

Copyright is owned by the Author of the thesis. Permission is given for a copy to be downloaded by an individual for the purpose of research and private study only. The thesis may not be reproduced elsewhere without the permission of the Author.

**STUDIES OF RADIOPAQUE MARKERS IN CATS AND DOGS**

**A THESIS PRESENTED IN PARTIAL FULFILMENT OF THE  
REQUIREMENTS FOR THE DEGREE OF MASTER OF VETERINARY  
SCIENCE AT MASSEY UNIVERSITY**

**SARA J BRUCE  
2000**

## Abstract

Radiopaque markers (RM) have been used to gain understanding of and assess gastrointestinal motility disorders in human medicine for some time. Development and validation of their use in veterinary medicine has commenced. The purpose of the present work was to further the knowledge and understanding of the use of RM in dogs and cats.

The physiology of gastrointestinal motility, the influence of fibre on the gastrointestinal tract and the gastric emptying of indigestible solids was reviewed to aid the reader in the interpretation of the experimental data. The disease processes affecting motility and the different methods used to diagnose dysmotilities were also summarised.

Reference values for the gastric emptying, small intestinal transit and large intestinal transit of a proprietary RM (BIPS, NZ Vet, Christchurch) fed in a high fibre diet (Hills Prescription Diet r/d) to healthy dogs were determined. The information was presented as box plots for veterinarians to use as reference curves in clinical practice.

Factors other than size and density may influence how indigestible particles empty from the stomach, such as the strength of antral contractions induced by the diet ingested. The objective of the next study was to investigate whether the size of the pieces of meat ingested along with indigestible particles (RM) affected how they emptied from the stomach.

The 50%, 75% and 90% gastric emptying times (GET) of each size of marker with each size of steak were compared by the Wilcoxon Sign Rank test. In addition, the area under the gastric emptying curves (AUC) of the RM were compared by a two-factor ANOVA. Fisher's Least Significant Difference (LSD) test was then used to compare means for the test meals.

The 50% GET of the small RM was found to be significantly faster than the large RM in the 10 mm<sup>3</sup> steak meal. The 50% and 75% GET of the small RM were significantly faster than the large RM in the 1 mm<sup>3</sup> and 20 mm<sup>3</sup> steak meals.

The mean AUCs of the large RM were significantly different between the test meals ( $p < 0.0068$ ). The large RM left the stomach significantly faster in the 10 mm<sup>3</sup> steak compared to the 20 mm<sup>3</sup> steak ( $p = 0.0029$ ).

The size steak fed with the large RM can influence how they empty from the stomach. An increased lag time appeared to be responsible for the slower emptying of the RM with the 20 mm<sup>3</sup> steak compared to the 10 mm<sup>3</sup>.

Preliminary veterinary use of RM in the assessment of gastrointestinal transit is encouraging. The objective of the last study was to assess the situations in which RM have been most often used in veterinary medicine, assess the motility abnormalities they highlight and assess how useful they have been to the diagnostic outcome. The case records of 120 dogs and 67 cats admitted to Massey University Veterinary Teaching Hospital which had undergone RM studies were utilised.

Vomiting was most common presenting sign resulting in a RM study being carried out. About half of both canine and feline studies were considered abnormal. Of the abnormal studies, delayed gastric emptying (DGE) was the most common finding. A wide range of diagnoses were associated with DGE. Other radiopaque marker patterns observed in cats and dogs were: rapid orocolic transit, adynamic ileus, delayed colonic transit (cats only) and bunching pattern.

In general, RM only rarely diagnosed primary gastrointestinal dysmotilities but regularly highlighted secondary dysmotilities. Knowledge of the gastrointestinal motility in a particular patient may allow the clinician to provide more tailored therapy to each patient. They are also useful to rule out physical obstructions in vomiting animals and have a place in the full work up of an animal with gastrointestinal disease.

## Acknowledgements

I would like to thank my supervisor Grant Guilford for his guidance, patience and encouragement in helping me to achieve this goal. Grant's enthusiasm and interest in my work was a great source of motivation for me and kept me going through the tough times, especially towards the end.

Special thanks to my mother, who flew half way around the world to help out with childcare, while I was in the finishing stages of this thesis. Her support and encouragement proved vital in the completion of my thesis.

Thank you also to Frazer Allan and Elizabeth Lee for your additional help and guidance.

Special thanks also to Linda Barter, Miho McHauley, Laurinda Oliver, Sarah Taylor and Eloise Jillings who spent many long, long nights radiographing dogs.

## Table of Contents

### Chapter One

### Introduction

### Chapter Two

### The Physiology of Gastrointestinal Motility

2.1	Introduction.....	1
2.2	The Function and Motility of the Stomach.....	5
	<i>Proximal Stomach</i> .....	6
	<i>Distal Stomach</i> .....	7
	<i>Neural and Hormonal Input</i> .....	8
	<i>Summary</i> .....	10
2.3	Small Intestinal Function and Motility.....	11
	<i>Individual Phasic Contractions</i> .....	12
	<i>Organised Groups of Contractions</i> .....	14
	<i>Special Propulsive Contractions</i> .....	15
	<i>Specific Intestinal Reflexes</i> .....	15
	<i>Hormonal and Neural Input</i> .....	16
	<i>Summary</i> .....	17
2.4	Colonic Function and Motility.....	17
	<i>Electrical Activity of Muscle Layers</i> .....	18
	<i>Types of Contractions</i> .....	19
	<i>Proximal Colon</i> .....	20
	<i>Middle Colon</i> .....	21
	<i>Distal Colon</i> .....	21
	<i>Neural and Hormonal Input</i> .....	22
	<i>Other Factors Influencing Colonic Transit</i> .....	22
	<i>Summary</i> .....	24

### Chapter Three Effects of Fibre on the Gastrointestinal tract

3.1	Introduction.....	25
3.2	Classification of Fibres.....	25
3.3	Effects of Fibre on Gastric Emptying.....	27
3.4	Effects of Fibre on Small Intestinal Function.....	28
	<i>Summary</i> .....	30
3.5	Effects of Fibre on the Colon and Faeces Production.....	31
	<i>Summary</i> .....	33

### Chapter Four The Gastric Emptying of Solids

#### Digestible Solids

4.1	Introduction.....	34
4.2	The lag phase.....	35
4.3	The emptying phase.....	36
	<i>Trituration</i> .....	37
	<i>Control of Gastric Emptying</i> .....	39
	<i>The Role of the Pylorus in Gastric Emptying</i> .....	40
4.4	Summary.....	41

#### Indigestible Solids

4.5	Introduction.....	42
4.6	Emptying of Indigestible Particles From an Empty Stomach.....	43
4.7	Influence of Particle Size on the Gastric Emptying of Indigestible Solid Particles.....	43
4.8	Influence of Particle Density on the Gastric Emptying of Indigestible Solid Particles...	45
4.9	Influence of Gastric Chyme on the Gastric Emptying of Indigestible Solid Particles....	46
4.10	The Hydrodynamic Theory of Gastric Emptying.....	48
4.11	Other possible factors influencing indigestible particle emptying.....	52



## Chapter Five

## Gastrointestinal Motility Diseases and their Diagnosis

## Diseases Affecting Intestinal Motility

5.1	Introduction.....	53
5.2	Gastric Motility Disorders.....	55
	<i>Gastric Motility Disorders Resulting in Accelerated Emptying</i> .....	58
	<i>Gastric Motility Disorders Resulting in Retrograde Transit</i> .....	59
5.3	Intestinal Motility Disorders.....	59
	<i>Adynamic Ileus</i> .....	60
	<i>Irritable Bowel Syndrome</i> .....	61
	<i>Intestinal Pseudo-Obstruction</i> .....	62
	<i>Dysautonomia</i> .....	64
	<i>Megacolon</i> .....	65

## Diagnosis of Motility Disease

5.4	Introduction.....	67
5.5	Plain and Contrast Radiography.....	67
5.6	Radiopaque Markers.....	68
	<i>RM Use in Humans</i> .....	68
	<i>RM use in Animals - Barium Impregnated Polyethylene Spheres</i> .....	73
5.7	Scintigraphy.....	79
5.8	Magnetic Resonance Imaging.....	81
5.9	Ultrasonography.....	83
5.10	Manometry.....	84
5.11	Less Common Methods of Assessing Gastrointestinal Motility.....	85
5.12	Summary.....	87

**Chapter Six                    Development Of Reference Intervals For The Gastric Emptying,  
Small Intestinal Transit And Colonic Transit Of Radiopaque Markers  
Fed With A High Fibre Diet To Dogs**

<b>6.1</b>	Introduction.....	88
<b>6.2</b>	Materials and Methods.....	90
	<i>Dogs</i> .....	90
	<i>Diet</i> .....	91
	<i>Radiopaque Markers</i> .....	91
	<i>Administration of the Radiopaque Markers</i> .....	92
	<i>Radiography</i> .....	92
	<i>Radiographic Interpretation</i> .....	93
	<i>Statistical Analysis</i> .....	93
<b>6.3</b>	Results.....	96
	<i>Experimental Protocol</i> .....	96
	<i>Gastric Emptying</i> .....	96
	<i>Small Intestinal Transit Time</i> .....	96
	<i>Colonic Filling Times</i> .....	97
	<i>Colonic Transit Times</i> .....	97
<b>6.4</b>	Discussion.....	98

**Chapter Seven    Influence of the Size of Pieces of Food in a Meal on the Gastric Emptying of  
Indigestible Solid Particles**

<b>7.1</b>	Introduction.....	109
<b>7.2</b>	Materials and Methods.....	111
	<i>Test Meals</i> .....	111
	<i>Indigestible solid particles</i> .....	111
	<i>Dogs</i> .....	113
	<i>Experimental design</i> .....	113
	<i>Radiography and radiographical interpretation</i> .....	114
	<i>Statistical analysis</i> .....	115
<b>7.3</b>	Results.....	116
<b>7.4</b>	Discussion.....	118

**Chapter Eight            A Retrospective Study of the Use of Radiopaque Markers in Dogs and  
Cats With Gastrointestinal Problems 1993 – 1998**

<b>8.1</b>	Introduction.....	124
<b>8.2</b>	Objectives.....	125
<b>8.3</b>	Materials and Methods.....	125
	<i>Case records</i> .....	125
	<i>Radiopaque markers</i> .....	125
	<i>Information collected from the case records</i> .....	126
	<i>RM study assessment</i> .....	126
<b>8.4</b>	Results.....	128
	<i>Signalment</i> .....	128
	<i>Clinical signs manifested by animals undergoing RM studies</i> .....	128
	<i>Indications for RM studies</i> .....	129
	<i>Administration techniques</i> .....	129
	<i>Radiographic findings of RM studies</i> .....	131
	<i>Survey radiographs</i> .....	132
	<i>Final diagnoses - Delayed gastric emptying pattern</i> .....	132
	<i>Final Diagnoses- Adynamic ileus pattern</i> .....	133
	<i>Final Diagnoses- Bunching pattern</i> .....	134
	<i>Final Diagnoses- Rapid orocolic transit pattern</i> .....	134
	<i>Final Diagnoses - Delayed colonic transit pattern (cats only)</i> .....	134
	<i>Diagnostic procedures used with RM</i> .....	134
<b>8.5</b>	Discussion.....	136
<b>Chapter Nine</b>	<b>Summary and Conclusions.....</b>	<b>147</b>

## List of Tables

<b>Table 6.1</b>	Average nutritional analyses of the diet.....	102
<b>Table 6.2</b>	Gastric emptying times.....	102
<b>Table 6.3</b>	Small intestinal transit.....	102
<b>Table 6.4</b>	Colonic filling times.....	103
<b>Table 6.5</b>	Mean residence times.....	103
<b>Table 7.1</b>	Gastric emptying times for all studies.....	121
<b>Table 7.2</b>	Area under the curve data.....	121
<b>Table 8.1</b>	Sex of the dogs.....	142
<b>Table 8.2</b>	Sex of the cats.....	142
<b>Table 8.3</b>	Clinical signs manifested by animals undergoing a RM study.....	143
<b>Table 8.4</b>	Final diagnoses associated with studies showing the delayed gastric emptying pattern .....	144
<b>Table 8.5</b>	Final diagnoses associated with studies showing adynamic ileus.....	145
<b>Table 8.6</b>	Additional radiographic abnormalities found on RM radiographs.....	146

## List of Figures

<b>Figure 6.1</b>	Box Plot Depicting the Gastric Emptying of the Small RM at different times after administration.....	104
<b>Figure 6.2</b>	Box Plot Depicting the Gastric Emptying of the Large RM at different times after administration.....	104
<b>Figure 6.3</b>	Box Plot Depicting the Colonic Filling of the Small RM at different times after administration.....	105
<b>Figure 6.4</b>	Box Plot Depicting the Colonic Filling of the Large RM at different times after administration.....	105
<b>Figure 6.5</b>	Box Plot Depicting the Percentage of Small RM in the Proximal Colon at Different Times after Administration.....	106
<b>Figure 6.6</b>	Box Plot Depicting the Percentage of Large RM in the Proximal Colon at Different Times after Administration.....	106
<b>Figure 6.7</b>	Box plot Depicting the Percentage of Small RM in the Distal Colon at Different Times after Administration.....	107
<b>Figure 6.8</b>	Box Plot Depicting the Percentage of Large RM in the Distal Colon at Different Times after Administration.....	107
<b>Figure 6.9</b>	Box Plot Depicting the Percentage of Small RM in the Total Colon at Different Times after Administration.....	108
<b>Figure 6.10</b>	Box Plot Depicting the Percentage of Large RM in the Total Colon at Different Times after Administration.....	108
<b>Figure 7.1</b>	The percent gastric emptying of the small RM for each test meal as a function of time with standard deviation bars.....	122
<b>Figure 7.2</b>	The percent gastric emptying of the large RM for each test meal size as a function of time with standard deviation bars.....	123

## **CHAPTER ONE**

### ***INTRODUCTION***

Since the beginning of this century, researchers have been working to understand the complex process of the gastrointestinal transit of food. Radiopaque markers (RM) have been used in human medicine to develop an understanding of gastrointestinal motility and to investigate gastrointestinal motility disorders. More recently, exploration of the use of RM in veterinary medicine has commenced. Most studies carried out so far in animals have concentrated on validation of the technique. Reference intervals have also been determined to allow application of the RM technique to a variety of clinical situations. The work presented in this thesis further develops the RM technique.

Chapter Two provides a review of the physiology of gastrointestinal motility. The passage of food through the gastrointestinal tract is complex. The co-ordination of gastric emptying and the transit of food through the small and large intestines consist of multiple interactions between intrinsic and extrinsic nerves, hormones, intestinal smooth muscle and the food ingested. A thorough understanding of gastrointestinal transit is necessary to interpret the experimental work described in this thesis. In particular, knowledge of the influence of fibre on gastrointestinal transit is important. Accordingly, a detailed description of the effect of fibre on gastrointestinal motility is provided in Chapter Three of this thesis.

The gastric emptying of solid particles from the stomach is complex and differs from the gastric emptying of liquids. This is because indigestible solids can become suspended in triturated gastric chyme and empty along with it. The gastric emptying of indigestible solids can be predicted on the basis of their size and density relative to that of the gastric chyme. A detailed description of how solids empty from the stomach is provided in Chapter Four to aid the reader understand the gastric emptying of indigestible solids such as RM.

A variety of different disease processes can disrupt gastrointestinal transit. These diseases are described in Chapter Five and include physical obstructions to flow of gastrointestinal contents, primary gastrointestinal neuromuscular or functional abnormalities and secondary dysmotilities resulting from a diverse range of other diseases. Knowledge of the different disease entities aids in interpretation of RM studies, in clinical situations.

The clinical signs associated with abnormal transit are often non-specific and include signs such as reduced appetite, vomiting, diarrhoea and alteration in frequency of defaecation. For this reason, gastrointestinal dysmotilities will be overlooked unless specific tests of gastrointestinal motility or transit are undertaken. The variety of different tests that used to diagnose dysmotilities are described in Chapter Five. Some of these tests directly measure gastrointestinal motility and others focus on gastrointestinal transit, the end point of gastrointestinal motility. Many of these tests are not suitable for use in clinical patients and few have been validated for use in the dog. A clinically-relevant test that has received considerable attention in the

veterinary literature is the use of RM. Chapter Five reviews also the previous work that has validated this technique in humans and animals.

In order to use RM in clinical practice reference intervals are required. Reference intervals have been produced for the gastrointestinal transit of RM<sup>a</sup> without food and mixed with a variety of diets in healthy dogs and cats. Increasing the fibre content of the diet results in greater quantities of faeces and may assist the delineation of the large intestine on radiographs. Fibre is also thought to regulate colonic motility in healthy animals. This property may assist the diagnosis of colonic dysmotility by leading to more uniform reference intervals. Because varying the amount of fibre in the diet can alter the gastrointestinal transit of food, separate reference intervals are required for the gastrointestinal transit of RM fed in diets of differing fibre content. The development of reference intervals for the gastric emptying, small intestinal transit and large intestinal transit of RM<sup>a</sup> mixed in a high fibre diet<sup>b</sup> is described in Chapter Six.

It is possible that factors other than size and density may influence the gastric emptying of indigestible solid particles. For example, if indigestible solid particles, such as RM, are ingested along with large pieces of food that require extensive trituration, the size and density of the indigestible solid particles may become less important. This is because it is likely that the particles will be kept in suspension in the gastric chyme via the muscular action of the stomach, regardless of their size or density, thus speeding their exit from the stomach. The influence of the size of the

---

<sup>a</sup> Barium Impregnated Polyethylene Sheres, MedID, Grand Rapids

<sup>b</sup> Prescription Diet r/d, Hills Pet Products, Topeka, KA



pieces of food ingested along with RM on the gastric emptying of the RM is investigated in Chapter Seven.

In order to evaluate the usefulness of a diagnostic technique it is important to assess how it is being used, the diagnostic information it provides and the contribution this information makes to the diagnostic outcome. The usefulness of RM in a veterinary clinical setting was evaluated by a retrospective study into the use of RM at Massey University. This study is described in Chapter Eight of this thesis.

## CHAPTER TWO

### ***THE PHYSIOLOGY OF GASTROINTESTINAL MOTILITY***

#### **2.1 Introduction**

As previously mentioned, the physiology of gastrointestinal motility is complex. It involves the interaction of intestinal smooth muscle with hormones, neurotransmitters, intrinsic and extrinsic nerves and nutrients present in the intestinal lumen. The presence of food can influence this interaction and consequently gastrointestinal motility.

#### **2.2 The Function and Motility of the Stomach**

The function of the stomach is to act as a reservoir for ingested food and to continue the process of digestion initiated by saliva in the mouth. The stomach grinds food into smaller particles before slowly releasing it into the duodenum. Gastric emptying is a carefully controlled process delivering ingesta to the duodenum in a manner that optimises nutrient absorption (Wingate *et al*, 1994). Gastric emptying will be explored in greater depth in Chapter Four and what follows here is a brief description of the physiological processes involved.

The stomach is divided functionally, but not anatomically, into two regions (Kelly, 1980; Hall *et al*, 1988). The proximal region comprises the fundus and proximal third of the body of the stomach. The distal stomach is made up of the antrum, pylorus and

distal two thirds of the body. The function of the proximal stomach is to store solids and expel liquids. The distal stomach is involved primarily in the trituration, or breaking down, of food particles and the emptying of solids.

### ***Proximal Stomach***

As food is swallowed, the lower oesophageal sphincter and proximal stomach relax to receive the bolus via a brief reflex called receptive relaxation. Distension of the stomach by the bolus then produces a longer lasting reflex relaxation called accommodation (Kelly, 1980; Hall *et al*, 1988). Liquids are expelled from the stomach via the action of the proximal stomach. By varying intragastric pressure, a gradient is set up between the pressures in the stomach and the duodenum so the rate of emptying of liquids can be controlled (Kelly, 1980; Hall *et al*, 1988). The pylorus offers little resistance to the flow of liquids (Hall *et al*, 1988). The rate of emptying is also affected by the viscosity of the fluid which, in turn, is dictated by the composition of the ingesta. For example, some fibres increase the viscosity of chyme, delaying gastric emptying (Russell and Bass, 1985a).

Variation in intragastric pressure of the fundus is achieved by fast and slow phasic contractions occurring on top of slow, sustained, tonic contractions (Kelly, 1980). Proximal stomach smooth muscle cells have a stable resting potential and do not exhibit the property of spontaneous depolarisation like the smooth muscle cells of the distal stomach (Hall *et al*, 1988). The resting potential of proximal smooth muscle cells is usually less negative than the threshold for contraction. Therefore these cells exhibit a degree of muscle contraction, or tone, even at rest. Phasic contractions are

influenced by neural input, with the slow contractions occurring in response to neural stimulation and the faster ones occurring during the periods of neural quiescence (Hall *et al*, 1988).

### ***Distal Stomach***

The contractions of the distal stomach that triturate food and empty the ground food particles into the duodenum are initiated by slow waves. Slow waves are generated by the spontaneous rhythmical depolarisation of the smooth muscle cells of the distal stomach (Kelly, 1980; Hall *et al*, 1988). The frequency of slow waves is the primary determinant of the frequency of smooth muscle contractions, although not every slow wave results in muscle contractions. Muscle contractions will only occur if the depolarisation caused by a slow wave is augmented by rapid membrane depolarisations referred to as “spike potentials”. Spike potentials are similar to the action potentials that initiate contraction of striated muscle. Neural and hormonal input to the distal stomach modifies muscle contraction rate by influencing the frequency of occurrence of spike potentials (Kelly, 1980; Hall *et al*, 1988).

Slow waves can be generated by smooth muscle cells at any site in the distal stomach although they are usually initiated by a pacemaker along the greater curvature of the body. The pacemaker undergoes more rapid spontaneous depolarisation than other areas of the stomach resulting in a faster frequency of slow wave production (Kelly, 1980; Hall *et al*, 1988). The inherent frequency of slow wave production decreases progressively towards the pylorus (Hall *et al*, 1988).

The pattern of slow wave production dictates the pattern of muscle contraction, thereby controlling and co-ordinating it. Hence, slow waves are also termed 'electrical control activity' or 'pacesetter potentials'. In the dog, the gastric pacemaker generates 4 - 5 slow waves per minute (Kelly, 1980; Hall *et al*, 1988). The resultant contractions sweep particulate matter towards the pylorus.

Transpyloric flow of solids is a function of pyloric resistance and terminal antral pressure (Wingate *et al*, 1994; Quigley, 1996). The rate of flow is modulated by feedback mechanisms operating further along the gastrointestinal tract. The feedback is stimulated by the presence of nutrients in the small intestinal lumen, intestinal mucosa and circulation (Lin *et al*, 1989; Lin *et al*, 1990; Wingate *et al*, 1994). Feedback inhibition increases with the concentration of nutrient, the length of intestine involved and the more aboral the site of intestine involved (Lin *et al*, 1990; Stanghellini *et al*, 1994). Mediators involved in these feedback mechanisms may be neural or humoral and possibly involve cholecystokinin (CCK) via modulation of the vago-vagal reflex (Jin *et al*, 1994; Stanghellini *et al*, 1994). This feedback slows the rate of gastric emptying (Read, 1994; Stanghellini *et al*, 1994; Wingate *et al*, 1994) and is known as the 'ileal brake' mechanism.

### ***Neural and Hormonal Input***

Neural and hormonal activity have an important influence on smooth muscle contraction. The enteric nervous system coordinates the functions of the gastrointestinal tract via nerve plexi in the submucosa and between the muscle layers (Hall *et al*, 1988). Interneurons connect these plexi and relay information from the

sensory neurons to the motor neurons. Enteric nervous system function can be influenced by the central nervous system (Hall *et al*, 1988).

The proximal stomach requires external neural input to regulate its activity because no spontaneous depolarisation occurs in this area. The distal stomach is also dependant on external neural input to potentiate its actions otherwise the amount of spontaneous contractile activity is low (Kelly, 1980). The proximal stomach responds differently than the distal stomach to some stimuli. Vagal input to the proximal stomach promotes relaxation therefore increasing gastric accommodation (Kelly, 1980), whereas sympathetic stimulation increases muscular contraction. In contrast, input from the sympathetic nervous system to the distal stomach is inhibitory and parasympathetic input can be inhibitory or stimulatory.

The hormones gastrin and cholecystinin (CCK) promote relaxation of the proximal stomach, although gastrin may not do this at physiological concentrations (Kelly, 1980; Hall *et al*, 1988). CCK acts in the gastrointestinal tract both directly and via neural stimulation. It results in relaxation of the fundus via a vago-vagal inhibitory reflex (Grider, 1994). Motilin increases muscular contraction in the proximal and the distal stomach (Kelly, 1980; Hall *et al*, 1988). Gastrin and CCK also promote muscular contraction of the distal stomach, in contrast to their actions on the proximal stomach. Gastrin also increases the frequency of the pacemaker cycle (Hall *et al*, 1988). Secretin, glucagon, vasoactive intestinal polypeptide (VIP) and somatostatin have been found to be antagonists to muscular contraction in the distal stomach and may also regulate activity in the proximal stomach (Hall *et al*, 1988). The response of the pylorus to enteric hormones appears to be different to the distal stomach. It is

stimulated to contract by secretin (Hall *et al*, 1988) and CCK, and by the presence of acid in the duodenal lumen (Daniel *et al*, 1994). The exact roles of hormones and paracrine agents in the modulation of gastric motility have still to be fully elucidated, however.

Variation in the nutrient composition, viscosity, consistency, energy density, temperature and pH of the food can alter gastric emptying rate by affecting gastric motility (Tadesse, 1986; Levanon *et al* 1998 ). The effects of some of these dietary factors are discussed more fully in Chapter Three and Four.

### ***Summary***

In summary, the stomach is comprised of a proximal region, responsible for the storage of ingesta and the emptying of liquids, and a distal region which grinds and empties food. These regions differ physiologically. The proximal stomach requires neural stimulation to maintain intragastric pressure, whereas the distal stomach exhibits spontaneous activity. This is initiated by slow waves that are modulated by hormonal and neural stimulation. The proximal stomach relaxes following vagal stimulation and contracts following sympathetic stimulation, whereas the distal stomach relaxes following sympathetic stimulation. Gastrin and CCK generally relax the proximal stomach but induce contraction of the distal stomach. Motilin stimulates muscular contraction of both the proximal and distal stomachs. The composition of the food ingested also affects gastric motility.

### **2.3 Small Intestinal Function and Motility**

The small intestine is a long, muscular tube 1.8 to 4.8 metres in length in the dog (Strombeck, 1996). Its function is to transport ingesta to the colon in a manner which optimises the mixing and propulsion of intestinal contents and the absorption of nutrients. During fasting, it is also responsible for the removal of debris, secretions and bacteria from the gastrointestinal tract (Otterson and Sarr, 1993). Anatomically, it is composed of four layers. From the luminal side to the outermost layer these are: the mucosa, submucosa, muscularis (comprising of an outer longitudinal and inner circular muscle layers) and serosa (Weisbrodt, 1987).

The passage of ingesta through the intestine is controlled by a combination of myogenic, hormonal and neural activity. As in the distal stomach, muscle contraction in the small intestine is controlled by electrical control activity (slow waves) (Bortoff, 1976). There is a pacemaker region in the proximal duodenum that drives or “paces” the distal intestine (Otterson and Sarr, 1993). The slow waves in this region are more frequent, more organised, have greater amplitudes and propagate over greater distances than slow waves in other regions of the intestine (Makhlouf, 1994). The slow waves propagate further because of tighter electrical coupling between the smooth muscle cells in the upper small intestine allowing good cell-to-cell transmission (Bortoff, 1976; Otterson and Sarr, 1993). More distally, the slow wave activity of the small intestine is less frequent and there is poorer electrical coupling between muscle cells. As a result, the propulsive contractions of the distal small



intestine are less coordinated and propagate over shorter distances. As a consequence of all of these factors, transit through the upper small intestine is quicker than transit through the distal small intestine (Otterson and Sarr, 1993).

Contractile activity in the small intestine can be divided into three major categories: individual phasic contractions, organised groups of contractions and special propulsive contractions (Otterson and Sarr, 1993).

### ***Individual Phasic Contractions***

Two types of individual phasic contractions occur in both the fed and fasted states: segmentation and peristalsis (Bortoff, 1976). Peristalsis result from well propagated slow wave activity, producing a ring of contraction that travels for a short distance in an aboral direction. Segmentation results from poorly propagated slow waves that produce stationary rings of contractions. These increase resistance to the flow of ingesta allowing time for the digestion and absorption of nutrients. Because electrical coupling, and hence slow wave propagation, is more effective in the upper small intestine, duodenal motility consists predominantly of peristalsis. In contrast, segmentation is the predominant feature of ileal contractile activity (Bortoff, 1976; Otterson and Sarr, 1993).

Nutrients in the intestinal lumen influence the frequency and type of individual phasic contractions (Bueno *et al*, 1981; Schemann and Ehrlein, 1986). A study by Schemann and Ehrlein (1986) demonstrated that “non-nutrient meals” are transported rapidly through the intestine with frequent, well propagated peristaltic waves in contrast to

“nutrient meals” which induce a higher proportion of segmenting contractions. In addition, certain nutrients were found to produce specific contraction patterns. For example, an oleic acid meal produced a high incidence of clusters of stationary and migrating contractions. This study also found that transit time through the intestine was better correlated to length of spread of the peristaltic waves than contraction frequency. As the length of spread of the peristaltic waves increased, the transit time through the intestine decreased. Interestingly, all single nutrient meals used in this study had similar intestinal transit times in spite of provoking markedly different motility patterns. This occurred because meals inducing a higher contraction frequency had a shorter length of spread of contraction waves and *vice versa*. Other studies also have found that small intestinal transit is relatively constant when different meals are ingested (Read *et al*, 1982; Davis *et al*, 1984b). However, small intestinal transit can be hastened by the addition of non-absorbable solutes such as lactulose to the meal (Davis *et al*, 1984b).

The mechanisms responsible for coordinating specific contraction patterns for certain nutrients were not determined by Schemann and Ehrlein’s study. However, the authors suggested that the interaction of hormones, osmoreceptors and chemoreceptors producing reflexes similar to those controlling gastric emptying were likely to be involved.

### *Organised Groups of Contractions*

Contractions also occur in organised groups in the small intestine (Otterson and Sarr, 1993). Organised groups of contractions are responsible for the interdigestive migrating motility complex (MMC) which occurs during the fasted state. The MMC consists of waves of peristalsis which move aborally down the intestines clearing any indigestible debris and bacteria from the lumen. It is thought to be modulated by the central nervous system with the hormone motilin possibly initiating or coordinating it (Otterson and Sarr, 1993). However, the exact roles of motilin and the central nervous system remain controversial.

The MMC occurs as cycles of different phases of contractile activity. During phase 1, there is no activity. In the dog, this phase lasts for approximately one hour and is followed by about 15 to 40 minutes of phase 2 activity. Phase 2 has a level of peristaltic activity similar to the fed motility pattern. Phase 3 is characterised by a burst of intense contractile activity which lasts 4 to 8 minutes and results in rapid transport of intestinal contents in an aboral direction (Weisbrodt, 1987). Phase 4 is a brief phase of reduced motility which merges into the quiescence of Phase 1.

During feeding, the MMC is interrupted and a level of muscular activity similar to phase 2 activity is instituted (Weisbrodt, 1987). This switch of motility is brought about by the release of CCK that occurs in response to detection of protein and fat

digestion products by the mucosa of the small intestine (Rodriguez-Membrilla and Vergara, 1997). The duration of this fed response varies with the physical and chemical composition of the food (Schemann and Ehrlein, 1986; Weisbrodt, 1987). For example, fibre has been found to prolong this response (Bueno *et al* 1981). In normal dogs, the switch from fed to fasted motility patterns occurs from 6.4 to 16 hours after feeding (Hall *et al*, 1988). MMC patterns are found in the stomach and down the entire length of the bowel. Cats do not generate a typical cycle of MMC activity but have more random bursts of activity during fasting (Weisbrodt, 1987).

### *Special Propulsive Contractions*

Special propulsive contractions also occur in the small intestine (Otterson and Sarr, 1993). These are involved in rapid transit of intestinal contents over large distances in either direction, for example, during vomiting or diarrhoea.

### *Specific Intestinal Reflexes*

Specific intestinal reflexes have been identified. Long intestinal reflexes alter the muscular activity of areas of intestine distant to the area stimulated (Strombeck, 1996a). Examples include, the ileal “brake” mechanism, mentioned previously, and the gastro-colic reflex in which food in the stomach stimulates a peristaltic response in the colon. The intestino-intestinal inhibitory reflex is another example of a long intestinal reflex. This reflex results in inhibition of intestinal motility (adynamic ileus) following any adverse stimuli to the intestines. Such stimuli include rough handling

of intestines during abdominal surgery or intestinal distention due to an obstruction (Guilford and Strombeck, 1996b).

### ***Hormonal and Neural Input***

The enteric nervous system is responsible for coordinating and regulating the contractile activities of the small bowel. As in the stomach, there is a network of neurons connecting plexi in the muscle and submucosal layers which synapse with extrinsic neurons (Weisbrodt, 1987).

Hormones and extrinsic neural activity have little effect on the frequency of slow waves in the small intestine because this is primarily determined by the inherent spontaneous electrical activity of the smooth muscle itself. However, spike burst amplitude and duration are influenced by neurohumoral factors (Bortoff, 1976; Weisbrodt, 1987; Otterson and Sarr, 1993). Therefore, although myogenic activity determines whether an intestinal contraction can occur, neurohumoral factors influence whether it will occur (Otterson and Sarr, 1993). Contraction of small intestinal smooth muscle is enhanced by vagal stimulation and reduced by sympathetic nervous input. Gastrin, motilin and CCK will increase smooth muscle contraction whereas secretin, glucagon, VIP and gastric inhibitory polypeptide decrease contractions.

Electrolyte imbalances and disease states also can affect intestinal motility. For example, slow wave activity can be reduced by hypokalaemia (Strombeck, 1996a).

## **Summary**

In summary, small intestinal smooth muscle contraction is triggered by slow wave activity occurring in association with spike potentials. Neurohumoral activity influences spike potentials but not slow waves. The number, type and strength of smooth muscle contractions varies with the area of the intestine, the presence of food, and the prevailing hormonal and neural activity. Individual phasic motility occurs during fed and fasting states and produces peristaltic or segmenting contractions. Certain nutrients have been shown to produce specific contraction patterns. However, the rate of transport of ingesta through the small intestine is usually constant. Organised groups of contractions underpin the MMC, a cycle of peristaltic activity which occurs during fasting. Special propulsive contractions occasionally occur in the small intestine and result in rapid transit of intestinal contents over large distances. Motility in one region of the gastrointestinal tract can be affected by events in other regions via long intestinal reflexes.

## **2.4 Colonic Function and Motility**

The colon completes the absorption of fluid and electrolytes but it also acts as a reservoir. The proximal colon retains contents for slow release into the middle and distal colons (Strombeck, 1996b) and the rectum stores faeces until defaecation is appropriate. The progression of intestinal contents through the colon is much slower than through the small intestine. The slow transit allows efficient water and electrolyte absorption to occur (Sarna, 1993).

### ***Electrical Activity of Muscle Layers***

Slow waves or pacemaker potentials are generated by the circular muscle layer in the colon, not the longitudinal layer as in the stomach and small intestine (Christensen, 1994). Slow wave generation by the circular layer requires the submucosa and the innermost layer of the circular muscle layer to be intact (Durdle *et al* 1983). In general, as in the distal stomach and small intestine, phasic contractions of the circular muscle layer are initiated by slow waves that carry a spike potential (El-Sharkawy, 1983).

The slow waves are poorly propagated throughout the colon because electrical coupling between smooth muscle cells is almost absent (Durdle *et al* 1983; Sarna, 1993). This results in uncoordinated contractile activity that serves to mix and agitate the colonic contents.

The longitudinal muscle layer of the colon appears to have a totally different pattern of electrical activity (El-Sharkawy, 1983). It exhibits periods of electrical activity alternating with periods of electrical quiescence. The electrical activity in the longitudinal muscle layer occurs in the form of oscillations and as the amplitude of these oscillations increases, spike bursts occur. The periods of electrical activity with spike bursts are associated with tonic contractions of the longitudinal muscle layer (El-Sharkawy, 1983).

Although the two muscle layers have differing electrical activity, there appears to be co-dependancy between the two layers. Most circular muscle contractions result from slow waves produced during the periods of electrical activity of the

longitudinal layer (Durdle *et al* 1983; El-Sharkawy, 1983). In addition, the longitudinal layer appears to require excitatory input to stimulate its electrical activity, for example, stretch or neural stimulation (El-Sharkawy, 1983). The exact relationship of the two muscle layers is yet to be fully elucidated.

### *Types of Contractions*

Different types of contractions also occur in the colon. These include individual phasic contractions, ultrapropulsive contractions and organised groups of contractions (Sarna, 1993). In the colon, unlike the small intestine, individual phasic contractions are of two types, short and long duration. Short duration contractions last less than 15 seconds and long duration contractions last approximately 40 to 60 seconds (Sarna, 1993). Each type of contraction may occur independently. Alternatively, short duration contractions may occur on top of long duration contractions (Sarna, 1993). Long duration contractions can propel colonic material in either an oral or aboral direction or they can remain stationary. Therefore they can produce peristaltic or segmental activity. Short duration contractions usually occur in a random fashion (Sarna, 1993), producing segmental activity. Segmentation mixes colonic material and regulates its passage through the entire colon. It has been proposed that short duration activity may be associated with circular muscle layer contractions and long duration activity with contractions of the longitudinal muscle layer (El-Sharkawy, 1983).

The colon also undergoes periods of organised groups of contractions, resembling the MMC activity of the stomach and small intestine. The MMC cycle in the colon is not



coordinated with the preceding intestine (Christensen, 1994), nor does ingestion of a meal disrupt the colonic MMC, although it will affect its cycle length (Sarna and Lang, 1989). This difference between the colonic and upper gastrointestinal MMC is likely due to the fact that even during fasting the colon is rarely empty.

### *Proximal Colon*

The reservoir function of the proximal colon is brought about by a characteristic motility pattern. In the feline proximal colon, rings of contractions move in an oral direction at a rate of about five per minute. These continue for periods of two to eight minutes with breaks of about 15 minutes. This mixes the contents preventing aboral passage of the material and facilitating fluid and electrolyte absorption. The slow wave activity that underlies these oral contractions is initiated by a pacemaker in the distal part of the proximal third of the colon. It generates slow waves at about 6 per minute in the dog and cat (Christensen, 1994). The anti-peristaltic action of the proximal colonic pacemaker opposes the aborally directed waves produced by the ileocolic pacemaker. The latter occur at about 4.5 per minute. The contrary actions of the ileocolic and proximal colonic pacemakers encourage bowel contents to be transiently retained in the caecum and proximal colon (Christensen, 1994).

### *Middle Colon*

Material entering the middle colon from the proximal colon stimulates contraction by distending the bowel (Christensen, 1994). The predominant contractile pattern in the middle colon is peristalsis. The peristalsis is similar to that of the proximal colon but it occurs in an aboral direction, slowly propelling the colonic contents towards the distal colon.

### *Distal Colon*

In the distal colon, ultrapulsive contractions, also called 'mass movements', are produced by strong contractions of the circular muscle layer (Christensen, 1994; Sarna, 1993). These occur intermittently between periods of segmentation activity. They result from giant migrating contractions (Sarna, 1993) or migrating spike bursts (Christensen, 1994) which occur at intervals of several hours (Christensen, 1994). Mass movements transport the colonic contents rapidly over large distances and can empty the colon. They are produced by a prolonged burst of spikes unrelated to slow wave activity (Christensen, 1994). These spikes are initiated in the middle colon and move aborally (Christensen, 1994). Before mass movements can occur, segmentation activity must be absent in the area of the colon that will provide the colonic contents and the area into which the contents will pass. Segmentation activity returns quickly

to the portion of colon receiving the faeces. Mass movements are thought to occur more often during feeding (Christensen, 1994).

### ***Neural and Hormonal Input***

Determination of extrinsic and intrinsic neural input to the colon has not been elucidated as clearly as for the stomach and small intestine. It is known that extrinsic nerves alter colonic motility but their mechanisms of action have not been completely determined. In general, parasympathetic activity stimulates segmentation and sympathetic input is usually inhibitory (Strombeck, 1996b). The primary inhibitory pathways are noncholinergic and noradrenergic involving mediators such as adenosine triphosphate (ATP), VIP and gamma-aminobutyric acid (Christensen, 1994). It is thought that hormones also affect colonic motility, especially during eating (Christensen, 1994).

### ***Other Factors Influencing Colonic Transit***

Transit through the colon is influenced by the resistance to flow of the faecal material. As in the small intestine, resistance to flow is determined by the degree of segmentation. Intracolonic and extracolonic factors influence the level of segmental activity. Distention of the colon is the primary intracolonic mechanism for stimulation of segmentation. This response is mediated by intrinsic neural reflexes (Strombeck, 1996b). Adding fibre to the diet will increase the amount of undigested matter reaching the colon and will increase segmentation and propulsive activity. Extracolonic factors affecting segmental activity are generally neurally mediated and

are usually inhibitory, possibly to allow mass movements to occur (Christensen, 1994). Diarrhoea is usually associated with a hypomotile intestine that provides no resistance to flow of ingesta. This is due to disruption of the oral gradient of motor activity and the initiation of multiple pacemakers in the proximal colon which stimulate aboral contractions (Christensen, 1994). In contrast, constipation is usually associated with increased segmentation resulting in increased resistance to flow and preventing mass movements (Christensen, 1994). Lastly, colonic slow wave activity can be affected by electrolyte imbalances. For example, both hyperkalaemia and hypokalaemia reduce slow wave activity (Strombeck, 1996b).

### *Summary*

In summary, slow wave activity, similar to that occurring in the distal stomach and small intestine, is a feature of the circular muscle of the colon. The longitudinal muscle layer produces periods of electrical oscillations and spiking activity interspersed with periods of quiescence. The activity of the muscle layers appears to be coordinated, although the precise mechanisms are not yet understood. Aborad peristalsis is the predominant activity in the proximal half of the colon and promotes the absorption of fluid and electrolytes. In the middle colon, peristalsis is the principal contraction pattern, slowly shifting the colonic contents towards the distal colon. Mass movements occur intermittently in the distal colon and are associated with movement of a large amount of colonic material and with defaecation. They are stimulated by eating. Segmentation activity prevents mass movements from occurring and slows transit time through the colon. Segmentation activity is affected by intracolonic factors such as distention, which is stimulatory, and by extracolonic factors that are usually neural and inhibitory.

## CHAPTER THREE

### ***EFFECTS OF FIBRE ON THE GASTROINTESTINAL TRACT***

#### **3.1 Introduction**

Fibre is the portion of plant material present in food that is resistant to process of digestion by monogastrics. The influence of fibre on human and animal gastrointestinal function has been thoroughly investigated. Adding fibre to the diet affects the transit of food (Burkitt *et al*, 1972; Harvey *et al*, 1973; Payler *et al*, 1975; Wyman *et al*, 1976; Spiller, 1994; Bueno *et al*, 1981; Burrows *et al*, 1982; Jenkins and Jenkins, 1984; Tadesse, 1986; Kritchevsky, 1988; Reppas *et al*, 1991; Tomlin *et al*, 1993; Benini *et al*, 1995), nutrient absorption (Jenkins and Jenkins, 1984; Jenkins *et al*, 1986; Kritchevsky, 1988; Eastwood, 1992) and stool volume and consistency (Burkitt *et al*, 1972; Payler *et al*, 1975; Cummings *et al*, 1976; Wyman *et al*, 1976; Spiller *et al*, 1980; Burrows *et al*, 1982; Kritchevsky, 1988; Eastwood, 1992; Roberfroid, 1993).

#### **3.2 Classification of Fibres**

Fibres are usually grouped according to their solubility in the upper gastrointestinal tract or their fermentability. Insoluble fibres, such as lignin or cellulose, are found in bran and rye fibres whereas soluble fibres, such as pectin, guar gum and hemicellulose, are abundant in psyllium husks, oats, barley and some fruit and

vegetable matter (Dimski and Buffington, 1991; Stephen, 1994; Guilford, 1996).

These types of fibre differ in their effects on gastric emptying, nutrient absorption, intestinal motility, water absorbing capacity, stool consistency and weight (Cummings *et al*, 1976; Spiller *et al*, 1980; Burrows *et al*, 1982; Rainbird and Low, 1986; Tadesse, 1986; Roberfroid, 1993; Tomlin *et al*, 1993).

In general, the soluble, or “gel-forming”, fibres absorb water to form gels which increase the viscosity of the intestinal contents. The gel-forming fibres tend to affect the upper intestine by delaying gastric emptying and intestinal transit. They are usually poor bulking agents and are often highly fermented by colonic bacteria. Additional effects include slowing glucose absorption and changing the composition of the caeco-colonic microbial flora.

In contrast, as a general rule, insoluble fibres do not form gels or delay gastric emptying but exert most of their effects on lower gastrointestinal transit and on faecal bulk. They act as mild buffers of gastric contents, have minimal effects on nutrient absorption and are not fermented in the colon. Generally, non fermentable fibres are good bulk forming agents increasing faecal weight and diluting colonic contents. Due to the multitude of chemical compositions of the different types of fibre, overlap between the effects of soluble and insoluble fibre occur. For this reason, some authors prefer the terms gel-forming and non-gel-forming and fermentable or non-fermentable fibres to classify fibres (Guilford, 1996b). Contrasting responses to the same types of fibres have been reported in the literature presumably in part due to the use of fibres varying slightly in chemical structure (Tadesse, 1986).

### 3.3 Effects of Fibre on Gastric Emptying

In general, gel-forming fibres prolong gastric emptying whereas non-gel-forming fibres do not influence gastric emptying (Kritchevsky, 1988; Reppas *et al* 1991; Eastwood, 1992, Roberfroid, 1993; Tomlin *et al*, 1993). Gel-forming fibres delay gastric emptying by increasing the viscosity of the gastric contents (Russell and Bass, 1985a; Kritchevsky, 1988; Reppas *et al* 1991; Tomlin *et al*, 1993; Spiller, 1994; Cherbut, 1995). The gastric emptying time of liquids increases in a linear fashion with increasing viscosity (Reppas *et al*, 1991). In contrast, increasing viscosity can, under certain circumstances, result in faster emptying of large indigestible particles from the stomach. The increasing viscosity slows the sedimentation of particulate solids in the stomach, helping ensure the particles are carried from the stomach in the flow of chyme (see next chapter for a fuller explanation of this phenomenon) (Meyer *et al*, 1986).

Gastric and small intestinal contractile patterns are altered by the presence of viscous liquids (Bueno *et al*, 1981; Prove and Ehrlein, 1982; Cherbut, 1995) resulting in fewer mixing and propulsive movements. This may affect the absorption of nutrients (Jenkins *et al*, 1986; Reppas *et al* 1991; Eastwood, 1992). Gel-forming fibre is also thought to delay gastric emptying by delaying fat absorption in the small intestine (Benini *et al*, 1995). The presence of fat in the small intestine has been shown to delay gastric emptying in a dose dependant manner (Lin *et al*, 1990).

Non-gel-forming fibres are not soluble and therefore remain as discrete particles in the gut. Conflicting results on the effects of this type of fibre on gastric



emptying are found in the literature. Non-gel-forming fibres have been found to speed (Tadesse, 1986; Kritchevsky, 1988), slow (Bueno *et al*, 1981; McIntyre *et al*, 1997) or have no effect on the gastric emptying of solids (Rainbird and Low, 1986).

Conflicting results observed in studies examining the effects of fibre on gastric emptying may be due to differences in chemical structures of the fibres used in the various studies, differences in the processing of the fibres prior to use, or variations in the experimental designs (Tadesse, 1986; Spiller, 1991; Stephen, 1994).

### **3.4 Effects of Fibre on Small Intestinal Function**

Fibre affects the rate of small intestinal transit. The effects on the rate of transit, however, are not uniform and vary according to the level of the intestine and the fibre type (Cherbut, 1995). Gel-forming fibres generally delay intestinal transit primarily by increasing the viscosity of the intestinal content. This effect follows the laws of luminal hydrodynamics (Reppas *et al*, 1991). In addition, gel-forming fibres modestly slow the rate of nutrient absorption. This may be due to the fibre increasing the thickness of the unstirred water layer adjacent to the brush border of the enterocyte which is thought to inhibit diffusion (Jenkins and Jenkins, 1984; Jenkins *et al*, 1986; Eastwood, 1992). Viscous luminal contents are more resistant to the turbulence induced by intestinal contractions. As a result, viscous luminal contents mix less with digestive enzymes and fewer food particles come into contact with the intestinal epithelium (Jenkins *et al*, 1986; Eastwood, 1992).

Non-gel-forming fibres, in general, speed intestinal transit (Jenkins and Jenkins, 1984; Kritchevsky, 1988; Roberfroid, 1993; Spiller, 1994; McIntyre *et al*, 1997), although conflicting results have been reported (Bueno *et al*, 1981; Cherbut, 1995). It has been suggested that alteration in small intestinal function may be mediated by the edges of the particles directly stimulating mucosal receptors (Edwards and Read, 1990). It is noteworthy, that the particle size of the fibre can be important. For example, coarse bran decreases transit time and increases stool weight more so than fine bran (Payler *et al*, 1975; Kritchevsky, 1988; McIntyre *et al*, 1997). Bran has also been reported to “normalise” transit (ie, hasten slow transit and retard rapid transit) in the small and large intestine of dogs and humans (Harvey *et al*, 1973; Payler *et al*, 1975; Burrows *et al*, 1982).

A study by McIntyre *et al* (1997), demonstrated that not only coarse bran but also inert plastic particles significantly quicken small intestinal transit. This observation suggests the effect of coarse bran on small intestinal transit could be via mechanical stimulation of enteric sensory nerves and need not be related to the water holding capacity (see below) or chemical composition of the bran.

The effects of fibre on gastrointestinal motility were investigated by Bueno *et al* in 1981. Strain gauge transducers were inserted into the antrum, duodenum and jejunum of dogs and then meals containing different types of fibre (guar, bran or cellulose) were fed, either added to a canned food (control diet) or fed on their own diluted in water. It was found that all three fibres increased the duration of the fed motility pattern associated with gastric emptying and small intestinal transit. The guar exerted the longest effect, suggesting the slowest transit time.

The amplitude of contractions induced by the fibres in this study was decreased compared with the control diet, especially by the guar. In addition, the types of contractions were altered. The bran and cellulose induced an increase in the number of propagated contractions and fewer single contractions. In contrast, guar produced a continual series of low amplitude single contractions. When the fibres were fed diluted in water they were found to induce similar motility patterns to when the fibres were fed with food, but of shorter duration. These findings contrast to the study by Russel and Bass (1985) in which the fibre meals did not interrupt the interdigestive motility pattern. However, in the study by Bueno *et al*, much more concentrated solutions of fibre were used and it was postulated that it was purely the bulking effect of the fibre that stimulated the fed motility pattern.

### ***Summary***

In summary, the effect of fibre on upper gastrointestinal transit is mainly a function of the fibre's solubility. The solubility varies with the chemical composition of the fibre. Solubility influences the viscosity of the chyme which affects the hydrodynamics of the gastrointestinal contents and the amplitude and type of intestinal contractions. As a general rule, gel-forming fibres tend to slow orocolic transit and non-gel-forming fibres speed transit.

### 3.5 The Effect of Fibre on the Colon and Faeces

The non-gel-forming (non-fermentable) fibres usually speed colonic transit (Kritchevsky, 1988; Roberfroid, 1993; Gatti, 1995). They are good bulk forming agents, increasing faecal weight and diluting colonic contents. This is due to their resistance to digestion and their water holding capacity. Normal colonic motility requires sufficient residue present to stimulate colonic smooth muscle contractions. Increasing faecal weight speeds colonic transit time. However, a critical point is reached when there is no further influence of increasing faecal residue on transit time (Eastwood and Morris, 1992).

Fibre is the main dietary constituent that affects faecal weight. The principle way fibre affects faecal weight is by altering faecal water holding capacity. Faecal water holding capacity decreases with its fermentability, e.g., bran increases faecal weight substantially (Cummings *et al*, 1976; Devroede, 1978; Eastwood, 1992; Roberfroid, 1993; Spiller, 1994). The non-gel-forming fibres may also increase faecal weight by increasing the free water content of faeces. They do this by speeding colonic transit therefore reducing the time for water reabsorption. Fermentable fibres increase faecal weight to a lesser degree than non-fermentable fibres. Fermentable fibres increase faecal weight primarily by increasing the bacterial mass (see below).

The influence of faecal bulk on the colon has been demonstrated by Cherbut and Ruckebusch (1985) in a study in which they added indigestible particles to the diet of dogs and pigs. Both transit time and colonic motility were measured. It was found

that increasing the bulk of the colonic contents with indigestible particles reduced the transit time by 30% in the dogs and 28% in the pigs. Faecal dry matter output was also increased. This increase in the dry matter output was found to be more than the dry matter added as indigestible particles. As no fermentation was occurring, the authors felt this illustrated that particles were acting purely through their mechanical properties to influence faecal bulk and colonic transit.

Faecal weight and transit in humans is similarly affected by indigestible particles (Tomlin and Read, 1988). Bran causes acceleration of colonic transit to a proportionately greater degree than it increases faecal weight (Spiller, 1994). This suggests that faecal bulk has a direct effect on colonic motility.

Colonic motility was also measured in the study by Cherbut and Ruckebusch (1985) and surprisingly it was found to decrease. Others have also noted a decrease in colonic motility with increasing bulk of colonic contents (Burrows and Merritt, 1983). More specifically, this study found that long spike burst activity in the proximal colon was decreased while short and migrating spike burst activity was unchanged. It was therefore concluded that the individual or small groups of long spike burst activity noted in this study appeared to result in a braking action on the colonic contents. In addition, there was a slight increase in the distal colonic motility possibly corresponding to the increase in faecal output.

The effect of fermentable fibres on colonic motility and transit varies and is not predictable based on their solubility. Gel-forming fibre is rapidly fermented by colonic bacteria to produce short chain fatty acids (SCFA) in the proximal colon

(Eastwood and Morris, 1992; Roberfroid, 1993; Spiller *et al*, 1980). These are well absorbed by the proximal colon or are utilised by the colonic bacteria. Therefore, gel-forming fibre results in stools containing a higher proportion of bacteria (Kritchevsky, 1988). Different fibres produce varying amounts of the different SCFA acetate, propionate and butyrate (McIntyre *et al*, 1993). The SCFA provide nutrition to the colonic enterocytes (Eastwood, 1992), promoting their multiplication and resulting in an increase in colonic weight.

### ***Summary***

In summary, non-gel-forming fibres increase faecal weight due to their water holding capacity. Their bulking effect speeds colonic transit, increasing the free water content of the faeces. The bulking effect is associated with a decrease in motility in the proximal colon. Presumably the decreased motility results in more rapid transit by causing a preferential decrease in the “braking” mechanisms of the proximal colon such as anti-peristaltic or segmenting contractions. The gel-forming fibres are fermented to SCFA and have only modest effects on faecal weight and colonic transit.

## CHAPTER FOUR

### *THE GASTRIC EMPTYING OF SOLIDS*

#### *DIGESTIBLE SOLIDS*

##### **4.1 Introduction**

The gastric emptying of solids consists of two phases, the lag phase and the emptying phase (Camilleri *et al*, 1985; Collins *et al*, 1988; Houghton *et al*, 1988; Siegel *et al*, 1988; Collins *et al*, 1991). To achieve the task of emptying solids, the stomach has two functionally distinct areas, the proximal and distal stomachs. The former consists of the fundus and part of the body while the latter includes the distal body and the antrum (Kelly, 1980). During the lag phase, solids are ingested and stored in the proximal stomach until redistribution into the distal stomach.

Following transfer from the proximal to the distal stomach, the trituration of solids occurs. As a wave of peristalsis reaches the terminal antrum, the lumen of the pylorus is occluded preventing passage of large solid particles into the duodenum. These particles reflux in an oral direction through the narrow lumen of an advancing antral contraction. This process creates high pressure turbulent flow that grinds larger particles. Once reduced in size, the solid particles become small enough to pass through the pylorus into the duodenum along with the liquid chyme. Solid particles empty from the stomach at a steady rate during the emptying phase.

## 4.2 The Lag Phase

The proximal stomach stores solids while the liquid component of a meal empties (Camilleri *et al*, 1985; Collins *et al*, 1988; Houghton *et al*, 1988). This is referred to as the 'liquid emptying phase' or the solid 'lag phase'. Houghton *et al* (1988), found a close correlation between the lag period and the time taken for 80% of the liquid to be emptied from the stomach. During this time, most of the solid component of a meal was found to remain in the fundus (Houghton *et al*, 1988). This study demonstrated the importance of the liquid portion of the meal in determining the start of solid emptying. That is, the emptying of solids does not usually begin until most of the liquid portion of the meal has left the stomach. Therefore if liquid emptying is delayed, for example if a viscous liquid is ingested, the lag period will be increased and hence solid emptying will be delayed.

Others have confirmed that the emptying of the liquid portion of a meal influences the emptying of solids (Collins *et al*, 1988; Collins *et al*, 1991; Brown *et al*, 1993). A study by Brown *et al* (1993) using real time ultrasound in humans proposed a "sedimentation and decanting" theory. The theory proposes that the effect of gravity results in the settling of solids in the greater curvature, a dependent portion of the stomach, while the liquid portion is "decanted" through the pylorus. As the liquid empties from the stomach, the fundus gradually lifts to a less dependent position, moving the solid portion nearer to the antrum in readiness for the emptying of solids.

In both studies by Collins *et al* (1988 and 1991), photoscintigraphs were produced of gastric emptying in humans demonstrating the presence of a 'transverse ligament' or



band that physically held the solid in the fundus until near the end of the liquid emptying phase. This ligament or band is thought to be a physiological phenomenon as it is only apparent in stomachs distended with food (Moore *et al*, 1986). Other studies have supported this finding (Collins *et al*, 1988; Houghton *et al*, 1988). A similar structure has been identified in dogs, pigs and monkeys (Moore *et al*, 1986).

It is thought that the duration of the lag phase is also dependent on the time required to reduce the solid component of the meal into small particles which can pass through the pylorus (Camilleri *et al*, 1985; Siegel *et al*, 1988; Horowitz *et al*, 1994). Antral motility is inversely correlated to the duration of the lag phase (Camilleri *et al*, 1985; Collins *et al*, 1988). An increase in antral motility decreases the length of the lag phase (Camilleri *et al*, 1985). This suggests that increased trituration during the lag phase more quickly reduced the solid particles into a size small enough to pass through the pylorus. Additional factors influencing the length of the lag period were suggested by Siegel *et al*, 1988. These included the caloric content of the meal and the method used to measure gastric emptying.

### **4.3 The emptying Phase**

The stomach retains larger solids and allows smaller particles to pass through the pylorus (Malagelada, 1977; Meyer *et al*, 1979; Kelly, 1980; Meyer *et al*, 1981; Weiner *et al*, 1981; Becker and Kelly, 1983; Camilleri *et al*, 1985; Brown *et al*, 1993). Pieces of food undergo repeated antral propulsion, grinding and retropulsion that break down the large particles and thoroughly mix the gastric contents. This vigorous

motility results in sufficiently small solid particles becoming suspended in and emptying with the fluid chyme (Camilleri *et al*, 1985; Hall *et al*, 1988; Kelly, 1980; Quigley, 1996; Malagelada, 1977).

The emptying phase commences when the antrum reaches maximum diameter (ie. is filled maximally), following redistribution of the solid from the proximal stomach (Collins *et al*, 1988). Fundic tone is thought to prime the antral 'pump' by supplying the antrum with solid (Camilleri *et al*, 1985; Collins *et al*, 1991). Antral distention induces increased antral contractions initiating the trituration and emptying of the solid ingesta (Houghton *et al*, 1988). Close coordination of terminal antral and pyloric peristaltic contractions is important for the efficient trituration and sieving of chyme (Hinder and San-Garde, 1983; Hall *et al*, 1988; Haba and Sarna, 1993).

### ***Trituration***

The grinding action of the stomach is facilitated by the action of the pyloric musculature. The pyloric muscle is composed of two loops in dogs (Hinder and San-Garde, 1983; Hall *et al*, 1988). The proximal loop is derived from a slight thickening of the circular muscle layer. The distal loop forms a thick muscular protrusion resulting from fusion of the circular and longitudinal muscle layers along with the muscularis mucosae. The distal loop is responsible for most of the occlusion of the pylorus at the gastroduodenal junction. Gastric contents that arrive in the pyloric region during peristalsis are trapped between and orad of the pyloric loops and only liquids and solid particles smaller than 2 mm can pass through into the duodenum. Shearing and mixing forces are then applied to the gastric contents as they are

repelled into the terminal antrum which remains patent during a peristaltic contraction (Hall *et al*, 1988). Trituration of large solid particles into small ones has been demonstrated ultrasonographically (Brown *et al*, 1993).

The efficiency of the process of size discrimination by the stomach has been highlighted in a study by Meyer *et al*, 1979. This study compared the effects of antral grinding on 0.25 mm and 10 mm pieces of liver and showed that the canine stomach emptied most particles as a size less than one mm. A similar finding was reported in humans (Meyer *et al*, 1981; Holt *et al*, 1982). The 0.25 mm particles emptied more quickly than the 10 mm particles from the stomach. Interestingly, the 0.25mm particles were found to exit the stomach as discrete particles of 0.25 mm or less whereas most of the 10 mm particles left the stomach as solubilized liver. Others (Malagelada *et al*, 1977; Weiner *et al*, 1981) have also demonstrated this phenomenon.

Trituration is initiated by propagation of a contraction from the antrum to the pylorus (Haba and Sarna, 1993). The pylorus starts to contract about 2 seconds after the antrum. The antral and pyloric contractions lasts approximately 11 seconds. As a result, the pylorus and antrum contract together for about 7 seconds, due to the overlap between the onset and termination of the contraction in each area (Haba and Sarna, 1993). Haba and Sarna (1993) believe that the retropulsion of gastric contents back into the antrum and corpus occurs due to the sequential contraction of antrum and pylorus and the greater resistance to flow of the pylorus compared to the antrum. The pylorus has a greater resistance to flow because it has a smaller diameter and a greater contraction amplitude. Haba and Sarna (1993) also observed the gastric

emptying of solid contents to occur in the period just before retropulsion. Emptying occurs if the proximal duodenum is relaxed but not if it is contracting at the same time as the antral contraction. Gastric emptying is negatively correlated to non-propagated duodenal contractions (Haba and Sarna, 1993).

### *Control of Gastric Emptying*

Control of the gastric emptying rate of solids is complex. In a study by Haba and Sarna (1993), the frequency of gastric contractions and the percentage of these contractions that propagated at least 5 cm in the stomach were the only gastric contraction parameters found to correlate to gastric emptying. The propagated contractions are thought to be important because they are responsible for bringing solid food to the pylorus for emptying and they play a role in the trituration process. Interestingly, in this study amplitude and duration of contractions did not correlate with gastric emptying. Gastric emptying rate was also correlated to the number of contractions that propagated into the proximal duodenum from the corpus, antrum or pylorus. It was suggested that the antrum, pylorus and proximal duodenum were acting together as a “peristaltic pump” to regulate the gastric emptying of solids.

Haba and Sarna (1993) also observed that gastric emptying rate was directly proportional to the percentage of propagated contractions in the distal duodenum. It was postulated that rapid removal of chyme from the duodenum would increase gastric emptying by decreasing the inhibitory neurohormonal feedback from the duodenum to the stomach, and by the removal of the mechanical obstruction to gastric emptying created by the physical presence of chyme in the duodenum. Gastric

emptying rate also depends on caloric density of the meal (Hunt and Stubbs, 1975; Hunt *et al*, 1978; Hall *et al*, 1988) and is independent of meal size (Hunt and Stubbs, 1975; Meyer *et al*, 1988). Early gastric emptying is, however, influenced by meal size until feedback inhibition is established (Hunt *et al*, 1985).

### *The Role of the Pylorus in Gastric Emptying*

The exact role of the pylorus is controversial. It has been shown that performing pyloroplasty does not significantly affect the sieving mechanism of the antrum (Meyer *et al*, 1979; Hinder and San-Garde, 1983). It has also been shown that the pylorus is often patent during a terminal antral contraction (Prove and Ehrlein, 1982). This suggests that the pylorus is not important in preventing passage of large pieces of ingesta. However, combining pyloroplasty with distal vagotomy does result in an impairment of the gastric sieving mechanism, supporting the important role of the antrum (Meyer *et al*, 1979). Paradoxically, however, performing an antrectomy while preserving the pylorus also does not significantly affect the sieving mechanism of the distal stomach, whereas, removal of the entire distal stomach does (Hinder and San-Garde, 1983). This suggests that an intact antrum may take on the functions of an absent pylorus and vice versa. Presence of one or the other, however, appears to be important for normal sieving function.

The work of Haba and Sarna (1993) found the pylorus to be an important regulator and promoter of the gastric emptying of solids. The mean frequency, duration and amplitude of pyloric contractions correlated positively with gastric emptying. They found that the gastric emptying of solids increased with increasing numbers of

contractions which initiated in the antrum or pylorus and were propagated into the proximal duodenum. The consequences of removal of either the pylorus or antrum was not investigated, however.

#### **4.4 Summary**

The mechanism by which solids empty from the stomach is complex. The distal stomach has a primary role in the gastric emptying of solids. The proximal stomach, however, does influence the gastric emptying of solid food by storing and then redistributing it to the distal stomach. The distal stomach has been shown to be an efficient triturator of solid particles and a regulator of solid emptying. It does this via propagated antropyloric and antropyloroduodenal contractions. Gastric emptying of solids increases with increasing frequency and propagation of gastric contractions and with increasing propagated distal duodenal contractions. The presence of an intact antrum and/or pylorus is important for the trituration of solid particles.

## **INDIGESTIBLE SOLIDS**

### **4.5 Introduction**

The gastric emptying of indigestible solid particles has been studied for a number of years. The particles have been found to behave in different ways depending on their physical properties and the properties of the meal in which they are dispersed. In some situations they may mix with, become suspended in and empty with the food in the stomach. In other situations, they remain in the stomach until the end of the emptying of the triturable solids and are removed from the stomach by the migrating motility complex.

A number of factors that influence the gastric emptying rate of different types of indigestible particles have been identified. These factors include the presence or absence of food in the stomach, the size and density of the indigestible particle, and the viscosity and flow velocity of the gastric chyme in which the particles are suspended. The shape and the surface area of the indigestible particles appear not to affect their gastric emptying (Meyer *et al*, 1985). It has been reported that soft particles empty more quickly than hard particles (Meyer *et al*, 1989). However, in this study the softer particles were also less dense which may have played a role in their faster gastric emptying.

#### **4.6 Emptying of indigestible particles from an empty stomach**

Administration of indigestible particles to a fasting animal will almost always result in the particles being driven into the duodenum by the strong contractions of the migrating motility complex at a rate irrespective of their size or density (Gruber *et al*, 1987). An exception to this general rule has been reported in the literature. In a study by Russell and Bass (1985b) 1-3 mm particles of fibre were administered to fasting dogs and were found to induce a motility pattern characteristic of the fed state. The fibre used was polycarbophil which readily absorbs water but which is also pliable and easily moulded into a bolus. This bolus is readily redispersed when mixed with water again. A relatively large amount of fibre was used. The authors proposed that the fibre was mixing with gastric secretions and behaving like a digestible solid in the stomach. The small size of the particles would allow emptying through the pylorus during the fed state motility pattern. Not surprisingly, very large, inflexible objects (size 2-12 cm) are usually retained by the canine stomach, even following the action of the MMC (Cargill *et al*, 1988).

#### **4.7 Influence of Particle Size on the Gastric Emptying of Indigestible Solid Particles**

Large indigestible solid particles are usually retained in the stomach until the onset of the MMC. As a result, large diameter radiopaque markers have been found useful to determine when the stomach has emptied of food (Feldman *et al*, 1984; Smith and Feldman, 1986), and to identify the end of the fed motility pattern and the onset of the



migrating motility complex (Hinder and Kelly, 1977; Kelly, 1980; Feldman *et al*, 1984; Mojaverian *et al*, 1985; Smith and Feldman, 1986; Gruber *et al*, 1987). The gastric residence time of these large particles is a function of meal size, meal frequency and dietary energy content (Davis *et al*, 1984a; Davis *et al*, 1984b; Mojaverian *et al*, 1985). In these studies the radiopaque markers were at least 7 mm in diameter. Particles of this size or above are retained by the sieving mechanisms of the distal stomach that operate during the fed motility pattern. Large radiopaque markers, such as these, also have been found to be a useful method to detect delayed gastric emptying in human diabetics (Feldman *et al*, 1984).

Smaller indigestible particles have been found to empty from the stomach before the onset of the fasting motility pattern (Russell and Bass, 1985b; Itoh *et al*, 1986; Meyer *et al*, 1986; Meyer *et al*, 1988; Sirois *et al*, 1990; Brogna *et al*, 1992). A study using indigestible spheres of varying sizes demonstrated that gastric emptying time increased in proportion to the size of the sphere, provided the density of the spheres remained constant (Meyer *et al*, 1985). In this study the spheres were fed along with liver and it was noted that the smallest diameter spheres (0.015mm and 1.1 mm) began emptying before the liver and at similar rates to each other. The 1.6 mm spheres emptied in a similar fashion to the liver and the larger 2.4 mm, 3.2 mm and 5 mm spheres took progressively longer to empty. This study, therefore, revealed that between certain critical diameters (1.1 and 5mm), the gastric emptying of an indigestible particle is influenced by its size.

In a similar study in dogs, markers greater than 5 mm were found to be retained in the stomach until the end of the fed motility pattern and the onset of the MMC (Itoh *et al*,

1986). In humans, the size of sphere that was found to empty along with liver was 1.4 mm +/-0.3 mm (Meyer *et al*, 1988). Another study in humans, however, reported that radiopaque markers made of tubing 2 mm by 5 mm also were found to empty along with a concurrently ingested meal (Brognia *et al*, 1992). The density of the tubing was not reported in this study, however.

Size is therefore important in influencing the gastric emptying of indigestible particles. In certain situations, when particle size is between 1 and 5 mm, gastric emptying time increases with size. However, as discussed below, the critical size above which the gastric emptying of a particle is delayed until the onset of the MMC will vary according to particle density (Sirois *et al*, 1990).

#### **4.8 Influence of Particle Density on Gastric Emptying of Indigestible Solid Particles**

In the study mentioned above (Meyer *et al*, 1985), the gastric emptying rate of the spheres increased as the sphere size decreased. However, when spheres of the same size but different densities were compared, it was found that spheres of a similar density to liver emptied faster than spheres of a greater or lesser density. In this case, the 2.4 mm spheres of density 1.0 gcm<sup>-3</sup> (close to that of the liver) emptied faster than the spheres of density <0.6 gcm<sup>-3</sup> and 2.0 gcm<sup>-3</sup>. These observations collectively suggest that factors affecting the buoyancy of particles in chyme are important in determining how particles empty from the stomach. These concepts have been confirmed by Sirois *et al* (1990), who demonstrated that the combination of size and

density of the indigestible particles is important in determining their gastric emptying rate (see below).

Visual confirmation of the phenomenon was achieved with the aid of gamma camera images (Meyer *et al*, 1988). These showed that the larger or more dense particles occupied the dependent portion of the greater curvature for longer periods of time compared with the smaller and less dense ones which were dispersed throughout the antral region. The settling of solid particles in the dependent part of the stomach has also been demonstrated ultrasonographically by Brown *et al* (1993) (see previous section on the gastric emptying of a mixed liquid - solid meal).

In contrast, studies by Davis *et al* (1984) and Bechgaard *et al* (1985) found the gastric emptying of pellets of density  $0.94\text{gcm}^{-3}$  and  $1.96\text{gcm}^{-3}$  to be the same. However, the size of the pellets was small, 0.7 – 1 mm, and the meals consumed along with the pellets were not uniform. These results may reflect differences in the meals consumed. More likely, however, they indicate that for particles of 1 mm diameter or less, particle density is a less important determinant of the rate of gastric emptying than it is for particles of larger diameter.

#### **4.9 Influence of Gastric Chyme on Gastric Emptying of Indigestible Particles**

The buoyancy of particles in chyme is dependent not just on the density and size of the particles but also on the properties of the chyme. The density of the chyme relative to the particles and the viscosity of the chyme has an important influence on the

buoyancy of particles mixed in it. The effects of chyme viscosity on the gastric emptying of spheres was investigated by Meyer *et al* (1986). The gastric emptying of dense spheres fed with saline and liver was compared to the gastric emptying of the same spheres fed with guar, a viscous liquid, and liver. When the saline was exchanged for guar, the dense spheres were found to empty more quickly than when they were mixed with saline and liver. In fact, in the guar mixture, many of the spheres left the stomach before the liver, whereas they followed the liver in the presence of the saline. It was suggested that in the presence of guar the spheres were adhering to the laws of hydrodynamics. The spheres took longer to sediment out in the guar and so passed out through the pylorus with the fluid, as opposed to being retained to empty with, or behind, the liver.

The velocity of fluid outflow from the stomach has been proposed as another influence on indigestible particle emptying (Amidon, 1985; Meyer *et al*, 1986). This variable was also investigated in Meyer's study, mentioned above. This was achieved by instilling different volumes of fluid into dogs' stomachs. Two hundred or 800 ml of fluid (saline or guar) was administered along with the spheres and liver to create different rates of fluid outflow from the dogs' stomachs. The results suggested the gastric emptying rate of the spheres was influenced by the outflow velocity of the fluid but the difference was not statistically significant.

The inter-relationship between the factors that are known to influence the gastric emptying of indigestible solids has been determined by Sirois *et al* (1990). This study illustrated that in certain situations neither the particle size, particle density nor the viscosity of the chyme alone dictate the rate of gastric emptying of indigestible

particles. However, in combination, these factors are instrumental in determining the gastric emptying rate of indigestible particles. For example, if the size of the particle is so large that it will not empty from the stomach during the fed motility pattern then its density or the viscosity of the chyme will be irrelevant. If the particles are less than 1 mm, they will all empty equally well, regardless of density (Bechgaard *et al*, 1985). Likewise, if the particles are so dense or light that they will constantly tend to sink or float in the chyme, having an optimal size will not speed gastric emptying. Therefore, if the particles are of optimum size (1.6 mm) and density (similar to that of food) they should empty from the stomach at a similar rate to that of the food ingested.

#### **4.10 The Hydrodynamic Theory of Gastric Emptying**

Hydrodynamics is the science concerned with the mechanical properties of fluid. It can therefore be applied to the gastric emptying of liquid material. If it is assumed that particle emptying is aided by concurrent fluid emptying, hydrodynamics can also be applied to solid particle emptying. For example, during the gastric emptying of a mixed solid – liquid meal, if a solid particle is present in the antrum, it is likely to become suspended in the liquid chyme and empty from the stomach. In contrast, a solid particle that has settled out in the fundus will tend to remain there instead of being carried along by the movement of the emptying chyme.

Size and density of a solid particle will influence the ability of a particle to be in an optimal location for emptying. Nutrient content and viscosity of the fluid in the stomach are also important because these factors affect the gastric emptying rate of liquids and the buoyancy of particles (Sirois *et al*, 1990). From this it can be seen that

a small particle of similar density to the chyme will empty at a similar rate to chyme. In contrast, progressively larger particles will empty at slower rates to the chyme and this effect will be enhanced if particle density differs markedly from that of the chyme.

The hydrodynamic theory of gastric emptying assumes that the antrum and pylorus are the primary regions of the stomach involved in the emptying of solids. It also assumes that the flow of fluid and suspended particles through this region occurs as it does through a pipe. When flow is laminar, the fluid does not travel through the pipe at uniform velocity. The velocity depends on the radial position of the fluid, (ie. its position with respect to the centre of the pipe). The fluid near the walls of the pipe will, therefore, travel at a slower velocity than fluid at the centre of the pipe due to pipe wall friction. If viewed in cross section, the fluid produces a parabolic velocity profile (Wilkinson, 1960) which is represented by the equation:

$$V_r = 2v_{av}(1 - [r/R]^2) \quad (1)$$

where  $V_r$  is the fluid velocity at a given distance  $r$  from the pipe axis;  $v_{av}$  is the average linear fluid velocity and  $R$  is the pipe radius.

If a particle moving in the fluid is considered, then its velocity within the pipe will depend on its buoyancy. If it is neutrally buoyant, it will travel along the centre of the pipe at maximum velocity. However, if it tends to sink or float in the fluid it will tend to travel closer to the pipe wall at a slower velocity. The buoyancy of a particle is determined by its sedimentation velocity that is described by Stokes' law

$$V_t = g(\rho_f - \rho_p)D_p^2/\eta \quad (2)$$

where  $V_t$  is the sedimentation velocity;  $g$  is the gravitational constant,  $9.8\text{m/s}^2$ ,

$\rho_f$  and  $\rho_p$  are the fluid density and particle densities respectively;

$D_p$  is the particle diameter and  $\eta$  is the viscosity of the fluid

It can be seen that the above formula incorporates the equation for buoyancy  $g(\rho_f - \rho_p)$ . Therefore, the horizontal velocity (or the velocity in the direction of fluid flow) of a particle with respect to its vertical velocity (sedimentation velocity) depends on its radial position (or its proximity to the pipe wall). This is dictated by the buoyancy of the particle that in turn dictates its velocity relative to that of the fluid. Therefore, if a particle tends to sink or float in a fluid, the velocity of the particle will tend to be slower relative to the velocity of the fluid. The distance a particle will flow through the pipe is a function of the ratio of  $V_t$  to  $v_{av}$ . This means that a particle in the stomach with a smaller ratio of vertical to horizontal velocities would tend to pass out through the pylorus more quickly than a particle with a larger ratio.

This ratio dictates the particle emptying coefficient (PEC).

$$PEC = [g(\rho_f - \rho_p)D_p^2/\eta] v_{av} \quad (3)$$

It can be seen that different combinations of particle size, particle density and fluid density, viscosity and velocity will give similar PEC ratios. The ability of the PEC ratios to determine how quickly particles will exit from the stomach illustrates the importance of hydrodynamics in indigestible particle emptying. However, the above formula applies to laminar flow through a pipe. The stomach is not a rigid tube. As the stomach contracts and relaxes, its diameter changes which likely results in unsteady flow and alters particle proximity to the wall. In addition, particle sedimentation is impaired when the ratio of pipe to particle diameter falls below a critical value. Sirois *et al* (1990) partly accounted for these “wall factors” by modifying the equation (3) above with the ratio of average estimated pyloric diameter,  $D_{py}$  to particle diameter,  $D_p$  creating the gastric emptying coefficient (GEC)

$$GEC = (D_{py} / D_p) [g(\rho_f - \rho_p)D_p^2]/[\eta v_{av}] \quad (4)$$

This formula illustrates that particle size and density, and fluid viscosity and velocity combine with “wall factors” to determine the gastric emptying of particles from the stomach. A limitation to this theory is that values for pyloric diameter and contraction strength had to be estimated for the GEC formula. Therefore, the ability of the GEC to predict particle emptying will vary between individuals. However, in general, the gastric emptying of indigestible particles can be predicted, in part, by hydrodynamics.



#### **4.11 Other Possible Factors Influencing Indigestible Particle Emptying**

The hydrodynamic theory of gastric emptying does not completely explain the mechanisms involved in the emptying of particulate material from the stomach. This is because the previously described “wall factors” may vary between different diets. Variable contraction strengths and frequencies are induced by different nutrients, as described earlier in the Chapter. The contribution such “wall factors” may make to the gastric emptying of indigestible particles is investigated in Chapter Seven.

## **CHAPTER FIVE**

### ***GASTROINTESTINAL MOTILITY DISEASES AND THEIR DIAGNOSIS***

#### ***DISEASES AFFECTING INTESTINAL MOTILITY***

##### **5.1 Introduction**

A variety of diseases affect the motility of the gastrointestinal tract. The signs associated with dysmotility of the intestine can include vomiting, diarrhoea, constipation, altered frequency of defaecation, anorexia, abdominal pain, weight loss and/or dehydration (Malagelada and Stanghellini, 1985; Von Der Ohe, 1992; Guilford, 1996a). Similar clinical signs can be caused by a number of different diseases making diagnosis of motility disorders difficult.

Diseases affecting gastrointestinal transit can be physical or functional. Physical disruptions to gastrointestinal transit result from narrowing of the intestinal lumen which increases resistance to the flow of intestinal contents or results in complete obstruction of the bowel. They can result from a variety of causes including intraluminal foreign bodies, intramural masses (such as, neoplasia, granulomas, haematomas and strictures) and extramural compression from adhesions, hernias and intussusceptions (Guilford and Strombeck, 1996b).

Functional motility diseases occur due to disruption of the control mechanisms of gastrointestinal motility and can result in faster or slower gastrointestinal transit.

Functional obstructions occur when gastrointestinal motility is markedly depressed resulting in decreased propulsion of intestinal contents. Functional motility disorders can be primary or secondary.

Primary gastrointestinal dysmotilities result from disruption of any of the factors involved in the control of gastrointestinal motility. As described previously, the control of motility is complex, involving interaction between intrinsic and extrinsic nervous systems, intestinal smooth muscle and hormones. Dysfunction of the enteric nervous system is one of the more common causes of primary dysmotility. Diseases such as myenteric ganglionitis and degenerative diseases of the enteric ganglia are amongst those reported to cause intestinal dysmotilities in dogs and cats (Guilford, 1990). A variety of autoimmune conditions affecting enteric nerve and muscle have been identified in humans and result in defective propulsive activity, sphincter spasticity and loss of cyclical fasting activity (Milla, 1999). It has also been proposed that functional gastrointestinal motility disorders may be brought about by an alteration in the sensory pathways of the intestinal wall. For example, an increase in the discharge of the visceral sensory afferents in the presence of normal intestinal distension could result in an increase in the reflex propulsive responses and a sensation of discomfort (Gwee and Read, 1994).

Secondary gastrointestinal motility disorders of varying severity can result from virtually any disease of the gastrointestinal tract (Gwee and Read, 1994). For example, dysmotilities can result from diseases that primarily affect absorption or

secretion in the gastrointestinal tract. Distension of the intestines due to hypersecretion or malabsorption induces propulsive small intestinal activity and the presence of unabsorbed fat and bile acids in the colon can induce colonic propulsion (Gwee and Read, 1994). Inflammatory diseases of the gastrointestinal tract, such as food hypersensitivity and inflammatory bowel disease, can result in motility derangements (Vermillion, 1987; Milla, 1999). The dysmotility appears to be mediated by the enteric nervous system (Guilford, 1990). Emotional states can affect gastrointestinal motility of humans (Milla, 1999). Fear and depression have been shown to delay gastric emptying whereas anger and aggression have been shown to enhance motor activity (Cann *et al*, 1983; Ewart and Wingate, 1983).

Motility disorders impair propulsion of gastrointestinal contents or, conversely, result in unrestrained propulsion causing gastric dumping or rapid transit of food. Overly rapid transit compromises digestion and absorption of food (Gwee and Read, 1994), whereas impaired gastrointestinal motility results in gastric stasis or bacterial overgrowth (Husebye, 1995). Both impaired and overly rapid gastrointestinal transit can lead to vomiting and diarrhoea.

## **5.2 Gastric Motility Disorders**

Disorders of gastric motility can be categorised into delayed transit caused by obstruction, delayed transit caused by defective propulsion and disorders causing accelerated transit (Hall *et al*, 1990). Obstructive disorders can be further divided into intrinsic pyloric lesions (eg, antral pylorohypertrophy syndrome and pyloric

neoplasia), obstructive pyloric lesions (eg, foreign bodies and antral polyps) and extra-gastric lesions (eg, hepatic or pancreatic abscesses, compression from adjacent intra-abdominal tumours) (Hall *et al*, 1990). Antral pylorohypertrophy syndrome is a cause of gastric outflow obstruction commonly seen in male, young to middle-aged, brachycephalic or small breeds of dog (Hall and Washabau, 1999). It is rarely seen in the cat. Primary gastric neoplasia is a not uncommon cause of gastric outflow obstruction. Adenocarcinoma and lymphoma are the most common malignant gastric neoplasms in the dog and cat, respectively (Hall and Washabau, 1999).

Less commonly, delayed gastric emptying is documented in the absence of any detectable organic disease. These functional disorders of gastric emptying occur due to abnormalities in myenteric neuronal or gastric smooth muscle function, or due to abnormalities in antralpyloroduodenal coordination (Hall and Washabau, 1999). The latter abnormality is usually due to gastric dysrhythmias. The lack of coordination between antral, pyloric and duodenal contractions reduces the antropyloroduodenal pressure gradient and has been proposed as the cause of delayed gastric emptying in these cases (Guilford and Strombeck, 1996a). It seems probable that dogs previously diagnosed with “pylorospasm” on the basis of delayed gastric emptying in the presence of a normal pyloric outflow tract and normal antral contractions were suffering from a gastric dysrhythmia (Guilford, 1990).

Gastric dysrhythmias result from an abnormality of gastric electrical rhythm, (Kim *et al*, 1987; Koch and Stern, 1996) affecting the spread of slow waves over the stomach. Bradygastria is thought to occur due to a dysfunction of the gastric pacemaker resulting in a decrease in the frequency of slow waves and therefore a decrease in

antral contraction frequency. Tachygastria is defined as abnormally fast slow wave rhythm with cycles occurring at more than five per minute in humans (Minami and McCallum, 1984). Tachygastria results from ectopic gastric pacemakers (Kim *et al*, 1987). It results in delayed gastric emptying because slow waves are propagated in an oral direction from an ectopic antral pacemaker producing weak or absent gastric contractions. Occasionally, a highly irregular gastric rhythm is observed. This is termed gastric arrhythmia (Guilford, 1990).

Gastric dysrhythmias can, however, be present in normal fasting dogs, or they can be spontaneous or induced by drugs eg. anticholinergics (Hall *et al*, 1990; Qian *et al*, 1999), hormones eg. glucagon, oestrogen, progesterone (Koch and Stern, 1996) and local prostaglandins (Kim *et al*, 1987). They have been observed in dogs recovering from gastric dilatation-volvulus (GDV) (Burrows, 1997) resulting in delayed gastric emptying (Hall and Washabau, 1999). It is not known whether the delayed gastric emptying is the cause of the GDV or if the delayed gastric emptying is occurring secondary to ischaemia-reperfusion injury of the stomach.

Gastric motility disorders can also occur due to infiltrative or inflammatory diseases of the stomach. These result in defective gastric propulsion by impairing the ability of the stomach to relax, distend or contract properly (Burrows, 1997). They can also cause pyloric outflow obstruction. Examples include chronic hypertrophic gastritis and severe eosinophilic gastritis (Hall and Washabau, 1999). Gastric ulcers and radiation gastritis can also result in delayed gastric emptying (Hall and Washabau, 1999).

Gastric motility disorders can occur secondary to systemic conditions. These include: acute stress, trauma, pain, pancreatitis, peritonitis, electrolyte imbalances (eg, hypokalaemia), metabolic disorders (eg, acidosis, hypothyroidism, hyperadrenocorticism, diabetes mellitus, hypergastrinaemia, uremia etc), brain tumours, abdominal surgery or irradiation, starvation and drugs (Rock *et al*, 1981, Hall *et al*, 1990 and Hall and Washabau, 1999).

### ***Gastric Motility Disorders Resulting in Accelerated Emptying***

Gastric motility disorders can also be associated with accelerated transit (gastric dumping). These disorders are less common. In dogs and cats, gastric dumping most often follows gastric surgery (Hall *et al*, 1990). The disorder is usually subclinical or it results in maldigestion and osmotic diarrhoea (Guilford and Strombeck, 1996a). Humans with gastric dumping often have symptoms of abdominal pain, nausea, vomiting, diarrhoea and weakness shortly after eating. The pathophysiology of gastric dumping in humans was thought to involve a drop in plasma volume secondary to the osmotic draw of large volumes of fluid into the intestine by the 'dumped' food (Ralphs *et al*, 1978). It is now, however, been shown that these symptoms are associated with a brief early period of upper intestinal hypermotility combined with tachycardia and peripheral vasodilation (Snook, *et al*, 1989).

Rapid gastric emptying in humans has been associated with duodenal ulcers, gastrinoma and hyperthyroidism (Rock *et al*, 1981). A case of rapid gastric emptying and intestinal transit has been documented in a dog with myenteric ganglionitis (Willard *et al*, 1988) and cats with hyperthyroidism have been shown to have a

shortened orocolic transit time (Papasouliotis *et al*, 1993). As mentioned previously, chronic mucosal disease of the small intestine could theoretically hasten gastric emptying by impairing the enterogastric reflex which is involved in the control of gastric emptying (Guilford and Strombeck, 1996a). Gastric emptying could also theoretically be accelerated in exocrine pancreatic insufficiency because maldigestion of fats would result in less fatty acids in the upper small intestine. Fatty acids are more potent inhibitors of gastric emptying than triglycerides (Hall *et al*, 1990).

### ***Gastric Motility Disorders Resulting in Retrograde Transit***

These disorders include vomiting, as the most extreme form of retrograde transit, gastroesophageal reflux, duodenogastric reflux and bilious vomiting syndrome (Hall and Washabau, 1999). Duodenogastric reflux can be a normal physiological occurrence and bilious vomiting syndrome is an idiopathic disorder in which duodenogastric reflux occurs following a fast. The usual clinical presentation is dogs that vomit bile in the morning following an overnight fast.

### **5.3 Intestinal Motility Disorders**

There are a number of functional motility diseases that affect the small bowel, most of which result in a reduction in gastrointestinal motility.



### ***Adynamic Ileus***

Adynamic ileus is a condition resulting in a transient and reversible lack of motility to the stomach and small and large intestine. It often results in a complete functional obstruction of the gastrointestinal tract. Adynamic ileus can occur due to a variety of reasons (Guilford and Strombeck, 1996b). These include handling of the intestines during abdominal surgery, peritonitis, unrelieved mechanical obstructions, intestinal ischaemia, electrolyte imbalances and sepsis. Adynamic ileus also is a common complication following parvoviral enteritis and acute pancreatitis (Guilford and Strombeck, 1996b). Adynamic ileus must be differentiated from anatomical bowel obstructions that require surgical rather than medical management.

The pathogenesis of adynamic ileus involves interaction between humoral, neural and metabolic factors to cause inhibition of peristalsis (Livingstone and Pessaro, 1990; Wood, 1987). Spike bursts and contractile activity in the circular muscle layer do not occur in response to the normal slow wave activity in the longitudinal muscle layer. The inhibition of spike burst activity is possibly due to membrane hyperpolarisation (Livingstone and Pessaro, 1990). In addition, there is an increased discharge of tonic inhibitory neurons, possibly associated with increased sympathetic tone (Livingstone and Pessaro, 1990; Wood, 1987). However, adrenalectomy does not prevent the development of adynamic ileus (Livingstone and Pessaro, 1990) and nor do  $\alpha$ - and  $\beta$ -adrenergic blocking drugs given postoperatively (Wood, 1987). Hypokalaemia resulting from vomiting may also contribute to the pathogenesis of some patients with adynamic ileus (Guilford and Strombeck, 1996b).

### ***Irritable Bowel Syndrome***

Irritable bowel syndrome (IBS) is the most common gastrointestinal motility disease of humans but a relatively rare disease of dogs and cats (Guilford, 1997). The cause of this functional bowel disease is unknown but several pathogeneses have been proposed. These include altered sensory perception of normal intestinal physiology and exaggerated enteric responses to various normal stimuli situated both internal and external to the gut (Mayer and Gebhart, 1994; Accarino *et al*, 1995; Maxwell *et al*, 1997).

Most sensory information from the gut is part of the reflex activity of digestion and does not reach conscious perception. The visceral-afferent pathways and the corresponding efferent pathways are constantly being modulated by the central nervous system. Evidence suggests that long term changes in the thresholds and modulation of the visceral-afferent pathways occurs in IBS. This is called visceral hyperalgesia (Mayer and Gebhart, 1994). Hypersensitivity of intestinal mechanoreceptors in response to balloon dilation of the jejunum has been documented in humans with irritable bowel syndrome (Accarino *et al*, 1995).

Various myoelectric and motility abnormalities have been reported in people with IBS (Maxwell *et al*, 1997). It has been shown that the interval between migrating motor complexes (MMC) is shorter in IBS patients than in controls and that this difference is absent during sleep (Kellow *et al*, 1990). Discrete clustered contractions in the small bowel during phase II of the MMC have been noted to occur more frequently in IBS patients than in controls (Kellow *et al*, 1990). These are thought to

represent an exaggerated response of the bowel to certain normal stressors in patients with IBS.

Motility abnormalities differ depending on whether constipation or diarrhoea is the predominant symptom of IBS. One study showed that patients with IBS demonstrated an abnormal propagation pattern of individual pressure waves in the duodenum and hypermotility in the upper gut (Simren *et al*, 1999). These motility abnormalities were found to be less pronounced in the constipation predominant IBS sufferers compared with the diarrhoea predominant patients (Simren *et al*, 1999).

Stress may play a role in triggering IBS, as may food hypersensitivities. In addition, a recent study has found that non-psychiatric IBS patients have a hyperreactivity to auditory stimuli. As it is known that the later elements of stimulus processing are influenced by emotions and personality traits, the authors proposed that the abnormal perception of visceral stimuli could be due to the brain hyperreactivity (Blomhoff *et al*, 1999). This would suggest that IBS could be a gastrointestinal expression of brain dysfunction.

### ***Intestinal Pseudo-Obstruction***

Intestinal pseudo-obstruction is a syndrome in which the clinical and radiographic signs are suggestive of a physical obstruction but no physical blockage of the intestines is identified at a subsequent exploratory laparotomy. Intestinal pseudo-obstruction syndrome can result from any disorders affecting the control mechanisms of gastrointestinal motility, such as enteric smooth muscle or the myenteric plexus

(Schuffler, 1981). Pseudo-obstruction in humans can occur secondary to diseases such as progressive systemic sclerosis and amyloidosis, or it can be idiopathic (Schuffler, 1981; Quigley, 1996).

Pseudo-obstruction can involve all or parts of the gastrointestinal tract, including oesophagus, stomach and colon. In humans, all patients generally have mild to severe distention of their duodenum. Distention of the bowel occurs because the enteric smooth muscle cannot contract to maintain tone because of abnormalities of the smooth muscle or enteric nervous system. Most reported human cases are due to familial or spontaneous myopathies or neuropathies (Schuffler, 1981). Two additional cases have been reported in humans describing progressive fibrosis of the intestinal wall, one following radiotherapy and another due to a form of scleroderma (Daum *et al*, 1989).

This condition is rare in the dog and cat. It has been reported in a dog found to have a dilated segment of jejunum associated with hypoplasia of the tunica muscularis without fibrosis, inflammation or myenteric plexus involvement (Arrick and Kleine, 1978). Pseudo-obstruction has been reported in dogs in association with sclerosing enteropathy (Moore and Carpenter, 1984; Swayne *et al*, 1986) and as a result of a congenital neuronal defect of the small intestinal myenteric plexi (Aroch *et al*, 1997).

### ***Dysautonomia***

Dysautonomia is a rare condition of the autonomic nervous system of cats, dogs and horses (Sharp, 1990; Schulze *et al*, 1997). Dysautonomia has occurred in pockets of disease throughout the world. An outbreak of the disease occurred in cats in the UK from 1982-1986 and small numbers of cases were reported in Scandinavia, parts of Europe, New Zealand and the United States (Longshore *et al*, 1996).

Younger animals are predominantly affected. The clinical signs include mydriasis, dry mucous membranes, bradycardia, regurgitation, vomiting, constipation and dysuria (Sharp, 1990; Wise and Lappin, 1990). Megaoesophagus is present in cats and delayed gastric emptying is present in both cats and dogs. Diarrhoea is more common in dogs with the disease than in cats (Wise and Lappin, 1990).

The cause is as yet unknown and extensive work has attempted to isolate an infectious or toxic agent without success. One report of a cluster of cases occurring in a closed colony of cats appears to have ruled out a dietary toxin as being the cause (Symonds *et al*, 1995). The selective chromatolytic degeneration of the sympathetic, parasympathetic and enteric nervous systems that occurs is unique to this condition (Sharp, 1990; Wise and Lappin, 1990).

## ***Megacolon***

Megacolon refers to colonic dilation and can be acquired or congenital in dogs and cats. Megacolon is more common in the cat, affecting predominantly middle aged males. Constipation or megacolon results in decreased frequency of defaecation, with occasional loss of appetite and vomiting due to overdistension of the colon and impaired colonic motility (Guilford, 1996a). Constipation is usually an early manifestation of megacolon and some animals may have episodes of constipation without progression to megacolon (Washabau and Holt, 1999). Animals with megacolon have permanent loss of colonic structure and function (Hasler and Washabau, 1997).

Acquired megacolon can be caused by a number of conditions including: chronic constipation, pelvic fractures, pelvic masses, strictures, foreign bodies, neoplasia, tail pull neuropathy and intestinal pseudo-obstruction (Guilford, 1996a). Idiopathic megacolon is common in cats and accounts for the majority of cases of feline megacolon. The pathogenesis of idiopathic megacolon remains to be fully elucidated but it appears to be associated with a generalised dysfunction of colonic smooth muscle (Washabau and Holt, 1999). Neurogenic megacolon, resulting from spinal cord or pelvic nerve injury, accounts for a small number of cases of megacolon and feline dysautonomia accounts for even fewer (Washabau and Holt, 1999).

Congenital megacolon is usually due to a congenital absence of myenteric and submucosal plexi in the caudal part of the colon (Guilford, 1996a), similar to

Hirschsprung's disease in humans. It may also be due to congenital sacral spinal cord deformity in the Manx cat (Washabau and Holt, 1999).

## **DIAGNOSIS OF MOTILITY DISEASE**

### **5.4 Introduction**

There are a wide variety of techniques currently employed to evaluate gastrointestinal motility. The methods differ in the parameters of gastrointestinal motility they assess. They expose the patient to differing amounts of radiation and vary in their invasiveness. Techniques that have been used in clinical settings include plain and contrast radiography, radiopaque markers, scintigraphy, magnetic resonance imaging, ultrasonography, manometry and a variety of less commonly used techniques.

### **5.5 Plain and Contrast Radiography**

Plain and contrast radiography has been used for many years to assess gastrointestinal motility (Kleine, 1979; Miyabayashi and Morgan, 1984; Armbjerg, 1992; Steyn and Twedt, 1994), in particular gastric emptying. Plain radiographs are suggestive of a gastric motility abnormality when a distended or abnormal shaped stomach is evident or the pylorus is distended, fluid filled or in an abnormal position (Kleine, 1979).

Assessment of gastric emptying rate by using plain radiography to subjectively observe the progressive reduction in stomach diameter has been described (Armbjerg, 1992). In this study, the stomach was considered to be empty when only air was present in the gastric lumen.

Mixing a barium suspension with food to evaluate gastric emptying rate has been attempted (Miyabayashi and Morgan, 1984; Steyn and Twedt, 1994). Unfortunately,



however, the barium suspension separates from the food (Miyabayashi and Morgan, 1984) and leaves the stomach predominantly in the liquid phase of the meal prior to the emptying of the solid food. Although useful for the assessment of mucosal abnormalities, such as gastric ulcers, tumours and foreign bodies (Kleine, 1979), barium is a liquid and therefore primarily gives information on the transit of liquids in the gastrointestinal tract. As previously described, the physiology of the gastrointestinal transit of liquids is different from that of solids. To assess the gastrointestinal transit of solids, other diagnostic methods should be used.

## **5.6 Radiopaque Markers**

### *RM Use in Humans*

The earliest radiopaque marker studies used barium impregnated polythene pellets or radiopaque polythene tubing to assess total gut transit times (Hinton *et al*, in 1969). Gastrointestinal transit was observed by collecting and radiographing the subjects' stools. The transit of the radiopaque markers (RM) was compared to the transit of carmine and  $^{51}\text{Cr}$  labelled sodium chromate and it was found that the time at which all of these gastrointestinal markers first appeared in the faeces was the same.

Hinton and Lennard-Jones (1968) investigated constipation by taking serial abdominal radiographs of patients who had ingested RM. Hinton *et al* (1969) later modified this procedure calculating gut transit times from faecal radiographs taken following administration of RM. Radiographs were continued until 80% of the markers had been passed.

Subsequently, a RM method to estimate total gut transit from the analysis of a single stool was described (Cummings and Wiggins, 1976). This study used three sets of RM of different shapes and sizes. Each set was given on three consecutive days with breakfast. The first stool passed on the fourth day following ingestion of the first set of markers was collected and radiographed. Total gut transit time was calculated from the number of markers present in the stool and the time elapsed since administration of the marker. Two of the three types of marker (designated  $s_1$  and  $s_2$ ), and their times since administration (designated  $t_1$  and  $t_2$ ), were used in the calculation. The two types of marker chosen for the calculation were the types present in the highest number in the stool. Total transit was calculated by dividing the sum of  $s_1 \times t_1$  and  $s_2 \times t_2$  by the sum of  $s_1$  and  $s_2$ .

More recently, RM have been found to be as accurate as the 'gold standard' scintigraphy for the assessment of total colonic transit (Stivland, *et al*, 1991; van der Sijp *et al*, 1993). They have also been shown to produce repeatable results (Bouchoucha *et al*, 1992).

RM can be used to assess motility in different segments of the colon (Metcalf *et al*, 1987; Stivland, *et al*, 1991; Bouchoucha *et al*, 1992; van der Sijp *et al*, 1993). Initial studies required daily abdominal radiographs following the ingestion of a different type of radiopaque markers on three consecutive days. Radiographs were taken 24 hours after the ingestion of the first set of radiopaque markers and then daily until all the markers had been passed. Simplified techniques using a single abdominal radiograph were then described (Metcalf *et al*, 1987; Bouchoucha *et al*, 1992). One

technique describes taking an abdominal radiograph on the fourth study day following ingestion of the first of the three types of RM (Metcalf *et al*, 1987). It has been validated for the determination of total and segmental colonic transit in healthy controls (Metcalf *et al*, 1987) and constipated patients (Casasnovas *et al*, 1991). Another technique involves taking an abdominal film 24 hours after ingesting ten of the same type of RM every day for six consecutive days (Bouchoucha *et al*, 1992). This technique has been validated in healthy subjects and those with irritable bowel syndrome for the assessment of total and segmental colonic transit.

Comparison of RM with scintigraphy for the assessment of segmental colonic transit, however, has revealed differences in the transit of the two marker types in the ascending and transverse colon (Stivland, *et al*, 1991; van der Sijp *et al*, 1993). RM were found to pass through the ascending and transverse colon faster than radioactive pellets in one study (Stivland, *et al*, 1991). The procedure used in this study to assess segmental colonic transit of the RM was the same as described by Metcalf *et al* (1987). The difference in transit through the ascending colon may be related to the larger size of RM compared to the size of the radioactive marker. It has been noted in other studies that particles of larger size pass through the ascending colon faster than smaller ones (Proano *et al*, 1990; Bruce *et al*, 1999; Chandler *et al*, 1999).

In the study by van der Sijp (1993), significant difference was found between the RM and the scintigraphic method of determining colonic transit. The RM were consistently found to be moving ahead of the radioisotope in each case. The authors suggested this may be due to a true difference in transit between the two types of particles or it may have been due to a difference in the way the transit was calculated.

The calculations differed between the two methods because of the small number of radiographs taken compared to large number of scans taken.

Radiopaque markers have also been used to investigate gastric emptying in humans. Some RM have been shown ultrasonographically to empty from the human stomach along with digestible solids (Broгна *et al*, 1992; Brown, 1993). In these studies, RM were swallowed during a meal and their gastric emptying, as assessed fluoroscopically, was compared to antral diameter, measured ultrasonographically. Measurements were taken at 30 then 60 minute intervals. Gastric emptying was considered complete when the antral diameter had returned to its fasting size. The RM were shown to have all emptied by this time, although at 180 and 240 minutes they were emptying significantly more slowly than the digestible solids. This discrepancy in the gastric emptying rate of the food and RM may have related to the size (2 x 5 mm) and density (not stated) of the RM used in this study.

RM have been used to detect delayed gastric emptying in two studies of human diabetics with suspected diabetic gastroparesis (Bertrand *et al*, 1982; Feldman *et al*, 1984). Both investigators highlighted that the RM studies were repeatable and identified that it was the solid phase, as opposed to the liquid phase, of gastric emptying that was delayed. In the former study, RM emptied along with the solid phase of the meal. In the latter study, the author used large RM (1 cm tubing of 0.2 cm diameter) to identify the onset of the migrating motor complex following the emptying of the meal.

More recent gastric emptying studies in humans have compared the RM technique to scintigraphy (Poitras *et al*, 1997; Stotzer *et al*, 1999). In the study by Poitras *et al* (1997), the two techniques were carried out on patients on separate occasions within a two month period and the results were reviewed retrospectively. Patients had been diagnosed with a range of conditions including dyspepsia, diabetes mellitus, multiple sclerosis, amyloidosis, systemic sclerosis and pseudoobstruction. The medication or the clinical signs did not change during the time between studies. The RM used were quite large (0.4cm – 0.5cm pieces of radiopaque tubing (12 French).

The RM method was found to correlate well to the scintigraphic gastric emptying studies. In fact, the RM studies were found to be more sensitive than scintigraphy in the detection of delayed gastric emptying. Meal size and composition varied between the two studies, however, which compromises direct comparison of the results. In the study by Stotzer *et al* (1999), comparison of RM and scintigraphy was done prospectively. The RM used were 3 mm cubes of density 1.13 g/cm<sup>3</sup> and their emptying from the stomach was assessed fluoroscopically. The RM were ingested along with an omelette in which the radioisotope had been bound. Measurement of the gastric emptying of the RM and radioisotope was performed simultaneously in healthy volunteers and in patients with diabetes mellitus and small intestinal bacterial overgrowth. The results of the RM technique and the scintigraphic technique were significantly correlated in both the healthy volunteers ( $r = 0.468$ ) and the patients ( $r = 0.686$ ), some of whom were documented to have delayed gastric emptying.

Radiopaque markers have been shown to be more sensitive than enteroclysis for the detection of partial bowel obstruction in four patients (Johnston *et al*, 1996). In these

patients, RM were observed radiographically to cluster in the area of small bowel just oral to the partial obstruction. This was confirmed later at surgery.

### ***RM use in Animals - Barium Impregnated Polyethylene Spheres***

Use of radiopaque markers to assess gastric emptying in animals was first reported by Hall *et al*, (1992) in a study of dogs surgically treated for gastric dilatation-volvulus. The radiopaque markers used were 2 mm segments of 1 mm diameter polyvinyl tubing. The study demonstrated delayed gastric emptying in the dogs that had undergone surgical correction of gastric dilatation- volvulus in comparison to sham-operated healthy controls.

A similar type of RM has been used to assess colonic transit times in cats (Fucci *et al*, 1995). The radiopaque tubing used in this study had a larger diameter (3.7 mm) and length (3 mm) than that used by Hall *et al* (1992). Colonic transit time was determined to be approximately 40 hours.

The majority of RM studies in animals have used commercially-available barium-impregnated polyethylene spheres (BIPS<sup>a</sup>). These RM are packaged in sets of 30 x one mm radiopaque spheres and ten x five mm radiopaque spheres. The RM studies reported in the present dissertation used BIPS because of the previously published work to validate the use of these RM (see below) and their consistent size and density. As previously discussed, the size and density of particles are 2 parameters that strongly influence their gastric emptying rate.

Reference intervals for the gastric emptying and orocolic transit times of BIPS in fasted cats and cats fed two different low residue commercial diets (Prescription Diet feline d/d, Hills Pet Products, Topeka, USA and Whiskas, Pedigree Petfoods) are available (Chandler and Guilford, 1995; Sparkes *et al*, 1997). Gastric emptying, small intestinal and colonic transit times have also been evaluated for cats fed a high fibre diet (Prescription Diet feline r/d (Hills Pet Products, Topeka, USA) (Chandler *et al*, 1999). The mean residence times of the RM in the colons of the cats reported by Chandler *et al* (1999) was approximately 25 hours for the small RM and 28 hours for the large RM which is considerably shorter than the 40 hours reported by (Fucci *et al*, 1995). The discordance between these two studies could be due to a variety of factors including the different diets fed, the different markers used and the different methods employed to calculate the transit times.

Reference intervals for the gastric emptying of BIPS in fasted dogs and dogs fed a low residue commercial diet<sup>g</sup> have been reported (Allan *et al*, 1996, BIPS booklet, NZ Vet, Christchurch, NZ). Reference intervals for the gastric emptying, small intestinal transit and colonic transit of BIPS in dogs fed a high fibre diet (Prescription Diet canine r/d (Hills Pet Products, Topeka, USA) are reported in Chapter 6 of this thesis and have recently been published (Bruce *et al*, 1999). The authors of the studies using high fibre diets (Chandler *et al*, 1995; Bruce *et al*, 1999) have proposed that this type of diet is preferably to low residue diets when the primary focus of the RM study is on the assessment of colonic transit or the detection of subtle partial obstructions.

The influence of sedation with acepromazine on the gastrointestinal transit of BIPS in cats has been investigated (Chandler and Guilford, 1995). The study was performed

because sedating uncooperative cats aids radiography but sedatives have been previously reported to affect gastrointestinal motility (Stick *et al*, 1987; Greene and Thurman, 1988). The results of the study demonstrated that acepromazine at 0.1mg/kg accelerates the gastric emptying rate of BIPS without affecting small intestinal transit time.

The effect of intravenous injection of low-dose diazepam on the gastrointestinal transit of BIPS in cats has been reported (Chandler *et al*, 1999). The injection of IV diazepam is occasionally necessary to encourage cats to promptly eat meals containing RM. The purpose of the study was to determine if this practice altered the gastrointestinal transit of BIPS. There was no significant difference in the total gastrointestinal transit of the markers in cats given intravenous diazepam compared to the non-treated cats. However, it was found that the large markers emptied from the stomach more quickly in the treated cats compared to the non-treated cats. The authors proposed this could have been due to the decreased anxiety levels of the treated cats.

Studies to validate the use of BIPS for assessing gastrointestinal transit in animals have been performed. The repeatability of the technique has been evaluated by comparing BIPS studies carried out on three separate occasions in the same ten dogs (Allan *et al*, 1996). No significant differences were found. The same study evaluated observer variation between two veterinarians with different radiological expertise (Allan *et al*, 1996). Very little observer variation was revealed.



A study has been performed to assess the correlation between the presumed position of BIPS in the gastrointestinal tract as determined by radiography with their actual position as determined by necropsy (Guilford *et al*, 1997). This study was performed by euthanising dogs at different time points following ingestion of the RM in a meal. The gastrointestinal tract from each of the dogs was then removed. Each section of the gastrointestinal tract was tied off and radiographed separately so that the precise number of RM present in the stomach, small intestine and colon could be determined. The results established that veterinarians experienced with RM studies are able to accurately determine the location of BIPS in the gastrointestinal tract by abdominal radiography.

The study by Guilford *et al* (1997) evaluated also the correlation between the gastric emptying of the RM and that of a commercial diet (Prescription Diet canine d/d (Hills Pet Products, Topeka, USA). The contents of the stomachs of each dog were removed and the percentages of wet and dry matter of the food left in the stomach were determined and compared to the percentages of markers remaining in the stomach. The authors concluded the RM were a reliable indicator of the gastric emptying of the particular type of food used in the study.

Clinical use of BIPS has recently been reported. A preliminary study of the use of BIPS over a 20 month period at the Massey University Veterinary Teaching Hospital has been published (Burbidge and Guilford, 1996). The majority of RM studies reviewed in this report were performed in vomiting animals and approximately 40% of the studies were abnormal. Delayed gastrointestinal transit of BIPS was associated with inflammatory bowel disease, uraemia, pancreatitis, pyloric disorders, physical

obstructions, parvovirus enteritis, surgically corrected gastric dilatation-volvulus and megacolon. The BIPS were found to bunch in one region of the small intestine in animals with a physical obstruction. A more detailed evaluation of the clinical use of BIPS at the Massey University Veterinary Teaching Hospital is reported in Chapter 9 of this thesis.

The use of BIPS to document delayed gastric emptying in two chronically vomiting dogs was described by Nelson *et al* (1996). One dog was found to have inflammatory bowel disease and the other dog was found to have gastric carcinoma. A recent review outlines the different clinical situations in which BIPS can be used and describes the radiographic patterns produced by the BIPS along with the clinical significance of these patterns (Robertson and Burbidge, 2000). This study concluded that RM have a place in the diagnosis of gastrointestinal disease, especially chronic conditions.

An attempt has been made to compare the accuracy of BIPS studies to scintigraphy in cats and dogs for the assessment of gastric emptying (Goggin *et al*, 1999; Lester *et al*, 1999). The former study found the gastric emptying of the RM to be significantly slower than the radioisotope in cats. A different diet was used in these studies, compared to that recommended by the manufacturer, however. The discrepancy in gastric emptying of the BIPS and the radioisotope may have been due to the failure of the RM to remain suspended in the diet with which they were mixed or because of insufficient mixing of the RM with the food. As illustrated in the previous chapter, the type of diet used with the RM is important. The diet must have the necessary

characteristics to keep the RM suspended in it in order for the RM to leave in parallel with the food.

The study by Lester *et al* (1999) also found the BIPS to empty significantly later than the radioisotope in dogs. This study used the canned diet recommended by the manufacturer, however, there were flaws in the experimental design. Firstly, the binding of the radioisotope was not checked. Secondly, the radioisotope was bound to egg that was then added to the canned diet. This suggests that the radioisotope was therefore depicting the emptying of the egg and not the canned diet. Thirdly, no attempt was made to check if the emptying of the egg and the canned diet was closely correlated. Egg is more trituratable than canned dog food and would therefore be expected to empty ahead of it. One study in humans comparing the gastric emptying of egg compared to liver found the egg to empty from the stomach significantly faster than the liver (Poitras *et al*, 1997).

In summary, RM studies using the commercially-available radiopaque markers BIPS, first described by Allan *et al* (1993), has been shown to be a simple and accurate method to assess gastrointestinal transit in dogs and appears also to be valuable for this purpose in cats. Many questions remain, however, some of which are the focus of the studies reported later in this thesis.

## 5.7 Scintigraphy

Scintigraphy is regarded as the “gold standard” for the measurement of gastrointestinal transit (Sica, 1998). It is accurate, noninvasive and exposes the patient only to a low dose of radiation that remains constant regardless of the number of scans taken. It provides a quantitative assessment of physiological transit and so is very useful for the diagnosis of gastrointestinal dysmotilities.

Scintigraphy, however, is an expensive procedure requiring a large amount of specialised equipment. In addition, the isotope can become separated from the food (Camilleri *et al*, 1998) during the procedure. Although, generally only about 2-5% becomes separated, this can result in erroneously rapid gastric emptying times as the isotope, once separated, may rapidly empty from the stomach with the liquid portion of the meal. It must also be noted that, due to the variation in the preparation of the radiolabel, variation in test meal and the method of data acquisition and processing used, studies completed at different institutions cannot be directly compared (Parkman *et al*, 1995).

Scintigraphy has long been advocated as a highly accurate technique for the assessment of gastric emptying (Collins *et al*, 1983; Hveem *et al*, 1996) and colonic motility (Camilleri and Zinsmeister, 1992; Notghi *et al*, 1994; Proano *et al*, 1990; Stivland *et al*, 1991; Van der Sijp *et al*, 1993) in humans. It has also been used to assess simultaneous liquid and solid gastric emptying (Collins *et al*, 1983) and whole gut transit (Charles *et al*, 1995), giving separate measurements for gastric emptying, small intestinal transit and large intestinal transit. The study by Collins *et al*, (1983)

revealed scintigraphy to be a reproducible technique in humans, although a wide inter-subject range for normal gastric emptying times was found.

Gastric emptying has also been assessed in cats (Steyn *et al*, 1995; Goggin *et al*, 1998; Costello *et al*, 1999) and dogs (Burrows *et al*, 1985; Kunze *et al*, 1998) using scintigraphy. Meaningful comparison between the scintigraphy studies and between scintigraphy and RM studies is difficult because different meal sizes and diets and a variety of different radiolabels were used in the studies.

Colonic motility has been assessed following ingestion of <sup>111</sup>Indium either as a resin or in pellets (Proano *et al*, 1990; Stivland *et al*, 1991; Van der Sijp *et al*, 1993; Notghi *et al*, 1994). Various protocols for the assessment of transit through different regions of the colon have been described, as mentioned below. Measurement of colonic transit in healthy people (Proano *et al*, 1990) and in those with idiopathic constipation (Stivland *et al*, 1991) has been achieved. The use of scintigraphy for the regional assessment of colonic motility in humans has been proposed as being more accurate than RM used for this purpose (Van der Sijp *et al*, 1993), due to the rapid transit of the RM through the ascending colon.

The above mentioned studies all required scans to be taken one or more times daily over three to seven days to obtain accurate results for segmental colonic motility. Notghi *et al*, (1994) have developed a more simplified technique which requires only three images to be taken over three days. Further simplification of this technique has been described (Camilleri and Zinsmeister, 1992; Charles *et al*, 1995). One method requires only 2 scans taken over a 24 hour period to determine if colonic transit is

rapid, normal or delayed (Camilleri and Zinsmeister, 1992). Another method requires four scans over a 24 hour period to determine gastric emptying, small bowel and large bowel transit (Charles *et al*, 1995).

## **5.8 Magnetic Resonance Imaging**

The development of Magnetic Resonance Imaging (MRI) has provided a non-invasive, radiation free alternative to scintigraphy for the assessment of gastrointestinal transit. MRI has been shown to be as accurate as scintigraphy in the assessment of gastric emptying of liquids in normal humans and those with gastric emptying disorders (Schwizer *et al*, 1992). It also allows the measurement of meal emptying while viewing a three dimensional image of the anatomical configuration of the stomach. The three dimensional images are produced by computer summation of the transverse images at each time point.

MRI has been found to be highly specific but less sensitive than RM for the detection of delayed gastric emptying in human diabetics (Lehmann, *et al*, 1996). Caution is required when interpreting this study, however, because the gastric emptying of a solid meal using RM was compared to the gastric emptying of a liquid meal with MRI.

The development of echo planar MRI scanners has allowed the faster production of images and therefore increased the frequency at which they can be taken. More rapid image production has allowed the sequential imaging of gastric and duodenal

contractions as they move in an aboral direction (Evans *et al*, 1993; Schweizer *et al*, 1996). MRI has also been used to observe the gastric emptying of a mixed solid-liquid meal (Evans *et al*, 1993). This study observed both the fasted and fed state motility patterns. Different phases of the migrating motor complex could be distinguished in the fasting state and the image separation of the solid and liquid portions of the meal was observed during early gastric emptying.

MRI has also been used to measure proximal and distal stomach motility simultaneously during gastric emptying (Schweizer *et al*, 1996). Liquid emptying, using a MRI liquid marker, was assessed in this study and the correlation between gastric wall motion and gastric emptying demonstrated, the first study of its kind in humans.

MRI has a number of advantages over scintigraphy. The technique is radiation free. The possibility for systematic error is reduced because no calculations for image attenuation are required and errors due to overlap of the small intestine are eliminated because the surrounding abdominal organs can be clearly delineated on the MRI scan (Schwizer *et al*, 1992). MRI also has advantages over ultrasonography as patients of all shapes and sizes can be assessed and the presence of gas in the stomach does not affect the results (Schwizer *et al*, 1992). Gastric acid inhibition is also not required, as in applied potential tomography (Schwizer *et al*, 1992).

Following development of a solid MRI marker and development of the technique to allow for normal breathing and positioning during imaging, MRI could become the method of choice for the assessment of gastric emptying in the future in humans

(Sica, 1998). In veterinary practice, however, the requirement for highly specialised equipment and the requirement for general anaesthesia to prevent the animal from moving restricts the use of MRI at present, especially for the assessment of gastrointestinal motility.

## **5.9 Ultrasonography**

Abdominal ultrasound has been used to assess gastric and upper small intestinal motility in humans (Holt *et al*, 1980; King *et al*, 1984). Motility has been subjectively assessed by direct observation of the contractions of the stomach and segments of the intestine. The direction and rate of flow of gastric contents has also been visualised (King *et al*, 1984). In this study, small bran particles were suspended in orange juice allowing subjective assessment of gastric emptying by observing the number and speed of particles passing through the pylorus at any time.

Direct measurement of the gastric emptying of liquids has also been achieved using ultrasound (Bateman and Whittingham, 1982). This method used similar calculations of total gastric volume to those used in MRI studies of gastric emptying. Computer-generated summations of transverse ultrasound “slices” of the stomach were produced at one centimetre intervals every five minutes and used to calculate the change in gastric volume over time. The reduction in gastric volume over time represented gastric emptying. Ultrasound has been shown to be as sensitive as scintigraphy in the measurement of gastric emptying of liquids (Hveem *et al*, 1996).



The gastric emptying of solid food also has been observed ultrasonographically (Brognia *et al*, 1992; Brown *et al*, 1993). The study by Brognia *et al* (1992), measured gastric emptying of a solid meal by assessing the diameter of the gastric body, the antrum and the pylorus. Measurements were taken before, immediately after and then sequentially following ingestion of the meal. The decrease in diameter from the maximum recorded immediately following ingestion of the meal was used to determine the percentage gastric emptying of the solid food.

Ultrasound has an advantage over other imaging modalities in that it can highlight thickening of the wall of the gastrointestinal tract or abdominal masses causing physical obstructions (Lamb, 1999). In humans, ultrasound is not suitable for all patients due to obesity or individual anatomic variation (King *et al*, 1984) and is dependant on a competent operator (Lamb, 1999; Sicca, 1998).

### **5.10 Manometry**

Manometry has been used to measure pressure changes in the stomach and upper small intestine for the assessment of gastric emptying (Malagelada *et al*, 1980). Strain gauge transducers attached to polyvinyl intestinal tube are placed into the gastric antrum, duodenum and jejunum and detect the presence and strength of intestinal contractions. Manometry has been used to highlight intestinal motor abnormalities in humans with post surgical gastroparesis and diabetic gastroparesis (Malagelada *et al*, 1980), and functional disorders of the upper intestine (Malagelada and Stanghellini, 1985).

The clinical value of manometry has been assessed over a six year period (Soffer and Thongsawat, 1996). This study concluded that although manometry could not give a specific diagnosis, it often helped in the choice of therapy, especially if surgery was being considered. For example, in patients with constipation displaying abnormal small intestinal motility, surgery is unlikely to be helpful. Manometry is of use only if organic disease has been ruled out (Camilleri *et al*, 1998). However, manometry is invasive, requires tolerant patients (Sicca, 1998) and is unlikely to be useful in veterinary clinical practice.

### **5.11 Less Common Methods of Assessing Gastrointestinal Motility**

Less common methods used for the assessment of gastrointestinal motility include electrogastrograms, the breath hydrogen test, plasma sulfapyridine concentrations, the octanoic acid breath test, biomagnetics, radiotelemetry and applied potential tomography.

Electrogastrograms (EGG) can be used to assess gastric emptying. An abnormal postprandial EGG has been shown to predict delayed gastric emptying, as verified by scintigraphy (Chen *et al*, 1996). Decreased numbers of slow wave cycles and/or a decrease in the dominant power of the EGG occurred in the postprandial period of patients with delayed gastric emptying. In the study by Chen *et al* (1996), however, a normal EGG did not rule out delayed gastric emptying and fasting EGGs were similar in patients with and without delayed gastric emptying.

The breath hydrogen test has been used to accurately assess small intestinal transit in humans (Read *et al*, 1980) and cats (Papasouliotis *et al*, 1998). It has also been shown to be a reproducible test in dogs (Bisset *et al*, 1998). In addition to oro-caecal transit time it can be used to assess carbohydrate malabsorption (Spohr *et al*, 1999) and small intestinal bacterial overgrowth (German *et al*, 1998). One study has used the breath hydrogen test to document more rapid oro-caecal transit time in cats with hyperthyroidism, as compared to healthy cats (Papasouliotis *et al*, 1993).

Plasma sulfapyridine concentrations (Kellow *et al*, 1986) have been found to be both accurate and reproducible in the assessment of small intestinal transit. This test requires serial withdrawal of blood samples following the oral administration of sulfasalazine.

The octanoic acid breath test is another method by which gastric emptying has been assessed in humans. Octanoic acid, combined with salt and then added to food, has been found to be sufficiently sensitive to detect drug induced changes in gastric emptying rates of solids (Maes *et al*, 1994). However, it does not produce consistent results when compared to scintigraphy (Choi *et al*, 1997).

A biomagnetic technique has been described whereby a metal object is swallowed which emits electromagnetic radiation and its passage through the gastrointestinal tract is followed using a metal detector (Basile *et al*, 1992). Radiotelemetry, using a Heidelberg capsule that detects the pH of its surroundings and transmits the information to a receiver on a belt around the body, is another technique used for the measurement of gastric emptying (Mojaverian *et al*, 1985). Applied potential

tomography involves placing multiple electrodes around the abdomen and measuring changes in electric conduction of the stomach following ingestion of a meal. This can be used to assess both liquid and solid gastric emptying (Avill *et al*, 1987).

## **5.12 Summary**

There are a wide variety of techniques to measure gastrointestinal transit. From a veterinary clinical perspective, the method used to determining gastrointestinal transit must be accurate, repeatable and non-invasive and should not require specialised equipment, heavy sedation or general anaesthesia. Radiopaque markers appear to fulfil the above criteria, although more work is required to fully validate their use in veterinary medicine. That is the focus of the next three chapters of this thesis.

## CHAPTER SIX

### **DEVELOPMENT OF REFERENCE INTERVALS FOR THE GASTRIC EMPTYING, SMALL INTESTINAL TRANSIT AND COLONIC TRANSIT OF RADIOPAQUE MARKERS FED WITH A HIGH FIBRE DIET IN DOGS**

#### **6.1 Introduction**

As described earlier, the gastrointestinal transit of food is complex and can be disrupted by a variety of different disease processes. Furthermore, the clinical signs associated with these disruptions are often nonspecific. For these reasons, tests of gastrointestinal motility are required to arrive at a definitive diagnosis.

Radiopaque markers (RM) have been found to be a useful technique in the assessment of gastric motility (Bertrand *et al*, 1982; Feldman *et al*, 1984; Brogna *et al*, 1992; Brown, 1993; Poitras *et al*, 1997; Stotzer *et al*, 1999), large intestinal motility (Metcalf *et al*, 1987; Proano *et al*, 1990; Casasnovas *et al*, 1991; Stivland *et al*, 1991; Bouchoucha *et al*, 1992; Camilleri and Zinsmeister, 1992; Von der Ohe and Camilleri, 1992; Van der Sijp *et al*, 1993) and total gut transit in humans (Hinton *et al*, 1969; Cummings and Wiggins, 1976), mimicking the movement of indigestible particles of food along the gastrointestinal tract.

Previous studies in dogs have found RM to be a simple and effective method of assessing gastrointestinal motility (Allan *et al*, 1996, Chandler *et al*, 1997; Chandler and Guilford, 1997; Guilford and Lawoko, 1997). The studies have been described in detail in Chapter 5 and validate the use of a particular type of radiopaque marker (Barium Impregnated Polyethylene Spheres (BIPS), MedID, Grand Rapids, USA) in select circumstances. They include a study determining the accuracy of the radiographic assessment of the position of RM in the gastrointestinal tract and the correlation between the gastric emptying of the food and the RM (Guilford and Lawoko, 1997). Another study confirms repeatability of the technique and provides reference ranges for the gastric emptying of the markers in healthy dogs fed a particular diet (Prescription Diet canine d/d (Hills Pet Products, Topeka, USA) (Allan *et al*, 1996).

In contrast to the previous studies, the present study examines the gastrointestinal transit of RM in dogs fed along with a diet with a high content of non-fermentable fibre. Faecal bulk is increased when high fibre diets are fed and it was hoped that this would more clearly delineate the colon on radiographs. In addition, the high fibre diet may facilitate detection of subtle partial intestinal obstructions because the indigestible fibre tends to trap RM proximal to an obstruction<sup>a</sup>.

As described in Chapter 3, the presence of fibre in the diet affects the complex physiological mechanisms regulating transit of food through the gastrointestinal tract. Therefore, the gastric emptying and colonic transit times of RM fed with a high fibre diet are likely to differ from those of RM fed with other diets. Reference intervals for

---

<sup>a</sup> Allan FJ and Guilford WG, Unpublished Observations, 1995

the gastric emptying and colonic transit of RM in cats fed a high fibre diet have been established (Chandler *et al*, 1997). The same values are not yet available for dogs.

Reference intervals for the gastric emptying and small intestinal transit of RM in dogs fed a high fibre diet will assist interpretation of RM studies performed with high fibre diets in the hope of detecting subtle partial obstructions of the small intestine.

Reference intervals for the colonic transit of RM in dogs are necessary before RM studies can be usefully applied to the investigation of colonic disorders, such as constipation or large bowel obstructions.

The objective of this study was to develop reference intervals for the gastric emptying, small intestinal transit, colonic filling and, in particular, the colonic transit of RM fed with a high fibre diet to dogs.

## **6.2 Materials and Methods**

### *Dogs*

Ten collie-cross dogs were supplied by the Animal Health Services Centre of Massey University. They ranged in age from 8 months to 69 months and weighed between 14 and 28 kg (mean 20.2 kg). Nine of the dogs were unspayed females and one dog was a male. None of the dogs had a history of previous gastrointestinal disease and all had been fully vaccinated and regularly wormed. No abnormalities were detected following a thorough clinical examination. The animals were housed in kennels at the Massey University Veterinary Teaching Hospital (MUVTH) and were exercised for 10 minutes three times daily. They had access to water at all times but were fasted for

24 hours prior to the study. The Massey University Animal Ethics Committee approved the experimental protocol.

### ***Diet***

A commercial high fibre diet was used (Prescription Diet canine r/d, Hills Pet Products, Topeka, USA) (Table 6.1). The majority of the fibre present in the diet is non-fermentable, insoluble and non-gel forming. On the day of the study, the dogs were fed enough to satisfy 25% of the dogs' daily caloric intake. This was calculated using the formula below to determine the amount of food, to the nearest gram, to be fed to each dog:

$$\frac{(33 \times W^{0.75})}{0.585}$$

In the formula, W is the weight of the dog in kg converted to body surface area, which is referred to as 'metabolic size' (Kleiber, 1975), and 0.585 is the energy density of the food in kcal/g. The 33 in the formula represents 25% of 132, the constant used to estimate the daily energy requirements of dogs (National Research Council, 1985).

### ***Radiopaque markers***

A commercial RM was used (Barium Impregnated Polyethylene Spheres (BIPS), MedID, Grand Rapids, USA). These are inert, radiopaque polyethylene spheres. One 'dose' of RM consists of 30 small (1.5-mm diameter) and 10 large (5-mm diameter)



spheres, contained in gelatin capsules. This is the standard number of RM used in previous studies.

### ***Administration of the Radiopaque Markers***

The capsules were split and the RM were mixed thoroughly in the food. Any RM not eaten were administered directly by mouth. In two dogs that refused to voluntarily consume the r/d diet, the entire meal was hand-fed.

### ***Radiography***

Radiographs were taken using a Philips® super 120 x-ray machine (Philips NZ Ltd, PO Box 41021, Auckland, New Zealand) and a focus grid of 8:1 ratio with film focus distance of 100cm. The film (Fuji) was contained in Kodak® X-Omatic™ cassettes with Kodak® lanex™ fast screens of size 35cm by 43 cm and Kodak® lanex™ regular screens of size 30cm by 40 cm. Films were developed using Kodak® RP X-Omat™ automatic processor (Model M6B, Kodak NZ Ltd, PO Box 2198, Auckland, New Zealand).

The dogs were restrained manually in left lateral and ventro-dorsal positions. No chemical restraint was used. Abdominal radiographs were taken two hours after feeding and then at two hourly intervals until 90% of the small and large spheres had left the colon and entered the rectum (ie, when they were caudal to the cranial border of the iliac crest on the lateral radiograph). Left lateral and ventro-dorsal positioning for radiography was chosen to comply with previous studies (Allan *et al*, 1996). To

increase animal comfort and support, a foam cradle was placed underneath the dogs during radiography.

### ***Radiographic Interpretation***

Every radiograph was studied and the total number of small and large RM counted. Each radiopaque marker counted was allocated into specific areas of the gastrointestinal tract. These areas consisted of: stomach, small intestine, proximal (ascending and transverse) and distal (descending) colon. Proximal and distal colons were differentiated on the ventro-dorsal view. Any radiopaque marker present in, or caudal to, the left colic flexure were counted as being in the distal colon. RM were determined to be in the rectum when they had passed the pelvic inlet on the lateral radiograph. When the location of a particular radiopaque marker could not be determined, no allocation was made and the radiopaque marker was excluded from future calculations for that time period.

### ***Statistical Analysis***

The gastric emptying rate of the small RM, expressed as a percentage, was calculated by counting the number of small RM which had left the stomach at each time point, dividing this by the total number of small RM ingested and multiplying by 100. This was repeated for the large RM. A box plot depicting a gastric emptying curve was constructed for each size of RM by plotting the median values, upper and lower quartiles and the range of gastric emptying percentages at each time point following administration. The box plots were produced as reference curves for use in clinical

practice. The median 50%, 75%, and 90% gastric emptying times (GET) and upper and lower quartiles for each size of RM were calculated by interpolation. The median 50%, 75% and 90% gastric emptying times of the small and large RM were compared by the Wilcoxon Sign Rank Test.

The median times (and upper and lower quartiles) for 50%, 75% and 90% of both sizes of RM to enter the colon ('colonic filling') were calculated. The colonic filling times for large and small RM were compared by the Wilcoxon Sign Rank Test. The percentage of RM that had entered the colon was plotted as a function of time after administration of the RM.

Small intestinal transit times (SITT) for both sizes of RM were determined by calculating the area between the gastric emptying and colonic filling curves. SITT of the small and large RM were also compared by the Wilcoxon Sign Rank Test. Linear interpolation and the trapezoidal rule were used to calculate this area from the two hourly observations.

Reference curves were produced for 'colonic transit' through the proximal, distal and total colon. The median percentages of each size of RM in the proximal, distal and total colon (exclusive of the rectum) at each time point were calculated and expressed as box plots as described for the gastric emptying curves.

The colonic transit rate of the RM was also quantified by assessing the mean residence times (MRT) of each size of RM in the proximal colon, distal colon and total colon. In this analysis, proximal, distal and total colons were considered

separately. Curves were drawn of the percentage of RM present in each space over time. For each space, the MRT of the RM was then calculated from the area under the curve.

This is equivalent to the standard formula for MRT in a single compartment model (Veng-Pederson, 1989<sup>1+2</sup>):

$$\text{MRT} = \frac{\int_0^{\infty} (Fxt) dt}{\int_0^{\infty} (F)dt},$$

Where F is the fraction of administered RM remaining in each area of the colon and t is the time measured in hours from the time of first entry of the RM into the proximal colon.

Finally, the MRT's for the small and large RM in the proximal, distal and total colon were compared using the Wilcoxon Sign Rank Test. A p-value of less than 0.05 was considered significant for all analyses.

## **6.3 Results**

### ***Experimental Protocol***

All the dogs remained healthy during the study. All the dogs ate the test meal except two dogs that had to be hand fed. The initial radiographs of three dogs revealed that sufficient mixing of the RM through the test meal had not been achieved.

Consequently, the data from these dogs was omitted from the gastric emptying study.

### ***Gastric Emptying***

The median gastric emptying times of the RM are shown in Table 6.2. The 50% and 75% GET of the small and large RM were not significantly different. Although not statistically significant, the time for 90% of the large RM to empty from the stomach tended to be longer ( $p = 0.055$ ) than the 90% gastric emptying time of the small RM.

The box plots for use as gastric emptying reference intervals are shown in Figures 6.1 and 6.2.

### ***Small Intestinal Transit Time***

The median SITT of the two sizes of RM are shown in Table 6.3. The SITT for the small and large RM were not significantly different.

### ***Colonic Filling Times***

The median colonic filling times (CFT) are shown in Table 6.4. The 50% and 75% CFT of the large and small RM were not significantly different. The 90% CFT of the large RM tended to be longer ( $p = 0.055$ ) than that of the small RM.

The box plots for use as reference intervals for the mean total colonic filling of the small and large spheres are shown in Figures 6.3 and 6.4.

### ***Colonic Transit Times***

The mean residence times of the small and large RM are shown in Table 6.5. There were no statistical differences between the MRT of the small and large RM in the distal and total colon but the small RM were present in the proximal colon for a significantly longer time than the large RM ( $P = 0.0039$ ).

Reference curves depicting the percentage of RM in the proximal, distal and total colons at different time points after administration are shown in Figures 6.5 – 6.10.

## 6.4 Discussion

This study has provided reference intervals for the gastric emptying, small intestinal transit, colonic filling and large intestinal transit times of RM in dogs fed a high fibre diet. These have been produced as a series of reference curves (Figures 6.1 - 6.10) to aid clinicians to evaluate intestinal transit. It is anticipated that the primary value of these curves will be the diagnosis of colonic motility disorders.

The reference curves must be interpreted with caution. Firstly, this study was designed to obtain reference curves in a manner relevant to clinical situations (ie. the dogs were kennelled in unfamiliar surroundings and were not accustomed to being radiographed). It is possible that the gastrointestinal transit times of RM in dogs trained to the radiographic procedure may be different. Secondly, the reference values are likely to be specific to the high fibre diet used. The presence and type of fibre in the diet has been found to have an effect on gastric emptying and intestinal transit. In general, intestinal transit is accelerated by the type of non-gel-forming fibres present in the diet used in this study (Burrows *et al*, 1982; Jenkins and Jenkins, 1984; Kritchevsky, 1988).

The shape of the gastric emptying curve in the present study was found to be similar to a previous RM study of gastric emptying in dogs (Allan *et al*, 1996). In the present study, the GET of the small RM tended to be shorter than the large RM for 90% gastric emptying. A likely explanation for this is that some of the large RM were retained in the stomach until near the end of gastric emptying. The retention of larger insoluble particles by the pylorus has been previously reported in dogs (Becker and

Kelly 1983). This phenomenon has been observed in previous studies of cats using the same type of RM (Chandler *et al*, 1999 and Chandler and Guilford, 1995) and a study of dogs that examined the simultaneous gastric emptying of different sized spheres (Meyer *et al*, 1985). The 50% GET for the small RM fed with the high fibre diet was faster than that of RM fed with a lower fibre diet in a previous study (Allan *et al*, 1996). This is consistent with studies in humans that have shown that diets high in insoluble fibre speed gastrointestinal transit (Kritchevsky, 1988; Tadesse, 1986).

The lack of difference between small intestinal transit times of the two sizes of RM supports the view that the stomach exercises most control over oro-caecal transit times (Read *et al*, 1982).

The colonic filling curves shown in Figures 6.3 and 6.4 can be used as reference curves for the orocolic transit of RM fed in a high fibre diet. The colonic filling curves assist in the interpretation of the RM studies of colonic transit because they allow the differentiation of delayed upper gastrointestinal transit from delayed colonic transit. The 90% colonic filling time of the large RM tended to be longer than the small RM, presumably due to the retention of some of the large RM in the stomach until near the end of gastric emptying (see above).

The reference curves for the percentage of RM in the different regions of the colon allow veterinarians in clinical practice to take only two or three sets of abdominal radiographs when assessing colonic motility. Our preliminary clinical experience, based on the use of these reference ranges, suggests that lateral and ventro-dorsal



radiographs taken at 24, 36 and 48 hours following ingestion of the RM are sufficient to detect delayed colonic filling and delayed proximal or distal colonic transit<sup>8</sup>.

Wide variation in colonic transit in humans has been noted (Metcalf *et al*, 1987). As can be seen from these results, there is also much individual variation in gastrointestinal transit between healthy animals, and therefore, only marked abnormalities in transit can be detected. Experience with clinical cases at the author's clinic to date, however, indicates that patients with colonic motility disorders do not, in general, present to veterinarians until their dysmotilities are severe.

There were no significant differences between the MRTs of the small and large RM in the distal colon and the total colon but it was found that the MRT of the small RM was significantly greater than that of the large RM in the proximal colon. The observation is consistent with a previous study of colonic transit of RM in cats (Chandler *et al*, 1997) and a study comparing the transit times of 1mm and 6mm particles through the right colon of humans (Proano and others 1990). The reason for this phenomenon is unknown. We speculate, however, that larger diameter particles are less likely than smaller particles to 'reflux' in an orad direction through a peristaltic ring progressing in an aborad direction. As a result, larger diameter particles would be carried more quickly in an aborad direction. In the proximal colon the faeces are subject to significant dehydration. It is noteworthy, therefore, that the rapid passage of large particles through the proximal colon would have little adverse consequence to colonic water reabsorption because of their small contribution to the osmolality of faecal matter.

---

<sup>8</sup> Guilford WG, unpublished observations, 1997

In conclusion, this study provides reference intervals for the gastric emptying, small intestinal transit, colonic filling and large intestinal transit times of a commercial RM in healthy dogs fed a high fibre diet. These reference intervals may prove to be of value in diagnosing partial obstructions of the gastrointestinal tract, assessing the severity of colonic dysmotility, and determining if constipation is due to a segmental or generalised colonic dysfunction.

**Table 6.1 Nutritional Analysis of the Diet Fed to the Dogs Along with the RM\***

Nutrient	As Fed	Dry Matter
Protein	6.2	25.6
Fat	1.7	7.0
Carbohydrate	8.6	35.5
Fibre	6.4	26.4

**\* Data provided by the manufacturer.**

**Table 6.2 Median Gastric Emptying Times (in Hours) of the Small and Large Radiopaque Markers Fed to Dogs with a High Fibre Diet**

%GE	Small RM			Large RM		
	Median (hrs)	Q1-Q3	Range (hrs)	Median (hrs)	Q1-Q3	Range (hrs)
50%	6.75	4.40-8.82	1.76-7.09	7.00	6.00-8.00	5.20-9.00
75%	9.21	6.83-12.25	5.67-12.25	10.38	7.50-13.67	7.00-15.00
90%	10.67	9.00-13.71	7.60-14.50	14.50	12.00-17.00	8.00-20.00

%GE = Percent Gastric Emptying, RM= Radiopaque Marker, Q1-Q3= Upper and Lower Quartiles

**Table 6.3 Median Small Intestinal Transit Times (in Hours) of the Small and Large Radiopaque Markers Fed to Dogs with a High Fibre Diet**

	Median (hrs)	Q1-Q3	Range
Small RM	2.03	1.88-2.12	1.73-3.07
Large RM	2.00	1.65-2.75	1.60-3.00

SITT= Small Intestinal Transit Time, RM= Radiopaque Marker, Q1-Q3= Upper and Lower Quartiles

**Table 6.4 Median Colonic Filling Times (in Hours) of the Small and Large Radiopaque Markers Fed to Dogs with a High Fibre Diet**

Colonic Filling Times						
%CF	Small RM			Large RM		
	Median (hrs)	Q1-Q3	Range (hrs)	Median (hrs)	Q1-Q3	Range (hrs)
50%	8.38	6.50-10.92	3.64-13.78	9.33	8.30-9.46	7.33-13.00
75%	11.60	9.88-14.01	7.67-18.33	13.67	11.13-16.83	9.00-18.33
90%	13.23	12.13-15.13	10.00-19.33	16.67	14.33-19.00	12.00-22.00

%CF= Percent Colonic Filling, RM= Radiopaque Marker, Q1-Q3= Upper and Lower Quartiles

**Table 6.5 Mean Residence Times (in Hours) of the Small and Large Radiopaque Markers Fed to Dogs with a High Fibre Diet**

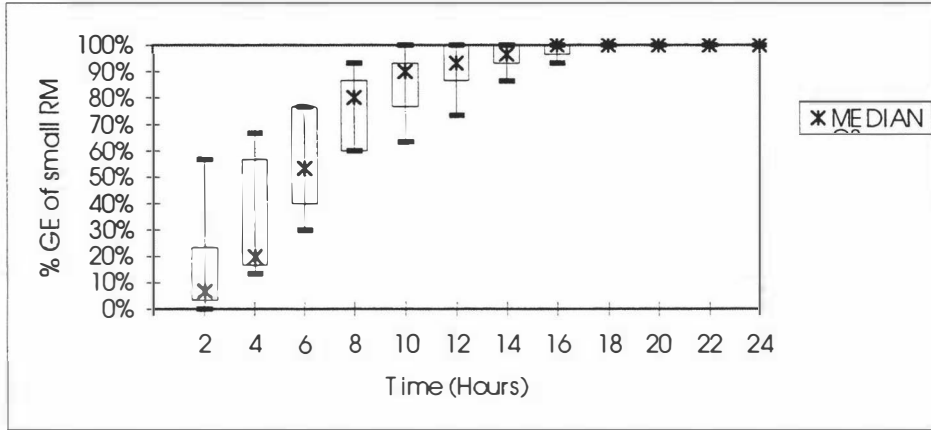
	Small RM			Large RM		
	Median (hrs)	Q1-Q3	Range	Median (hrs)	Q1-Q3	Range
Proximal Colon	3.07	2.53-4.98	2.00-16.27	2.50	2.05-3.55	1.60-9.40
Distal Colon	6.13	5.27-7.50	3.40-13.87	5.50	4.40-11.05	3.60-17.60
Total Colon	9.70	8.53-10.83	5.47-28.13	8.10	6.85-13.25	5.20-26.60

**\*Statistically significant difference (p<0.01) between small and large RM.**

MRT= Mean Residence Time, RM= Radiopaque Marker, Q1-Q3= Upper and Lower Quartiles

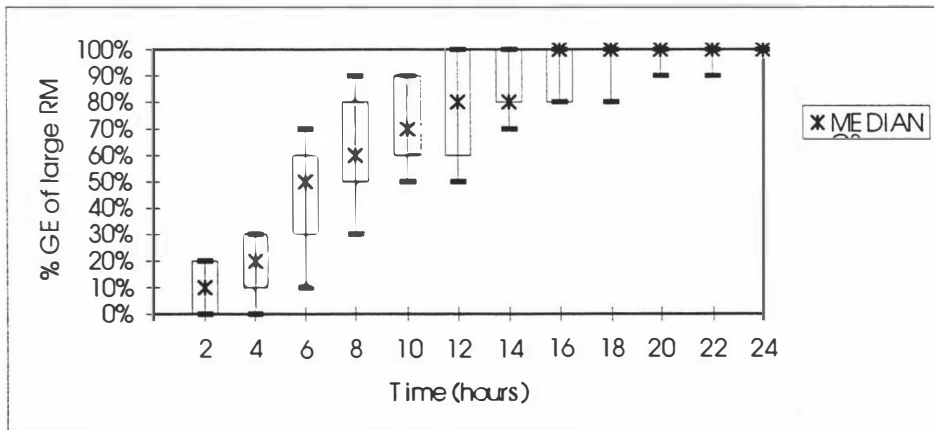
**Figure 6.1** Box plot depicting the gastric emptying of the small RM at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



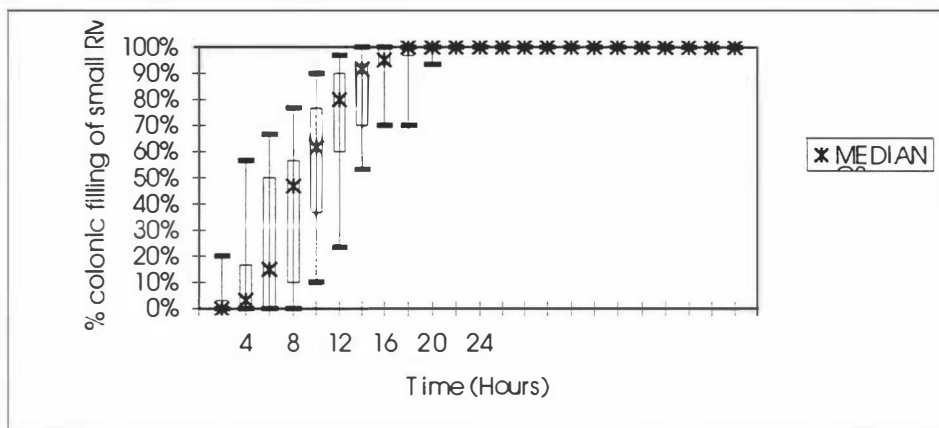
**Figure 6.2** Box plot depicting the gastric emptying of the large RM at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



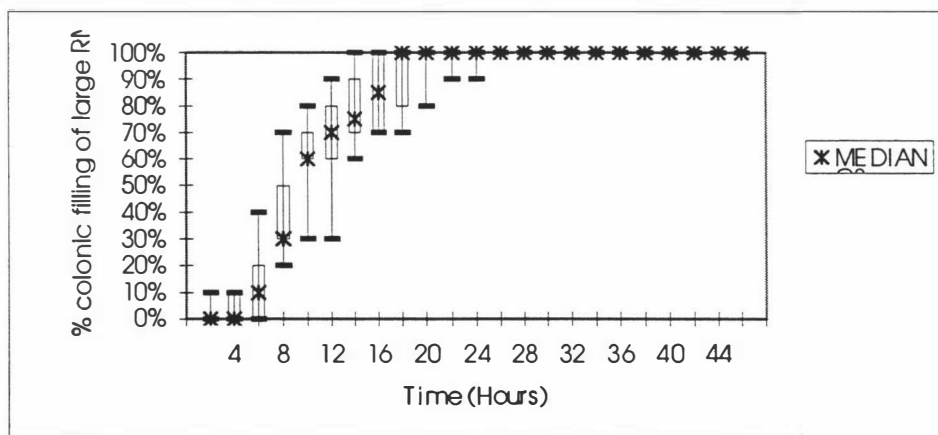
**Figure 6.3** Box plot depicting the colonic filling of the small RM at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).

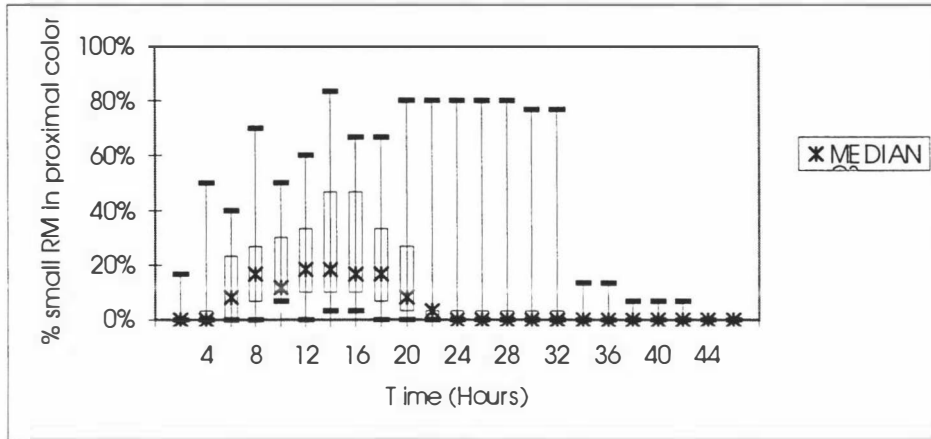


**Figure 6.4** Box plot depicting the colonic filling of the large RM at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



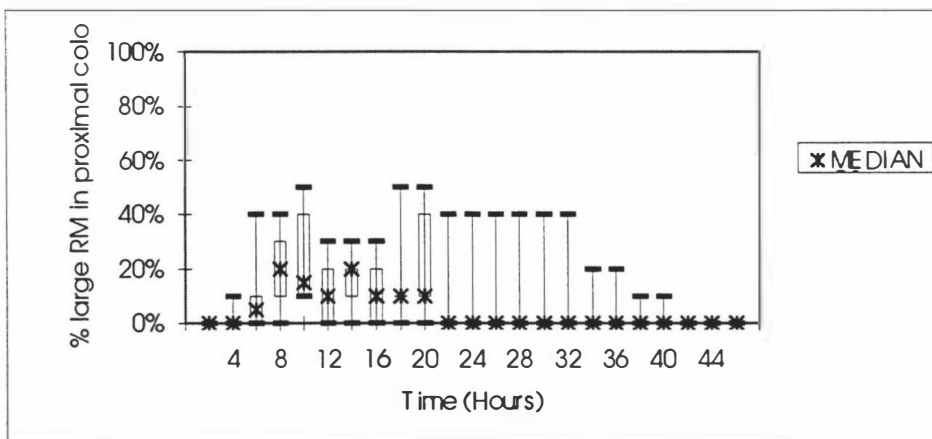
**Figure 6.5** Box plot depicting percentage of small RM in the proximal colon at different times after administration.



The graph shows median values, upper and lower quartiles (bars) and range (lines).

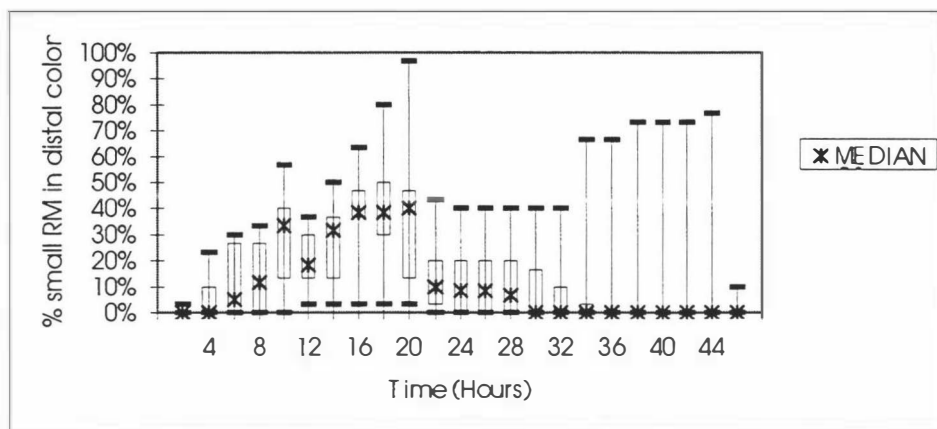
**Figure 6.6** Box plot depicting percentage of large RM in the proximal colon at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



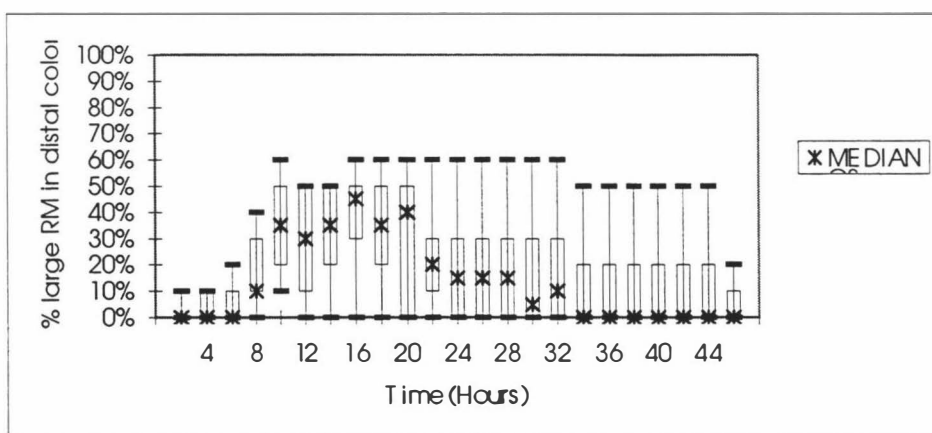
**Figure 6.7** Box plot depicting percentage of small RM in the distal colon at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



**Figure 6.8** Box plot depicting percentage of large RM in the distal colon at different times after administration.

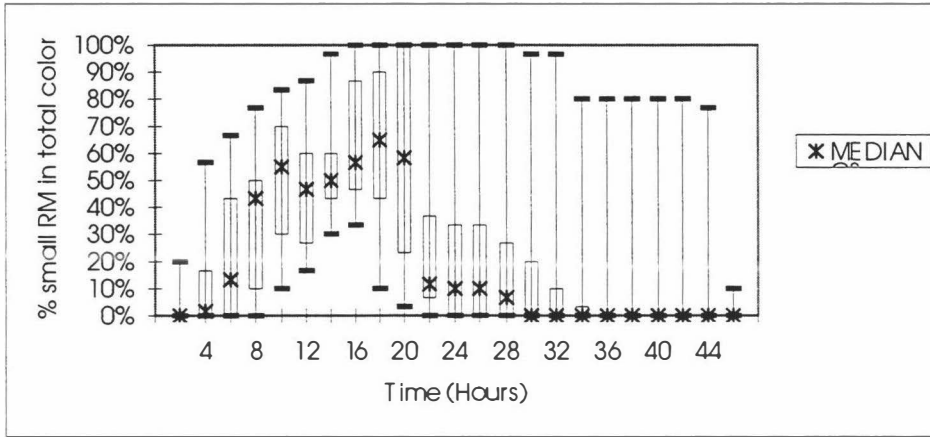
The graph shows median values, upper and lower quartiles (bars) and range (lines).





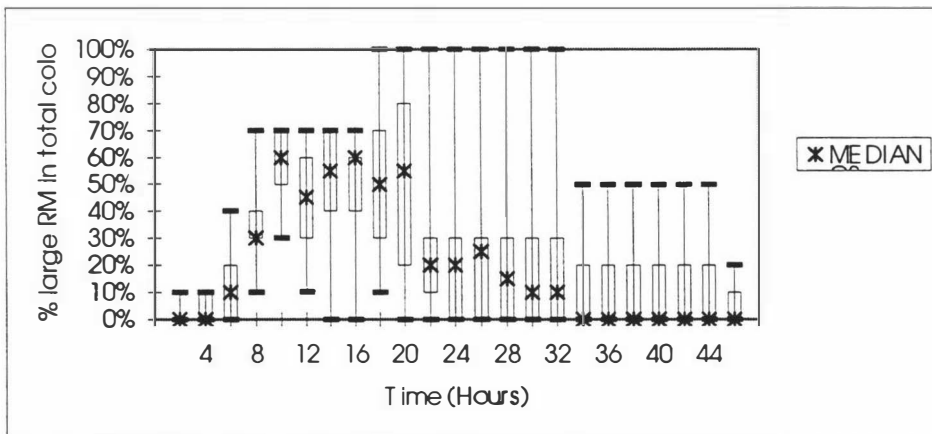
**Figure 6.9** Box plot depicting percentage of small RM in the total colon at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



**Figure 6.10** Box plot depicting percentage of large RM in the total colon at different times after administration.

The graph shows median values, upper and lower quartiles (bars) and range (lines).



## CHAPTER SEVEN

### ***INFLUENCE OF THE SIZE OF PIECES OF FOOD IN A MEAL ON THE GASTRIC EMPTYING OF INDIGESTIBLE SOLID PARTICLES***

#### **7.1 Introduction**

The stomach deals with a variety of types of ingesta simultaneously. It is capable of distinguishing between the different physical properties of liquids, digestible solids and indigestible solids. Knowing how indigestible solids empty from the stomach is useful because it assists in the understanding of the pathogenesis of gastric motility diseases. In addition, it aids manipulation of the gastric residence time of drugs to alter their pharmacokinetics.

As described in Chapter Four, the solid portion of a meal settles in the proximal stomach and from there it is transferred to the distal stomach to be exposed to the grinding action of the antrum. Once the digestible solid particles are small enough to become suspended in the liquid chyme they pass out through the pylorus (Camilleri *et al*, 1985; Hall *et al*, 1988; Kelly, 1980; Quigley, 1996; Malagelada, 1977). Indigestible solid particles may also become suspended in the liquid portion of the gastric contents and leave the stomach with the digestible solid particles (Russell and Bass, 1985b; Itoh *et al*, 1986; Meyer *et al*, 1986; Meyer *et al*, 1988; Sirois *et al*, 1990; Brogna *et al*, 1992). Alternatively, they may be retained until the stomach is empty of digestible food to be expelled by the action of the migrating myoelectric complex (MMC).

There are a variety of factors that affect the gastric emptying of indigestible solids from the stomach. Several of these factors have been incorporated into the hydrodynamic theory of gastric emptying (Sirois *et al*, 1990). These include the size and density of the indigestible particle and the density and velocity of flow of the gastric chyme. As described in Chapter Four, however, the hydrodynamic theory does not completely explain the mechanisms involved in the emptying of particulate material from the stomach. In particular, 'wall factors' such as the strength and frequency of contractions induced by different diets may play an important role.

The size of the pieces of food ingested may influence the gastric emptying rate of particulate material. Large pieces of food require extensive trituration in the stomach (Hinder and Kelly, 1977,), particularly if the food has a firm texture that resists trituration (Poitras *et al*, 1997). The muscular activity of the antrum is likely to facilitate the suspension of particles in the chyme and could potentially reduce the influence of particle density and chyme viscosity on the gastric emptying rate of indigestible particles. In contrast, finely ground food requires little trituration and may not induce as great antral muscular activity as larger food pieces. Indigestible particles ingested with finely ground material may be more likely to settle in the fundus until the digestible material has emptied from the stomach.

In support of this hypothesis, it has been shown that small particles of liver (up to three mm diameter) will empty from the stomach faster than a similar quantity of liver fed in pieces of ten mm diameter (Hinder and Kelly, 1977; Holt *et al*, 1982). This is thought to be due to the time required to triturate the ten mm pieces of liver into

particles small enough to pass through the pylorus. It has also been shown that pieces of liver introduced into the stomach which are small enough to pass through the pylorus will do so unchanged whereas large pieces that must be first triturated are found to exit the stomach as almost liquified material (Meyer *et al.* 1979). It is likely, therefore, that ingestion of large pieces of food may result in increased antral grinding compared with the same food ingested in a finely-ground form.

The objective of the present study was to determine if the size of pieces of food ingested in a meal along with an indigestible solid affects the gastric emptying rate of the indigestible solid.

## **7.2 Materials and Methods**

### ***Indigestible Solid Particles***

A commercially available radiopaque marker (RM) was used (BIPS, MedID, Grand Rapids, USA) as the indigestible solid particle in this study. Thirty small (1.5 mm) and 10 large (5 mm) RM of density 1.37 g/ml were administered to each dog for each gastric emptying study.

### ***Test Meals***

The test meals were prepared from fresh steak ('gravy beef') and rice. Each of the three test meals contained pieces of steak of only one size; either <math>1 \text{ mm}^3</math>,  $10 \text{ mm}^3</math> or  $20 \text{ mm}^3</math>. Steak was used in the test meals on the assumption its firm consistency$$

would require extensive trituration and because it would not disintegrate when being diced or hand fed to the dogs. The steak was prepared immediately prior to each gastric emptying study. Sinew was removed and the meat was diced into 10 mm or 20 mm cubes using a sharp knife and a ruler or placed in a food processor for one minute until the meat had been ground to pieces no bigger than one mm<sup>3</sup>. The steak and RM were then thoroughly mixed with rice. White rice was boiled in water until soft and then refrigerated or frozen until use.

The amount of steak and rice fed was enough to satisfy 20% and 5% respectively of the daily caloric requirement. The weights (grams) of steak and rice to be fed were calculated by the formulae:

Steak:  $(26.4 \times W^{0.75}) / 3.83$

Rice:  $(6.6 \times W^{0.75}) / 1$

Where  $W^{0.75}$  is the 'metabolic size' (Kleiber, 1975), of the dog and 3.83 and 1 represent the energy density of gravy beef steak and rice respectively in kcal/g. The values 24.6 and 6.6 represent 20% and 5% respectively of 132, the constant used to estimate the daily energy requirements of dogs (National Research Council, 1985).

The required amounts of steak and rice were weighed out and the RM were added. Care was taken to ensure thorough mixing of the RM throughout the meal. The meals were then offered to the dogs. Most meals had to be hand fed.

## ***Dogs***

Ten collie-cross or Labrador-cross dogs were supplied by the Animal Health Services Centre for phase one of the study. They ranged in age from 13 months to 91 months and weighed between 17.2 kg and 35 kg (mean 22.9kg). Nine of the dogs were unspayed females and the other dog was a male. Ten collie-cross or Labrador-cross dogs supplied by the Animal Health Services Centre were used for phase two of the study. They ranged in age from nine months to 60 months and weighed between 18 and 28.5kg. Two of the dogs were unspayed females, four were spayed females and one of the four males was neutered. Two of the dogs used in phase one of the study were available to participate in phase two of the study.

None of the dogs had a history of previous gastrointestinal disease and all had been vaccinated and wormed regularly. No abnormalities were detected following a thorough clinical examination.

The dogs were housed and exercised as described in Chapter Six. They had access to water at all times but were fasted for 24 hours prior to the study. The experimental protocol was approved by the Massey University Animal Ethics Committee.

## ***Experimental Design***

The experiment was conducted in two phases. The first phase was designed to prevent variability being introduced within each test meal group as a result of batch-to-batch variation of meat texture. Ten dogs completed a separate gastric emptying study for

each test meal. The studies were carried out one week apart and each test meal was prepared from the same batch of fresh steak. The constraint of using the same batch of fresh steak for each test meal necessitated all dogs in the first phase of the experiment receiving the test meals in the same order. The order of the test meals was randomly chosen as follows. The first test meal studied was the meal containing the 10 mm<sup>3</sup> pieces of steak. The second test meal studied was the meal containing the food processed steak and the last test meal studied was the meal containing the 20 mm<sup>3</sup> steak.

The second phase of the study was designed to control temporal effects that had the potential to confound the first phase of the experiment. In this phase, the order in which the dogs received the test meals was varied. Two orders that differed from the order used in the first phase of the experiment were arbitrarily chosen. Five dogs were randomly assigned to receive the test meal containing the one mm<sup>3</sup> steak pieces followed by that containing the 10 mm<sup>3</sup> and then 20 mm<sup>3</sup> steak pieces. Another five dogs were randomly allocated to receive the test meal containing the 20 mm<sup>3</sup> steak pieces followed by that containing the one mm<sup>3</sup> and then the 10 mm<sup>3</sup> steak pieces. Steak from a different batch was used for this study.

### ***Radiography and Radiographic Interpretation***

The radiographic equipment and radiographic positioning used in this study was identical to that used in the previous chapter. Two radiographs were taken, one in left lateral recumbency and one in ventro-dorsal recumbency. Radiographs were taken immediately following ingestion of the meal and then hourly thereafter until all of the

RM had left the stomach. Each radiograph was studied and the total number of small and large RM noted. Each RM was allocated to either an intragastric position or an extragastric position. If the position of a RM could not be determined, no allocation was given and the RM was excluded from the total counted and future calculations.

### *Statistical Analysis*

Gastric emptying times (GET) of the RM were calculated from the radiographs as described in the previous chapter. No statistically significant differences were found in the gastric emptying rate of each test meal between phase one and phase two of the experiment. As a result, the data from phase one and phase two were combined for analysis.

Mean (and SD) gastric emptying curves were constructed for the small and large RM fed with each of the three test meals. The mean 50%, 75% and 90% gastric emptying times for the small and large RM were calculated by interpolation and compared (within each test meal group) by the Wilcoxon Sign Rank Test.

In addition, the area under the gastric emptying curves (AUC) was calculated, using linear interpolation and the trapezoidal rule, for each size of RM in each dog for each test meal. The AUC data was used to compare the length of time the RM remained in the stomach with each test meal. A smaller area was considered to indicate more rapid gastric emptying. The small and large RM were analysed separately. Analysis of Variance (ANOVA) with two factors (the test meal and the order in which the test meals were fed) and the dog as a blocking variable was



used. The data satisfied the distributional assumptions required of a parametric ANOVA. Fisher's Least Significant Difference (LSD) test was used to compare means for the test meals if the 'meal-effect' was significant.

### **7.3 Results**

Unfortunately, it became necessary to remove one of the dogs from phase one of the study as it was found to have an abnormally long gastric emptying time. RM were observed to remain in the stomach up to 48 hours after administration - more than twice the length of time of all of the other dogs. For this reason it was decided that the dog may have had a previously undetected gastric abnormality and therefore should not be included in the experiment.

The mean gastric emptying times (GET) of the small and large RM fed with the three different meals are shown in Table 7.1. The 50% GET of the small RM was significantly faster than the large RM in the test meal containing the ten mm<sup>3</sup> steak pieces. The 50% and 75% GET of the small RM were significantly faster than those of the large RM in the meals containing the one mm<sup>3</sup> and 20 mm<sup>3</sup> steak. There were no significant differences between the 90% gastric emptying times of the small and large RM in any of the meals.

The mean gastric emptying curves for the small and large RM fed with the three test meals are shown in Figures 7.1 and 7.2. The area under the gastric emptying curve (AUC) data is shown in Table 7.2.

For the small RM data, there was no significant interaction between the order of feeding the test meals and the size of the pieces of steak on the area under the gastric emptying versus time curve. The size of the pieces of steak did not influence the rate of gastric emptying of the small RM. The order of feeding the test meals did not influence the rate of gastric emptying.

For the large RM data, there was no significant interaction between the order of feeding the test meals and the size of the pieces of steak on the area under the gastric emptying versus time curve. The order of feeding the test meals did not influence the rate of gastric emptying. There was, however, a significant effect of the size of the piece of steak on the area under the gastric emptying versus time curve ( $p= 0.0068$ ). The large RM left the stomach significantly faster in the meal containing the  $10 \text{ mm}^3$  steak compared to the meals containing the  $20 \text{ mm}^3$  steak ( $p= 0.0029$ ). They also tended to leave the stomach faster in the meal containing the  $10 \text{ mm}^3$  steak compared to the meal containing the  $1 \text{ mm}^3$  steak ( $p=0.07$ ). There was no significant difference between the area under the gastric emptying versus time curves for the  $20 \text{ mm}^3$  steak and the  $1 \text{ mm}^3$  steak.

## 7.4 Discussion

The mean gastric emptying times (GET) of the small and large RM fed with the three test meals are similar to the mean GETs previously reported when the RM have been fed with other diets (Allan *et al*, 1996; Bruce *et al*, 1999).

In general, the large RM emptied more slowly than the small RM. This is in agreement with previous studies (Itoh *et al*, 1986; Meyer *et al*, 1985; Sirois *et al*, 1990; Bruce *et al*, 1999; Chandler *et al*, 1999). The slower emptying of the large RM compared to the small RM may be explained by the hydrodynamic theory of gastric emptying (Sirois *et al*, 1990). This study showed that indigestible particles leave the stomach along with digestible solids if they are of suitable size and density, relative to the density and viscosity of the fluid in which they are suspended. Sirois *et al* (1990) also showed that indigestible particles of similar density to the fluid in which they are suspended will empty from the stomach progressively more slowly as their size increases from 1.6 mm to 4 mm. Both sizes of RM used in this study are of similar density (1.37g/ml) to gastric chyme and are therefore of optimal density to empty with the digestible solids. It is therefore not surprising that the 5 mm diameter RM left the stomach more slowly than the 1.5 mm diameter RM.

The gastric emptying curves observed in the present study have similar shapes to previous RM studies (Allan *et al*, 1996; Chandler *et al*, 1999; Lester *et al*, 1999) and other studies observing the gastric emptying of digestible solids (Hinder and Kelly, 1977; Camilleri *et al*, 1985; Collins *et al*, 1988; Houghton *et al*, 1988). The gastric emptying curves have a lag phase followed by a period of linear emptying similar to

that described for the gastric emptying of digestible solids (Camilleri *et al*, 1985; Collins *et al*, 1988; Houghton *et al*, 1988). This supports the assumption that the RM are emptying along with the solid phase of the meal.

The results of this study support the hypothesis that the size of the pieces of food ingested influence the gastric emptying rate of particulate material. The reason the large RM emptied faster in the meal containing the 10 mm<sup>3</sup> steak than the 20 mm<sup>3</sup> steak appears to be due primarily to a shorter lag phase. In Figure 7.2 it can be seen that it took about one hour longer to empty more than 20% of the large RM from the stomach when fed with the meal containing the 20 mm<sup>3</sup> steak compared to the 10 mm<sup>3</sup> steak. The duration of the lag phase has been correlated to the time required to reduce the solid component of a meal into small enough particles which can pass through the pylorus (Camilleri *et al*, 1985, Horowitz *et al*, 1994 and Siegel *et al*, 1988). It is probable that the 20 mm<sup>3</sup> steak meal would have taken longer to triturate into sufficiently small particles than the 10 mm<sup>3</sup> steak meal. It is noteworthy, however, that the lag phase was less evident for the small RM. This may be because, due to their smaller size, the small RM may have started to empty immediately from the stomach during trituration.

The large RM may have tended to leave the stomach faster when the meal with the 10 mm<sup>3</sup> steak was consumed than when the one mm<sup>3</sup> steak was consumed due to the increased amount of trituration required by the stomach to empty the 10 mm<sup>3</sup> steak. The increased amount of trituration required for the larger pieces of steak may have kept the RM suspended in the chyme leaving the stomach thereby hastening their emptying. The gastric emptying of indigestible particles is described by the

hydrodynamic theory of gastric emptying in part only (Sirois *et al*, 1990). In particular, ‘wall factors’ such as the strength and frequency of contractions induced by different diets may play an important role in influencing the suspension of indigestible particles in gastric chyme. The present study suggests that the size of the pieces of food ingested in the meal may influence the ‘wall factors’ that Sirois *et al* (1990) described because larger food particles increase trituration and may therefore increase the suspension of larger indigestible. It is unclear why the same effect was not seen with the small RM. A possible explanation is that the small RM remained suspended in the gastric chyme more easily than the large RM, lessening the importance of trituration in maintaining their suspension.

In conclusion, the size of the pieces of food ingested in a meal along with an indigestible solid particle appear to affect the gastric emptying rate of the indigestible solid particle.

**Table 7.1 Mean Gastric Emptying Times (in Hours) for RM Ingested with Steak of Size <1 mm, 10 mm and 20 mm**

% gastric emptying of RM	Size of RM	Test Meal					
		Steak Size <1mm		Steak Size 10mm		Steak Size 20mm	
		Mean time (hrs)	SD	Mean time (hrs)	SD	Mean time (hrs)	SD
GE50%	Small	6.48*	3.04	5.87*	2.28	5.65*	3.38
	Large	9.11	3.01	8.13	2.38	9.66	3.05
GE75%	Small	7.95*	2.92	7.57	2.25	7.22*	3.10
	Large	9.68	2.83	8.60	2.45	10.41	3.04
GE90%	Small	9.13	2.57	8.74	2.44	9.03	2.65
	large	10.19	2.65	8.87	2.48	10.76	3.00

\*Denotes emptying time to be significantly shorter compared to the large spheres fed with the same test meal (p<0.05)

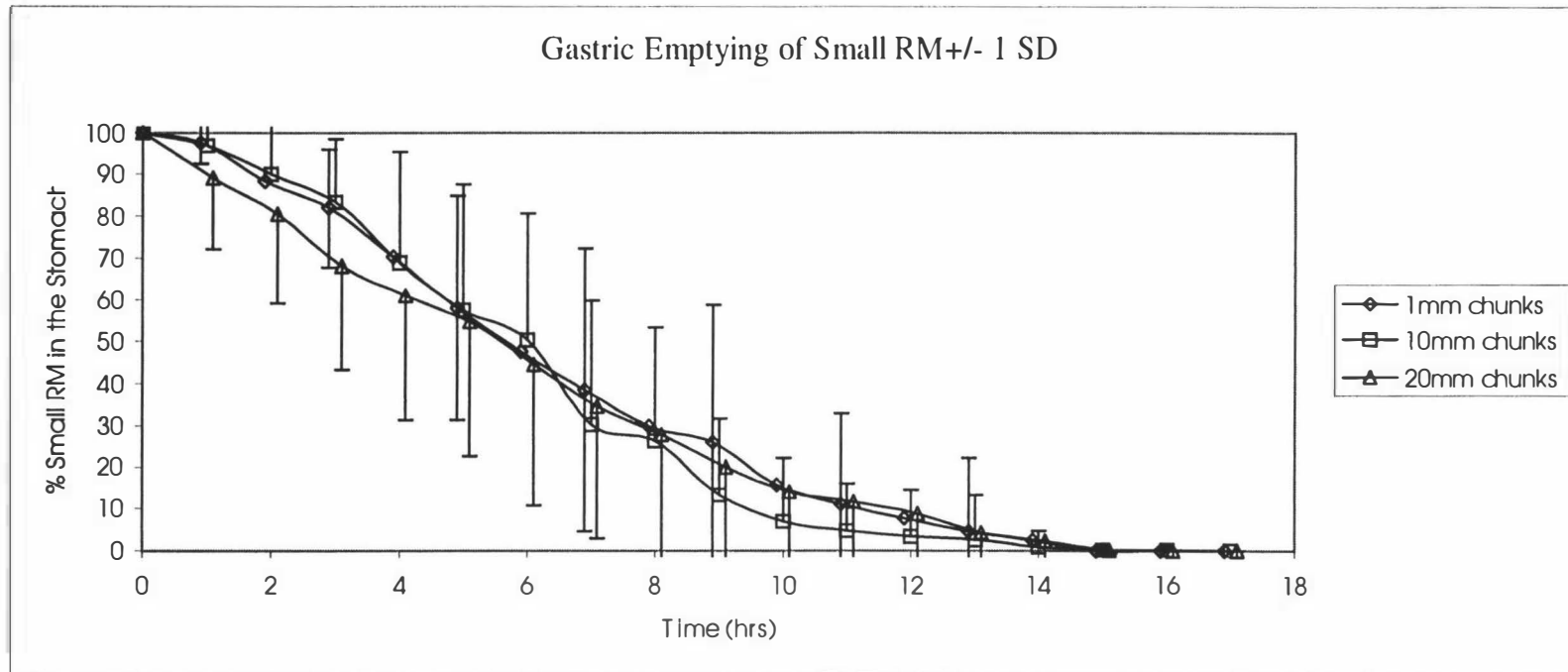
GE= gastric emptying, RM= radiopaque marker, SD= standard deviation

**Table 7.2 Area Under the Curve Data from the Gastric Emptying Curves for RM Ingested with Steak of Size <1 mm, 10 mm and 20 mm**

Test Meal	Small RM		Large RM	
	LS Mean AUC*	SD	LS Mean AUC*	SD
1 mm <sup>3</sup>	4.92	1.14	7.87	2.68
10 mm <sup>3</sup>	5.64	1.46	7.53	1.99
20 mm <sup>3</sup>	4.46	1.73	9.26	2.34

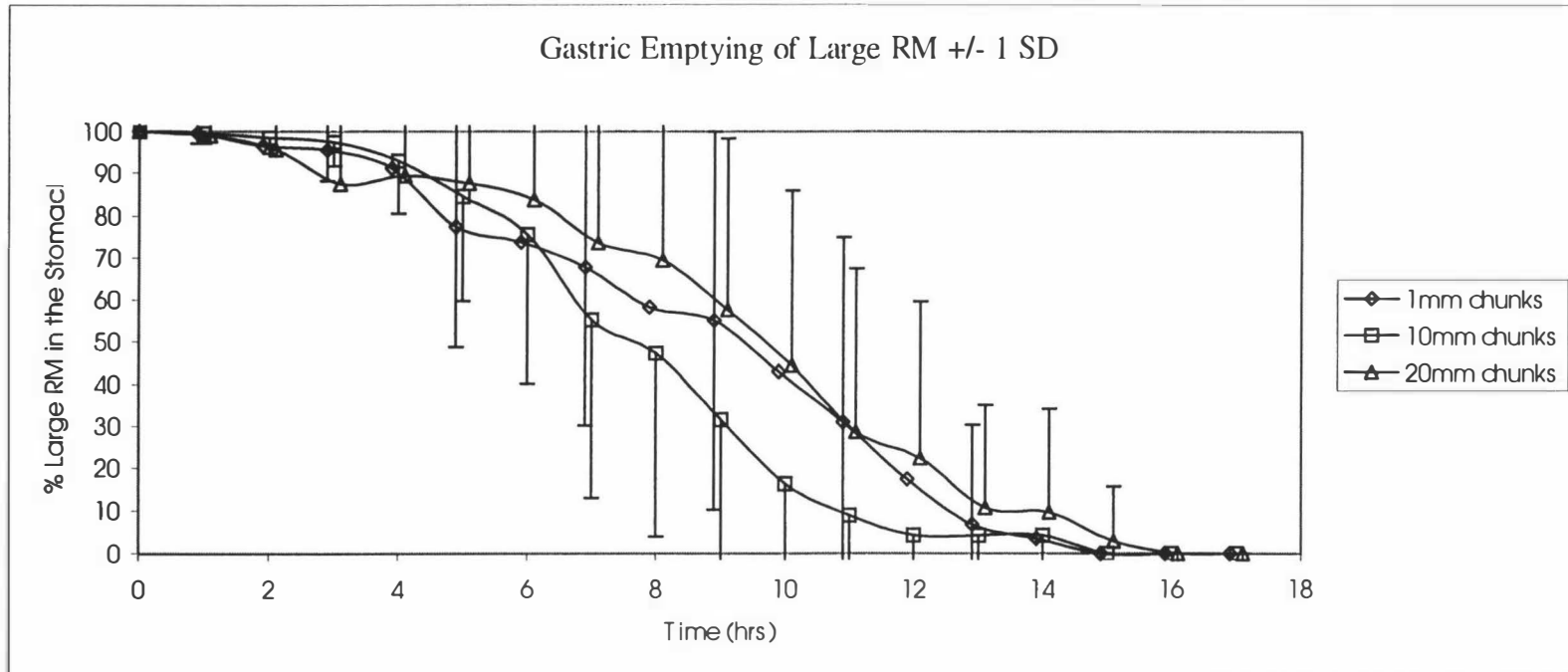
\* Least Squares (LS) Means (SAS/Stat User Guide, 1990, Cary, North Carolina) are presented. A smaller area is suggestive of more rapid emptying.

**Figure 7.1** The percent gastric emptying of the small RM for each test meal as a function of time with standard deviation bars.\*



\* The upper SD bar from the 20mm test meal data, the lower SD bar from the 10mm test meal data and every second upper and lower SD bar from the 1mm test meal data have been removed to make interpretation easier.

**Figure 7.2 The percent gastric emptying of the large RM for each test meal as a function of time with standard deviation bars.\***



\* The upper SD bar from the 10mm test meal data, the lower SD bar from the 20mm test meal data and every second upper and lower SD bar from the 1mm test meal data have been removed to make interpretation easier.



## CHAPTER EIGHT

### **A RETROSPECTIVE STUDY OF THE USE OF RADIOPAQUE MARKERS IN DOGS AND CATS WITH GASTROINTESTINAL PROBLEMS 1993-1998**

#### **8.1 Introduction**

Radiopaque markers (RM) have been used for a variety of diagnostic purposes in human gastroenterology for some time. These include measurement of total gastrointestinal transit (Hinton *et al*, 1969), detection of diabetic gastroparesis (Bertrand *et al*, 1982), detection of partial small bowel obstruction (Johnson *et al*, 1996) and the assessment of colonic transit (Bouchoucha *et al*, 1992; Camilleri and Zinsmeister, 1992; Casanovas *et al*, 1991; Metcalf *et al*, 1987; Stivland, *et al*, 1991; van der Sijp *et al*, 1993; von der Ohe and Camilleri, 1992). More recently, RM have been used in veterinary medicine.

Publications to date have largely focused on validation of the technique and the development of reference ranges (Allan *et al*, 1996; Bruce *et al*, 1999; Chandler *et al*, 1999; Fucci *et al*, 1995; Sparkes *et al*, 1997,<sup>a</sup>)(see Chapters 1 and 2). Preliminary evidence that RM have a useful role in veterinary gastroenterology has been presented (Guilford *et al*, 1997; Nelson *et al*, 1996).

---

<sup>a</sup> BIPS Booklet, NZ Vet, Christchurch, NZ

## **8.2 Objectives**

The objectives of this retrospective study were: to record the type of clinical situations in which RM have been used at the Massey University Veterinary Teaching Hospital; to record the different radiographic RM patterns produced and their interpretation; to review the final diagnoses of the patients investigated with RM; and to assess the contribution that the studies made to the diagnostic outcome.

## **8.3 Materials and Methods**

### *Case Records*

The case records from 120 dogs and 67 cats that had undergone RM studies at Massey University Veterinary Teaching Hospital (MUVTH) over a five year period were reviewed. Some animals had been studied multiple times. As a result, 142 canine studies and 73 feline studies were available for evaluation.

### *Radiopaque Markers*

A commercial radiopaque marker (Barium Impregnated Polyethylene Spheres BIPS (Med ID, Grand Rapids, USA) was used in all studies. In most cases 30 small (1.5mm) and 10 large (5mm) RM were given to each animal.

### ***Information Collected from the Case Records***

The following information was collected: signalment, body weight, clinical signs, previous drug administration, method of RM administration, radiographic RM pattern observed, presence or absence of survey radiographs, radiographic abnormalities present, radiographic diagnosis, final diagnosis, all tests carried out to attain the final diagnosis, usefulness of RM study and the number of studies carried out. The radiographic abnormalities noted were those obtained from the radiologist's report, contained in the case record. The usefulness of the study was determined by subjective assessment of how the results of the RM study affected management of the case.

### ***RM Study Assessment***

All RM study radiographs and survey radiographs were reviewed by the author with the exception of those of five dogs and two cats that were not available for review. These five dogs and two cats, all of which had undergone one RM study each, were removed from the review. RM studies were considered to be normal when the markers passed through the gastrointestinal tract of the dog or cat within the appropriate published reference interval for that species<sup>a</sup>. RM studies that fell outside the published reference interval were considered to be abnormal.

The 'pattern' of the abnormality was described according to the location of the RM in the gastrointestinal tract and the rapidity of gastric emptying or orocolic transit of the RM.

There were a variety of RM patterns observed, including prolonged RM retention in the stomach (referred to as 'delayed gastric emptying' pattern), delayed gastric and intestinal transit with RM scattered throughout the stomach and small intestines, (referred to as 'adynamic ileus' pattern), delayed orocolic transit with RM bunched in one area of the small intestines (referred to as 'bunching' pattern), rapid orocolic transit and delayed colonic transit.

The ability to distinguish between delayed gastric emptying (DGE) and adynamic ileus relied on the timing of the radiographs. In several cases a distinction could not be made because insufficient radiographs had been taken to evaluate the rate of transit of the RM through the intestine. These patients were recorded as having a DGE pattern.

RM studies were recorded as inconclusive when insufficient radiographs had been taken following RM administration, or if they had been taken at times which did not allow differentiation between normal and abnormal gastrointestinal transit.

## 8.4 Results

### *Signalment*

A wide range of ages of dog were studied from 1 month to 14 years (mean 4.5 years).

The age range of cats studied was 2 months to 15 years (mean 6.25 years). The most commonly represented breeds of dog to undergo RM studies were Labrador Retrievers, cross breeds and German Shepherds with 15, 13 and 10 of those respectively.

Rottweilers, Poodles and Boxers were also quite commonly represented with six, five and five of those included in the study. A wide range of other breeds of dogs also underwent RM studies. Domestic short and long haired cats were the most common breed of cat that underwent RM studies with 46 of those included in the study along with seven Siamese, four Burmese, three Persian, two Birman and one each of the Chinchilla, Havana and Exotic breeds. The sexes of the dogs and cats studied are shown in Tables 8.1 - 8.2. The mean weight of the dogs was 20.3 kg (range 1.1 – 54.5 kg). The mean weight of cats was 3.9 kg (range 1 – 9 kg).

### *Clinical Signs Manifested by Animals Undergoing RM Studies*

The most common clinical sign exhibited by dogs and cats undergoing RM studies was vomiting. The second and third most common clinical signs observed in dogs undergoing RM studies were diarrhoea and anorexia, respectively. In cats, the second and third most common clinical signs were anorexia and weight loss. The variety of clinical signs

manifested by animals undergoing RM studies are shown in Table 8.3. The more unusual clinical signs noted were always accompanied by some of the classical clinical signs of gastrointestinal dysfunction such as vomiting.

### ***Indications for RM Studies***

RM studies were used to assess gastrointestinal motility in animals with clinical signs suggestive of gastrointestinal disease, such as vomiting and diarrhoea. RM studies were also used to rule out a diagnosis, usually a suspicion of a physical obstruction. They were used for this purpose mainly in the vomiting animal. Additionally, RM studies were used to evaluate success of medical therapy (eg, erythromycin treatment for a dog with intestinal pseudo-obstruction) or surgical therapy (eg, following Y-U Plasty).

### ***Administration Techniques***

In general, the method of administration of the RM depended on the presenting complaint and clinical signs of the animal. For example, if the animal was vomiting acutely or was ill such that the ingestion of food would be unlikely or impractical, the RM were administered on an empty stomach. Otherwise, the RM were generally administered mixed in a diet recommended by the manufacturer.

In 30 (22%) canine studies, the RM were administered on an empty stomach. In 70 (51%) canine studies the RM were given with a diet recommended by the manufacturer

(Prescription diet canine d/d, Hills Pet Products). On one occasion the RM were given with dog roll and on another they were given with a gruel. In the remaining 37 (27%) canine studies the method of administration could not be determined from the records. Of these studies, the recording of 25 (18%) studies as normal or abnormal was not affected by whether the reference intervals (BIPS Booklet, NZ Vet, Christchurch, NZ) used were for fed or fasted dogs. In nine studies, the only conclusion that could be drawn from the information present was that no physical obstruction was present. The remaining five of the canine studies were inconclusive and were not used further in the review.

In 16 (23%) feline studies the RM were administered without food. Thirty-three (46%) cats were given the RM with food. In 26 studies cats were given the RM with the diet recommended by the manufacturer (Prescription Diet feline d/d, Hills Pet Products). In three studies the RM were given with a high fibre diet (Prescription Diet feline r/d, Hills Pet Products) and in four studies, cats were given the RM with another canned commercial diet. In 22 (31%) cases it could not be determined from the records how the RM were administered to cats. However, in eight of these studies the results of the RM study were not altered by whether the reference intervals (BIPS Booklet, NZ Vet, Christchurch, NZ) used were for fed or fasted cats. In eight studies the only conclusion that could be made was that no physical obstruction was present. The remaining seven of the feline studies were inconclusive and were not used further in the review.

### ***Radiographic findings of RM Studies***

Of the 142 canine studies available for evaluation, ten were eliminated from further consideration because the radiographs were not available for review by the author or because the studies were inconclusive. Of the remaining 132 studies carried out on dogs, 69 (52%) RM studies were considered abnormal, 60 (45%) were considered normal and 3 (2%) were considered inconclusive. Of the abnormal studies in dogs, 46 (66%) of them showed delayed gastric emptying (DGE), 13 (19%) showed adynamic ileus, 4 (6%) revealed a bunching pattern and 4 (6%) indicated rapid orocolic transit. The remaining 2 (3%) of studies showed miscellaneous patterns, ie, one study revealed rapid oro-rectal transit and another showed rapid gastric emptying of the RM but slow orocolic transit.

Of the 73 feline studies available for evaluation, nine were eliminated from further consideration because the radiographs were not available for review by the author or because the studies were inconclusive. Of the remaining 64 feline studies, 32 (50%) RM studies were abnormal and 32 (50%) were normal. Of the abnormal studies, 14 (44%) showed delayed gastric emptying, 6 (18%) showed rapid orocolic transit, 4 (12%) showed adynamic ileus, 5 (16%) showed delayed colonic transit and 3 (9%) showed a bunching pattern.

In some of the RM study radiographs, other radiographic abnormalities were noted. The most common abnormalities in dogs were dilated bowel loops, ventral spondylosis and splenomegaly. In cats, the most common abnormalities observed were dilated bowel



loops, abnormal gastric shadow and hepatomegaly. A complete description of additional radiographic abnormalities noted in the RM radiographs is provided in Table 8.6. All the RM studies showing a physical obstruction pattern had other radiographic signs suggestive of obstruction based on standard radiographic signs, eg, dilated bowel loops and gravelling.

### ***Survey Radiographs***

Survey radiographs were taken in some animals in addition to the RM study radiographs. This occurred in 24 (17%) canine studies and 9 (12%) feline studies. The survey radiographs did not give any additional information that could also be provided by the RM radiographs. However, 17/24 (71%) of the RM study radiographs in dogs and 8/9 (88%) of RM study radiographs in cats provided more information than the survey radiographs. The additional information was either the identification of a motility abnormality (12/24 canine cases, 5/9 feline cases) or the definitive exclusion of a diagnosis of a physical obstruction (6/24 canine cases, 3/9 feline cases).

### ***Final Diagnoses - Delayed Gastric Emptying Pattern***

Of the 46 dogs with a DGE pattern, 33 (72%) had pathology present in the intestine +/- the stomach, whereas 13 (28%) had pathology exclusively in the stomach. Nineteen (41%) dogs with a DGE pattern were diagnosed with inflammatory bowel disease, 5 (11%) had a gastrointestinal foreign body [2 (4%) gastric foreign body], 4 (9%) had

gastrointestinal neoplasia [2 (4%) gastric neoplasia], and 4 (9%) had antral pyloro-hypertrophy syndrome. The rest of the dogs with DGE had a variety of gastrointestinal and other disorders that are shown in Table 8.4.

In cats, the final diagnoses associated with a DGE pattern were also varied. Of the 14 cats with a DGE pattern, only four (29%) had pathology exclusively in the stomach. Five (36%) cats with a DGE pattern were diagnosed with IBD with or without other conditions. Two (14%) cats had an intestinal foreign body and 2 (14%) had gastritis. The remainder of diagnoses associated with the DGE pattern are shown in Table 8.4.

#### ***Final Diagnoses - Adynamic Ileus Pattern***

Of the 13 dogs with a RM pattern suggestive of adynamic ileus, 3 (23%) were diagnosed with intestinal neoplasia, 3 (23%) had enteritis (parvoviral or nonspecific) and 2 (15%) had inflammatory bowel disease alone, or in combination with other disease processes. The remainder of diagnoses associated with an adynamic ileus RM pattern are shown in Table 8.5.

Of the four cats with a RM pattern suggestive of adynamic ileus, one was found to have IBD, one food allergy, one intestinal neoplasia and in one cat the diagnosis was open, as shown in Table 8.5.

### ***Final Diagnoses - Bunching Pattern***

Of the four dogs with a bunching pattern, two were diagnosed with an intestinal foreign body, one had an intestinal adenocarcinoma and one had inflammatory bowel disease. All three cats with a bunching pattern were found to have intestinal neoplasia.

### ***Final Diagnoses - Rapid Orocolic Transit Pattern***

Three out of the four dogs showing a rapid orocolic transit pattern were found to have IBD and one dog remained undiagnosed. Four out of the six cats with a rapid orocolic transit pattern were diagnosed with IBD or chronic gastritis and two cats remained undiagnosed.

### ***Final Diagnoses - Delayed Colonic Transit Pattern (cats only)***

Three of the five cats with this pattern were diagnosed with idiopathic constipation, whereas one cat had a colonorectal stricture and one cat had constipation in association with a 'tail- pull neuropathy'.

### ***Diagnostic Procedures used with RM***

Approximately half the animals underwent RM studies as part of a complete work up for gastrointestinal disease. The diagnostic procedures included a complete blood count, serum biochemistry profile, assay of serum TLI, serum T<sub>4</sub>, FeLV test, FIV test, urinalysis, faecal analysis, gastroduodenoscopy with biopsy and breath hydrogen test. In this situation, the RM studies often broadened the diagnostic findings by detecting

delayed gastric emptying but the definitive diagnosis was obtained by one or more of the other diagnostic procedures. In 39 of the 69 dogs that underwent endoscopy and a RM study, the RM study indicated that altered motility was present. In the remaining 30 dogs a diagnosis of a partial intestinal obstruction was ruled out. In 16 of the 33 cats that underwent endoscopy and RM studies, the RM indicated that altered motility was present. In the remaining 17 cats a partial obstruction was ruled out. Exploratory laparotomy also was used in conjunction with RM studies. Exploratory laparotomies were primarily performed to confirm or refute a suspected intestinal obstruction after the observation of a bunching RM pattern.

## 8.5 Discussion

The most common RM pattern observed in both dogs and cats was delayed gastric emptying (DGE). Disorders of the stomach, such as antral pylorohypertrophy syndrome, gastric neoplasia, gastritis and gastric dysmotilities, accounted for less than one third of the animals with the DGE pattern. More commonly, the delayed gastric emptying was associated with intestinal disorders such as enteritis, enteropathy and, in particular, inflammatory bowel disease (IBD). The cause of the modest DGE observed in the animals with IBD and gluten enteropathy may have been due to activation of the 'ileal brake' by the malabsorption associated with these conditions (see Chapter Two).

Importantly, foreign body obstruction of the intestine often resulted in a DGE pattern in dogs and cats instead of the more characteristic bunching RM pattern. This was most likely due to the foreign body initiating a degree of adynamic ileus (Guilford and Strombeck, 1996b). Adynamic ileus may have contributed also to the DGE pattern observed in the animals with enteritis. As mentioned previously, it was sometimes difficult to differentiate the DGE pattern from the adynamic ileus pattern because some of the RM studies were not continued long enough to demonstrate delayed intestinal transit over and above delayed gastric emptying.

Only a small number of dogs and cats with a bunching RM pattern were observed. The low prevalence of physical obstructions of the bowel is probably a reflection of the type

of cases that were referred to MUVTH. The small number of animals with this pattern makes it difficult to draw conclusions about the diagnostic accuracy of the pattern. Nevertheless, the specificity of the bunching pattern for physical obstruction appears to be high (75% [3/4] in dogs and 100% [3/3] in cats in our study).

The cause of the bunching pattern in one dog was not established. This dog had clinical signs of weight loss and large bowel diarrhoea. The RM arrested at the ileocolic valve for a period of 24 hours and were associated with a dilated small bowel loop. Exploratory laparotomy did not detect any gross abnormalities of the ileocolic area. A biopsy sample was not taken from the area due to the cachexic state of the dog. The only abnormality detected on a subsequent gastroduodenoscopy and colonoscopy was a mild lymphocytic duodenitis. The dog responded rapidly to dietary manipulation. Either a transient partial obstruction (foreign body or intussusception) of the ileocolic valve, an ileitis or a motility disorder of the ileocolic area may have been present in this case.

The sensitivity of the bunching pattern for the detection of physical bowel obstruction was more difficult to assess because it was dependent on radiographs being taken after allowing sufficient time for the RM to leave the stomach and collect orad of the obstruction. In some of the animals with physical obstructions, the RM study was terminated because evidence on the first set of radiographs, such as dilated small intestinal loops or a radiopaque foreign body, immediately led to an exploratory laparotomy. If 8 hours was arbitrarily selected as an adequate duration for an RM study

and all studies terminating earlier than this were excluded, the sensitivity of the bunching pattern for physical bowel obstruction was 100% (3/3) in dogs and 50% (3/6) in cats.

As discussed above, a contributing factor to the absence of the bunching pattern in some animals with bowel obstruction appeared to be an associated adynamic ileus that trapped the RM in the stomach. It is noteworthy, however, that no animal with a physical obstruction of the bowel had a normal RM study (3/8 dogs and 3/6 cats had a bunching pattern, 5/8 dogs and 2/6 cats had DGE, and 1/6 cats had an adynamic ileus pattern). Similarly, no animal that had a normal RM study was subsequently shown to have a physical obstruction of the bowel.

Collectively, these observations suggest that clinicians can usually rule out physical obstructions in animals with a normal RM study (ie. The negative predictive value of the test is high). In addition, if a bunching pattern occurs, a physical obstruction is highly likely. Lastly, if a DGE or adynamic ileus pattern occurs, motility disorders are most likely but physical obstructions cannot be ruled out until such time as the RM (particularly the large RM) arrive in the colon.

Rapid orocolic transit occurred in a small number of cats and dogs in association with IBD. The most likely cause for the rapid transit was interference with the 'enterogastric reflex' controlling gastric emptying (see Chapter Two). In particular, it has been proposed that chronic duodenal inflammation can alter the release of hormones such as CCK that mediate gastric emptying (Hall *et al*, 1990; Guilford and Strombeck, 1996a).

The apparent paradox that IBD can be associated with rapid gastric emptying in some animals and delayed gastric emptying in others (see above) may have a number of explanations. In theory, variation in the severity of the mucosal inflammation and the area of gastrointestinal tract affected could result in quite different effects on transit. Animals with IBD primarily affecting the duodenum are more likely to have rapid gastric emptying through interference with the 'enterogastric reflex'. In contrast, in animals with more generalised IBD, the malabsorbed nutrients reaching the ileum can be expected to stimulate the 'ileal brake' mechanism and delay gastric emptying.

Unfortunately, the area of the intestine most severely affected by IBD in the dogs and cats reviewed in the present study was usually not determined. In addition, the presence of concurrent disease along with IBD in some of the dogs in the present review made comparison of the cases with rapid orocolic transit to those with delayed orocolic transit difficult. Nevertheless, the observation that IBD can be associated with rapid or delayed orocolic transit suggests that patients with the disease may benefit from tailored nutritional or drug therapies aimed at either slowing or quickening orocolic transit respectively.

Survey radiographs, when taken, rarely gave any additional information to that which was obtained from the RM study. Indeed, it was usual to obtain more information from the RM study. This was because all abdominal abnormalities viewed on the survey radiographs were also observed on the RM radiographs and, in addition, the RM radiographs provided information on gastrointestinal motility and/or ruled out a physical



obstruction. These observations suggest that, unlike contrast studies with barium suspensions, survey radiographs are not required prior to RM studies. Furthermore, it appears that administering RM several hours (preferably 8 hours or more) prior to taking survey radiographs will allow clinicians to derive more information of relevance to diagnosis and case management than survey radiographs not preceded by RM administration.

The RM studies in the present review provided a definitive diagnosis only in a small number of patients. These patients were diagnosed with physical obstructions of the bowel and primary dysmotilities such as a case of intestinal pseudo-obstruction in a dog. In many other patients, the RM studies highlighted a secondary dysmotility allowing the clinician to consider symptomatic management of the patient's dysmotility (eg. with prokinetic drugs or gruels for DGE) or waiting for the dysmotility to be controlled by attention to the patient's primary problem. Determining from the case records what criteria triggered clinicians to symptomatically treat dysmotilities was difficult, however. RM studies appeared to be useful also in ruling out partial obstructions of the bowel and to assess response to medical or surgical treatment of delayed gastric emptying and constipation.

In summary, RM studies were performed primarily in animals with vomiting, diarrhoea, anorexia or weight loss to rule out physical obstructions of the gastrointestinal tract (particularly partial obstructions) and to detect motility disorders. The most common RM pattern observed in both dogs and cats was delayed gastric emptying (DGE). Other

patterns included the adynamic ileus pattern and the bunching pattern. If a delayed gastric emptying or an adynamic ileus RM pattern was observed, a dysmotility was the most likely cause but a physical obstruction could not be ruled out until such time as the RM (particularly the large RM) arrived in the colon. A physical obstruction of the bowel was highly likely if RM bunched in the small intestine and very unlikely if the orocolic transit of the RM was within the reference intervals. Only a small number of primary dysmotilities were diagnosed but secondary dysmotilities appeared common. They were readily detected with RM ensuring the clinician considered the option of symptomatic management of the dysmotility. RM were also used to monitor response to treatment. In conclusion, the results of this study suggest RM are useful in the diagnostic work up and management of cats and dogs with gastrointestinal problems.

**Table 8.1 Sex of the Dogs Undergoing RM Studies**

	Male	Female
Entire	50	21
Neutered	24	28
Total	74	49

**Table 8.2 Sex of the Cats Undergoing RM Studies**

	Male	Female
Entire	6	5
Neutered	29	26
Total	35	31

**Table 8.3 Clinical Signs Manifested by Animals Which Resulted in a RM Study being Carried Out**

Clinical Signs	Dogs	Cats
Vomiting	92	45
Diarrhoea	50	18
Anorexia	32	29
Weight Loss	31	20
Lethargy	18	7
Depression	15	4
Gastric Dilatation-Volvulus (GDV) / post surgical GDV	11	2
Abdominal pain	7	0
Melaena	6	0
Tenesmus	6	3
Regurgitation	5	1
Failure to Thrive	4	1
Abdominal Bloating	4	1
Haematemesis	3	1
Borborygmus	3	0
Polyuria/Polydipsia	3	4
Flatulence	2	0
Haematochezia	2	0
Weakness	2	0
Restless	2	0
Shaking	2	0
Arching back	2	1
Dyschezia	2	3
Poor Coat Quality / Skin Disease	2	5
Obstipation	1	1
Dehydrated	1	0
Excessive Swallowing	1	0
Constipation	1	4
Dysphagia	1	2
Post prandial pain	1	0
Repeat Study	1	0
Retching	1	1
Praying Position	1	0
Halitosis	1	0
Cough	1	2
Shifting Lameness	1	0
Icterus	0	1
Distress	0	1
Collapse	0	1
Polyphagia	0	1
Ptyalism	0	1

**Table 8.4 Final Diagnoses Associated with RM Studies Showing the Delayed Gastric Emptying Pattern**

Final Diagnosis	Dogs		Cats	
	No. Studies	(% Studies)	No. Studies	(% Studies)
Inflammatory Bowel Disease	19	(41%)	5	(36%)
Foreign body - gastric	2	(4%)		
- intestinal	2	(4%)	2	(14%)
- later passed	1	(2%)		
Neoplasia - gastric	2	(4%)		
- intestinal	2	(4%)	1	(7%)
Antral pyloro-hypertrophy syndrome	4	(9%)	1	(7%)
Nonspecific enteritis	3	(7%)	1	(7%)
Disordered antral motility	2	(4%)	0	(0%)
Wheat gluten enteropathy	2	(4%)	0	(0%)
Parvoviral enteritis	2	(4%)	0	(0%)
Idiopathic gastric dilatation	2	(4%)	0	(0%)
Chronic atrophic gastritis	1	(2%)	0	(0%)
Low grade peritonitis	1	(2%)	0	(0%)
Thoracic Fibrosarcoma	1	(2%)	0	(0%)
Gastritis	0	(0%)	2	(14%)
Primary gastric dysmotility and				
Secondary gastritis	0	(0%)	1	(7%)
Open	0	(0%)	1	(7%)

**Table 8.5 Final Diagnoses Associated with Studies Showing Adynamic Ileus**

Final Diagnosis	Dogs		Cats	
	No. Studies	(% Studies)	No. Studies	(% Studies)
Intestinal neoplasia	3	(23%)	1	(33%)
Pseudo-obstruction syndrome	3*	(23%)	0	(0%)
Enteritis (parvo/nonspecific)	3	(23%)	0	(0%)
Inflammatory Bowel Disease +/- secondary conditions	2	(15%)	1	(33%)
Colonic stricture	1	(8%)	0	(0%)
Hypothyroidism and polyneuropathy	1	(8%)	0	(0%)
Food Sensitivity	0	(0%)	1	(33%)

\*these studies were all carried out in the same dog

**Table 8.6 Additional Radiographic Abnormalities Found on RM Radiographs**

Radiographic abnormality	Dogs	Cats
	No. studies abnormality present in	No. studies abnormality present in
Dilated bowel loops	30	5
Ventral spondylosis	14	3
Splenomegaly	9	1
Abnormal gastric shadow	8	5
Hepatomegaly	7	5
Stacked Small Intestinal loops	3	4
Small liver	2	0
Gravelling Sign	2	1
Dystrophic calcification of liver	2	0
Megacolon/constipation	2	2
Lumbar vertebral anomalies	2	1
Bladder calculi	2	0
Displaced S.I.	1	0
Colonic narrowing at pelvic inlet	1	0
Sentinel loop	1	2
Dilated oesophagus	1	0
Renomegaly	1	1
Caecal impaction	1	0
Fractured Tail	0	2
Radiodense Mass	0	2
Rectal Stricture	0	1
Small Kidneys	0	1
Kyphosis	0	1
Inguinal Lymphadenopathy	0	1

## **CHAPTER NINE**

### ***SUMMARY AND CONCLUSIONS***

As described in Chapters Two to Four of this thesis, the transit of food through the gastrointestinal tract is complex and is controlled through a combination of neurogenic, myogenic and hormonal factors that are triggered by different properties of the food. The gastric emptying of solids, in particular, remains to be fully explained. The physiology of gastrointestinal motility, the effects of fibre on gastrointestinal motility and the intricate mechanisms governing the gastric emptying of solids were outlined in these Chapters.

In Chapter Five, the different disease processes capable of disrupting gastrointestinal transit were described. These diseases include physical obstructions to flow of gastrointestinal contents, primary gastrointestinal neuromuscular abnormalities and secondary dysmotilities resulting from a diverse range of other diseases. The Chapter outlined the diverse tests that have been used to diagnose dysmotilities in humans. Few of these diagnostic methods were considered to be feasible in veterinary practice with the exception of the radiopaque marker (RM) method. The Chapter concluded with a summary of the previous literature describing the development and validation of a RM technique for clinical use in dogs and cats.

The objective of the experimental work described in Chapters Six was to develop reference intervals for the gastric emptying, small intestinal transit and large intestinal



transit of RM fed with a high fibre diet to dogs. It was considered that administering RM in a high fibre diet would assist the delineation of the large intestine on radiographs and might help “normalise” colonic motility leading to more uniform reference intervals. Because varying the amount of fibre in the diet can alter the gastrointestinal transit of food, separate reference intervals to those already published for the gastrointestinal transit of RM fed with other (lower fibre) diets were required. The reference intervals were presented graphically as gastric emptying, colonic filling and colonic transit curves. In the future, these curves may assist clinicians investigate colonic motility disorders. In addition, RM used with high fibre diets may prove to be more sensitive for the detection of subtle partial obstructions of the small intestine in comparison to RM used with low fibre diets.

The aim of the study reported in Chapter 7 was to improve understanding of the factors affecting the gastric emptying rate of indigestible solid particles. The hydrodynamic theory of gastric emptying has previously clarified how the size and density of indigestible particles influence their emptying rate from the stomach by affecting the ease with which the particles are suspended in the tritiated portion of the food. In addition, the gastric emptying rate of indigestible particles is thought to be influenced by ‘wall factors’, such as the grinding action of the gastric antrum. In the present study, it was proposed that the size of the pieces of food ingested along with indigestible solid particles could influence the emptying of the particles by altering the vigour of antral grinding. Specifically, it was hypothesised that larger chunks of food would result in more vigorous grinding, favouring the suspension of indigestible particles in the chyme and hastening their emptying.

The results of the study demonstrated that large RM (5 mm diameter) emptied from the stomach significantly more quickly when fed with 10mm<sup>3</sup> pieces of steak than when fed with 20 mm<sup>3</sup> pieces of steak. There was no significant difference between the emptying of the small RM (1.5 mm) in any of the meals. The study suggested that the size of the pieces of food ingested in the meal influence the 'wall factors' that Sirois *et al* (1990) described. It is unclear why the same effect was not seen with the small RM. A possible explanation is that the small RM remain suspended in the gastric chyme more easily than the large RM lessening the importance of wall factors on their gastric emptying rate. The increased emptying time of the RM fed with the 20 mm<sup>3</sup> steak appeared to be related to the longer lag time. The duration of the lag phase has been correlated to the time required to reduce the solid component of a meal into small enough particles to pass through the pylorus. It is also probable that the 20 mm<sup>3</sup> steak meal would have taken longer to triturate into sufficiently small particles than the 10 mm<sup>3</sup> and 1 mm<sup>3</sup> steak meals.

The objective of Chapter 8 was to assess the contribution RM have made to the diagnosis of gastrointestinal disease at Massey University Veterinary Teaching Hospital by determining the type of clinical situations in which they have been used, summarising the different RM patterns observed and reviewing the final diagnoses reached in patients investigated with RM. All RM studies carried out at Massey University Teaching Hospital over a five year period were reviewed. This study revealed that vomiting was the most common clinical sign in cats and dogs that resulted in a RM study being performed. About half of all the studies in dogs and cats were abnormal and delayed gastric emptying was the most common RM pattern observed in both dogs and cats. A wide range of diagnoses were associated with

delayed gastric emptying. Other RM patterns observed were adynamic ileus pattern, rapid orocolic transit, bunching pattern and delayed colonic transit (cats only).

Only a small number of dogs and cats with a bunching RM pattern were observed. The small number of animals with this pattern made it difficult to draw conclusions about the diagnostic accuracy of the pattern. Nevertheless, the specificity of the bunching pattern for physical obstruction appeared to be high (75% [3/4] in dogs and 100% [3/3] in cats). The sensitivity of the bunching pattern for the detection of physical bowel obstruction was more difficult to assess because it was dependent on radiographs being taken after allowing sufficient time for the RM to leave the stomach. If 8 hours was arbitrarily selected as an adequate duration for a RM study, the sensitivity of the bunching pattern for physical bowel obstruction was 100% (3/3) in dogs and 50% (3/6) in cats.

If a bunching pattern was observed, therefore, a physical obstruction was highly likely. If a delayed gastric emptying pattern or an adynamic ileus pattern was observed, a dysmotility was most likely but a physical obstruction could not be ruled out until such time as the RM (particularly the large RM) arrived in the colon. In no animal in which the RM reached the colon was a physical obstruction subsequently diagnosed. Most RM studies provided more information than survey radiographs in the animals in which survey radiographs were also taken.

In general, RM studies infrequently diagnosed primary gastrointestinal dysmotilities but regularly highlighted secondary dysmotilities. It was interesting to note that IBD was found to be associated with rapid gastric emptying in some animals and delayed

gastric emptying in others. In theory, variation in the severity of the mucosal inflammation and the area of gastrointestinal tract affected could result in quite different effects on transit by altering the enterogastric reflex and/or the ileal brake mechanism. Knowledge of the gastrointestinal motility in a particular patient may allow the clinician to tailor therapy to each patient.

In conclusion, the results of the study reported in Chapter 8 suggest RM procedures are useful to assist clinicians diagnose primary or secondary dysmotilities and rule out physical obstructions of the gastrointestinal tract in dogs and cats with gastrointestinal problems.

## REFERENCES

- Accarino AM, Azpiroz F and Malagelada JR. Selective dysfunction of mechanosensitive intestinal afferents in irritable bowel syndrome. *Gastroenterology* 108, 636-43, 1995.
- Allan FJ, Guilford WG and Robertson ID. Gastric emptying of solid radiopaque markers in healthy dogs. Poster; Am Col Vet Int Med 1993, Washington DC.
- Allan FJ, Guilford WG and Robertson ID. Gastric emptying of solid radiopaque markers in healthy dogs. *Veterinary Radiology and Ultrasound* 37, 336-344, 1996.
- Amidon GL. Fluid mechanics and intestinal transit. (letter to the Editor) *Gastroenterology* 88, 858, 1985. Cited in: Meyer JH, Gu Y, Elashoff J, Reedy T, Dressman J and Amidon G. Effects of viscosity and fluid outflow on postcibal gastric emptying of solids. *American Journal of Physiology* 250, G161-164, 1986.
- Arnbjerg J. Gastric emptying time in the dog and cat. *Journal of the American Animal Hospital Association* 28, 77-81, 1992.
- Aroch I, Nyska A, Gal R and Bark H. Functional intestinal hypomotility in association with neuronal damage in a dog. *Journal of Small Animal Practice* 38, 119-23, 1997.
- Arrick RH and Kleine LJ. Intestinal pseudoobstruction in a dog. *Journal of the American Veterinary Medicine Association* 172(10), 1201-5, 1978.
- Avill R, Mangnall YF, Bird NC, Brown BH, Barber DC, Seagar AD, Johnson AG and Read NW. *Applied Potential Tomography Gastroenterology* 92, 1019-26, 1987.
- Basile M, Neri M, Carriero A, Casciardi S, Comani S, Del Gratta C, Donato LD, Luzio SD, Macri MA, Pasquarelli A, Pizzella V and Romani GL. Measurement of segmental transit through the gut in man. *Digestive Diseases and Sciences* 37(10): 1537-43, 1992.
- Bateman DN and Whittingham TA. Measurement of gastric emptying by real-time ultrasound. *Gut* 23, 524-27, 1982.
- Bechaard H, Christensen FN, Davis SS, Hardy JG, Taylor MJ, Whalley DR and Wilson CG. Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. *Journal of Pharmaceuticals and Pharmacology* 37, 718-721, 1985.
- Becker JM and Kelly KA. Antral control of gastric emptying of solids. *American Journal of Physiology* 245, G334-8, 1983.
- Benini L, Castellani G, Brighenti F, Heaton KW, Brentegani MT, Casiraghi MC, Sembenini C, Pellegrini N, Fioretta A, Minni G, Porrini M, Testolin G and Vantini I. Gastric emptying of a solid meal is accelerated by the removal of dietary fibre naturally present in food. *Gut* 36, 825-30, 1995.

- Bertrand J, Dorval ED and Platel A. Gastric emptying time as measured by radiopaque markers in control and diabetic patients. In: *Motility of the Digestive Tract*, Wienbeck, Raven Press, New York, 1987. Pp363-367.
- Bisset SA, Spohr A, Guilford WG and Haslett SJ. Reproducibility of breath hydrogen concentration measurements in dogs after change of diet. *American Journal of Veterinary Research* 59(12), 1523-1525, 1998.
- Blomhoff S, Jacobsen M, Spetalen S Dahm, Vatn M and Malt UF. Brain information processing: the core of the irritable bowel syndrome? Abstract 31<sup>st</sup> Nordic Meeting on Gastroenterology, 22<sup>nd</sup> SADE meeting on Gastrointestinal endoscopy and 10<sup>th</sup> SAGIM Scientific Session on Gastrointestinal Motility, Tromso, Norway, 2-5<sup>th</sup> June 1999.
- Bortoff A. Myogenic control of intestinal motility. *Physiological Review* 56, 418-34, 1976.
- Bouchoucha M, Devroede G, Arhan P, Strom B, Weber J, Cugnenc P, Denis P and Barbier J. What is the Meaning of Colonorectal Transit Time Measurement? *Diseases of the Colon and Rectum* 35, 773 - 782, 1992.
- Brogna A, Catalano F, Mangimeli A, Monello S, Ferrara R, Bucceri AM and Marletta A. Simultaneous measurement of gastric emptying of digestible and indigestible solids in healthy humans. *Italian Journal of Gastroenterology* 24, 188-91, 1992.
- Brown BP, Schulze-Delrieu K, Schrier JE and Abu-Yousef MM. The configuration of the human gastroduodenal junction in the separate emptying of liquids and solids. *Gastroenterology* 105, 433-40, 1993.
- Bruce SJ, Guilford WG, Hedderley DI and McCauley M. Development of reference intervals for the large intestinal transit of radiopaque markers in dogs. *Veterinary Radiology and Ultrasound* 40(4), 472-6, 1999.
- Bueno L, Praddaue F, Fioramonti J and Ruckebusch Y. Effect of dietary fiber on gastrointestinal motility and jejunal transit time in dogs. *Gastroenterology* 80, 701-7, 1981.
- Burbidge HM, Guilford WG. Barium-impregnated polyethylene spheres (BIPS): clinical observations. *Vet Radiology and Ultrasound* 37, 79, 1996.
- Burkitt DP, Walker ARP and Painter NS. Effect of dietary fibre on stools and transit times, and its role in the causation of disease. *The Lancet*, December 30, 1408-1411, 1972.
- Burrows CF. Disorders of gastrointestinal motility: more common than you think. *Proceedings 15<sup>th</sup> ACVIM Forum*, Gainesville, Florida, 1997

- Burrows CF, Bright RM and Spencer CP. Influence of dietary composition on gastric emptying and motility in dogs: potential involvement in acute gastric dilatation. *American Journal of Veterinary Research* 46(12), 2609-12, 1985.
- Burrows CF, Kronfeld DS, Banta CA and Merritt AM. Effects of fiber on digestibility and transit time in dogs. *Journal of Nutrition* 112, 1726-32, 1982.
- Burrows CF and Merritt AM. Influence of  $\alpha$ -cellulose on myoelectric activity of proximal canine colon. *American Journal of Physiology* 245, G301-306, 1983.
- Camilleri M, Malagelada J-R, Brown ML, Becker G and Zinsmeister AR. Relation between antral motility and gastric emptying of solids and liquids in humans. *American Journal of Physiology* 249, G580-585, 1985.
- Camilleri M and Zinsmeister AR. Towards a relatively inexpensive, noninvasive, accurate test for colonic motility disorders. *Gastroenterology* 103, 36-42, 1992.
- Camilleri M, Hasler WL, Parkman HP, Quigley EMM and Soffer E. Measurement of gastrointestinal motility in the GI laboratory. *Gastroenterology* 115, 747-62, 1998.
- Cann PA, Read NW, Cammack J, Childs H, Holden S, Kashman R, Longmore J, Nix S, Simms N, Swallow K and Weller J. Psychological stress and the passage of a standard meal through the stomach and small intestine in man. *Gut* 24, 236-40, 1983.
- Cargill R, Caldwell LJ, Engle K, Fix JA, Porter PA and Gardner CR. Controlled gastric emptying. 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. *Pharmaceutical Research* 5 (8), 533-536, 1988.
- Casasnovas AB, Varela Cives R, Villanueva Jeremias A, Castro-Gage M, Cadranel S and Tojo Sierra R. Measurement of Colonic Transit Time in Children. *Journal of Paediatric Gastroenterology and Nutrition* 13 : 42 - 45, 1991.
- Chandler ML and Guilford WG. Assessment of gastric emptying and small intestinal transit in cats using radiopaque markers. *Abstract Journal of Veterinary Internal Medicine* 9(3), 192, 1997.
- Chandler ML, Guilford WG, Lawoko CRO and Whittam T. Gastric emptying, small intestinal and colonic transit times of radiopaque markers in cats fed a high fibre diet with and without low dose intravenous diazepam. *Veterinary Radiology and Ultrasound* 40(1), 3-8, 1999.
- Charles F, Camilleri M, Phillips SF, Thomforde GM and Forstrom LA. Scintigraphy of the whole gut: clinical evaluation of transit disorders. *Mayo Clinic Proceedings* 70, 113-8, 1995.
- Chen JDZ, Lin Z, Pan J and McCallum RW. Abnormal gastric myoelectrical activity and delayed gastric emptying in patients with symptoms suggestive of gastroparesis. *Digestive Diseases and Sciences* 41(8), 1538-45, 1996.

Cherbut C. Role of gastrointestinal motility in the delay of absorption by dietary fibre. *European Journal of Clinical Nutrition* 49 (Supp 3), S74-S80, 1995.

Cherbut C. and Ruckebusch Y. The effect of indigestible particles on digestive transit time and colonic motility in dogs and pigs. *British Journal of Nutrition* 53, 549-557, 1985.

Choi M, Camilleri M, Burton DD, Zinsmeister AR, Forstrom LA and Nair KS. Octanoic acid breath test for gastric emptying of solids: accuracy, reproducibility and comparison with scintigraphy. *Gastroenterology* 112, 1155-62, 1997.

Christensen J. Motility of the Colon. In: *Physiology of the Gastrointestinal Tract* (third edition). Raven Press, New York. 1994: Pp991 - 1024.

Collins PJ, Horowitz M and Chatterton BE. Proximal, distal and total stomach emptying of a digestible solid meal in normal subjects. *British Journal of Radiology* 61, 12-18, 1988.

Collins PJ, Horowitz M, Cook DJ, Harding PE and Shearman DJC. Gastric emptying in normal subjects – a reproducible technique using a single scintillation camera and computer system. *Gut* 24, 1117-25, 1983.

Collins PJ, Houghton LA, Read NW, Horowitz M, Chatterton BE, Heddle R and Dent J. Role of the proximal and distal stomach in mixed solid and liquid meal emptying. *Gut* 32, 615-619, 1991.

Conover WJ and Iman RL. Rank transformations as a bridge between parametric and nonparametric statistics. *The American Statistician*. Pp 124-9, 1981.

Costello M, Papasouliotis K, Barr FJ, Gruffydd-Jones TJ and Caney SMA. Determination of solid- and liquid- phase gastric emptying half times in cats by use of nuclear scintigraphy. *American Journal of Veterinary Research* 60(10), 1222-6, 1999.

Cummings JH, Hill MJ, Jenkins A, Pearson JR and Wiggins HS. Changes in fecal composition and colonic function due to cereal fiber. *American Journal of Clinical Nutrition* 29, 1468-73, 1976.

Cummings JH and Wiggins HS. Transit through the gut measured by analysis of a single stool. *Gut* 17, 219 - 23, 1976.

Daniel E, Tougas G, Allescher H, Vergara P and Fox-Threlkeld J. Mediators and enteric nerve pathways controlling gastric emptying. *Digestive Diseases and Sciences* 39(12Supp), 63S-68S, 1994.

Daum R, Nutzenadel W, Roth H and Zachariou. Motility malfunction of the gastrointestinal tract by rare diseases – fibrosis of the intestinal wall. *Progress in Paediatric Surgery* 24, 193-201, 1989.



Davis SS, Hardy JG, Taylor MJ, Whalley DR and Wilson CG. The effect of food on the gastrointestinal transit of pellets and an osmotic device (osmet). *International Journal of Pharmaceutics* 21, 331-40, 1984a.

Davis SS, Hardy JG, Taylor MJ, Stockwell A, Whalley DR and Wilson CG. The in-vivo evaluation of an osmotic device (osmet) using gamma scintigraphy. *Journal of Pharmacy and Pharmacology* 36, 740-2, 1984b.

Davis SS, Stockwell AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG, Bechaard H and Christensen FN. The effect of density on the gastric emptying of single and multiple-unit dosage forms. *Pharmaceutical Research* 3(4), 208-213, 1986.

Devroede G. Dietary fiber, bowel habits, and colonic function. *American Journal of Clinical Nutrition* 31, S157-160, 1978.

Dimski DS and Buffington CA. Dietary fiber in small animal therapeutics. *Journal of the American Veterinary Medicine Association* 199(9), 1142-46, 1991.

Durdle NG, Kingma YJ, Bowes KL and Chambers MM. Origin of slow waves in the canine colon. *Gastroenterology* 84, 375-82, 1983.

Eastwood MA. The physiological effect of dietary fiber: an update. *Annual Review of Nutrition* 12, 19-35, 1992.

Eastwood MA and Morris ER. Physical properties of dietary fiber that influence physiological function: a model for polymers along the gastrointestinal tract. *American Journal of Clinical Nutrition* 55, 436-42, 1992.

Edwards CA and Read NW. Fibre and small intestinal function. In: *Dietary Fibre Perspectives*. AR Leeds. 1990, Pp 52-75. London: John Libbey. Cited in: Cherbut C. Role of gastrointestinal motility in the delay of absorption by dietary fibre. *European Journal of Clinical Nutrition* 49 (Supp 3), S74-S80, 1995.

El-Sharkawy TY. Electrical activities of the muscle layers of the canine colon. *Journal of Physiology* 342, 67-83, 1983.

Evans DF, Lamont G, Stehling MK, Blamire AM, Gibbs P, Coxon R, Hardcastle JD and Mansfield P. Prolonged monitoring of the upper gastrointestinal tract using echo planar magnetic resonance imaging. *Gut* 34, 848-852, 1993.

Ewart WR and Wingate DL. Central representation and opioid modulation of gastric mechanoreceptor activity in the rat. *American Journal of Physiology* 244, G27-32, 1983.

Feldman M, Smith HJ and Simon TR. Gastric emptying of solid radiopaque markers: studies in healthy subjects and diabetic patients. *Gastroenterology* 87, 895-902, 1984.

- Fragar D, Baer JW, Medwid SW, Rothpearl A and Bossart P. Detection of intestinal ischemia in patients with acute small bowel obstruction due to adhesions or hernia: efficacy of CT. *American Journal of Roentgenology* 166, 67-71, 1996.
- Fucci V, Pechman RD, Hedlund CS and Venugopalan CS. Large bowel transit times using radiopaque markers in normal cats. *Journal of the American Animal Hospital* 31, 473-77, 1995.
- Galil MA, Critchley M and Mackie CR. Isotope gastric emptying tests in clinical practice: expectation, outcome and utility. *Gut* 34, 916-19, 1993.
- Gatti E. Clinical effects of a dietary fibre supplement. A review. *European Journal of Clinical Nutrition* 49(supp3), S199-200, 1995.
- German AJ, Martin MA, Papasouliotis K and Hall JA. Assessment of a breath collection technique and portable breath hydrogen monitor for use in cats and dogs. *Research in Veterinary Science* 65, 173-5, 1998.
- Goggin JM, Hoskinson JJ, Butine MD, Foster LA and Myers NC. Scintigraphic assessment of gastric emptying of canned and dry diets in healthy cats. *American Journal of Veterinary Research* 59(4), 388-92, 1998.
- Goggin JM, Hoskinson JJ, Kirk CA, Jewell D and Butine MD. Comparison of gastric emptying times in healthy cats simultaneously evaluated with radiopaque markers and nuclear scintigraphy. *Veterinary Radiology and Ultrasound* 40(1), 89-95, 1999.
- Greene SA and Thurmon JC. Xylazine – a review of its pharmacology and use in veterinary medicine. *Journal of Veterinary Pharmacology and Therapeutics* 11, 295-313, 1988.
- Grider JR. Role of Cholecystokinin in the regulation of gastrointestinal motility. *Journal of Nutrition* 124, 1334S – 1339S, 1994.
- Gruber P, Rubinstein A, Li VHK, Bass P and Robinson JR. Gastric emptying of nondigestible solids in the fasted dog. *Journal of Pharmaceutical Sciences* 76 (2), 117-122, 1987.
- Guilford WG. The enteric nervous system: function, dysfunction and pharmacological manipulation. *Seminars in Veterinary Medicine and Surgery (Small Animal)* 5(1), 46-56, 1990.
- Guilford WG. Motility Disorders of the Bowel In: Strombeck's Small Animal Gastroenterology (third edition). WB Saunders Philadelphia PA. 1996a, Pp 532-6.
- Guilford WG. Nutritional Management of Diseases In: Strombeck's Small Animal Gastroenterology (third edition). WB Saunders Philadelphia PA. 1996b, Pp 892-3.
- Guilford WG. Irritable bowel syndrome. Myth or reality. *Proceedings 15th Am Col Vet Int Med Forum* 317-318, 1997.

Guilford WG, Lawoko CRO and Allan FJ. Accuracy of localizing radiopaque markers by abdominal radiography and correlation between their gastric emptying rate and that of a canned food in dogs.' *Journal of Veterinary Research* 58(12), 1359-63, 1997.

Guilford WG and StrombeckDR. Chronic Gastric Diseases. In: Strombeck's Small Animal Gastroenterology (third edition). WB Saunders Philadelphia PA. 1996a, Pp 299-302.

Guilford WG and StrombeckDR. Intestinal obstruction, pseudo-obstruction, and foreign bodies. In: Strombeck's Small Animal Gastroenterology (third edition). WB Saunders Philadelphia PA. 1996b, Pp 487-501.

Gwee KA and Read NW. Rolling review: disorders of gastrointestinal motility – therapeutic potentials and limitations. *Alimentary Pharmacology and Therapeutics* 8, 105-18, 1994.

Haba T and Sarna SK. Regulation of gastroduodenal emptying of solids by gastropyloroduodenal contractions. *American Journal of Physiology* 264, G261-271, 1993.

Haddad H and Devroede-Bertrand G. Large bowel motility disorders. *Medical Clinics of North America, Gastrointestinal Motility Disorders* 65(6), 1377-96, 1981.

Hall JA, Burrows CF, Twedt DC. Gastric Motility in Dogs. Part 1. Normal Gastric Function. *Compendium of Small Animals* 10(11), 1282-93, 1988.

Hall JA, Twedt DC and Burrows CF. Gastric motility in dogs. Part 2. Disorders of gastric motility. *The Compendium* 12(10), 1373–91, 1990.

Hall JA and Washabau RJ. Diagnosis and treatment of gastric motility disorders. *Veterinary Clinics of North America: Small Animal Practice* 29(2), 377-95, 1999.

Hall JA, Willer RL, Seim HB, Lebel JL and Twedt DC. Gastric emptying of nondigestible radiopaque markers after circumcostal gastropexy in clinically normal dogs and dogs with gastric dilatation-volvulus. *American Journal of Veterinary Research* 53(10), 1961-5, 1992.

Harvey RF, Pomare EW and Heaton KW. Effects of increased fibre on intestinal transit. *The Lancet*, June 9, 1278-80, 1973.

Hasler AH and Washabau RJ. Cisapride stimulates contraction of idiopathic megacolon smooth muscle in cats. *Journal of Veterinary Internal Medicine* 11(6), 313-318, 1997.

Hinder RA and Kelly KA. Canine gastric emptying of solids and liquids. *American Journal of Physiology* 233 (4), E335-340, 1977.

Hinder RA and San-Garde BA. Individual and combined roles of the pylorus and the antrum in the canine gastric emptying of a liquid and a digestible solid. *Gastroenterology* 84, 281-286, 1983.

Hinton JM and Lennard-Jones JE. Constipation: definition and classification. *Postgraduate Medical Journal* 44, 720-3, 1968 cited in: Hinton JM, Lennard-Jones JE and Young AC. A new method for studying gut transit times using radiopaque markers. *Gut* 10, 842-7, 1969.

Hinton JM, Lennard-Jones JE and Young AC. A new method for studying gut transit times using radiopaque markers. *Gut* 10, 842-7, 1969.

Holt S, McDicken WN, Anderson T, Stewart IC and Heading RC. Dynamic imaging of the stomach by real-time ultrasound- a method for the study of gastric motility. *Gut* 21, 597-601, 1980.

Holt S, Reid J, Taylor TV, Tothill P and Heading RC. Gastric emptying of solids in man. *Gut* 23, 292-296, 1982.

Horowitz M, Dent J, Sun W and Hebbard G. Role and integration of mechanisms controlling gastric emptying. *Digestive Diseases and Sciences* 39 (12 supp), 7S-13S, 1994.

Houghton LA, Read NW, Heddle R, Horowitz M, Collins PJ, Chatterton B and Dent J. Relationship of the motor activity of the antrum, pylorus and duodenum to gastric emptying of a solid - liquid mixed meal. *Gastroenterology* 94, 1285-91, 1988

Hunt JN, Cash R and Newland P. Energy density of food, gastric emptying and obesity. *American Journal of Clinical Nutrition* 31, S259-260, 1978.

Hunt JN, Smith JL and Jiang CL. Effect of meal volume and energy density on the gastric emptying of carbohydrates. *Gastroenterology* 89, 1326-30, 1985.

Hunt JN and Stubbs DF. The volume and energy content of meals as determinants of gastric emptying. *Journal of Physiology* 245, 209-225, 1975.

Husebye E. Gastrointestinal motility disorders and bacterial overgrowth. *Journal of Internal Medicine* 237, 419-27, 1995.

Hveem K, Jones KL, Chatterton BE and Horowitz M. Scintigraphic measurement of gastric emptying and ultrasonographic assessment of antral area: Relation to appetite. *Gut* 38, 816-21, 1996.

Itoh T, Higuchi T, Gardner CR and Caldwell L. Effect of particle size and food on gastric residence time of non-disintegrating solids in beagle dogs. *Journal of Pharmaceuticals and Pharmacology* 38, 801-806, 1986.

Jacobs LR. Effect of dietary fiber on colonic cell proliferation and its relationship to colon carcinogenesis. *Preventative Medicine* 16, 566-71, 1987.

Jenkins DJA and Jenkins AL. The clinical implications of dietary fiber. *Advances in Nutritional Research* 6, 169-202, 1984.

Jenkins DJA, Jenkins AL, Thomas MS, Wolever TMS, Thompson LH and Venkat Rao A. Simple and complex carbohydrates. *Nutrition Reviews* 44, 44-9, 1986.

Jin HO, Lee KY, Chang TM, Chey WY and Dubois A. Physiological role of cholecystokinin on gastric emptying and acid output in dogs. *Digestive Diseases and Sciences* 39(11), 2306-14, 1994.

Johnson PA, Miner PB, Geier D and Harrison LA. Value of radiopaque markers in identifying partial small bowel obstruction. *Gastroenterology* 110, 1958-63, 1996.

Kellow JE, Borody TJ, Phillips SF, Haddad AC and Brown ML. Sulfapyridine appearance in plasma after salicylazosulfapyridine. *Gastroenterology* 91, 396-400, 1986.

Kellow JE, Gill RC and Wingate DL. Prolonged ambulant recordings of small bowel motility demonstrate abnormalities in the irritable bowel syndrome. *Gastroenterology* 98, 1208-18, 1990.

Kelly KA. Gastric emptying of liquids and solids: roles of proximal and distal stomach. *American Journal of Physiology* 239, G71-6, 1980.

Kim CH, Zinsmeister AR and Malagelada JR. Mechanisms of canine gastric dysrhythmia. *Gastroenterology* 92, 993-9, 1987.

King PM, Adam RD, Pryde a, McDicken WN and Heading RC. Relationships of human antroduodenal motility and transpyloric fluid movement: noninvasive observations with real-time ultrasound. *Gut* 25, 1384-91, 1984.

Kleiber M. Body size and metabolic rate. In *the Fire of Life*, Publisher Robert E Kreiger Publishing Co, Huntingdon, Pp179-222, 1975. Cited in *Small Animal Clinical Nutrition* 3, Mark Morris Associates, Topeka, KA, Pp1-5, 1987.

Kleine LJ. Radiology of the stomach in the dog and cat. *Compendium on Continuing Education* 1(12), 936-44, 1979.

Koch KL and Stern RM. Functional disorders of the stomach. *Seminars in Gastrointestinal Disease* 7(4), 185-95, 1996.

Kritchevsky D. Dietary fiber. *Annual review of Nutrition* 8, 301-28, 1988.

Kunze CP, Hoskinson JJ, Butine MD and Goggin J. Evaluation of solid phase radiolabels of dog food for gastric emptying. *Veterinary Radiology and Ultrasound* 39(5), 169-73, 1998.

Lamb CR. Recent developments in diagnostic imaging of the gastrointestinal tract of the dog and cat. *Veterinary Clinics of North America: Small Animal Practice* 29(2), 307-42, 1999.

- Lehmann R, Borovicka J, Kunz P, Creiler G, Boesiger P, Fried M, Schwiser W and Spinaz GA. Evaluation of delayed gastric emptying in diabetic patients with autonomic neuropathy by a new magnetic resonance imaging technique and radiopaque markers. *Diabetes Care* 19(10), 1075-78, 1996.
- Lester NV, Roberts GD, Newell SM, Graham JP, Hartless CS and Stat M. Assessment of barium impregnated polyethylene spheres (BIPS) as a measure of solid-phase gastric emptying in normal dogs- comparison to scintigraphy. *Veterinary Radiology and Ultrasound* 40(4), 465-71, 1999.
- Levanon D, Zhang M, Orr WC and Chen JDZ. Effects of meal volume and composition on gastric myoelectrical activity. *American Journal of Physiology* 274, G430 – G434, 1998.
- Lin HC, Doty JE, Reedy JE and Meyer JH. Inhibition of gastric emptying by glucose depends on length of intestine exposed to nutrient. *American Journal of Physiology* 256, G404-11, 1989.
- Lin HC, Doty JE, Reedy JE and Meyer JH. The load to length principle in the inhibition of gastric emptying by intestinal feedback. *Gastroenterology* 98, 1387-88, 1990.
- Lin HC, Doty JE and Meyer JH. Inhibition of gastric emptying by sodium oleate depends on the length of intestine exposed to the nutrient. *American Journal of Physiology* 259, G1031-6, 1990.
- Livingstone EH and Passaro EP. Postoperative Ileus. *Digestive Diseases and Sciences* 35(1), 121-32, 1990.
- Longshore RC, O'Brien DP, Johnson GC, Grooters AM and Kroll RA. Dysautonomia in dogs: A retrospective study. *Journal of Veterinary Internal Medicine* 10(3), 103-9, 1996.
- McIntyre A, Gibson PR and Young GP. Butyrate production from dietary fibre and protection against large bowel cancer in a rat model. *Gut* 34, 386-391, 1993.
- McIntyre A, Vincent RM, Perkins AC and Spiller RC. Effect of bran, ispaghula and inert plastic particles on gastric emptying and small bowel transit in humans: the role of physical factors. *Gut* 40, 223-227, 1997.
- Maes BD, Hiele MI, Geypens BJ, Rutgeerts PJ, Ghoois YF and Vantrappen G. Pharmacological modulation of gastric emptying rate of solids as measured by the carbon labelled octanoic acid breath test: influence of erythromycin and propantheline. *Gut* 35, 333-7, 1994.
- Makhlouf GM. Neuromuscular function of the small intestine. In: Johnson LR, (ed). *Physiology of the Gastrointestinal Tract* (3<sup>rd</sup> edition). New York, Raven Press, 1994 Pp 977 – 990.

Malagelada J-R. Quantification of gastric solid-liquid discrimination during digestion of ordinary meals. *Gastroenterology* 72, 1264-1267, 1977.

Malagelada J-R, Rees WDW, Mazzotta LJ and Go VLW Gastric Motor Abnormalities in Diabetic and Postvagotomy Gastroparesis: Effects of Metoclopramide and Bethanechol. *Gastroenterology* 78, 286-93, 1980.

Malagelada J-R and Stanghellini V. Manometric evaluation of functional upper gut symptoms. *Gastroenterology* 88, 1223-31, 1985.

Maxwell PR, Mendall MA and Kumar D. Irritable bowel syndrome. *The Lancet* 350, 1691-5, 1997.

Mayer EA and Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 107, 271-93, 1994.

Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW and Wolff BG. Simplified Assessment of Segmental Colonic Transit. *Gastroenterology* 92, 40 - 47, 1987.

Meyer JH, Beglinger C, Neumayer M and Stalder GA. Physical characteristics of indigestible solids affect emptying from the fasting humans stomach. *Gut* 30, 1526-1529, 1989.

Meyer JH, Dressman J, Fink A and Amidon G. Effect of size and density on canine gastric emptying of nondigestible solids. *Gastroenterology* 89, 805-813, 1985.

Meyer JH, Elashoff J, Porter-Fink V, Dressman J and Amidon GL. Human postprandial gastric emptying of 1-3 millimeter spheres. *Gastroenterology* 94, 1315-1325, 1988.

Meyer JH, Gu Y, Elashoff J, Reedy T, Dressman J and Amidon G. Effects of viscosity and fluid outflow on postcibal gastric emptying of solids. *American Journal of Physiology* 250, G161-164, 1986.

Meyer JH, Ohashi H, Jehn D and Thomson JB. Size of liver particles emptied from the human stomach. *Gastroenterology* 80, 1489-1496, 1981.

Meyer JH, Thomson JB, Cohen MB, Shadchehr A and Mandiola SA. Sieving of solid food by the canine stomach and sieving after gastric surgery. *Gastroenterology* 78, 804-813, 1979.

Milla PJ. Acquired motility disorders in childhood. *Canadian Journal of Gastroenterology* 13(suppA), 76-84A, 1999.

Minami H and McCallum RW. The physiology and pathophysiology of gastric emptying in humans. *Gastroenterology* 86, 1592-1610, 1984.

Miyabayashi T and Morgan JP. Gastric emptying in the normal dog. *Veterinary Radiology* 25(4), 187-91, 1984.

Mojaverian P, Ferguson RK, Vlases PH, Rocci ML, Jr, Oren A, Fix JA, Caldwell LJ and Gardner C. Estimation of gastric residence time of the Heidelberg capsule in humans: effect of varying food composition. *Gastroenterology* 89, 392 – 7, 1985.

Moore R and Carpenter J. Intestinal sclerosis with pseudo-obstruction in three dogs. *Journal of the American Veterinary Medicine Association* 184(7), 830-3, 1984.

Moore JG, Dubois A, Christian PE, Elgin D and Alazraki N. Evidence for a midgastric transverse band in humans. *Gastroenterology* 91, 540-5, 1986.

Nelson OL, Jergens AE and Miles KG. Using barium-impregnated polyethylene spheres to document delayed gastric emptying. *Veterinary Medicine Nov/Dec* 984-98, 1996

Notghi A, Hutchinson R, Kumar D, Smith NB and Harding LK. Simplified method for the measurement of segmental colonic transit time. *Gut* 35, 976-82, 1994.

Nutritional requirements of the dog. National Research Council, Bethesda, MD, 1985 cited in: Ogilvie GK. Energy metabolism in diseased and critically ill dogs: New horizons. *Veterinary Clinical Nutrition Supplement*, 23-27, 1998.

Otterson MF and Sarr MG. Normal physiology of small intestinal motility. *Surgical Clinics of North America* 73(6), 1173-92, 1993.

Papasoulliotis K, Muir P, Gruffydd-Jones TJ, Galloway P, Smerdon T and Cripps PJ. Decreased oro-caecal transit time, as measured by the exhalation of hydrogen, in hyperthyroid cats. *Research in Veterinary Science* 55, 115-8, 1993.

Papasoulliotis K, Sparkes AH, Gruffydd-Jones TJ, Cripps PJ and Harper EJ. Use of the breath hydrogen test to assess the effect of age on oro-caecal transit time and carbohydrate assimilation in cats. *American Journal of Veterinary Research* 59(10), 1299-1302, 1998.

Parkman HP, Miller MA and Fisher RS. Role of nuclear medicine in evaluating patients with suspected gastrointestinal motility disorders. *Seminars in Nuclear Medicine* 25(4), 289-305, 1995.

Payler DK, Pomare EW, Heaton KW and Harvey RF. The effect of wheat bran on intestinal transit. *Gut* 16, 209-13, 1975.

Poitras P, Picard M, Dery R, Giguere A, Picard D, Morais J, Plourde V and Boivin M. Evaluation of gastric emptying function in clinical practice. *Digestive Diseases and Sciences* 42(11), 2183-89, 1997.

Proano M, Camilleri M, Phillips S, Brown ML and Thomforde GM. Transit of solids through the human colon: regional quantification in the unprepared bowel. *American Journal of Physiology* 258, G856-862, 1990.



Prove J and Ehrlein HJ. Motor function of gastric antrum and pylorus for evacuation of low and high viscosity meals in dogs. *Gut* 23, 150-6, 1982.

Qian L, Lin X and Chen JDZ. Normalization of atropine-induced postprandial dysrhythmias with gastric pacing. *American Journal of Physiology* 276, G387-92, 1999.

Quigley EMM. Gastric and small intestinal motility in health and disease. *Gastroenterology Clinics of North America* 25(1), 113-45, 1996.

Rainbird AL and Low AG. Effect of various types of dietary fibre on gastric emptying in growing pigs. *British Journal of Nutrition* 55, 111-21, 1986.

Ralphs DNL, Thomson JPS, Haynes S, Lawson-Smith C, Hobsley M and Le Quesne LP. The relationship between the rate of gastric emptying and the dumping syndrome. *British Journal of Surgery* 65, 637-41, 1978.

Read NW. Feedback regulation and sensation. *Digestive Diseases and Sciences* 39(12Supp), 37S-40S, 1994.

Read NW, Cammack J, Edwards C, Holgate AM, Cann PA and Brown C. Is the transit time of a meal through the small intestine related to the rate at which it leaves the stomach? *Gut* 23, 824-28, 1982.

Read NW, Miles CA, Fisher D, Holgate AM, Kime ND, Mitchell MA, Reeve AM, Roche TB and Walker M. Transit of a meal through the stomach, small intestine and colon in normal subjects and its role in the pathogenesis of diarrhoea. *Gastroenterology* 79, 1276-82, 1980.

Reppas C, Meyer JH, Sirois PJ and Dressman JB. Effect of hydroxypropylmethylcellulose on gastrointestinal transit and luminal viscosity in dogs. *Gastroenterology* 100, 1217-23, 1991.

Roberfroid M. Dietary Fiber, Inulin and Oligofructose: a review comparing their physiological effects. *Critical Reviews in Food Science and Nutrition* 33(2), 103-48, 1993.

Robertson ID and Burbidge HM. Pros and cons of barium-impregnated polyethylene spheres in gastrointestinal disease. *Veterinary Clinics of North America: Small Animal Practice* 30(2), 449-465, 2000.

Rock E, Malmud L and Fisher RS. Motor disorders of the stomach. *Medical Clinics of North America, Gastrointestinal Motility Disorders* 65(6), 1269-89, 1981.

Rodriguez-Membrilla A and Vergara P. Endogenous CCK disrupts the MMC pattern via capsaicin-sensitive vagal afferent fibers in the rat. *American Journal of Physiology* 272, G100-5, 1997.

Russel J and Bass P. Canine gastric emptying of fiber meals: influence of meal viscosity and antroduodenal motility. *American Journal of Physiology* 249,G662-7, 1985a.

Russel J and Bass P. Canine gastric emptying of polycarbophil: an indigestible, particulate substance. *Gastroenterology* 89, 307-12, 1985b.

Sarna SK. Colonic motor activity. *Surgical Clinics of North America* 73(6), 1201-23, 1993.

Sarna SK and Lang IM. Colonic motor responses to a meal in dogs. *American Journal of Physiology* 257, G830-5, 1989.

SAS/Stat User Guide, 1990, Cary, North Carolina, Chapter 24, Pp 893-993.

Schemann M, Ehrlein H-J. Postprandial patterns of canine jejunal motility and transit of luminal content. *Gastroenterology* 90, 991-1000, 1986.

Schuffler MD. Chronic Intestinal Pseudo-obstruction Syndromes. *Medical Clinics of North America* 65(6), 1331-1357, 1981.

Schulze C, Schanen H and Pohlenz J. Canine dysautonomia resembling the key-gaskell syndrome in germany. *Veterinary Record* 141, 496-7, 1997.

Schweizer W, Fraser R, Borovicka J, Asal K, Crelier G, Kunz P, Boesiger and Fried M. Measurement of proximal and distal gastric motility with magnetic resonance imaging. *American Journal of Physiology* 271, G217-22, 1996.

Schwizer W, Maecke H and Fried M. Measurement of gastric emptying by magnetic resonance imaging in humans. *Gastroenterology* 103, 369-76, 1992.

Sharp NJH. Feline dysautonomia. *Seminars in Veterinary Medicine and Surgery* 5(1), 67-71, 1990.

Sica GT. MR Imaging for assessment of gastric motility disorders: has its time come? *Radiology* 207, 9-10, 1998.

Siegel JA, Urbain J-L, Adler LP, Charkes ND, Maurer AH, Krevsky B, Knight LC, Fisher RS and Malmud LS. Biphasic nature of gastric emptying. *Gut* 29, 85-89, 1988

Simren M, Abrahamsson H and Bjornsson ES. Motility abnormalities in the duodenum in constipation predominant irritable bowel syndrome. Abstract 31<sup>st</sup> Nordic Meeting on Gastroenterology, 22<sup>nd</sup> SADE meeting on Gastrointestinal endoscopy and 10<sup>th</sup> SAGIM Scientific Session on Gastrointestinal Motility, Tromso, Norway, 2-5<sup>th</sup> June 1999.

Sirois PJ, Amidon GL, Meyer JH, Doty J and Dressman JB. Gastric emptying of nondigestible solids in dogs: a hydrodynamic correlation. *American Journal of Physiology* 258, G65-72, 1990.

Smith HJ and Feldman M. Influence of food and marker length on gastric emptying of indigestible radiopaque markers in healthy humans. *Gastroenterology* 91, 1452-1455, 1986.

Snook JA, Wells, AD, Prytherch DR, Evans, DH, Bloom SR and Colin-Jones DG. Studies on the pathogenesis of the early dumping syndrome induced by intraduodenal instillation of hypertonic glucose. *Gut* 30, 1716-20, 1989.

Soffer E and Thongsawat S. Clinical value of duodenojejunal manometry. *Digestive Diseases and Sciences* 41(5), 859-63, 1996.

SparkesAH, Papasouliotis K, Barr FJ and Gruffyd-Jones TJ. Reference ranges for gastrointestinal transit of barium-impregnated polyethylene spheres in healthy cats. *Journal of Small Animal Practice* 38, 340-3, 1997.

Spiller GA. Beyond dietary fiber. *American Journal of Clinical Nutrition* 54, 615-7, 1991.

Spiller RC. Pharmacology of dietary fibre. *Pharmacology and Therapeutics* 62, 407-27, 1994.

Spiller GA, Chernoff MC, Hill RA, Gates JE, Nassar JJ and Shipley EA. Effect of purified cellulose, pectin, and a low-residue diet on faecal volatile fatty acids, transit time and faecal weight in humans. *American Journal of Clinical Nutrition* 33, 754-9, 1980.

Spohr A, Guilford WG, Haslett SJ and Vibe-Petersen G. Use of breath hydrogen testing to detect experimentally induced disaccharide malabsorption in healthy adult dogs. *American Journal of Veterinary Research* 60(7), 836-840, 1999.

Stanghellini V, Borovicka J and Read N. Feedback regulation and sensation. *Digestive Diseases and Sciences* 39(12Supp), 124S-127S, 1994.

Stephen AM. Whole grains – Impact of consuming whole grains on physiological effects of dietary fiber and starch. *Critical reviews in Food Science and Nutrition* 34(5 & 6), 499-511, 1994.

Steyn PF and Twedt DC. 'Gastric emptying in the normal cat: a radiographic study.' *Journal of the American Animal Hospital Association* 30, 78–80, 1994.

Steyn PF, Twedt D and Toombs W. The Scintigraphic evaluation of solid phase gastric emptying in normal cats. *Veterinary Radiology and Ultrasound* 36(4), 327-31, 1995.

Stick JA, Chou MD, Derksen FJ and Arden WA. Effects of xylazine on equine intestinal vascular resistance, motility, compliance and oxygen consumption. *American Journal of Veterinary Research* 48(2), 198-203, 1987.

- Stivland T, Camilleri M, Vassallo M, Proano M, Rath D, Brown M, Thomforde G, Pemberton J and Phillips S. Scintigraphic measurement of regional gut transit in idiopathic constipation. *Gastroenterology* 101, 107-15, 1991.
- Stotzer P, Fjalling M, Gretarsdottir J and Abrahamsson H. Assessment of gastric emptying Comparison of solid scintigraphic emptying and emptying of radiopaque markers in patients and healthy subjects. *Digestive Diseases and Sciences* 44(4), 729-734, 1999.
- Strombeck DR. Motility: Small Intestine. In: Strombeck's Small Animal Gastroenterology (third edition). WB Saunders Philadelphia PA. 1996a, Pp 324-327.
- Strombeck DR Motility: Colon In: Strombeck's Small Animal Gastroenterology (third Edition). WB Saunders Philadelphia PA. 1996b, Pp327-9.
- Swayne DE, Tyler DE, Farrell RL and Cornelius LM. Sclerosing enteropathy in a dog. *Veterinary Pathology* 23, 641-3, 1986.
- Symonds HW, McWilliams P, Thompson H, Nash A, Sanchez S and Rozengurt N. A cluster of cases of feline dysautonomia (Key-Gaskell syndrome) in a closed colony of cats. *Veterinary Record* 136, 353-5, 1995.
- Tadesse K. The effect of dietary fibre isolates on gastric secretion, acidity and emptying. *British Journal of Nutrition* 55, 507-13, 1986.
- Taourel PG, Fabre JM, Pradel JA, Seneterre EJ, Megibow AJ and Bruel JM. Value of CT in the diagnosis and management of patients with suspected small bowel obstruction. *American Journal of Roentgenology* 165, 1187-92, 1995.
- Tomlin J, Brown N, Ellis A, Carlsson A, Bogentoft C and Read NW. The effect of liquid fibre on gastric emptying in the rat and humans and the distribution of small intestinal contents in the rat. *Gut* 34, 1177-81, 1993.
- Washabau RJ and Holt D. Pathogenesis, diagnosis and therapy of feline idiopathic megacolon. *Veterinary Clinics of North America: Small Animal Practice* 29(2), 589-603, 1999.
- Weiner K, Graham LS, Reedy T, Elashoff J and Meyer JH. Simultaneous gastric emptying of two solid foods. *Gastroenterology* 81, 257-266, 1981.
- Weisbrodt NW. Motility of the Small Intestine. *Physiology of the Gastrointestinal Tract* (second edition). Raven Press, New York. 1987, Pp 631-663.
- Wilkinson WL. Non-newtonian fluids. In: *Fluid Mechanics, Mixing and Heat Transfer*. London, Pergamon, 1960. P61-63.
- Willard MD, Mullaney T, Karasek S and Yamini B. Diarrhoea associated with myenteric ganglionitis in a dog. *Journal of American Veterinary Medicine Association* 193(3), 346-348, 1988.

Wingate DL, Stacher G and Kreiss C. Role and integration of mechanisms controlling gastric emptying. *Digestive Diseases and Sciences* 39(12Supp), 120S-123S, 1994.

Wood JD. Physiology of the enteric nervous system. In Johnston LR (ed) *Physiology of the Gastrointestinal Tract*. Raven Press, New York, 1987.

Wymann JB, Heaton KW, Manning AP and Wicks ACB. The effect on intestinal transit and the faeces of raw and cooked bran in different doses. *American Journal of Clinical Nutrition* 29, 1474-79, 1976.

Van der Sijp JRM, Kamm MA, Nightingale JMD, Britton KE, Mather SJ, Morris GP, Akkermans LMA and Lennard-Jones JE. Radioisotope determination of regional colonic transit in severe constipation: Comparison with Radiopaque Markers *Gut* 34, 402-8, 1993.

Veng-Pederson P. Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (Part 1). *Clinical Pharmacokinetics* 17(5), 345-66, 1989.

Veng-Pederson P. Mean time parameters in pharmacokinetics. Definition, computation and clinical implications (Part 2). *Clinical Pharmacokinetics* 17(6), 424-40, 1989.

Vermillion D, Scicchitano R, Ernst P and Collins SM. Immunomodulation of gut motility: involvement of connective tissue mast cells in antigen-induced contraction of smooth muscle. Abstract, *Digestive Diseases and Sciences* 32(8), 931, 1987.

Von der Ohe, MR and Camilleri M. Measurement of small bowel and colonic transit: indications and methods. *Mayo Clinical Proceedings* 67, 1169-79, 1992.