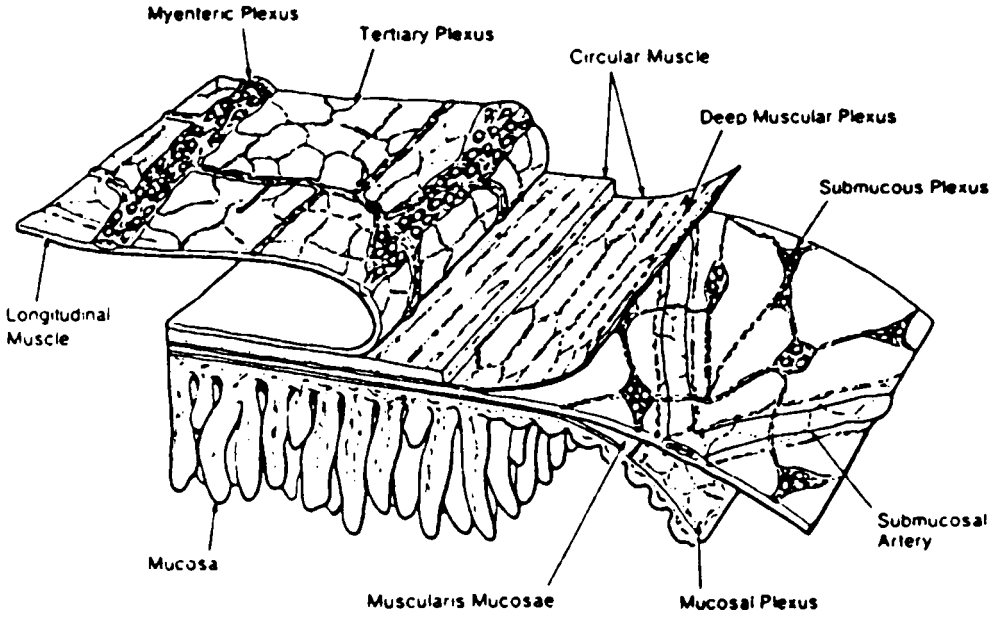

Figure 5: Diagrammatic representation of the enteric plexuses as they are seen in whole mounts of intestine (Reproduced from: *Furness* and *Costa*, 1987).

quency of the pacemaker area. When the difference in intrinsic frequency becomes too large or when the resistance to intercellular current spread increases, the more distal areas can no longer follow the slow wave frequency of the duodenal pacemaker. This area then will act as a pacemaker for more distal areas (*Bortoff*, 1976).

The small intestine, therefore, can be considered to consist of a series of functional units, each one being dominated by a pacemaker which imposes its rhythm on the segment below it.

Slow waves and pacemaker activity constitute an important myogenic control mechanism of smooth muscle contraction in that they facilitate contractions and thereby determine the normal temporal and spatial distribution of smooth muscle contractions, at least in the stomach and the small intestine. However, slow waves do not by themselves produce effective contractions.

THE ENTERIC NERVOUS SYSTEM AND NORMAL MOTILITY PATTERNS

The factors which determine the occurrence of spike potentials (and thus of contractions) are mainly neurogenic responses to stimulation of chemothermo- and mechanoreceptors in the intestinal wall and intestinal lumen. The enteric nervous system has an important role in the organisation of intestinal contractions into motility patterns.

The enteric nervous system

Figure 5 is a schematic drawing of the enteric nervous system with the myenteric plexus of Auerbach in between the longitudinal and circular muscle layers and the submucosal plexus (*Furness* and *Costa*, 1987).

The enteric nervous system is connected with the brain and the spinal cord

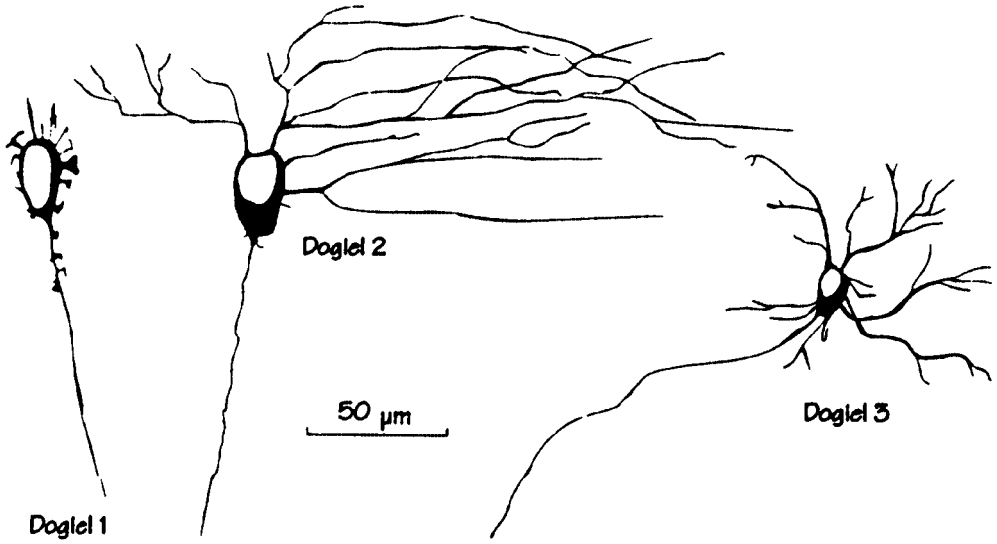

Figure 6: Diagrammatic representation of the three morphological categories of enteric neurons according to *Dogiel* (1899).

via the vagal nerve and the splanchnic and pelvic nerves.

However, the enteric nervous system has a remarkable independence from the central nervous system. It is the only division of the peripheral nervous system that is capable of mediating reflex activity in the absence of input from the brain and/or the spinal cord. It is now well established that the vast majority of the enteric neurons do not receive input from the central nervous system (there are only 2000 efferent fibres in the subdiaphragmatic vagus, versus 100 to 1000 million enteric neurons). Current concepts consider the enteric nervous system to be an independent integrative system that contains sensory neurons, interneurons and motor neurons which are all involved in the production of motility patterns (*Wood*, 1994).

On a morphological basis *Dogiel* (1899) identified 3 types of enteric neurons: type 1, 2 and 3 (Figure 6).

On the basis of their electrophysiological characteristics four types of enteric neurons have been identified (S/Type 1; AH/Type 2; types 3 and 4 (Table 1). S/Type 1 neurons of the small intestine discharge several action potentials, whereas AH/Type 2 neurons discharge only one action potential fol-

Table 1: Electrophysiological classification of enteric neurons

Properties	S/type 1	AH/type 2	Type 3	Type 4
Resting potentials	low	intermediate	high	intermediate
Input resistance	high	intermediate	low	intermediate
Spike discharge	repetitive	1 or more	none	one
Anodal-break discharge	yes	no	no	no
TTX-sensitive spikes	yes	no	-	yes
After-hyperpolarisation	no	yes	-	no

Table 2: Established and putative neurotransmitters present within the enteric nervous system

Amines:	acetylcholine norepinephrine histamine 5-hydroxytryptamine dopamine
Amino acids:	gamma-aminobutyric acid
Purines:	adenosine 5'-triphosphate
Non-related compounds:	nitric oxide?
Neuropeptides:	vasoactive intestinal polypeptide substance P enkephalins dynorphin calcitonin gene-related peptide somatostatin bombesin neurotensin neurokinin A cholecystokinin neuropeptide Y galanin gastrin-releasing peptide angiotensin adrenocorticotrophic hormone

lowed by a long after-hyperpolarisation. Studies of enteric neurons in different divisions of the digestive tract have revealed distinctive, region-specific electrical and synaptic properties (for example, AH/Type 2 neurons are absent from the oesophagus, the corpus of the stomach and the gallbladder). This variability probably reflects the adaptation of the microcircuits that control the specialized functions of different regions of the gastro-intestinal tract.

Over the past several years important information has been obtained regarding neurotransmitters and receptors for different neurotransmitters in the enteric nervous system.

Histochemical methods have allowed to visualize a large number of potential neurotransmitter substances or transmitter related enzymes in enteric neurons (*Costa* et al, 1987). These include amines (such as acetylcholine, 5HT and dopamine), amino acids (GABA), purines, nitric oxide.

There are also a large number of neuropeptides including VIP, substance P, enkephaline, etc. (Table 2).

Electrophysiological studies of enteric neurons and *in vitro* studies of enteric reflex activity have demonstrated a diversity of receptors for different neurotransmitters and messenger substances on enteric neurons. Some are ENS specific, some are confined to subclasses of neurons and there are regional differences in the presence of receptors.

The data, presented thus far only constitute a small fraction of the huge amount of data accumulated in recent years on the physiology of the enteric nervous system. It will be a major challenge for the future to put these data

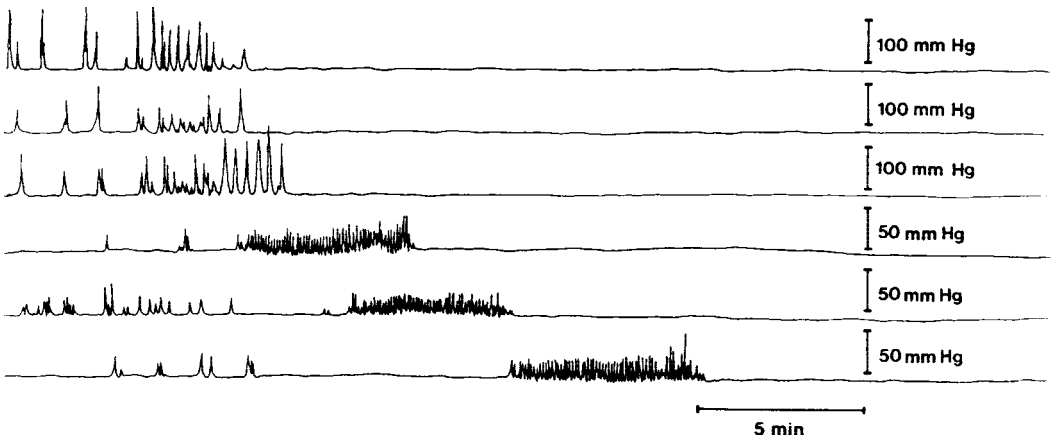

Figure 7: Manometric recording of the migrating motor complex (MMC) in man. The upper three traces were recorded in the antrum and the antropyloric region at 3 cm intervals; the lower three traces were recorded in the duodenum and upper jejunum (at 25 cm intervals).

all together in order to understand how the enteric nervous system really functions, and to determine the role of the enteric nervous system in the organisation of myogenically controlled contractions into specific motility patterns.

NORMAL AND ABNORMAL GASTRO-INTESTINAL MOTILITY PATTERNS

Recently it has become clear that well organized motility patterns occur in the small intestine in both the digestive and the interdigestive phases (*Code* and *Marlett*, 1975).

The best known interdigestive motility pattern is the migrating motor complex (MMC; Figure 7) and particularly phase 3 of this complex (the activity front). The burst of rhythmic contractions of phase 3 starts in the stomach. This burst of peristaltic contractions slowly migrates down the small intestine and dies out somewhere in the ileum. A new phase 3 then starts in the stomach. The duration of the MMC cycle is quite variable, but usually lasts between 90 and 120 min. This cyclic activity goes on and on until it is interrupted by food, which induces the so-called fed pattern. This fed pattern lasts for a variable period of time, depending upon the caloric load and composition of the meal.

At each level of stomach and small intestine the MMC comprises three phases. Phase 1 is a period of quiescence, with no or only very few contractions. During phase 2 the intensity of the motor activity gradually increases and contractions appear more and more frequently, until the burst of rhythmic, forceful contractions of phase 3 develops.

Distinct motility patterns have also been identified during phase 2 of the MMC i.e.: 1) single propagated (or peristaltic) contractions, 2) burst activity or clustered contractions (which may or may not be propagated); and 3) ultrarapid contractions of ultrarapid rushes (*Coremans*, 1987; *Vantrappen* et al., 1986).

Figure 8 is an example of an EMG

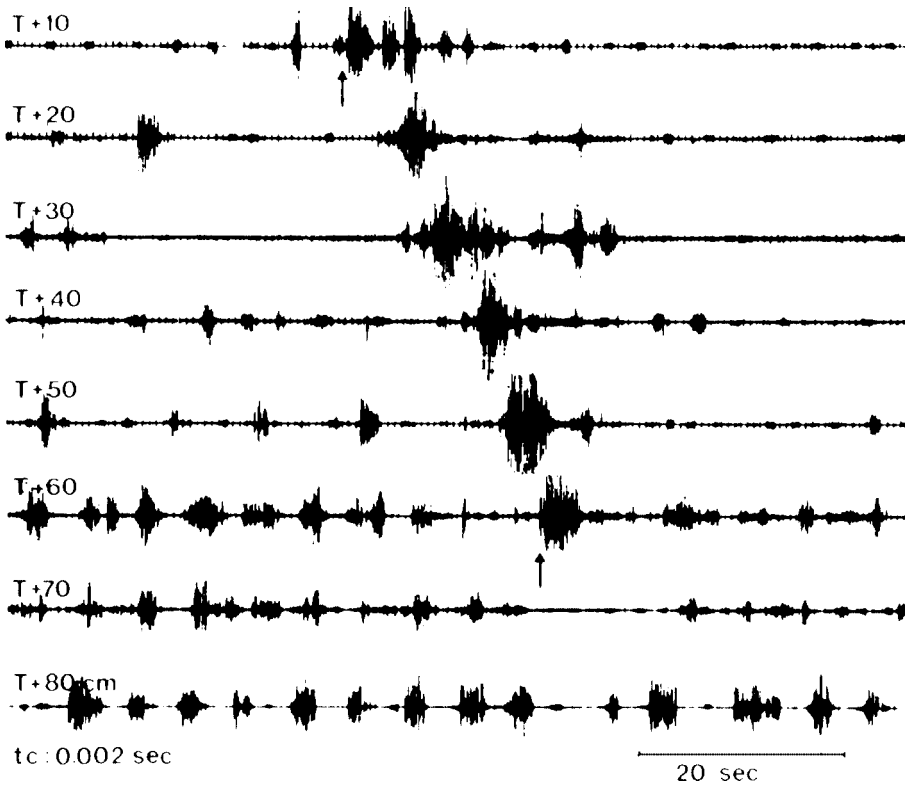

Figure 8: Electromyographic recording of a single propagated contraction i.e. a peristaltic contraction progressing from 10 cm below Treitz (T+10) to 60 cm below Treitz (T+60). The trace was recorded in a normal subject. (t.c.: time constant of the electrical recording).

recording of a single propagated contraction progressing from 10 cm below Treitz to 60 cm below Treitz.

On manometric examination a single pressure wave is seen to sweep down the intestine in a peristaltic way at a speed of 0.5 to 2.0 cm per second in the jejunum, but it is markedly slower in the ileum (0.2-1.8 cm/min). Such a lumen obliterating contraction results in propulsion of intestinal contents.

A second pattern observed during phase 2 of the MMC may be termed "clustered contractions". This pattern is characterized by the occurrence of a series of contractions which follow each other in close sequence and are separated from other contractions at that level by a period of quiescence before and after the cluster (Figure 9).

Clustered contractions may or may not be propagated. Propagated clusters are highly propulsive.

Both propagated single contractions and propagated clustered contractions occur rather infrequently in normal subjects. Their incidence is markedly increased in pathological conditions (*Coremans*, 1987). Stimulation of the small intestine by exposure of the mucosa to non-invasive bacteria results in an increased incidence of propagated single contractions, whereas exposure of the small intestine mucosa to invasive bacteria or other agents that cause mucosal damage induces propagated clustered contractions (*Mathias* et al., 1976; *Burns* et al., 1978).

An other type of motility pattern is: the retrograde giant contraction, which

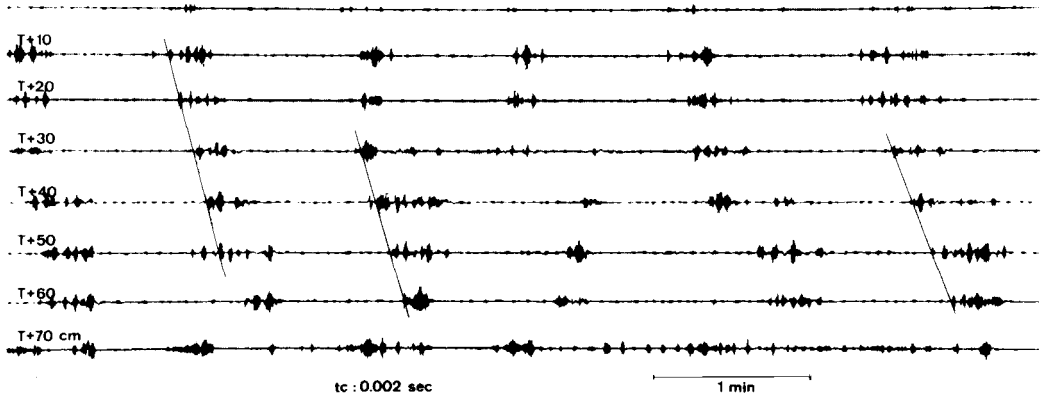

Figure 9: Electromyographic recording of clustered migrating contractions in the upper jejunum of a patient with diarrhoea (T+10: 10 cm below Treitz). Three clusters of propagated spike bursts are indicated by the oblique lines.

is one of the motor correlates of vomiting (*Lang* et al., 1986). It is a large-amplitude, long duration contraction that begins in the middle small bowel and rapidly migrates to the antrum. This retropulsive contraction precedes vomiting. Just prior to the occurrence of a giant retrograde contraction slow waves

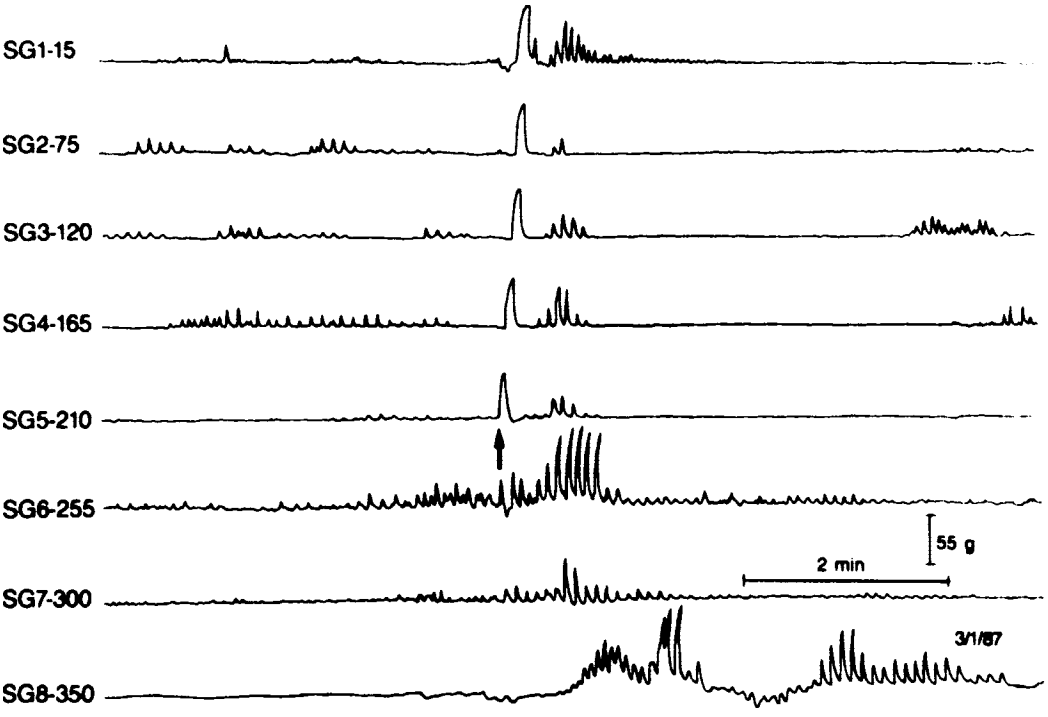

Figure 10: Retrograde giant contractions recorded from the canine small intestine. The arrow indicates the start of this contraction which migrated uninterruptedly from the mid small intestine to the proximal duodenum. SG1-SG8 are strain gauge transducers and the numbers indicate their distances from the pylorus. (From: *Sarna* and *Otterson*, 1989).

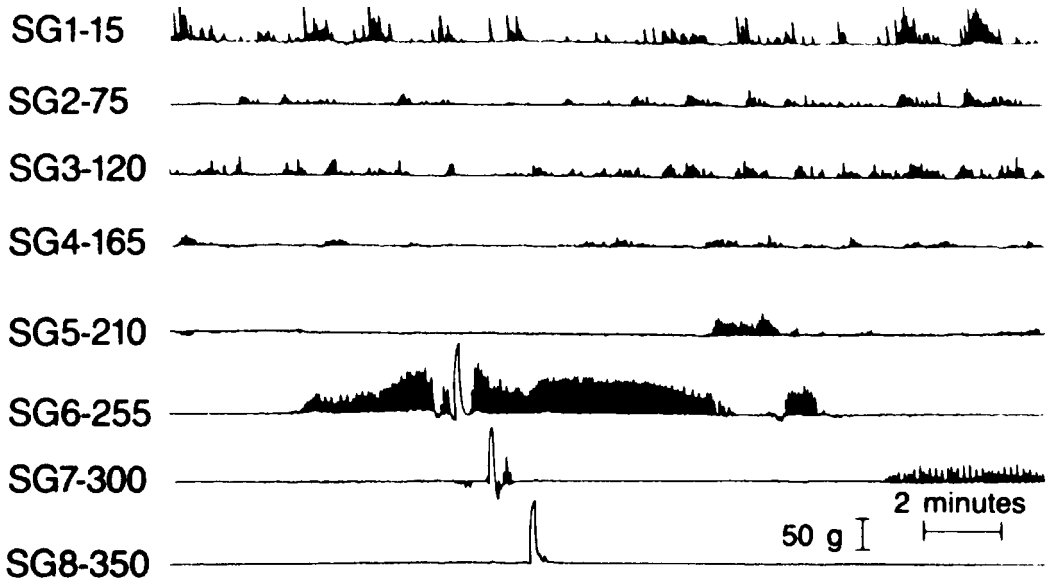

Figure 11: Giant migrating contractions recorded from the canine small intestine. The contraction started 255 cm distal to the pylorus and rapidly migrated to the terminal ileum. SG11-SG8 are strain gauge transducers and the numbers indicate their distances from the pylorus. (From: *Sarna* and *Otterson*, 1989).

disappear and phasic activity stops, apparently in order not to hamper the retropulsion of the intestinal contents into the stomach (Figure 10).

The giant migrating contractions (also called power contractions) also constitute a special motility pattern (*Sarna* and *Otterson*; 1989). These high amplitude, long duration contractions occur irregularly in the distal small intestine and migrate from their point of origin to the ileo-colonic junction and often into the colon (Figure 11).
These contractions occur only in the fasted state and can be initiated by a variety of stimuli including morphine, loperamide, erythromycin and intraluminal administration of short chain fatty acids. The function of the giant migrating contractions is probably to clean the distal ileum from food residues or refluxed colonic contents.

Abnormal pacemaker activity

If an intestinal distal pacemaker beats at an abnormally fast frequency i.e. at a frequency that is higher than the frequency of a more proximal pacemaker, there is an inversion of the slow wave frequency gradient. This then leads to a situation where contractions progress orally i.e. as antiperistaltic contractions which may cause chronic pseudo-obstruction (*Waterfall* et al., 1981).

A comparable situation may occur in patients with a Roux-en-Y type gastrectomy (*Vantrappen* et al., 1991). In studies on patients with a Roux-en-Y procedure we showed that 80% of the patients complaining of symptoms such as nausea and vomiting had a slow wave frequency in the distal part of the Roux limb that was higher than that of the more proximal parts. In other words they had an inversion of the slow wave frequency gradient in the Roux limb, the distal part of the Roux limb acting as a pacemaker for the more proximal parts.

Such a situation leads to the occur-

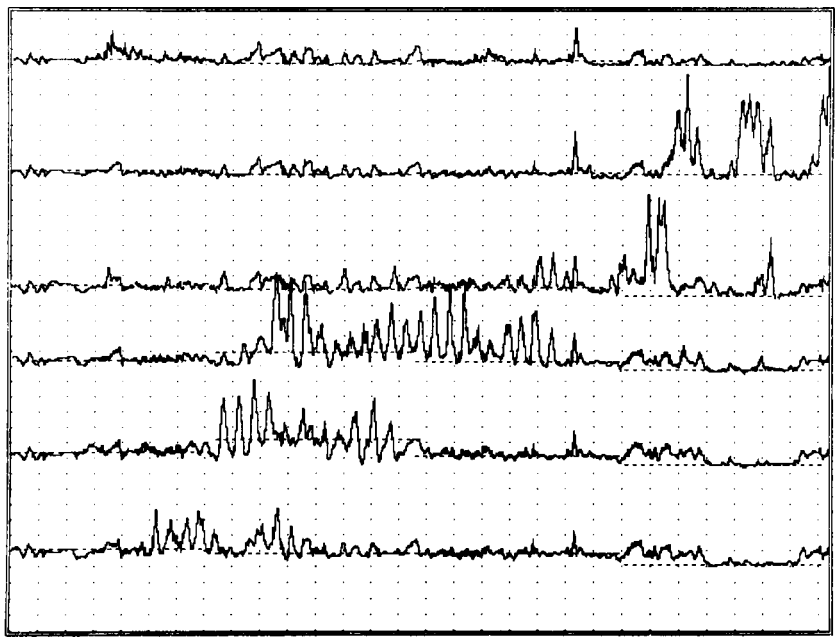

Figure 12: Retrograde phase 3-like contraction burst in a Roux-en-Y limb of a patient presenting with symptoms of nausea and vomiting after a Roux-en-Y procedure. Manometric recordings were made at 5 cm intervals in the Rouxlimb.

rence of antiperistaltic contractions and probably retropulsion. Even phase 3 of the MMC may move in an oral direction (Figure 12). This retrograde activity probably has a role in delaying gastric emptying and in the production of symptoms.

INTERACTION BETWEEN SMALL INTESTINAL MOTILITY AND SMALL INTESTINAL BACTERIA

There is a close interplay between the small intestinal microbial flora and small intestinal motility. Motility disorders may lead to bacterial overgrowth; conversely, exposure of the small intestinal mucosa to certain bacteria may lead to motility disorders.

Motility disorders may lead to bacterial overgrowth of the upper small intestine

Simultaneous manometric and radiocinematographic studies in dogs by *Code* and *Schlegel* (1974) and in man by our group had shown that the burst of peristaltic contraction waves of phase 3 are highly propulsive. They clear the bowel of all injected contrast material completely and quickly. *Code* and *Schlegel* (1974), therefore, proposed the concept that phase 3 of the MMC is the housekeeper of the small intestine and serves to keep the bowel clean. We speculated that, if the function of the MMC is to keep the bowel clean, absence of MMC's might result in stasis of food remnants, secretions and desquamated cells, thus creating an ideal culture medium for the development of small bowel bacterial overgrowth.

To test this hypothesis we studied

Table 3: Relation between presence or absence of phase 3 activity and bacterial overgrowth as demonstrated by bile acid studies

	Number	Phase 3 normal	Phase 3 absent or grossly abnormal
Normal subjects	18	18	0
Patients with negative bile acid breath test	9	9	0
Patients with positive breath test due to ileal malabsorption	6	6	0
Patients with positive breath test due to bacterial overgrowth	12	7	5

the interdigestive motor activity of the small bowel in 18 normal subjects, in 9 patients with various gastro-intestinal diseases but a normal 14CO2 bile acid breath test and in 18 patients with various gastro-intestinal diseases but a positive bile acid breath test (Table 3). In 6 of these 18 patients repeated bile acid breath tests after antibiotic treatment and radio-activity measurement in 24 h stool collections showed the positive bile acid breath test to be due to ileal bile acid malabsorption. In the remaining 12 patients the positive bile acid breath test seemed to be due to small intestinal bacterial overgrowth. In 7 of these 12 patients with bacterial overgrowth phase 3 of the MMC was normal; in 5 patients phase 3 was completely absent or grossly abnormal during recording periods of 6-8 hours. In other words, whenever phase 3 was absent or grossly abnormal there appeared to be bacterial overgrowth of the small intestine. Follow-up studies in these and in numerous other normal subjects and patients showed that: 1) absence of phase was always accompanied by a positive bile acid breath test that normalized after a course of antibiotics and was not accompanied by abnormal bile acid loss in the stool, and 2) when phase 3 had reappeared on later controls the evidence of bacterial overgrowth had disappeared.

That absence of phase 3 of the MMC may induce small bowel bacterial overgrowth was later proved experimentally by *Scott* and *Cahall* (1982). These authors treated rats with morphine or phenylephrine and cultured segments of the small bowel and its contents for aerobic and anaerobic bacteria. Opposite to its effect on the small bowel of man, morphine eliminated the activity front in rats and phenylephrine in the doses administered had the same effect. If the activity front was absent for more than 6 to 15 hours, the rats developed small intestinal bacterial overgrowth. If the rats were killed after the drugs had been stopped and the activity front had been allowed to reoccur, bacterial overgrowth was no longer present.

Bacteria in contact with the small intestinal mucosa may induce small intestinal motility disorders

Matthias et al. (1976) studied the myoelectrical pattern of the rabbit ileum in response to non-invasive diarrhoeagenic bacteria and their toxins. They noted in rabbit ileal loops exposed to live *Vibrio cholerae* or to cholera enterotoxin the occurrence of an abnormal electrical pattern they termed the "migrating action potential complex" (MAPC). It is a burst of spiking activity

of 2-5 seconds or longer which migrates down the ileal loop and propels the intraluminal contents in an aboral direction. This MAPC results in a single propagated (peristaltic) contraction. That this MAPC pattern was not merely a consequence of the increased intraluminal fluid secretion was suggested by the fact that the MAPC activity began 4 hours after loop inoculation, a time well beyond the well-known intestinal secretory effect of cholera enterotoxin.

These propagated single contractions have been described in the literature under various terms: MAPC, peristaltic rush, propagated contractions of the jejunum, prolonged propagated contractions of the ileum, type IV contractions, giant migrating contractions and power contractions, depending upon the animal species examined and the method of investigation used. The main characteristic of these propagated single contractions is their propagation velocity which is similar or approaches the propagation velocity of the slow waves (± 2 cm/sec in jejunum). As they are produced by a single spike burst associated with a single slow wave, or by a single spike burst spanning several slow wave cycles, their duration varies from a few seconds to approximately half a minute, and their amplitude is also quite variable.

Single propagated contractions of this type occur rather rarely in the normal jejunum. They can be elicited in experimental animals by a variety of stimuli. Non-invasive micro-organisms or their toxins may elicit this motility pattern. This has been demonstrated for *Vibrio cholerae* and its enterotoxin, for various strains of *Salmonella typhimurium*, for live toxigenic *E. coli* and its heat-labile enterotoxin, and there may be several others. Chemical stimuli which do not cause damage to the mucosa such as ricinoleic acid and prostaglandins also may cause this motility pattern. In patients with secretory diarrhoea the incidence of propagated single contractions is markedly increased.

Burns et al. (1978) studied the effect of invasive strains of *E. coli* on the myoelectrical activity of the small intestine of New Zealand white rabbits. They found two distinct complex patterns: repetitive bursts of action potentials (RBAPs) occurring predominantly in the infected ligated ileal loop and MAPC activity occurring predominantly in the uninfected small bowel oral to the ligated ileal loop. The authors concluded that MAPC activity was characteristic of "non-invasion" and that RBAPs correlated with enterocyte injury. RBAPs en MAPC activity have also been described after *Shigella dysenteriae* I enterotoxin, *Clostridium perfringens* A enterotoxin and *Clostridium difficile* enterotoxin.

These studies indicate that, at least in animals, specific motor patterns can be induced by diarrhoeagenic bacteria and that their toxins may contribute to the diarrhoea in these diseases. Analogous studies have not been performed in man.

These repetitive bursts of action potentials have been described in the literature under various names: clustered contractions, type II peristalsis, ricinoleic acid pattern of dogs, and in case of prolonged sequences of clustered contractions, it has been termed "minute rhythm".

The incidence of clustered contractions is increased in a variety of pathological conditions. We observed it in patients with infectious diarrhoea. The outbreak of chronic diarrhoea in raw milk drinkers in Brainerd, Minnesota, also resulted in clustered contractions. We observed it also in the uninvolved jejunum of patients with inactive Crohn's disease. Interestingly, the jejunal motility pattern of these Crohn's disease patients was characterized by decreased phase III activity and an in-

crease in both propagated single and propagated clustered contractions. Whether this is due to the presence of an abnormal bacterial flora of to other causes remains unknown.

The interaction between small intestinal motility and small intestinal bacteria was recently further investigated in a series of elegant studies by E. Husebye (*Husebye*, 1995; *Husebye* and *Engedal*, 1992; *Husebye* et al., 1992, 1994). Studies in healthy subjects and patients with late radiation enteropathy showed that intestinal motility is the main line of defence against colonisation with Gram-negative bacilli in the upper gut. The role of gastric acid in host defence is confined to restriction of microbial growth and metabolism in the stomach. Husebye's studies further showed that proximal intestinal dysfunction, as indicated by abnormal motility patterns and colonisation with Gram-negative bacilli, plays a key role in the pathogenesis of late radiation enteropathy.

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