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AN INVESTIGATION INTO THE STRUCTURE AND FUNCTION OF THE ILEOCAECAL JUNCTION OF THE SHEEP

A Thesis presented in fulfilment of
the requirements for the degree of
MASTER OF SCIENCE
by thesis only
at Massey University.

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Abstract

The sheep ileocaecal junction has been shown to have sphincter-like properties, fulfilling the criteria for a gastrointestinal sphincter identified by Fisher and Cohen (1973). However the short zone of elevated pressure within the Ileocaecal Junction (ICJ) could be due to venous engorgement rather than tonic muscular activity, as the tip of the ileum examined histologically reveals an irregular musculature interspersed with a vascular loose connective tissue. A similarity is suggested to the human ileocaecal sphincter as described by Quigley, Borody, Phillips, Weinbeck, Tucker and Haddad (1984). This short (less than 5mm) zone of elevated pressure in the sheep would appear to work in conjunction with a valvular action as described by Kuman and Phillips (1987) for the human ICJ, preventing retrograde digesta flow from the caecum to the ileum.

EMG recordings of the ileocaecal region in the conscious sheep showed approximately 70-80% of the MMC phase 3 activity that reaches the distal ileum progresses as far as the ICJ. This appears to be the main motility pattern present in this region in the conscious sheep, and very little coordination was observed between patterns of caecal and ileal activity.

Feeding was found to decrease the amount of MMC activity in the distal ileum by lengthening the interval between successive MMC phase 3 patterns of motility. This effect of feeding on MMC activity appears not to be due to the levels of circulating gastrin, and could be due to either a reflex inhibition such as an intestino-intestinal reflex mediated by noradrenaline as has been described for cats, or humoral mechanisms involving another agent such as cholecystekinin, VIP or Substance P. Both the latter substances were shown to be present in nervous tissue within the ileum, though their role remains unclear.

Preface

The digestive tract of ruminants has long been of interest to biologists, chiefly due to the modified stomach or rumen (Hofmann, 1973). Studies of the rumen have resulted in many publications describing its function and physiology in detail (Kay, 1983).

There has been much less interest in the small intestine of the ruminant, probably because this part of the ruminant resembles that found in other mammals (Wyburn, 1981). The junction between the ileum and colon, in particular, is the least explored part of the gastrointestinal tract of any species, even though it represents an important transition zone (Quigley, Borody, Phillips, Weinbeck, Tucker and Haddad, 1984). The ileocaecal junction separates the abundant caecal flora from the ileum, and the failure of this function results in well documented pathological conditions (Gorbach, Plant, Nahas, Weinstein, Spanknebel and Levitan, 1967). In the sheep, activity in the distal small intestine and large intestine has been examined by means of electromyographic recordings (Fioramonti, 1981), and radiographically (Reid and Dellow, 1972). Both these studies were primarily concerned with large intestine activity, and gave only brief reference to the sheep ileocaecal junction. Current understanding of the function of the ileocaecal junction is due mainly to studies in dogs (Kelly, Gordon and DeWeese, 1966; Kruis, Azpiroz and Phillips, 1985), cats (Pahlin, 1975; Conklin and Christensen, 1975) and Humans (Quigley, Phillips and Dent, 1984; Quigley, Borody, Phillips, Weinbeck, Tucker and Haddad, 1984.)

These species are monogastric, and small intestine motility and digesta flow in such species differs from that seen in the ruminant. Regular, cyclic activity in the small intestine is only seen between meals in most monogastric species, but occurs continuously in the sheep, irrespective of feeding (Ruckebusche, 1970; Bueno, Fioramonti and Ruckebusche, 1975). Such a difference in small intestine activity could indicate differences in function. Code and Schlegel (1974) suggested the interdigestive activity of the small intestine gave it a `housekeeper' function, preventing bacterial overgrowth between meals. In species such as sheep, which show this type of activity constantly, this regular pattern of activity is responsible for the transit of digesta through the small intestine to the caecum. With digesta being propelled through the small intestine by different motility patterns in different species, it would not be prudent to extrapolate results from experiments on the small intestine of monogastric species to ruminants such as sheep. The ileocaecal junction (ICJ) of the sheep, about which very little has been published, warrants further investigation.

Acknowledgements

The development of this thesis has been a protracted affair which began even before its formal initiation in 1987, when my supervisor, Dr. Dave Carr made a remark about the lack of published material on this topic. In launching into this part-time project, I had little idea that I had embarked on an undertaking that would lead down many interesting paths and take until 1992 to complete! Many thanks to Dr Carr for his always supportive comments and patience. Thanks too to Dr. Gordon Reynolds for his help, particularly during Dr Carr's sabbatical absence; Dr Heather Simpson for having a gastrin assay running, and John Elgar and Jane Candy for running my samples through the assay. In the histology lab. I would have been lost without Roy Sparksman, a fount of wisdom and good humour, to whom I owe whatever expertise I have developed in histology.

I also would like to thank my wife Heather, and family: Andrew, Simon and Nicola. It can't have been much fun with Dad always juggling their needs with work commitments and THE THESIS. Thanks - it's done.

TABLE OF CONTENTS

LIST OF FIGURES between pages

CHAPTER 1

CHAPTER 2

CHAPTER 3

APPENDIX B between pages

LIST OF TABLES

APPENDIX B TABLES

LIST OF PLATES

CHAPTER 5 between pages

CHAPTER 1
Literature Review

1.1 The Ileocaecal Junction - Valve or Sphincter?

Pahlin (1975) attributes the first anatomical description of the ileocaecal region to Variolus, writing in 1573, although Bauhin in 1579 was the first to propose a valve-like function to the terminal part of the ileum. This valve action was thought to prevent the backflow of digesta from the caecum to the ileum, since it prevented the retrograde flow of water from the colon to the ileum in dead animals.

Much later, in 1904, Elliot reported that the ileocaecal junction (ICJ) in the cat lost its ability to separate ileal and caecal contents after it had been denervated. This suggested a muscular action, implying sphincter-like qualities within the terminal ileum since denervation led to a loss in muscle tone and thus incompetence. This raised a question as to whether the junction between the ileum and the caecum would be more appropriately described as a valve or as a sphincter. Certainly the description of the region in humans (Elliot, 1904), cats (Rosenberg and Dio Dio, 1969) and sheep (Fioramonti, 1981), as a protrusion of the terminal ileum into the colon, surrounded by colonic wall, would support the impression of a valve - like function (Figure 1.1).

A recent report from Kuman and Phillips (1987) further supports this concept. Using postmortem human specimens, Kuman and Phillips found that caeco-ileal reflux was prevented as long as the fibrous tissues responsible for the angulation between the ileum and the caecum were intact. They described these fibrous structures as the superior and inferior ileocaecal ligaments. ICJ valvular competency was maintained in all specimens up to 40

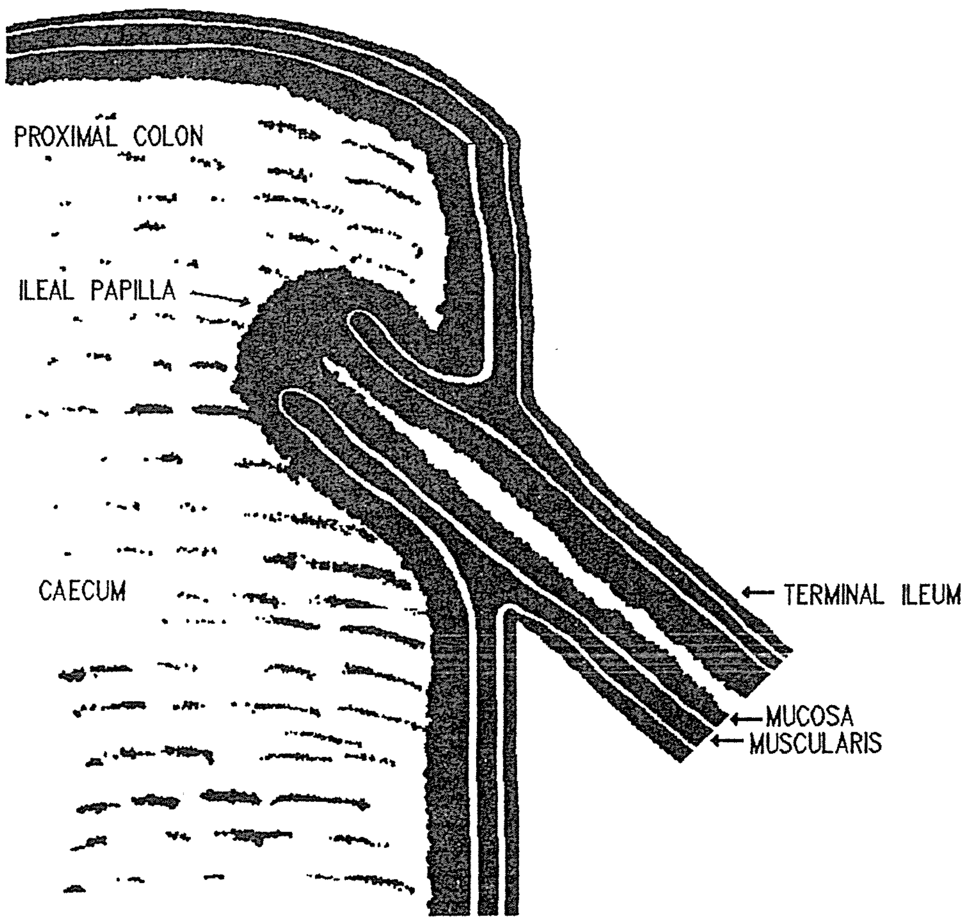

FIGURE 1.1 Schematic diagram of a section through the sheep Ileocaecal Junction.

mm Hg, and in most (10 of 12), 80 mm Hg with the ileocaecal ligaments intact. Cutting the ligaments rendered the junction incompetent, but surgical reconstruction of the ileocaecal angle restored competence.

Those species with an ileocaecal junction anatomically similar to humans, such as cats and sheep, could use the valve-like characteristics of the junction to prevent reflux of caecal contents into the ileum.

This valvular theory is not supported by the findings of Elliot, or by Rendleman, Antony, Davis, Buenger, Brooks and Beattie (1958), who reported that the ileal reflux of caecal contents increased with increasing intracaecal pressure in dogs and humans. This observation, supports the view that the ileocaecal junction has a sphincter - like action rather than a valvular action which would close more positively with an increase in pressure, until very high pressures were reached. Although this observation is at variance with Kuman and Phillips with respect to humans, in the dog the ileum is continuous with the proximal colon while the caecum protrudes as a blind sac from the side of this tube (see Figure 1.2). Such a structure would suggest sphincter action would be needed to separate colonic and ileal contents, and does not suggest a valvular action. Using direct observation in the dog, Hinrichsen and Ivy (1931) described a contracted ring around the ileocolic junction which remained closed except when the ileum was discharging its contents. This evidence is strongly supportive of a sphincter action.

Besides the ability to prevent retrograde digesta flow through either sphincter or valvular action (or a combination of both), the distal ileum has been shown in some species to use distinct patterns of motility to assist in this function. Kruis <u>et al</u> (1985) reported in

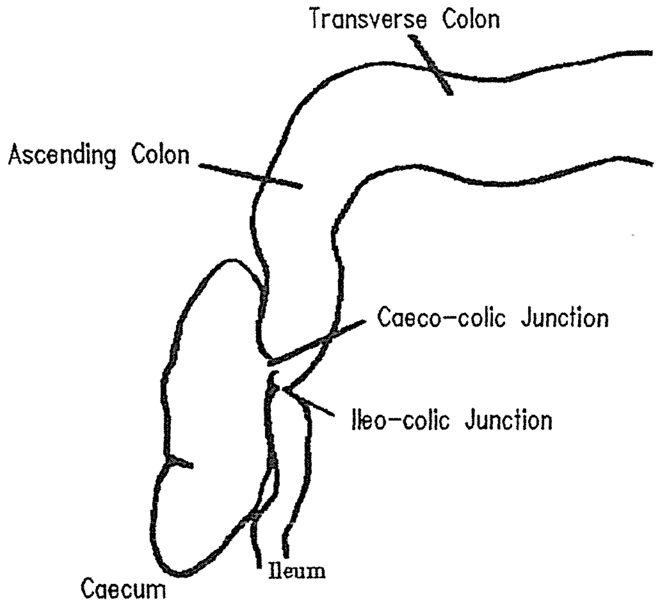

FIGURE 1.2 Schematic diagram of the canine ileocaecal region. (After Fioramonti, 1981).

dogs that the canine stool, when introduced into the ileum, provoked powerful propulsive contractions of the ileum. This would appear to be a mechanism utilizing the motility of the distal ileum to limit the amount of reflux from the large intestine.

In addition to preventing retrograde flow into the ileum, the ICJ also has been implicated in affecting the rate of flow of digesta from the ileum into the large intestine. Singleton, Redmond and McMurray, (1964) found only a small decrease in digesta transit time through the small intestine after ICJ excision in humans. However these workers also found that if the ICJ remained intact, up to 50% of the small intestine could be removed with digesta transit being largely unaffected, while the removal of both the ICJ and a large part of the small intestine results in a marked decrease in transit time through the small intestine.

Spiller, Brown and Phillips, (1987) studied digesta movement through the ICJ of humans using radioactive markers. They reported that while postprandial digesta movement showed a steady flow rate, during interdigestive periods ileocaecal transit became erratic and, at low flow rates, the ileum was able to act as a reservoir, at least for up to two or three hours. In dogs Spiller, Brown, Phillips and Azpiroz (1986) showed a similar phenomenon even postprandially, with the terminal ileum being cleared of about half its contents every 90-120 minutes. This may indicate that the ICJ is a more effective barrier in dogs than in humans. This precept is supported by published evidence indicating that the ICJ in dogs has a high tonic pressure (Kelly, Gordon and Deweese, 1965; Quigley, Phillips and Dent, 1983) whereas the same region in the human shows less tone (Quigley, Phillips and Dent, 1984; Nasmyth and Williams, 1985).

From the evidence reviewed here, the ICJ could have a valvular function only in those species with an appropriate anatomical configuration in this region, as present in humans, cats and sheep. This does not preclude the junction from having sphincter-like qualities as well, and the reports of Singleton et al (1964); Spiller, Brown, Phillips and Azpiroz, (1986); and Spiller, Brown and Phillips, (1987) suggest that motility patterns of the distal small intestine may be important to ICJ function.

1.2 Evidence for sphincter action at the Ileocaecal Junction.

Pahlin (1975) described a gastrointestinal sphincter as "a muscle which surrounds and serves to close an orifice. This serves to keep the gastrointestinal contents in one part of the alimentary canal for an appropriate time by preventing too rapid a passage or preventing regurgitation".

While some gastrointestinal sphincters such as the pyloric sphincter at the distal end of the stomach can be recognised anatomically, others are difficult to visually identify and their classification as sphincters is a functional one (Higgs, Shorter, and Ellis, 1965). Such sphincters can be demonstrated physiologically if they fulfil the criteria suggested by Cohen, Harris and Levitan (1968) and refined by Fisher and Cohen (1973):

a) A sphincter exhibits an intraluminal pressure greater than that of the cavities separated by the sphincter.
b) Appropriate stimulation proximal to the sphincter results in a consistent fall in the elevated pressure within the sphincter.
c) Appropriate stimulation distal to the sphincter results in a prompt rise in sphincteric pressure.

In order to establish the existence of a sphincter, these criteria outlined by Fisher and Cohen (1973) need to be met.

Kelly et al (1965) reported an area of high pressure in the terminal ileum of the dog. The average basal pressure was 19 cm H_2O (13.6 mmHg) above that of the non-actively contracting ileum or caecum. The length of this high pressure zone was found to vary between 0.5 cm and 3 cm, averaging 1.0 cm. Quigley et al (1983), also working with dogs, found an average pressure of 28.5 cm H_2O (23.6 mmHg). A similar zone has been described in cats (Conklin and Christensen, 1975). This zone of elevated pressure occurs in a region of thickening of the circular muscle in the terminal ileum of the cat, though such a visible anatomical feature of the ICJ has not been described for any other species.

While there seems to be little argument over the presence of a zone of elevated pressure at the ileocaecal junction in cats and dogs, reports from other species are less conclusive. Kelly et al (1965) did note that the pressure developed by the sphincter in the dog was greater with increasing diameter of the devices used to measure pressure, as had been reported in work on other sphincter regions in the dog. With much of the early work on sphincter pressure being performed with "pull through" saline filled balloons, this explains some of the discrepancies between results obtained by different workers. For instance, the ICS intraluminal pressure of 20 cm H_2O (14.3 mmHg) recorded by Cohen et al (1968) in humans could not be substantiated by Quigley, Phillips and Dent (1984), who only found intermittent periods of elevated pressure in the order of 1 - 2 mm Hg (1.4 - 2.7 cm H_2O) using fine multilumen flexible catheters for pressure recording. Quigley and co-workers were of the opinion that the pressures recorded were sufficient to compartmentalize the intestine adequately.

In order to be classified as a sphincter, though, the other two criteria proposed by Fisher and Cohen need to be examined - namely the effects of 'appropriate' stimulation proximal and distal to the ICJ.

Hannes (1920), Tönnis (1924) and Pahlin and Kerwenter (1975) found in cats that injecting fluids into ileal and colonic fistulas in dogs resulted in an increase in pressure of the proposed sphincteric region. Intraluminal pressure would, however, decrease before advancing waves of contraction as they moved down the ileum to the ICJ. Others working in this area in the dog reported that mean intraluminal ICJ pressure decreased with increasing volume of ileal contents, while distal ileal motor activity increased. (Short, (1919); Hinrichsen and Ivy, (1931); Kelly et al, (1966); Cohen et al, (1968); Quigley et al, (1983)).

Rubin, Cardwell, Ouyang, Snape and Cohen (1981) described the effects of ileal distension in the cat as being a consistent reduction in tonic pressure at the ICJ although this was frequently followed by a period of contraction and elevated pressure.

Although the intraluminal pressure at the ICJ has been reported by some as increasing in response to distention of the ileum proximal to the ICJ (e.g. Pahlin and Kerwenter, 1975) there is a consistent reported decrease (at least transiently) in pressure at the ICJ when an advancing wave of ileal activity approaches. Bueno et al (1975) described waves of activity in the small intestine pushing intestinal contents along before them. Such movement of digesta could provide the "appropriate stimulation proximal to the sphincter" that results in "a consistent fall in the elevated pressure within the sphincter". Fisher and Cohen's second condition would seem to have been met, even if the ICJ response to simple distention or bolus injection into the ileum seems to be variable.

Reports on the effects of caecal or colonic distention are much more consistent. There is an increase in tonic pressure in the ICJ in response to colonic distention in humans (Cohen et al, 1968) cats (Rubin et al, 1981) and dogs (Kelly et al, 1966). This response would clearly inhibit retrograde flow from the caecum into the ileum. From available evidence in dogs, cats and humans, the ICJ does fulfil the criteria proposed by Fisher and Cohen in 1973, and in these species can be considered a functional sphincter.

No published evidence relating to the characteristics of the ICJ in the sheep is readily available.

1.3 Motility patterns of the distal small intestine.

1.3.1 Evidence from Myoelectric recordings.

In 1969 Szurszewski described a cycle of myoelectric activity in the canine small intestine. Carlson, Bedi and Code (1972) further described this pattern of canine myoelectric activity as the Interdigestive Myoelectric Complex, identifying four phases. The first phase was a period of quiescence, which was replaced by a period of seemingly random activity (Phase 2). This developed into a period of intense activity (Phase 3), after which the activity passed through a Transition Phase (4) reducing back to Phase 1 (Quiescence). Carlson's fourth phase appears to be of short duration and occurs on an irregular basis, and is not always used when describing the activity

(Weisbrodt, 1981). The cycle of activity has been shown to sweep down the length of the small intestine, originating proximally in the duodenum.

Weisbrodt (1981) reviewed the descriptions of the patterns of cyclic activity described by a number of investigators, and argues that the term "Interdigestive Myoelectric Complex" is too specific a descriptor, as the activity does not necessarily occur only as an "Interdigestive" phase, nor can it be recorded only as myoelectric activity. Weisbrodt maintains that the cyclic activity of the small intestine should be described as a "Migrating Motility Complex", or MMC.

The arrival of the MMC at the ileocaecal junction has been shown to alter ileocaecal sphincter (ICS) activity in humans (Quigley et al, 1983). While the ICS often has a basal tone higher than the surrounding ileum or colon, the arrival of the MMC results in pressure peaks of 70-80 cm H_2O (50-58 mmHg) within the sphincter lumen. This supports the observation by Weinbeck and Janssen (1974) that coordinated spike activity moves freely across the ICJ from ileum to colon, but contrasts with reports by Balfour and Hardcastle (1975, 1978) of an electrically silent zone at the ICS.

In a later report, Quigley, Phillips and Dent (1984) observed that 90% of the MMC's developing in the canine small intestine would reach the ICJ, and 86% of these would pass over the ICJ into the colon. Other species have been more difficult to categorise. In humans, 90% of recorded MMCs appear to `disappear' into the `random activity of the ileum' (Quigley, Borody et al, 1984). It does appear that there are a number of changes in MMC activity that are consistent across species, however. These develop as the MMC progresses distally into the terminal ileum. Firstly the phase I periods (quiescence), which are typical of the duodenum, are much shortened and sometimes absent in the terminal ileum. Secondly, the random phase 2 contractions tend to group into discrete bursts. Quigley et al considered that both these features would give a more specialized propulsive function to phase 2 contractions in the distal small intestine. In addition, the phase 3 contractions of the MMC propagate more slowly in the distal regions of the small intestine compared to the proximal small intestine. Typical propagation speed in the ileum of the dog is 1.2 cm min^{-1}, as opposed to 2.1 cm min^{-1} in the duodenum. Bueno et al (1975) described a faster rate of MMC propagation (4.0± 1.5 cm min^{-1}) in the jejunum of the dog, and an even faster rate in the sheep jejunum (17.8± 5.7 cm min^{-1}), though these authors gave no data on rates of MMC migration in the ileum.

Kerlin, Zinsmeister and Phillips (1982) and Kruis et al (1985) correlated small intestine motor activity with chyme transit times, and found that flow is very slow during phase 1, and becomes progressively faster during phase 2 and phase 3. In addition to MMC activity, these workers and others (Quigley, Phillips and Dent, 1984) also identified two other contractile patterns that seem to be associated with the interdigestive phase of intestinal activity.

First, groups of clustered, rhythmic phasic activity were seen to propagate through the ileum during the phase 2 (irregular) activity of the MMC in dogs (Discrete Clustered Contractions, or DCC). Their occurrence was variable, from 3 per hour down to none during an 8 hour recording period. The DCC lasted from 30 seconds to 9.6 minutes, propagating at velocities of up to 60 cm min^{-1}. The effect of this pattern of contraction on chyme transit remains to be determined, since it is difficult to separate its effects from that of phase 2 activity of the MMC.

secondly, Kruis et al (1985) described a broad phasic wave of contraction which is rapidly propagated along the ileum. Speeds of up to 27 cm min.$^{-1}$ were recorded. Similar activity has been described by Quigley, Borody et al (1984) in dogs. Quigley et al described these as 'Prolonged Propagated Contractions', or PPCs, although a similar event has been described as a 'peristaltic rush' by White, Rainey, Monaghan and Harris (1934), and Code, Rogers, Schlegel, Hightower and Bargen (1957) in humans. The PPC has been shown to be evoked by ileal distention, and is able to empty the ileum in humans and dogs (Kruis et al 1985). The response is augmented when bile acid or fecal material is in the bolus creating the distention. Other possible equivalents of the PPC have been described in rabbits (Koch, Martin and Mathias, 1983) in response to cholera enterotoxin and other infectious agents. Others have simulated the electrical patterns typical of the PPC by ileal distention (Sjorgren, Wardolow and Charles, 1984) or by morphine administration (Sarna, 1984).

PPC's would appear to be very variable in occurrence. Quigley, Borody et al (1984) recorded none in some human subjects, up to a maximum rate of 3/hour in one subject. They occur in the last 20 - 30 cm of the ileum, with some crossing the ICJ. Their presence appears to ensure that ileal irritants such as cholera enterotoxin or colonic contents entering into the ileum are rapidly cleared into the large intestine, in a similar response to the secondary peristaltic waves clearing acid from the oesophagus following gastroesophageal reflux (Kruis et al 1985).

1.3.2 The ICJ of the sheep.

In sheep, the MMC occurs on a regular basis even after feeding (Bueno et al 1975). Since this cycle of activity is continuous in the sheep, the muscular activity it represents is responsible for the movement of digesta through the small intestine. Fioramonti (1981) endoscopically observed the ileal protuberance into the caecum of the sheep, noting an average contraction frequency of about 13 per minute, though this ranged from every few seconds to once every 2 or 3 minutes. This movement of digesta corresponded to EMG activity measured by ileal serosal electrodes placed 1cm from the end of the ileum, with the higher rate of contraction occurring at the same time as Phase 3 of the MMC, and the lower rates with Phase 2. (Fioramonti describes Phase 2 and Phase 3 of the MMC as Irregular Spiking Activity (ISA) and Regular Spiking Activity (RSA)). With each contraction 0.5 to 2mls of digesta was ejected into the caecum.

Fioramonti (1981) also described a period of caecal activity prior to the arrival of the MMC at the ileocaecal junction in sheep, proposing this as a mechanism to evacuate the caecum which then typically reduces it's level of activity for approximately 10 minutes as digesta is squirted through the ileocaecal orifice prior to the arrival of phase 3 MMC. Following this, caecal activity resumes, mixing the newly arrived digesta with caecal and proximal colon contents.

Reid and Dellow (1972) observed the activity of the terminal ileum radiographically. They described bursts of activity lasting from a few seconds up to 10 minutes, repeating 12 - 20 times every 24 hours. Bueno <u>et al</u> (1975) reported 15-20 MMCs per 24 hours from EMG recordings from sheep jejunum.

The movement of digesta across the sheep ICJ would appear to be linked to the arrival of Phase 3 MMC activity in the distal ileum.

1.4 Pharmacology of the Ileocaecal region.

1.4.1 Pharmacology of the ICJ In Vitro.

After three criteria for determining the existence of a sphincter had been proposed by Cohen _et al_ (1968), Bass, Ustach and Schuster (1970) suggested a fourth feature should be used to characterise gastro-intestinal sphincter regions: circular muscle strips should contract (in vitro) in response to adrenergic stimulation. (Non sphincteric gut muscle will not.)

The initial in vitro studies of muscle strips from the region of the ileocaecal junction were carried out by Gazet and Jarrett (1964). Their studies included samples from humans, monkeys, cats and dogs. Further work by Conklin and Christensen (1975) on the cat and opossum, and Cardwell, Rubin and Snape (1981) on the cat, consistently support the findings of Gazet and Jarrett. In summary, the isolated circular muscle strips from the ileocaecal sphincter (ICS) respond to sympathetic agonists such as adrenaline, noradrenaline and phenylephrine by contracting, while muscle from the adjacent regions of ileum and colon respond by relaxing. The ICS muscle response is blocked by phentolamine, suggesting an alpha-adrenergic receptor is involved in mediating this response. All the muscle strips (ileum, ICS and colon) are reported to respond to acetyl choline by contracting. In addition, Cardwell _et al_ also reported that circular muscle strips from the ICS showed no response to various humoral agents - secretin, gastrin, glucagon and CCK, while colonic and ileal circular muscle strips did respond. Colonic muscle was inhibited by glucagon and secretin and contracted in response to CCK and Gastrin, while ileal muscle was inhibited by glucagon and contracted in response to CCK and gastrin.

1.4.2 Pharmacology of the ICJ in Vivo.

Pahlin and Kerwenter (1975) showed in anaesthetised cats that sympathetic amines elicited an excitatory response from the ICS. This response could be blocked by alpha receptor blocking agents, but remained after a beta receptor blockade. In fact, in two thirds of the experiments, sympathetic amines injected after ß - blockade (propanolol) resulted in an enhanced response, suggesting a tonic inhibitory innervation mediated by beta receptors in the intact animal.

Rubin, Fournet, Snape and Cohen (1980), also reported similar responses from the ICS to catecholaminergic agonists and blocking agents.

Johnson (1977) discussed the likely involvement of gastrin in increasing the tone of the lower oesophageal sphincter, and Polak and Bloom (1981) reported gastrin containing nerves in the distal small intestine and proximal colon, suggesting a possible sensitivity of this region to gastrin.

1.5 Innervation of the muscularis externa of the small intestine.

The small intestine is intrinsically supplied by two plexuses of nerves, containing a variety of neurotransmitters (Polak and Bloom, 1981). Within the wall of the intestine, these two nervous networks are concentrated in two distinct areas - between the two layers of the muscularis externa (Myenteric, or Auerbach's, plexus) and in the submucosa (Submucosal, or Meissner's, plexus).

Gabella (1987) describes the myenteric plexus as forming a continuous network from the oesophagus to the anal canal in monogastric species. Harrison and Wathuta (1980) identified the myenteric plexus in the small intestine, colon and rectum of sheep.

The submucosal plexus is found right throughout the length of the ruminant intestine (Habel, 1956).

Within these plexuses are ganglia containing cell bodies of autonomic neurons which have been described as enteric neurons (Szurszewski and Weems, 1976). The two plexuses are interconnected, and the ganglia are thought to be able to integrate sensory input and contribute to intestinal motor control patterns (Wood, 1981). Recent studies have shown a variety of neurotransmitters are involved in this control (Polak and Bloom, 1981; Gabella, 1987). The actions of some of these in the intestine are fairly well established. Acetylcholine acting on smooth muscle cells has a stimulatory effect (Weisbrodt, 1987), while the effect of catecholamines is generally inhibitory except on sphincter muscle (see section 1.4). Other neurotransmitters, such as Vasoactive Intestinal Peptide (VIP), Substance P and Serotonin, are not so well understood.

VIP was discovered in 1970 by Said and Mutt in fractions of extract of porcine gut, and has since been found in large quantities throughout the entire length of the digestive tract of numerous species, including ruminants, with the majority of neurone cell bodies located in the submucosal plexus (Polak and Bloom, 1981; Harrison and Wathuta, 1980). VIP has been shown to relax intestinal smooth muscle (particularly circular muscle) in the cat (Sjöqvist and Fahrenkrug, 1987), and is thought to act as a neurotransmitter at interneuronal synapses (Costa and Furness, 1983), although its role as a neurotransmitter remains to be established.

Substance P is a powerful gut smooth muscle stimulant (Yau, 1978), and is thought to mediate non-cholinergic smooth muscle stimulation through interneurones within the myenteric plexus and branches into the circular muscle layer of the intestine (Katayama and North, 1978; Bornstein, North, Costa and Furness, 1984). However the lack of substance P in the interganglionic connections suggests that Substance P serves mainly a localized role within the muscularis of the intestine (Costa, Furness, Llewellyn-Smith and Cuello, 1981). Substance P may also be involved in sensory neurotransmission within the enteric nervous system (Polak and Bloom, 1981).

Serotonin (5-Hydroxytryptamine, or 5-HT) is thought to be the noncholinergic mediator of responses evoked relatively distant to ganglia within the enteric nervous system, as it is found in relative abundance in the plexuses between ganglia and has been shown to mediate contractile responses from intestinal muscle in response to nerve stimulation in guinea pigs (Erde, Sherman and Gershon, 1985). Wood and Meyer (1979) have also demonstrated that adrenergic stimulation of the small intestine inhibits serotonin release in the myenteric plexus.