MECHANICS OF GASTRIC EMPTYING AND THE INFLUENCE OF GASTRIC SURGERY

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by

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DECLARATION OF AUTHORSHIP

This work contains no material which has been accepted for the award of any degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Mehran Anvari

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With the following exceptions, all of the experiments described in this thesis were designed, performed and analyzed by myself. The initial experiments (described in Chapter 7.1) were designed by Professor Dent, and were performed by me, in collaboration with Dr. Tougas. However, much of the burden of the analysis of the radiological data was carried out by Dr. Tougas, who became the first author in the subsequent publication of the study. To the best of my knowledge, the material in this study has not been used by any of the other collaborators (including Dr. Tougas) towards a higher degree.

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ABSTRACT

Emptying of ingesta from the stomach is controlled by a complex mechanism which is affected by therapeutic gastric surgeries, and can lead to significant symptoms in patients following such surgery. The aim of this thesis was to identify some of the motor mechanisms involved in emptying of gastric contents, the effect of therapeutic gastric surgery on these motor mechanisms, and evaluation of new surgical techniques aimed at minimizing the effects of surgery on normal patterns of gastric emptying. The work has been carried out on human subjects and conscious pigs, using recently developed antropyloroduodenal manometric techniques concurrent with measurements of gastric emptying, transpyloric flow, and gastric wall motion or tension.

The studies performed found the following. Phasic contractions of the corpus and antrum are important in initiating pulses of transpyloric flow through pressurization of gastric cavity in a fluid-distended stomach. The pylorus acts as a major braking mechanism to regulate the volume of transpyloric flow pulses. The timing of gastric contraction in relation to ensuing pyloric contraction is a major determinant of the volume of gastric contents passing across the pylorus, this timing being in part regulated by antral intramural pathways which are often transected during surgery.

Posture was shown to influence gastric emptying through changes in gastric motility. And, CCK pathways were shown to be important in inhibition of gastric pumping and stimulation of pyloric braking mechanisms seen during delivery of lipids into the intestine.

Changes in antropyloric motility and gastric emptying were correlated in patients following vagotomy and pyloroplasty, highly selective vagotomy, and partial gastrectomy, confirming our earlier observations in pigs.

In a final series of studies, a one centimeter bridge of muscle was shown to be capable of preserving the relative timing of gastric and pyloric contractions, and a normal pattern of gastric emptying after otherwise complete antral transection, indicating that this bridge carried important control signals to the pylorus from the stomach.

The work presented in this thesis has helped to improve our understanding of the mechanics of gastric emptying and some of the control mechanisms involved in its regulation. Studies were also done on the disturbances to these mechanisms caused by various therapeutic gastric surgical procedures, and possible new techniques to minimize these.

DEDICATION

I would like to dedicate this thesis, in recognition of their personal sacrifices, to the three women who have shaped my life, my grandmother Homa, my mother Nouri, and my wife Sima.

Section A

Literature Review

Chapter 1

Introduction

One of the first reports of the contractions of the stomach was made by Wepfer in 1697, who studied gastric movements in vivisected cats, dogs and wolves. However, it was the pioneering work of Beaumont in 1833, that laid down some basic concepts regarding gastric motility and its relation to gastric emptying. Beaumont's careful observations of the movement of chunks of food placed in the stomach of Alexis St. Martin (who had a permanent gastrostomy high on the greater curvature, as a result of a gunshot wound), led him to conclude that the proximal stomach stored food while the distal stomach was responsible for trituration and expulsion of material from the stomach (Szurszewski 1985). His division of the stomach into two functional units, proximal and distal, had endured until recently (Kelly 1981, Minami & McCallum 1984). Lack of reliable measurement techniques has been a major factor for the domination of this old and simplistic view of gastric motor function. However, in the last decade, the development of sophisticated measurement techniques, which have allowed direct measurement of the motor function of the different regions of the stomach (Aspiroz & Malagelada 1985a, Heddle *et al* 1988a, King *et al* 1984) and their role in gastric emptying, have suggested a more complex integration of gastric motor mechanisms. In addition, the recent growth of knowledge of gastrointestinal hormones (Walsh 1987, Allescher 1990) and neurotransmitters (Wood 1990) has further improved our understanding of the controls of gastric motility and emptying.

Despite the advances in our knowledge of gastric motility and emptying, many questions still remain to be answered. This review will outline the current understanding of the controls of gastric motility and emptying, and the effect of various therapeutic and experimental surgical procedures on gastric function. Special emphasis will be given to gaps in current knowledge. Due to the range of topics covered by this review, an overview of available literature is provided, with more details given in areas which are the focus of the experimental work of this thesis. The review includes the literature available until 1991 when the design of the studies for this thesis was completed. On a few occasions when an abstract published or presented by 1991, and relevant to the design of the studies, was published after 1991 as a completed manuscript, the date of the published manuscript is quoted. Otherwise, works published later and relating to the studies, are discussed in the appropriate chapters.

Chapter 2

Electrical and Mechanical Properties of Gastric Muscle

Coordinated motor function of the stomach is controlled by interaction of myogenic, neural and humoral mechanisms. This arrangement provides nearly complete compensation and adaptation when one component is lost or altered. Myogenic mechanisms are the primary controllers of gastric smooth muscle function, while neural and hormonal controls modulate the basic myogenic mechanisms. This chapter discusses the current knowledge on the electrical and mechanical properties of gastric muscle, which form the basis of the myogenic control.

2.1 ELECTRICAL CONTROL ACTIVITY

In vitro studies of gastric smooth muscle cells by intracellular electrodes show that gastric muscle, in common with other areas of the gastrointestinal tract, undergoes periodic oscillations in resting membrane potential (Szurszewski 1987), except in the fundus. This electrical control activity (ECA), consists of initial depolarization, partial repolarization, a sustained plateau phase lasting 4 - 20 seconds, and repolarization (figure 2.1) (Szurszewski 1987, Sanders & Publicover 1988). The ECA is recorded extracellularly as slow waves (Hinder & Kelly 1977).

Figure 2.1: Electrical Control activity recorded from the different regions of the stomach (printed from Szurszewski 1987, with permission).

2.1.1 Electrical properties of muscle strips

The fundic muscle cells have a resting membrane potential of around -48 mV and exhibit no spontaneous electrical activity (Bury & Boev 1979, Hinder & Kelly 1977, Kelly *et al* 1969). Muscle cells from the corpus, antrum and pylorus have an intracellular resting membrane potential of -60 to -75 mV (Szurszewski 1987), with the resting potential becoming more negative towards the pylorus. They exhibit periodic episodes of spontaneous depolarization (Weber & Kohatsu 1970) known as ECA.

2.1.2 Spatial patterns of electrical control activity

Intracellular electrode studies on isolated muscle strips from dogs and humans have shown that the frequency and morphology of the ECA is dependent on the original site of the muscle strips (El-Sharkawy *et al* 1978). The frequency, duration and character of the spontaneous fluctuations in membrane potential vary with position along the stomach, with spontaneous discharges (ECA) being less frequent and of longer duration at more distal sites, and exhibiting a more complicated, oscillating pattern of spiking discharge (Bury & Boev 1979, Hinder & Kelly 1977). *In vivo*, all portions of the stomach oscillate at the same frequency, driven by a proximal pacemaker located at the greater curve, about two-thirds of the distance from the pylorus (Code & Carlson 1968, Code *et al* 1968).

2.1.3 Origin of ECA

Due to electrical properties of the fundic smooth muscle, no ECA is observed in the fundus of the stomach (Morgan *et al* 1981). The ECA can only be initiated by the cells of corpus, antrum, and the pylorus. The cells in the region of the upper corpus on the greater curvature have the highest intrinsic frequency of ECA (Kelly *et al* 1969). As the gastric smooth muscle behaves as an electrical syncytium, this region determines the

frequency of the ECA for the entire stomach, thus acting as a pacemaker, with the electrical activity spreading circumferentially around the stomach and more slowly in a longitudinal direction towards the pylorus (Kelly *et al* 1969, Hinder & Kelly 1977, Bury & Boev 1979). Pacesetter potentials cycle at 3 per minute in humans and pigs (Smout 1980) and 5 per minute in dogs (Hinder & Kelly 1977). Antral muscle can also develop a pacemaker potential spontaneously (Daniel & Irwin 1971), or it can be accelerated by lowering the resting potential artificially with applied current (Sarna & Daniel 1973, Szurszewski 1987), or by chemically induced depolarization (El-Sharkawy & Szurszewski 1978).

2.1.4 Interstitial Cells of Cajal

There is an accumulating body of indirect evidence from studies in dogs and humans, suggesting that the interstitial cells of Cajal (ICC), which have a higher density in the pacemaker region of the stomach, are responsible for establishing the pacesetter potential (Thuneberg 1982 &1989). However, to date no experimental evidence for this hypothesis exists.

The ICCs have been classified into two groups according to their position in the wall of the gastrointestinal tract: one is localized in the myenteric plexus, and the other is in the smooth muscle. As each type of cell forms a network with other interstitial cells, smooth muscle cells and neural structures, it has been suggested that ICC may be involved in the generation or neurotransmission of electrical control activity of the gastrointestinal tract (Thuneberg 1989). For instance, fluctuating electrical activity has been recorded from the interstitial cells in the colon of dogs (Barajas-Lopez *et al* 1989). In the colon, ECA originates at the inner border of the circular muscle, while in the intestine the ECA originates between the circular and longitudinal muscles, areas

rich in ICCs (Daniel & Allescher 1990). Removal of these cells leads to abolition of the ECA activity (Hara *et al* 1986). To date, however, there are no studies which have examined the function of these cells in the human or animal stomach.

2.2 ELECTRICAL RESPONSE ACTIVITY

During ECA depolarization, all cells may exhibit a sustained plateau potential on which spikes may be superimposed. The spikes are known as the electrical response activity (ERA) or action potentials (Figure 2.2) (Szurszewski 1987). *In vitro*, contractions occur without spikes and their strength is related to the amplitude and duration of the plateau potential. *In vivo*, large contractions are associated with spikes (Smout 1980). The first component of the gastric slow wave, the initial sharp depolarization, elevates the membrane potential above the threshold for contraction and induces a small initial muscle contraction (Szurszewski 1987, Daniel *et al* 1990). This initial contraction is followed by stronger and more prolonged secondary contraction if the plateau potential exceeds the voltage threshold for contraction (Szurszewski 1987, Daniel *et al* 1990). The cells of the terminal 2 to 3 cm of antrum and pylorus exhibit spike potentials during the plateau potentials. *In vivo*, contraction accompanies ERA, which can only occur during the ECA depolarization of the membrane, and therefore, the frequency of the ECA determines the maximal contraction frequency of the stomach. *In vitro*, the contractions are timed by the occurrence of plateaus so they also have the frequency of ECA. Thus, the maximum frequency of the contractions in humans and pigs is 3 per minute and in dogs is 5 per minute. It can, however, be driven faster by external electrical stimulation, for example 9 per minute in dogs (Sarna & Daniel 1973).

Whether pacesetter potentials (ECA) are followed by action potentials (ERA) depends on neural and humoral modulation. ERA may accompany the pacesetter potential as it

travels from the corpus to the pylorus, or it may appear over only part of the stomach, giving rise to contractions which occur only in the region of ERA activity; *e.g.* contractions in the corpus, dying out in the antrum, or contractions which start in the distal antrum and travel to the pylorus.

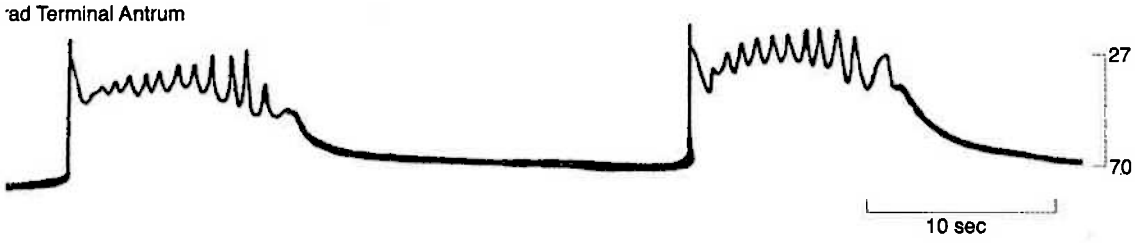


Figure 2.2: Electrical Response Activity (action potential) superimposed on an Electrical Control Activity in the antrum of a dog stomach (printed from Szurszewski 1987, with permission).

2.3 ELECTRICAL CONDUCTION ALONG THE STOMACH

Publicover & Sanders (1985) reported that the speed of conduction of potentials along the longitudinal axis was seven times slower compared to that along the transverse axis, suggesting that the spread around the stomach must be faster than the propagation distally toward the gastroduodenal junction. Furthermore, they demonstrated that the speed of propagation of the pacesetter potential of gastric muscle, studied in an organ bath, varies with muscle stretch. This suggests that gastric filling may be associated with an increase in the speed of propagation of the ECA and so the ERA, and thus, more area may contract concurrently, increasing the propulsive force. *In vivo*, the velocity of slow wave propagation increases towards the pylorus (Daniel 1965, Duthie *et al* 1971, Hinder & Kelly 1977). In patients undergoing cholecystectomy, Duthie *et al* (1972) demonstrated that the velocity of the slow wave increased from 0.5 cm per second in the proximal antrum to about 2 cm per second across the pylorus. The increase in the velocity of the gastric slow wave as it passes distally, together with the corresponding increase in duration of the plateau potential, may result in an increasing length of contracting muscle as it passes towards the pylorus (Code *et al* 1968).

2.4 TRANSMISSION OF ELECTRICAL ACTIVITY ACROSS THE PYLORUS

The ECA frequency recorded from the pyloric ring muscle is usually determined by the gastric pacemaker (Carlson *et al* 1966, Kelly *et al* 1969), but a number of studies have suggested that the pylorus may contract at a frequency approximating that of duodenal ECA (Aste *et al* 1979, Bertiger *et al* 1987, Allescher *et al* 1988). Studies in cats, dogs and other species have suggested that slow waves (ECA) can be transmitted across the pylorus in both directions, and that such transmission is myogenic, since it continues despite functional myenteric denervation (Bortoff & Davis 1968). Daniel & Allescher

(1990), have reported a close physical association between interstitial cells of Cajal and smooth muscle cells in the pylorus and have suggested that ICC may provide a pacemaker activity at the pylorus, and may be responsible for the faster rate of phasic activity occasionally observed at the pylorus. Further support for this theory comes from observations that tetrodotoxin (TTX), a neurotoxin, does not abolish either spontaneously-occurring slow waves in the pyloric region (El-Sharkawy *et al* 1978) or localized pyloric tone (Anuras *et al* 1974, Behar *et al* 1979, Telford *et al* 1979). Also, it either does not disturb, or enhances spontaneous pyloric pressure waves occurring in the absence of associated antral and duodenal pressure waves (Telford *et al* 1979, Bertiger *et al* 1987, Allescher *et al* 1988).

2.5 CONTRACTION PATTERNS OF GASTRIC MUSCLE

The contractile activity of the fundus differs from that of the rest of the stomach, reflecting the electrophysiological differences already discussed. The fundus has active tone at rest and was originally thought to be incapable of phasic contractile activity (Szurszewski 1987). The membrane potential of the fundic smooth muscle under resting conditions is above the voltage threshold for contraction, thus explaining the presence of basal tone (Morgan *et al* 1981). The fundic fibres partially depolarize and increase their tonic contraction after cholinergic neurostimulation, and hyperpolarize and decrease tonic contraction after noncholinergic, nonadrenergic vagally mediated stimuli (Morgan *et al* 1981). However, the fundus demonstrates some phasic contractile activity, which is believed to be due to regularly spaced periods of tonic increase (Szurszewski 1987). Lind *et al* (1961) reported phasic contractions of the fundus which produced prolonged elevations of pressure of 10-25 cm of water, lasting 1 to 6 minutes. These are now believed to be periodic changes in fundic tone which can be recorded with a gastric barostat (Azpiroz & Malagelada 1985a). In addition, increases in

fundic tone of shorter duration (10-15 sec), which raise the intra-gastric pressure by 5 cm water, have also been reported (Lind *et al* 1961). The mechanical and physiological significance of these periodic changes in fundic tone remains obscure.

The corpus, antrum and pylorus, on the other hand, exhibit mainly short duration (10 sec) phasic contractions which produce greater changes in intra-luminal pressure (10-150 mm Hg) (Heddle *et al* 1988a, Treacy *et al* 1990) than fundus, and appear as ring contractions on fluoroscopic examination (Smith *et al* 1957, Carlson 1962, Carlson *et al* 1966). The appearance of ring contractions derives from the rapid circumferential conduction of ECA described above.

The pylorus is capable of two types of motor activity: i) contractions coordinated with antral and/or duodenal contractions, and ii) isolated contractions occurring in the absence of associated antral or duodenal contractions (Heddle *et al* 1988a &1988b & 1988c, Treacy *et al* 1990). Antropyloric and antropyloroduodenal contractions can both propel material across the pylorus and retropel material back into the stomach (Smith *et al* 1957). It has been shown that isolated pyloric pressure waves are stimulated by infusion of nutrients into the duodenum, and are proposed to be involved in regulation of transpyloric flow (Heddle *et al* 1988b & 1988c, Treacy *et al* 1990). The mechanical significance of pyloroduodenal contractions is not well established, although it has been proposed that they help clear the duodenum, thus preventing duodenal distension and enhancing gastric emptying.

Chapter 3

Gastric Extrinsic Motor Neural Mechanisms

The neural modulation of gastric motor activity can be divided into two pathways: i) extrinsic and ii) intrinsic or intramural. The extrinsic neural mechanisms can be further subdivided into vagal and sympathetic pathways.

3.1 VAGAL EFFERENT MECHANISMS

3.1.1 Central projections

There is limited information available, but studies in cats and rats using retrograde tracer techniques with horseradish peroxidase and fast methyl blue (Yamamato *et al* 1977, Elfvin & Lindh 1982, Norman *et al* 1985), have suggested that the majority of the central nervous system projections to the stomach derive from the dorsal motor nucleus of the vagus. Two other brain centres, namely nucleus ambiguus and nucleus retroambiguus, have also been shown to send projections to the stomach (Gillis *et al* 1989). It has been reported that the gastric column within the vagus is subdivided into a medial column which supplies the antrum and pylorus, and a lateral column that supplies the fundus (Gillis *et al* 1989). The functional significance of this is unclear, although it is postulated that other parts of the CNS could have selective effects on specific parts of the dorsal motor nucleus of the vagus, and therefore, selective effects on specific parts of the stomach (Gillis *et al* 1989).

3.1.2 Anatomy

The vagus nerves (anterior and posterior trunks) to the abdomen derive from the oesophageal plexuses in the thorax and they exhibit considerable variability (Skandalakis *et al* 1980).

The anterior vagal trunk contains fibres mainly from the left vagus nerve, and most commonly forms a single trunk as it passes through the hiatus, but occasionally two or even three trunks are found. It separates into two divisions at or near the hiatus. The larger division, known as nerve of Latarjet (Latarjet 1922), continues parallel to the lesser curvature of the stomach. It sends 2-12 branches to the anterior gastric wall, and usually terminates at a variable point on the antrum without reaching the pylorus (95% of cases). The other division of the anterior trunk, known as the hepatic nerve, passes in the lesser omentum to the hilum of the liver. It gives off a branch, known as nerve of McCrea, which descends to the left of the hepatic artery and supplies the pylorus and first part of duodenum (McCrea 1924).

The posterior vagal trunk is formed mainly from right-sided vagal fibres of the oesophageal plexus. This trunk tends to parallel the anterior trunk but lies further to the right. It divides below the diaphragm with one division (coeliac division), carrying the major portion of its fibres, traveling backwards with the left gastric artery to the coeliac plexus. The other division, the posterior nerve of Latarjet, parallels the anterior nerve of Latarjet, but supplies fewer fibres to the antrum. Occasionally the first gastric branch arises in the hiatus or above, and crosses behind the oesophagus to the left to reach the fundus. This nerve is often referred to, perhaps somewhat melodramatically,

as the 'criminal nerve' of Grassi, as it can be missed during the performance of highly selective vagotomy for ulcer disease, leading to ulcer recurrence after surgery.

3.1.3 Composition

The vagi are composed of pre- and postganglionic afferent and efferent fibres. The vagus nerves carry the parasympathetic efferent fibres to the stomach, as well as some adrenergic fibres which enter at the level of the oesophageal plexus. The majority (80-90%) of fibres in the vagus nerves are afferent fibres (Hoffman & Schnitzlein 1969), carrying signals from sensory nerve endings in the gastric mucosa, muscle wall and serosa, and other viscera, in response to stretch, motility and chemical stimuli (Grundy & Scratcherd 1982 & 1984).

3.1.4 Types of vagal efferents

Vagal efferents are of two types: i) low threshold excitatory fibres and ii) high threshold inhibitory fibres (Roman & Gonella 1981). The low threshold fibres are cholinergic and blocked by atropine. They are also blocked by hexamethonium (ganglionic blocker), suggesting that they act through intramural ganglia (Jansson 1969). The high threshold fibres, on the other hand, are nonadrenergic, noncholinergic nerves (Gillespie 1982).

3.1.5 Neurotransmitters

Acetylcholine (ACh) is the neurotransmitter for the low threshold efferent fibres, but the exact neurotransmitter for the high frequency efferent nerves is unknown, although several substances, including nitric oxide (Christinck et al 1991), vasoactive intestinal polypeptide (VIP) (Schultzberg *et al* 1980) and adenosine triphosphate (ATP) (Gillespie 1982), have been proposed.

3.2 SYMPATHETIC CONTROL

3.2.1 Anatomy

The efferent preganglionic sympathetic supply to the stomach originates from the fifth to tenth thoracic segments of the spinal cord (Elfvin &Lindh 1982). It enters the coeliac ganglion, and the postganglionic fibres reach the stomach along the branches of the coeliac artery (Meyer 1987, Williams *et al* 1989).

3.2.2 Composition

Similar to the vagus, the majority of sympathetic fibres are afferents carrying signals from gastric mechanoreceptors (Allescher 1990). These afferents may take part in a number of reflexes modulating the gastric motor function.

3.2.3 Sympathetic efferents

Sympathetic efferents have an inhibitory effect on the gastric motility, either through inhibitory modulation at the level of myenteric plexus, or to a lesser degree by direct action at the muscle level (Grundy & Scratcherd 1982). The pylorus, however, is heavily innervated (Allescher *et al* 1988). Lerman *et al* (1981) reported an excitatory effect from splanchnic stimulation in the dog, but this effect was blocked by atropine and not affected by adrenoreceptor blockers, suggesting the activation of post-ganglionic cholinergic fibres.

3.2.4 Neurotransmitters

Acetylcholine (nicotinic) is the neurotransmitter in the preganglionic fibres, while the primary postganglionic neurotransmitters are noradrenaline, ATP, and NPY (Costa & Furness 1982).

Chapter 4

Gastric Intrinsic Motor Neural Mechanisms

4.1 ANATOMY

The stomach, like the rest of the GI tract, has both a myenteric (Auerbach's) and submucosal (Meissner's) plexus (Gabella 1987), which are believed to modulate the pattern of gastric motility. In the stomach, however, the submucosal plexus is very sparse in ganglia and nerve cell bodies (Gabella 1987). The two plexuses receive input from both the vagus and the sympathetic nerves (Gabella 1972 & 1987). There are neural connections between the myenteric and submucosal plexus (Gabella 1987) and both are continuous between the antrum and duodenum, but display considerable specialization at the pylorus (Daniel & Allescher 1990).

4.2 NEURAL PATHWAYS

There is limited knowledge of the various pathways which may operate in this rich network of neurons.

4.2.1 Descending inhibitory

Antral field stimulation has been shown to inhibit phasic and tonic pyloric contraction in anaesthetized dogs after bilateral vagotomy (Allescher *et al* 1988). This inhibition was unaffected by atropine, hexamethonium, naloxone and propanolol, reduced by phentolamine and abolished by tetrodotoxin and antral transection distal to the stimulating electrodes, suggesting the presence of inhibitory, intramural neural

pathways passing from the antrum to the pylorus. There are probably distal projecting inhibitory pathways within the stomach and ascending excitatory ones as well.

4.2.2 Ascending excitatory

Duodenal electrical field stimulation, on the other hand, was shown to induce phasic and tonic pyloric contraction unrelated to duodenal or antral pressure waves, a response blocked by atropine, hexamethonium and duodenal transection (Allescher *et al* 1988). This suggests the presence of ascending excitatory pathways between the duodenum and the pylorus. This was supported by a recent study in conscious pigs (Treacy *et al* 1992), which reported that the stimulation of isolated pressure waves by intraduodenal dextrose was markedly reduced after duodenal transection. There is, however, no evidence (not tested) as yet for the presence of ascending inhibitory pathways between the duodenum and the antrum.

Furthermore, little is known about similar local neural pathways in humans. Atropine has been shown to reduce tonic and phasic pyloric response to intraduodenal acid and dextrose (Valenzuela *et al* 1976, Fone *et al* 1989), while intravenous naloxone failed to block the stimulation of pyloric motility by intraduodenal lipid (Tougas *et al* 1990).

4.3 NEUROTRANSMITTERS

A large number of neurotransmitters have been shown to be present in enteric neural pathways. The excitatory neurotransmitters include acetylcholine, gastrin, CCK, substance P, neurokinin A, dynorphin, met-enkephelin, and leu-enkephalin. The inhibitory neurotransmitters include noradrenaline, neurotensin, VIP, ATP, secretin, and glucagon (Daniel *et al* 1989a & 1989b, Meyer 1987). In more recent years, the possibility that nitric oxide (NO) is the NANC inhibitory neurotransmitter has attracted

great attention and support. Recent studies have shown that nitric oxide synthase (NOS), the enzyme which synthesizes nitric oxide, is present in the enteric nervous system (Boeckxstaens *et al* 1990, Gustafsson *et al* 1990, Hata *et al* 1990, Toda *et al* 1990, Tottrup *et al* 1991). Enzymatic blockade of nitric oxide production, using various arginine analogs, either reduced or blocked the inhibitory NANC response in the lower oesophageal sphincter (Tottrup *et al* 1991) and ileocecal sphincter (Boeckxstaens *et al* 1990). Also, in non-sphincteric regions of the gut, such as opossum oesophagus (Daniel *et al* 1986) and canine circular intestinal smooth muscle (Stark *et al* 1991, Toda *et al* 1990), the NANC inhibitory action appears to be mediated by nitric oxide or a related compound. There is also *in vitro* evidence that NO plays a role in the NANC inhibitory innervation of other gastrointestinal smooth muscles such as the guinea pig ileum (Gustafsson *et al* 1990). To date (1991), there are no studies on the role of NO pathways in the regulation of gastric motor function.

Chapter 5

Afferent Neural and Integrative Controls of Gastric Motor Functions

Afferent fibres greatly outnumber efferent fibres in the autonomic nerves of the viscera, and play an important role in the gut function (Grundy 1988). The afferent fibres transmit information from sensory receptors in the gastric wall to the central nervous system, and also form important neural reflex arcs which modulate gastric motor function (Meyer 1987).

5.1 AFFERENT RECEPTORS

Both mechanical and chemical receptors are believed to be present in or immediately below the gastric mucosa and respond to a variety of luminal stimuli (Grundy & Scratcherd 1984). Mechanoreceptors are also present in the muscle wall, as well as in the serosa. The signals from these afferent receptors form a number of important neural reflexes.

5.2 NEURAL REFLEXES

5.2.1 Receptive relaxation

It has been long established that the stomach shows reflex relaxation with mechanical stimulation of the pharynx (swallowing), or oesophageal distension, which reduces intra-gastric pressure and is known as ***receptive relaxation*** (Cannon & Lieb 1911, Meyer 1987). This reflex is abolished by vagotomy (Jansson 1969).

5.2.2 Accommodation reflex

Another important reflex abolished by vagotomy is reflex relaxation of the gastric fundus to gastric distension, known as the ***accommodation reflex*** (Jansson 1969, Staadas 1970, Staadas 1975). This reflex allows for only small increases in intra-gastric pressure with gastric distention.

Both receptive relaxation and the accommodation reflex depend on nonadrenergic and noncholinergic mechanisms (Martinson & Murren 1963, Jansson 1969).

5.2.3 Antral Reflex

Andrews *et al* (1980) demonstrated in anaesthetized ferrets, that the distension of the proximal stomach increased action potentials along the efferent fibres to the antrum which had been transected from the proximal stomach, leading to stimulation of antral contractions. This reflex was abolished by antral vagal denervation and is termed the ***antral reflex.*** Vagotomy in dogs (Wilbur & Kelly 1973) and humans (Staadas & Aune 1970) also diminishes the antral response to gastric distension.

5.2.4 Enterogastric reflex

Enterogastric reflexes have also been described. Grundy & Scratcherd (1982) reported that distension of the duodenum and colon in the anaesthetized ferret inhibited gastric tone and phasic contractions, a response partially reduced by vagotomy or splanchnectomy alone, and totally abolished by both interventions together. Deponti *et al* (1987) reported that gastric relaxation caused by duodenal distension in conscious dogs, was not affected by intravenous atropine or combined phentolamine and propanalol, but was abolished by supradiaphragmatic vagal cooling or vagotomy. Thus, suggesting that in

dogs, a nonadrenergic, noncholinergic vagal pathway participates in gastric relaxation induced by duodenal distension. Furthermore, the inhibition of antral contraction by infusion of acid and glucose into the proximal intestine is inhibited by vagotomy, suggesting this effect is mediated through a vagal enterogastric reflex (Grundy & Stratcherd 1989).

5.3 INFLUENCE OF CENTRAL NERVOUS SYSTEM IN HUMANS

There is limited data concerning the influence of the central nervous system on gastric motor function in humans. Tumor infiltration of the medulla oblongata has been reported to result in abnormal fasting motor patterns and delayed gastric emptying in the absence of raised intracranial pressure (Wood *et al* 1985). Also, the basilar variant of migraine may present with nausea, vomiting and abdominal pain (Prensky 1976). Physical and mental stresses have also been reported to alter gastric motor function and delay gastric emptying (Fone *et al* 1990). The data on the effect of vagotomy on gastric motor function are discussed in Chapter 10.

Chapter 6

Humoral Control Mechanisms

An increasing number of gastrointestinal hormones and neuropeptides have been shown to influence gastric motility in pharmacological concentrations *in vivo* or *in vitro* (Walsh 1987, Allescher 1990). Cholecystokinin is, however, the only GI hormone which has been shown to have a major influence on the postprandial pattern of gastric motility in physiological concentrations. The current information available on the physiological relevance and the action of cholecystokinin (CCK) on gastric motility and emptying is reviewed below. The effects of other hormones are reviewed only briefly.

6.1 CHOLECYSTOKININ

6.2.1 *In vitro* action

In vitro studies indicate that CCK increases contractions and the amplitude of action potentials in canine antral circular muscle (Kuwahara *et al* 1986). The studies of Ludtke *et al* (1988) on muscle strips from different regions of human and dog stomach found that the excitatory effects of CCK_8 show great regional variation in quality and intensity depending on what region of the stomach the muscle strips originated.

6.1.2 *In vivo* action

Exogenous infusions of CCK_8 and CCK_{33}, designed to replicate the plasma concentrations of CCK occurring after ingestion of protein and fat-containing meals, slow gastric emptying in humans (Fried *et al* 1991a, Kleibeuker *et al* 1988a, Liddle *et al* 1986) and

animals (Debas *et al* 1975, Green *et al* 1988). Intravenous infusions of exogenous CCK analogues (CCK_8 or CCK_{33}) decrease proximal gastric tone and antral contraction, and stimulate pyloric contraction (Isenberg & Csendes 1972, Phaosawasdi & Fisher 1982, Yamagishi & Debas 1978, Fraser *et al* 1992). A recent study by Lopez *et al* (1991), reported that CCK_8 infusion intracerebroventricularly decreased postprandial pyloric spike activity in dogs, while CCK antagonist asperlicin produced an opposite effect, suggesting a different effect of centrally administered CCK.

6.1.3 Mode of action

The mechanism(s) by which CCK influences gastric and pyloric motor function is unclear. CCK receptors are found on smooth muscle cells throughout the gut as well as on the intramural neurons and central nervous system (Walsh 1987). Thus, CCK may act on the smooth muscle directly or indirectly through other pathways. Allescher *et al* (1989) reported that intra-arterial CCK_8 had both neural and direct effects on the pylorus of anaesthetized dogs, depending on the dose of CCK_8 infused. They reported that the pyloric motor response to CCK_8 was dependent on muscarinic (atropine sensitive) mechanisms. In contrast, Fraser *et al* (1993), studying intravenous CCK infusion in healthy volunteers, and using a similar sleeve manometric assembly, reported that CCK_8 stimulated localized pyloric contractions but that the response was not influenced by atropine. This latter observation may suggest that the relatively high doses of intravenous CCK_8 had a direct effect on pyloric smooth muscle, as earlier observations by the same group (Fraser *et al* 1992) indicate that the pyloric motor response to intraduodenal lipid is dependent on muscarinic mechanisms. The differences in observations of Allescher and Fraser may also be, in part, due to different routes of CCK administration *i.e.* local intra-arterial infusion (local effect) versus intravenous infusion with widespread effects.

Based on results obtained in rats, Forester *et al* (1990) has suggested that the site of action of CCK on the corpus and antrum is on primary afferent neurons that are also gastric mechanoreceptors, and that this causes activation of an inhibitory vago-vagal reflex pathway, which leads to relaxation of the body of the stomach.

6.1.4 Physiological role

The recent development of relatively specific peripheral CCK antagonists have allowed the role of endogenous CCK to be better evaluated. The specific CCK antagonist, loxiglumide, has been reported to accelerate gastric emptying of liquid and solid test meals in humans (Fried *et al* 1991b, Meyer *et al* 1989), although this result was not confirmed with a different CCK antagonist (Liddle *et al* 1989). There are two CCK receptors, CCK_A and CCK_B, and the relative contribution of each one in regulation of gastric motility and emptying in different animal species and in humans is still unclear.

The CCK antagonists, loxiglumide and L364,718 (later termed MK-329, primarily a CCK_A antagonist) prevent the retardation of gastric emptying by exogenous CCK infusion (Fried *et al* 1991b) and accelerate the emptying of meals containing fat, protein or glucose in humans (Fried *et al* 1991b, Ricci Maccarini *et al* 1991) and animals (Forester *et al* 1991, Green *et al* 1988). However, this effect of CCK antagonists on gastric emptying has not been a consistent observation by all experimenters (Corazziari *et al* 1990, Liddle *et al* 1989). The reasons for the discrepancy may include the fact that different doses of CCK-antagonists were used. These are competitive antagonists and their effects are dose dependent (Malesci *et al* 1990). It is also possible that differences in experimental techniques and use of antagonists with CCK_B or mixed CCK_A and CCK_B antagonistic action may have contributed to the discrepancies in the literature.

The above data suggests that cholecystokinin is an important mediator of the changes in gastric motility and emptying associated with the ingestion of meals (Kleibeuker *et al* 1988a, Liddle *et al* 1986). However, to date this has not been verified by concurrent measurements of gastric motility and emptying using selective antagonists.

The effect of CCK on gastric motility and emptying may constitute a feedback loop which regulates its release, as suggested by Liddle *et al* (1986). They demonstrated that the emptying of food into the proximal intestine stimulates the release of CCK, which in turn slows emptying. Several studies have suggested that this mechanism may also be important in the regulation of food intake in both humans and animals (Moran & McHugh 1982, McHugh & Moran 1986, Smith & Gibbs 1979).

6.2 GASTRIN

6.2.1 ***In vitro*** **action**: Gastrin has no effect on slow wave frequency (Ormsbee & Bass 1976, Schuurkes & Charbon 1978, Strunz *et al* 1979), but increases the amplitude and duration of action potentials (Szurszewski 1975).

6.2.2 ***In vivo*** **action:** Gastrin is known to induce antral and duodenal contractions (Gregory & Tracy 1964), and delay gastric emptying of liquids in pharmacological doses (Dozois & Kelly 1971, Cooke *et al* 1972). The effects of gastrin on pyloric motor function is still unclear due to lack of evidence using adequate techniques for recording pyloric activity.

6.2.3 **Mode of action:** It acts directly on gastric muscle, as well as acting on the neural pathways (Szurszewski 1975, Vizi *et al* 1973, Fox *et al* 1983). Whether its actions on the stomach are mediated through gastrin or CCK receptors is still unclear.

6.2.4 Physiological role: Gastrin is released in response to a meal and to a number of other stimuli. Its main physiological effect is to stimulate gastric acid secretion, but whether it has physiological effects on gastric motility is still uncertain.

6.3 SECRETIN

6.3.1 *In vitro* action: Secretin stimulates contractile activity in pyloric muscle (Lipshutz & Cohen 1972), but inhibits antral contractions produced by electrical field stimulation (Van Nueten & Shuurkes 1984).

6.3.2 *In vivo* action: It decreases gastric tone (Valenzuela 1976), inhibits postprandial gastric motility (Sarna *et al* 1978), stimulates pyloric contraction (Fisher *et al* 1973), and delays liquid and solid gastric emptying in physiological concentrations (Valenzuela & Defilippi 1981, Kleibeuker *et al* 1988b).

6.3.3 Mode of action: There is a possibility that secretin interacts with dopaminergic mechanisms (Van Nueten & Shuurkes 1984).

6.3.4 Physiological role: Secretin is released in response to increased delivery of acid into the duodenum following the ingestion of a meal and may act to regulate the rate of nutrient delivery into the intestine. Its relative contribution to other hormonal controls, particularly CCK, is not known.

6.4 MOTILIN

6.4.1 *In vitro* action: Motilin increases duodenal spiking activity without a change in slow wave frequency (Ruppin *et al* 1975).

6.4.2 *In vivo* action: Motilin increases gastric tone (Valenzuela 1976, Jennewein *et al* 1975), antropyloroduodenal motility (Jennewein *et al* 1975), and liquid and solid gastric emptying (Christofides *et al* 1979 & 1981, Fox *et al* 1984).

6.4.3 **Mode of action:** Neural and direct muscle action (Wingate *et al* 1976, Fox *et al* 1984).

6.4.4 **Physiological role:** There is some evidence supporting a physiological role of motilin in the occurrence of migrating motor complexes during the fasting phase (Lee *et al* 1983).

6.5 GLUCAGON

6.5.1 ***In vitro*** **action:** Glucagon inhibits both basal and stimulated electrical activity of the stomach (Bortolotti *et al* 1975).

6.5.2 ***In vivo*** **action:** It decreases intra-gastric pressure (Valenzuela 1976), inhibits antral contraction (Miolan & Roman 1975), and delays liquid gastric emptying in pharmacological doses (Chernish *et al* 1978).

6.5.3 **Mode of action:** It may act through the vagus nerve or through the release of catecholamines (Miolan & Roman 1975).

6.6 OTHER HORMONES

There are a number of other hormones and neuropeptides which have a direct or indirect action on gastric motility and emptying, in either pharmacological or physiological doses. These include somatostatin, pancreatic polypeptide, peptide YY, bombesin, enkephalins, VIP, substance P, GIP, and neurotensin (Walsh 1987, Allescher 1990). The known effects of these hormones have been tabulated in the next page (Table 6.6).

Table 6.6: The known effects on gastric motility and emptying of other hormones and neuropeptides.

Hormone	*In vivo*		*In vitro*
	Motility	***Emptying***	***Motility***
Bombesin	-increases antral electrical activity -causes contractions of antrum and pylorus	-delays solid emptying	-disrupts electrical activity -excitatory action on corpus, antrum and pylorus
Enkephalins	-inhibits antral contractions -stimulates pyloric contraction	-delays liquid emptying	
Gastric Inhibitory Polypeptide (GIP)	-inhibits motor activity in corpus & antrum -reduces intragastric pressure		
Neurotensin	-converts fasting MMC to fed pattern	-inhibits emptying of liquids & solids	-stimulates circular muscle (in dogs), contracts fundic muscle
Pancreatic Polypeptide (PP)	-increases motility in stomach & intestine -inhibits gastric MMC	-speeds gastric emptying	
Peptide YY	-no effect on MMC -no effect on postprandial motility	-inhibits gastric emptying of liquids	
Somatostatin	-inhibits normal MMC in stomach	-low doses: enhance emptying -high doses: inhibit emptying	
Substance P	-constricts smooth muscle -alters MMC (rabbit ileum)		-low dose: relaxes smooth muscle -high dose: contracts smooth muscle
Vasoactive intestinal peptide (VIP)	-antagonizes pentagastrin-induced muscle contractions		-inhibits antral contractions (dog) -inhibits pyloric motor activity

Chapter 7

Gastric Emptying Patterns

Close regulation of gastric motor function allows the stomach to act as a reservoir and an electromechanical pump, which regulates the orderly emptying of material into the proximal intestine.

7.1 EMPTYING PATTERNS OF DIFFERENT INGESTA

7.1.1 Non-nutrient liquids

Non-nutrient liquids empty from the stomach (animals and humans) in an exponential fashion (Hunt & Spurrell 1951, McHugh & Moran 1979, Collins *et al* 1983) suggesting that the speed of gastric emptying is determined by some volume dependent variable (first order kinetics).

7.1.2 Nutrient-rich liquids

Nutrient-rich liquids have a relatively linear gastric emptying rate (Collins *et al* 1983, Brener *et al* 1983) which allows for a constant rate of calorie delivery into the proximal intestine (McHugh & Moran 1979, Brener *et al* 1983). The rate of emptying of these liquids is dependent on the initial volume and the energy density of the meal (Hunt *et al* 1985).

With liquid meals, there may be no initial lag phase, or if any, a very short one (Meyer 1987).

7.1.3 Digestible solids

Digestible solids, on the other hand, have a sigmoid shaped gastric emptying time course (Meyer *et al* 1976, Collins *et al* 1988). It begins with a long initial lag phase during which no solid food is emptied (accompanying liquid meal may empty), followed by a prolonged linear phase of emptying (zero-order kinetics), and finally, when the stomach is nearly empty, by a much slower phase. The gastric emptying rate of digestible solids is increased by meal weight (Moore *et al* 1981), and decreased by increasing the caloric content of the meal (Moore *et al* 1984).

7.1.4 Indigestible solids

Indigestible solids with a diameter of less than 2 mm, empty with digestible solids at a rate which is dependent on their size and density (Meyer *et al* 1985). Particles with a larger diameter are retained until the regular migrating motor complex (MMC) is re-established after the meal, and are emptied from the stomach during phase III of the MMC cycle (Code & Marlett 1975).

7.2 INFLUENCE OF POSTURE ON GROSS PATTERNS OF EMPTYING

Gravity, as well as active pumping by the stomach and the duodenum, may help generate a transpyloric pressure gradient, which leads to emptying of food from the stomach. Burn-Murdock *et al* (1980) demonstrated that emptying of non-nutrient liquids of equal volume was faster when human subjects lie on the right side as opposed to when they were sitting or lying on the left side. Emptying of nutrient liquids (Hunt *et al* 1965) and solids (Moore *et al* 1988) are also accelerated in positions where the gravitational pull favours emptying. Whether the effect of posture is a direct effect of

gravity, or whether there are additional effects on gastric motor function which could alter emptying rate, is not known.

7.3 OTHER FACTORS WHICH INFLUENCE GROSS PATTERNS OF EMPTYING

Exercise (Moore *et al* 1990), volume of the meal (Collins *et al* 1991), and the age of the subject (Horowitz *et al* 1984), have been shown to effect gastric emptying rate. Gender also plays a role; Hutson *et al* (1989) reported that premenopausal women have a slower gastric emptying of liquids and solids, as compared to men of similar age, but that postmenopausal women have a similar rate of solid (but not liquid) gastric emptying to men.

7.4 SECOND TO SECOND TRANSPYLORIC FLOW

Fluoroscopic (Klein 1926, Carlson *et al* 1966), ultrasonic (King *et al* 1984), electromagnetic flow meter (Malbert & Ruckebusch 1991) and duodenal pH studies (Rhodes *et al* 1966) have shown that gastric emptying occurs primarily as pulses of transpyloric flow. Concurrent measurement of antropyloroduodenal motility and transpyloric flow (Smith *et al* 1957, Ehrlein & Hiesinger 1982, Malbert & Ruckebusch 1991, Treacy *et al* 1990) has suggested that pulsatile transpyloric flow is associated with lumen-occlusive antropyloric contraction sweeping the antral contents into the duodenum. However, King *et al* (1984), using real-time ultrasonic evaluation of transpyloric flow of liquids, reported that a significant portion of transpyloric liquid movement occurred prior to, or in absence of lumen occlusive antropyloric contractions. Furthermore, Malbert and Ruckebusch (1991) reported that terminal antral contraction occurred 0.9±0.29 seconds after the onset of transpyloric gush.

The second to second relationship between transpyloric flow and motor events in the stomach is still poorly understood. A major focus of this thesis is to establish the correlation between these two variables on a second to second basis, and to establish some of the control mechanisms operating to regulate transpyloric flow.

Chapter 8

Mechanical Functions of the Stomach

Anatomically, the stomach may be divided into four regions: fundus, corpus, antrum and pylorus, but functionally they interact closely. Normal control of gastric emptying depends on several motor mechanisms.

8.1 GASTRIC RESERVOIR FUNCTION

Gastric fundic muscle has an unusually large capacity for lengthening so that large volumes are accommodated within the fundus with minimal increases in intra-gastric pressure (high compliance) (Wilbur *et al* 1974). The smooth muscle of the fundus is capable of slow sustained contractions (Szurszewski 1987), and exhibits vagally mediated receptive relaxation in response to swallowing of food (Cannon & Lieb 1911). Using a gastric barostat, Azpiroz and Malagelada (1986) demonstrated that intestinal nutrients induce fundic relaxation by a vagally mediated, nonadrenergic noncholinergic mechanism. The slow changes in fundic tone are believed to regulate intra-gastric distribution of food within the stomach during the grinding, sieving and pumping action of the stomach (Sheiner *et al* 1980, Kelly 1981). But, a mid-gastric band (Beaumont 1833, Moore *et al* 1986) of relatively high tone may also be important, acting by forming a waist between the fundus and antrum without producing lumen occlusion. The mechanical consequences of the mid gastric band are still, however, unclear.

8.2 GASTRIC TRITURATION

Solids are retained in the stomach until they are broken down to particles of less than 2 mm in diameter, through softening by soakage, enzymatic action and gastric grinding (Meyer *et al* 1979, Mayer *et al* 1984), before being delivered into the duodenum. The grinding action of the stomach, with the resultant massive increase of food particle surface area, is important for small intestinal luminal digestion. It has been suggested that the retropulsive action of antropyloric contractions is important in the grinding mechanism (Smith *et al* 1957, Carlson *et al* 1966). This occurs when the pyloric lumen closes ahead of propagating antral contractions. Resection of the antrum in humans (Mayer *et al* 1982) and dogs (Hinder & San-Garde 1983) is associated with defective grinding. However, the fact that, in the absence of antrum, 60 to 70% of particles leaving the gastric remnant are still smaller than 1 mm (Meyer *et al* 1979), suggests that the antrum is not the exclusive site of trituration of solid food. The efficiency of gastric grinding may depend, in part, on appropriate intra-gastric distribution of food (Jacobs *et al* 1982, Collins *et al* 1988) *i.e.* orderly delivery of the meal from the proximal stomach to the distal stomach where grinding occurs.

8.3 GASTRIC SIEVING

The limitation of nutrient solid emptying to particles with diameter of 2 mm or less (Meyer *et al* 1981), is believed to be primarily the function of the antrum and the pylorus (Meyer 1987), but the mechanics are poorly understood. The sieving action of the stomach is lost in patients with distal gastrectomy (Mayer *et al* 1982), but this was found to be intact for the most part, in patients after proximal gastric vagotomy and vagotomy & pyloroplasty (Mayer *et al* 1984). These observations, together with earlier cineradiographic studies of the passage of plastic spheres in dogs, before and after antrectomy (Dozois *et al* 1971), have suggested that the antrum plays the predominant

role in the sieving of solids. Hinder & San-Garde (1983) demonstrated in dogs that pylorectomy alone, or antrectomy with pylorus preservation, cause minimal disturbance to the sieving of solid particles, but pylorectomy together with antrectomy (Billroth I gastrectomy) significantly disrupted the sieving ability of the stomach. Thus, suggesting that any operation which could preserve any of these two regions will cause less disturbance in the sieving action of the stomach.

8.4 GASTRIC PUMPING MECHANISM

8.4.1 Stomach as a dual mode pump

It can be argued that the stomach acts as a dual mode pump; pumping liquids or almost liquefied solids (<2 mm diameter) in the fed state (with feedback control), and indigestible solids of larger (>2 mm) diameter in the interdigestive phase (no feedback control). The lag phase observed after ingestion of a digestible solid meal, represents the time taken by the stomach to liquefy the meal.

The mechanics involved in each type of pumping are different and involve a close integration of the motor function of the fundus, corpus, antrum, and the pylorus.

8.4.2 Gastric pumping in the fed state

The rate of gastric emptying of chyme (dv/dt) is dependent on the pressure gradient between the stomach and the duodenum (P_s-P_d), and the pyloric resistance (R_p), *i.e.* [$dv/dt = (P_s-P_d)/R_p$] (Nelson & Kohatsu 1971). The mechanical forces which can produce the pressure gradient necessary to propel ingesta across the pylorus are still poorly understood. The fundus is capable of slow sustained contractions, and appears to be the primary determinant of the baseline intra-gastric pressure (Szurszewski 1987,

Morgan *et al* 1981). However, pulsatile flow is the primary pattern of emptying after ingestion of a liquid or solid meal. It is difficult to envisage how fundic tone alone could lead to this pattern of flow, for either liquids or liquefied solids. One theory, proposed by Schulze-Delrieu & Brown (1985), is that the fundic tone provides the driving force, the flow being repeatedly interrupted by the pylorus acting as a phasic distal resistance mechanism. Schulze-Delrieu & Brown stented the pylorus of the cat stomach both in situ and *in vitro* and found that in both settings the emptying of a saline test meal from the in situ or isolated feline stomach was hastened when the tip of the collecting duodenal cannula was across the pyloric segment rather than the duodenal bulb. The gastric outflow was continuous when the duodenal cannula was across the pyloric sphincter, whereas flow was intermittent when the tip was in the duodenal cap. However, others have shown that phasic motor activity of the pylorus can be independent of any antral activity (Heddle *et al* 1988a & 1988b) and that flow occurs during short periods of relaxation of the pylorus (Malbert & Ruckebusch 1991). But, there are no data to show that pulsatile transpyloric flow is caused purely by intermittent relaxation of the pylorus in the presence of a raised intra-gastric pressure (Rees *et al* 1979a & 1979b, Malbert & Ruckebusch 1991).

It is more plausible that the major expulsive force generated by the stomach is itself intermittent. Cineradiographic studies have demonstrated that propagated contractions of the corpus and antrum, which sweep towards the pylorus, propel ingesta through the pylorus into the duodenum (Cannon 1898, Thomas 1957, Wilbur & Kelly 1973). These propagated contractions empty only a small amount of material into the stomach while the rest of the material is retropelled back into the gastric cavity (Thomas 1957, Wilbur & Kelly 1973) and is important in grinding of food particles. Treacy et al (1990) showed that the volume of pulsatile gastric emptying over time was associated

with the frequency of antropyloric contractions. White *et al* (1981) reported that gastric emptying of saline was most rapid when antral, pyloric and duodenal pressure waves were sequentially propagated. Houghton *et al* (1988a), studying healthy volunteers, reported that the onset of emptying after ingestion of a solid meal was associated with an increase in the rate of occurrence of antral pressure waves, and that the half time for emptying (T_{50} minus lag period) was inversely correlated with the rate of propagated contractions of the antrum. Many of these observations are however, indirect, and do not provide evidence of an exact correlation between transpyloric flow and motor events.

It is now believed that the pumping of liquids and liquefied solids relies on a complex integration of fundic tone and gastric contractions in the body and antrum, although the relative contribution of each mechanism is still to be established.

8.4.3 Gastric pumping during interdigestive phase

The migrating motor complex (MMC) is a pattern of motor activity that occurs throughout the GI tract during the interdigestive phase (Sakamoto *et al* 1987). It is a burst of localized contraction, which migrates distally along the tract from the lower oesophageal sphincter into the stomach, duodenum and small intestine, usually ending in the ileum (Szurszewski 1969). In humans, MMC activity recycles every one and a half to two hours, and consists of four phases of activity, specifically phase I, relative absence of action potential activity, phase II, random action potential activity, phase III, sudden onset and continuous large action potentials on every slow wave, and phase IV, rapid decrease in action potentials. It has been suggested that the MMC is the intestinal housekeeper which periodically sweeps the bowel clean (Sakamoto *et al* 1987).

During phase III of the interdigestive migrating motor or myoelectric complex, non-digested food residues, cellular debris and secretions are expelled into the duodenum irrespective of their size (Moroz & Kelly 1977). Studies in dogs have shown that there is transient cessation of duodenal phase III contractions during strong antral contractions, an effect which may allow material to empty unimpeded from the stomach (Mearin *et al* 1987).

Chapter 9

Mechanics of Transpyloric Flow Retardation

Emptying is slowed by both the inhibition of pumping and stimulation of active motor mechanisms that oppose gastric emptying (Heddle *et al* 1989).

9.1 WITHDRAWAL OF PUMPING

Ingestion of nutrient meals or intraduodenal infusion of carbohydrates, lipids, and proteins are associated with inhibition of antral contractions and retardation of gastric emptying in both animals (Reynolds *et al* 1985, Treacy *et al* 1990) and humans (Hunt & Stubbs 1975, Cooke 1975, Brener *et al* 1983, Heddle *at al* 1988b, 1988c &1989, Fone *et al* 1989). The exact correlation between inhibition of antral contraction and retardation of transpyloric flow is currently lacking, and has been addressed in this thesis.

9.2 ACTIVATION OF RESISTANCES

9.2.1 Pyloric

The primary resistance to flow is believed to be exerted by the pylorus. The anatomy of the pylorus has, for centuries, lead to speculation that it controls gastric outflow, a view supported indirectly by radiological observations (Cannon 1898, Smith *et al* 1957). However, the inability of investigators to record a high pressure zone at the pylorus (Anderson & Grossman 1965, Atkinson *et al* 1957, Gaffney *et al* 1987), has cast doubts as to the physiological role of the pylorus as a true sphincter. In retrospect though, the

manometric techniques used for these studies were not adequate. Brink *et al* (1965) and Fisher & Cohen (1973) were the first investigators to demonstrate a high pressure zone at the pylorus. Adaptation of sleeve manometry for pyloric manometry has confirmed that the pylorus generates tonic and phasic motor activity independent of the antrum or the duodenum (Heddle *et al* 1988a). There is now a significant body of evidence derived from both animal and human studies which suggest that the pylorus is an important regulator of gastric emptying of solids and liquids (Edin *et al* 1980, Schulze-Delrieu & Brown 1985, Ruckebusch & Malbert 1986, Keinke & Ehrlein 1983, Heddle *et al* 1989, Treacy *et al* 1990). With the use of an electromagnetic flow meter, Malbert & Ruckebusch (1991) showed that the relationship between the pressure and flow across the gastroduodenal junction were never linear. During the interdigestive phase, highest flow occurred during the periods of lowest resistance, while after a meal resistance rose simultaneously with the flow rate, suggesting a feedback relationship between transpyloric flow and resistance offered by the pylorus.

9.2.2 Intestinal

An active mid-duodenal mechanism which resists gastric emptying has been proposed to be stimulated in anaesthetized dogs by small intestinal nutrient receptors (Miller *et al* 1981). This view is supported by the observation that selective resistance to the outflow of nutrients still persists after antropyloric resection in both dogs (Williams *et al* 1986) and humans (Berger 1969). However, the mechanical basis of this resistance has not been defined.

9.3 REGULATION OF THE MECHANISMS THAT RETARD EMPTYING

9.3.1 Intraluminal nutrients

The most important control of the 'gastric emptying slowing mechanisms' is in the small intestine (Hunt 1956 &1963), which has receptors along its length sensitive to osmolality and amount of fat, carbohydrate, protein and acid in the lumen (Meyer 1987). Infusions of acid (Quigley *et al* 1942, Hunt & Knox 1972, Cooke 1974 & 1977), hyperosmolar solutions (Meeroff *et al* 1975) and nutrients (Hunt 1956) have been shown to slow gastric emptying of test meals by reducing fundic tone (Azpiroz & Malagelada 1985b), inhibiting antral contractions (Gleysteen & Gohlke 1979, Heddle *et al* 1988b & 1989, Treacy *et al* 1990) and stimulating isolated pyloric contractions (Keinke & Ehrlein 1983, Heddle *et al* 1988b & 1989, Treacy *et al* 1990). In dogs, the inhibition of gastric emptying is proportional to the length of intestine exposed to nutrients, suggesting that the intensity of intestinal feedback is dependent on the number of receptors stimulated (Lin *et al* 1989, 1990a & 1990b). In addition, there is variable inhibition of gastric emptying by glucose, fat or acid, depending on which region of the intestine is exposed, consistent with specific localization of nutrient or acid receptors at different sites within the intestine (Lin *et al* 1989, 1990a&b).

This regulation is important in preventing duodenal over-distension and acidification, and maintaining a constant rate of delivery of nutrients and hyperosmolar solutions into the proximal small intestine.

9.3.2 Intravenous nutrients

The blood glucose concentration has been shown to be important in the regulation of gastric emptying. In healthy volunteers, hyperglycemia has been shown to slow gastric

emptying of a mixed meal (MacGregor *et al* 1976), and in diabetic patients, high blood glucose concentrations are associated with slow gastric emptying (Horowitz *et al* 1986 & 1989). The effect of low blood glucose concentrations on gastric emptying in healthy humans is unknown, although for patients with peptic ulceration, insulin-induced hypoglycemia has been reported to accelerate gastric emptying of water (Aylett 1962).

Chapter 10

Effect of Surgical Disruption or Removal of Gastric Motor Control Mechanisms on Gastric Emptying

10.1 INTRODUCTION

Almost any operation on the stomach performed for the purposes of either reducing acid output or removing a diseased segment, is associated with an alteration in gastric motility and emptying (Wittebol *et al* 1988) and is often followed by undesirable symptoms (Goligher 1970, Jamieson 1983). Significant long term morbidity has been reported in 25% of patients (Thompson & Wiener 1984), and includes symptoms such as early satiety, bloating, dumping and diarrhoea. These problems have been attributed to the alteration in the normal control of gastric motility and emptying subsequent to the various forms of gastric surgery (McKelvey 1970, Ralphs *et al* 1978, Parr *et al* 1988a, Fitch *et al* 1990), which either denervate the stomach, or resect and physically alter the stomach, or both.

Over the last 15 years with the development of radionuclide gastric emptying (Collins *et al* 1983), the effect of the different therapeutic surgical procedures on gastric emptying have been well studied and will be summarized in this review. However, there are no reported studies in which concurrent measurement of gastric motor function and emptying have been made in patients after gastric surgery. Thus, the current understanding of the effect of different procedures on gastric motility comes from

limited studies in animals, and indirectly from observations of changes in the pattern of gastric emptying after denervation or resective procedures in humans.

10.2 EFFECT OF VAGAL INTERRUPTION

Vagotomy performed clinically for the purpose of reducing acid output from the stomach disturbs not only the intended efferent fibres but also disrupts important afferent pathways. The effects of the vagus nerve on gastric motor function have been studied in animals and humans by either interrupting the nerve (surgical transection or by vagal cooling) at varying points or by stimulating it (Wilbur & Kelly 1973, Sarna & Daniel 1975, White *et al* 1984, Azpiroz & Malagelada 1986). Surgical interruption has been accomplished, for experimental or therapeutic reasons, by truncal vagotomy (at or above the level of the diaphragm, denervating all abdominal viscera), selective vagotomy (just distal to the hepatic branch; total denervation of the stomach and other viscera except the liver and the gallbladder), or by highly selective vagotomy (limited to the fibres supplying the fundus and corpus of the stomach; preserving the innervation to the antrum and the pylorus, as well as the other abdominal viscera), also known as proximal gastric vagotomy. The effects of these procedures on gastric emptying, and on antral and pyloric motor function, have been examined alone and in combination with other surgical procedures, such as fundectomy, antrectomy and pyloroplasty. While there is a great deal of information on the overall effect of the vagal denervation on gastric emptying, there is relatively little known of the effect on the various motor regions of the stomach.

10.2.1 Effect on fasting and fed patterns of myoelectric activity

There is conflicting data with regard to the effect of vagal interruption on gastric myoelectric activity. While most investigators (Kelly & Code 1969, Wilbur & Kelly

1973, Mroz & Kelly 1977, Hall *et al* 1986, Gleysteen *et al* 1988) have found that truncal vagotomy leads to interruption of normal fasting and fed patterns of myoelectric activity, a few have not (Spencer *et al* 1989). The discrepancies may be related in part to the different techniques of gastric denervation, the completeness of vagal disruption, and different recording methods used.

10.2.2 Effect on the fundic motor function and reservoir capacity

Unfortunately, very little work has been done to isolate the effects of interruption of vagal pathways to the fundus. Highly selective vagotomy, which denervates the fundus, corpus and proximal antrum (Wilbur & Kelly 1973) has been found to be associated with loss of accommodation and receptive relaxation reflexes and faster liquid emptying. Azpiroz and Malagelada (1986) using a vagal cooling technique in dogs, demonstrated that acute reversible disruption of vagal pathways at cervical or supradiaphragmatic level produced similar reductions in gastric (fundic) tone measured by a barostat. This effect was not altered by adrenergic blockade but was prevented by prior administration of bethanecol, suggesting a cholinergic pathway. Relaxation of the gastric (fundic) tone induced by intestinal nutrients, has however, been shown to be mediated through noncholinergic nonadrenergic vagal pathways (Azpiroz and Malagelada, 1986).

10.2.3 Effect on corpus and antrum

Wilbur & Kelly (1973) demonstrated that the electrical activity of the corpus and antrum in dogs was affected more by total gastric vagotomy than by highly selective vagotomy. Total denervation of the stomach results in slowed gastric emptying of solids, in association with the observed inhibition of antral contractions (Gleysteen *et al* 1988). It is generally recognized that interruption of vagal pathways to the stomach is associated with disruption of the gastric "pumping" mechanism, a function of the corpus

and antrum of the stomach. Highly selective vagotomy, in which innervation of the antrum and the pylorus is maintained, is believed to be associated with little change in antral contractions (Gleysteen *et al* 1988) and near normal patterns of solid emptying in humans (Mayer *et al* 1984), and dogs (Wilbur & Kelly 1973).

10.2.4 Effect on the pylorus

There is only limited literature available on the effects of vagotomy on the pylorus. Early use of truncal or selective vagotomy for treatment of peptic ulcer was associated with gastric retention in humans (Dragstedt *et al* 1947, Clarke *et al* 1972), thought to be, in part, due to pylorospasm, and relieved by pyloroplasty. Edin *et al* (1979) has used a technique of afferent and efferent vagal stimulation to assess the effect on pyloric function in anaesthetized cats. He demonstrated the presence of vago-vagal excitatory reflex to the pylorus by afferent vagal nerve stimulation. Later studies have suggested that vagal control of the feline pylorus is mediated via enkephalinergic neurons (Edin *et al* 1980).

10.2.5 Effect on intestinal regulation of stomach

DePonti *et al* (1987) used vagal cooling techniques to examine the reflex gastric relaxation response to duodenal distension in dogs. They demonstrated that this response was abolished by vagal cooling but not altered by either bethanocol or combined phentolamine and propanolol intravenous infusion, concluding that gastric relaxation elicited by duodenal distension is mediated by a nonadrenergic, noncholinergic vagal mechanism. Hall & Read (1970) used a dilution technique to compare gastric emptying of liquids in patients after truncal vagotomy without a drainage procedure, with a group of duodenal ulcer patients acting as controls. They found that truncal vagotomy did not alter the emptying of hypotonic sodium chloride, but led to faster emptying of 10%

glucose meal instilled into the stomach. They suggested that vagotomy disrupts the small bowel osmoreceptor mechanism in control of gastric emptying. Their failure to notice any change in rate of non-nutrient liquid emptying, may be related to the size of the meal used, and to the fact that in both groups of patients the test meal emptied very quickly.

Other investigators have demonstrated that after truncal vagotomy, although the rates of emptying of nutrients, acid and hyperosmolar solutions are faster, they are still significantly slower than the rate of non-nutrient isotonic solutions, in both dogs (Springfield *et al* 1974, Shahidullah *et al* 1975, Wilbur & Kelly 1977) and humans (Hall & Read 1970). This suggests that either sympathetic, intramural or humoral mechanisms may also be involved in the small bowel control of gastric emptying. There is currently little or no information on the relative roles of these mechanisms in this control.

10.2.6 Effect on the overall organization of gastric motor function and emptying

Truncal vagotomy has been shown to impair trituration and gastric pumping (Wilbur & Kelly 1973) and lead to stasis of solid food (Dragstedt *et al* 1947). However, its effect on liquid emptying is less consistent (Wilbur & Kelly 1973, Springfield *et al* 1974). Vagotomy alters the intra-gastric distribution of liquid (Lawaetz *et al* 1982) as well as solid meals (Calabuig *et al* 1988), it abolishes the accommodation reflex and receptive relaxation (Wilbur & Kelly 1973) of the fundus and is associated with higher intra-gastric pressures after ingestion of a liquid meal (Azpiroz & Malagelada 1987). The actions of gastrin (Okike & Kelly 1977) and CCK (Forester *et al* 1990) and other hormones (Becker & Kelly 1983), which relax the fundus may also be impaired by

vagotomy. Hinder & Bremner (1978) showed that vagotomy was only associated with a more rapid early emptying with higher volume test meals (40 ml/kg) and not with smaller volumes (10 or 20 ml/kg). The inconsistencies in the effects on liquid emptying may, therefore, be due to differences in the volumes of the meals tested, as well as the differences in the methodologies used. Furthermore, the vagal effects on the gastric "pumping" and pyloric "braking" mechanisms and their regulation of liquid gastric emptying are still poorly understood.

Selective vagotomy which produces total denervation of the stomach, pylorus and the small intestine, is believed to have similar effects on the gastric motor function and emptying to truncal vagotomy.

Highly selective vagotomy, although it denervates the fundus and body including the gastric pacemaker region, does not significantly alter either the cyclical generation of pacesetter potentials by the pacemaker or its distal propagation (Wilbur & Kelly 1973, Hinder & Kelly 1977). It does, however, impair receptive relaxation and accommodation of the fundus (Wilbur & Kelly 1973, Jahnberg *et al* 1975, Stadaas 1975)) and leads to more rapid liquid emptying (Faxen *et al* 1977, Wilbur & Kelly 1973, Lavigne *et al* 1979), but hyperosmolar and nutrient liquids continue to empty slower than non-nutrient isotonic solutions (Wilbur & Kelly 1973).

Highly selective vagotomy is associated with near normal patterns of trituration (Wilbur & Kelly 1973), sieving (Mayer *et al* 1984), and solid emptying (Howlett *et al* 1976, Lavigne *et al* 1979, Wittebol *et al* 1988). This is believed to be due to the importance of the antrum and the pylorus (which have an intact innervation), in the regulation of solid emptying (Becker & Kelly 1983). But, there is a possible role for

compensatory motor mechanisms in maintaining the normal pattern of solid gastric emptying, after highly selective vagotomy, that is unknown.

The incidence of post-operative dumping and diarrhoea after highly selective vagotomy is reported to be less than after truncal vagotomy and pyloroplasty (Humphrey *et al* 1972). However, Kaushik *et al* (1982), using a provocation test reported that incidence of dumping was similar to truncal vagotomy & pyloroplasty and distal gastrectomy. Thus, suggesting that although a patient with HSV may not experience dumping clinically (with his/her "regular" diet), under conditions that test the limits of gastric regulatory function (provocation test), the subject may exhibit more rapid liquid emptying and experience symptoms of dumping.

10.3 EFFECT OF DESTRUCTION OF PYLORIC FUNCTION OR PYLORIC REMOVAL

Destruction of the pyloric sphincter mechanism by pyloroplasty was first introduced to overcome the gastric stasis attendant on truncal vagotomy (Weinberg *et al* 1956). There are no clinical data concerning the isolated effect of pyloric destruction on gastric emptying.

Animal studies have shown that pyloric removal or destruction alone, with an intact antrum, is associated with impaired sieving of solids (Treacy *et al* 1988) and more rapid emptying of liquids and solids (Treacy 1991).

Isono & Kelly (1979) reported that antrectomy with pylorus preservation was associated with delayed emptying of digestible solids in dogs. This finding contrasts with

the finding in humans and dogs that distal gastrectomy, with removal of the pylorus and antrum, is associated with more rapid solid emptying (Mayer *et al* 1982, Hinder & San-Garde 1983). Together these studies suggest that the pylorus plays an important role in controlling the emptying of solids. Destruction or removal of the pylorus will also predispose to duodenogastric reflux of bile (Ehrlein *et al* 1980, Brough *et al* 1984).

10.3.1 Truncal vagotomy and pyloroplasty

The slowed emptying of solids caused by truncal vagotomy, is counteracted by the addition of a pyloroplasty (Cowley *et al* 1976), but emptying of liquids is still abnormal with a very rapid early emptying followed by a slow second phase. The net effect is that emptying remains close to normal or slightly delayed, in both dogs (Parr *et al* 1988b, Wilbur & Kelly 1973) and humans (Colmer *et al* 1973, Wittebol *et al* 1988, Calabuig *et al* 1988). Despite the early rapid emptying, nutrient and hyperosmolar solutions still empty more slowly than non-nutrient isotonic solutions (Wilbur & Kelly 1973, Miller *et al* 1986, Gough *et al* 1981).

In patients with truncal vagotomy and pyloroplasty (TV&P), gravity has been suggested to play a more significant role than gastric pumping, in determining the rate of liquid emptying (McKelvey 1970, Gulsrud *et al* 1980). The initial rapid emptying of liquids associated with TV&P has been proposed to be a cause of postoperative dumping and diarrhoea. McKelvey (1970) coined the term "gastric incontinence" to describe the rapid early gastric emptying after TV&P in the upright posture when gravity favours emptying. This view was supported by Colmer *et al* (1973) and Parr *et al* (1988a), who reported that patients with diarrhoea following TV&P, had more rapid initial phase of emptying compared to symptomless patients. It has also been suggested that early rapid emptying of liquids leads to post-vagotomy dumping syndrome. Ralphs *et al*

(1978) reported that gastric emptying of a hypertonic glucose solution was significantly faster in TV&P patients who experienced dumping symptoms, compared to patients who did not. It is not clear, however, why some patients develop these complications, while others do not. Concurrent measurements of gastric motor function made early and later after truncal vagotomy will help evaluate the possible compensatory mechanism which may be important in preventing the development of these complications in some patients.

Although pyloroplasty does hasten the emptying of solids from the stomach after truncal vagotomy (Wilbur & Kelly 1973, Cowley *et al* 1972), the rate and pattern varies among individual patients. This has led to discrepancies in observations with regard to the rate of solid emptying in TV&P patients relative to healthy controls (Howlett *et al* 1976, MacGregor *et al* 1977a, Wittebol *et al* 1988). The discrepancies in solid gastric emptying rates reported may also be related to the differences in calorie content, particle size, fat and sugar content of the test meal used, and the lack of uniformity in the methods of assessment of gastric emptying. Concurrent measurement of gastric motor function during solid gastric emptying should allow better evaluation of the factors responsible for this variability among TV&P patients.

10.4 EFFECT OF DISTAL GASTRECTOMY

Pyloric and antral resection is associated with rapid liquid and semisolid emptying (Dozois *et al* 1971, MacGregor *et al* 1977b, Hinder & San-Garde 1983, Smout *et al* 1987, Wittebol *et al* 1988) in both humans and animals. Small intestinal luminal receptors retain some regulatory inhibitory influence on gastric emptying, but are less effective (Ehrlein *et al* 1987b & 1988b, Buhner *et al* 1988).

Solid emptying after distal gastrectomy is also marked by a short lag phase and more rapid gastric emptying (MacGregor *et al* 1977a, Wittebol *et al* 1988), as well as impaired trituration (Dozois *et al* 1971) and sieving, with passage of larger particles (Meyer *et al* 1979) and more rapid gastric emptying (MacGregor *et al* 1977a, Wittebol *et al* 1988).

Smout *et al* (1987) demonstrated a positive correlation between the early rate of emptying of semi-solid meals and the intensity of postprandial nausea, vomiting, and vasomotor symptoms after distal gastrectomy. The jejunal contraction frequency differs from that of the duodenum in both Billroth II and Roux-Y gastrojejunostomies, and is associated with increased occurrence of non-propagated contractions (Ehrlein *et al* 1987a & 1989a). It has been suggested that the length of the Roux loop is important in determining the speed of gastric emptying, and in this supposition, longer loops were used for treatment of patients with significant dumping symptoms (Miedema & Kelly 1991). Non-propagating and retrograde contractions have been described in Roux loops (Ehrlein et al 1987a &1987b, Morrison *et al* 1990) with a higher incidence in longer lengths of the loop.

10.4.1 Distal gastrectomy with vagotomy

Addition of vagotomy to distal gastrectomy impairs the receptive relaxation and accommodation response of the fundus, and also impairs the small intestinal control of gastric emptying. These effects lead to even faster liquid emptying than gastrectomy alone, but solid emptying remains variable (Minami & McCallum 1984). Kalbasi *et al* (1975) reported that patients with duodenal ulcer who underwent a truncal vagotomy and antrectomy, had significant retardation of solid gastric emptying one month after surgery, which returned to near normal levels by the sixth month after surgery.

Wittebol *et al* (1988) reported marked acceleration of gastric emptying of a semisolid meal but significant retardation of gastric emptying of a solid meal in seven patients with truncal vagotomy and partial gastrectomy performed 2-12 years previously. All seven patients in the Wittebol series had significant vasomotor symptoms after liquid and semisolid meals, and severe symptoms of epigastric fullness after solid meals.

10.5 PYLORUS PRESERVING DISTAL GASTRECTOMY

10.5.1 Potential benefits

It has been postulated that preservation of the pyloric mechanism in gastric surgery leads to improved patterns of gastric emptying and thus fewer unwanted symptoms after the surgery.

10.5.2 Animal experiments

Flynn & Longmire (1960) and Killen & Symbas (1962) were the first to demonstrate that it is feasible to preserve the pylorus in dogs having distal gastrectomy. In 1967, Maki *et al* reported a technique of pylorus preservation during distal gastrectomy in dogs, with preservation of the vagal innervation to the pylorus (Nerve of McCrea), and maintaining a 1.5-2 cm cuff of antrum (Figure 10.5.2). They found that an antral cuff of 1 cm was associated with a hypotonic pylorus, while a 4 cm cuff was associated with a hypertonic pylorus. Maki and his colleagues, neither investigated nor proposed a possible reason for their observation with regard to the length of the antral cuff, but it is possible that differences in level of interruption of the enteric neural plexus and the completeness of vagal preservation may have influenced these observations. In 1979, Isono & Kelly reported their study of solid and liquid emptying in 5 dogs after pylorus preserving antrectomy and proximal gastric vagotomy. They found that the emptying of liquids and indigestible solids remained normal but that the emptying of digestible solids

was markedly delayed. They concluded that delayed solid emptying may cause stasis symptoms in patients. However, the dogs studied by Isono & Kelly had already had their stomachs altered with the creation of an Heidenhain pouch from the gastric pacesetter region, thus possibly affecting the normal electrical rhythm of the stomach.

10.5.3 Clinical experience

Maki and his colleagues (1967), were first to report the use of pylorus preserving gastrectomy in patients (Figure 10.5.2). Despite the use of a crude radiological technique to assess gastric emptying, their results in 50 patients were encouraging, with the majority (48/50) being found to have "normal" gastric emptying after surgery. There were no reported cases of dumping or other post-gastrectomy symptoms in these patients, but the methods of symptom assessment was subjective and lacked the necessary sensitivity to identify less debilitating symptoms.

A few years later, Griffith (1974) reported his experience with the pylorus-preserving antrectomy (Maki's procedure) added to selective vagotomy for treatment of duodenal ulcer. Although none of his patients experienced dumping, 7 out of 20 patients had symptoms attributed to gastric stasis, with one patient requiring surgical correction. Since then, there have been few reports of pylorus-preserving gastrectomy. This loss of enthusiasm has probably been due in part to the advent of effective anti-ulcer medications and subsequent reduction in the number of partial gastrectomies done for peptic ulcer disease, as well as to the lack of physiological data to provide a rationale for clinical use of pylorus preservation.

A few centres around the world, however, continued to employ this procedure. Hennessy *et al* (1974) reported their experience with 47 patients who had Maki's procedure for

duodenal ulcer. They reported no incidence of dumping, bile gastritis or stasis, with 40 of 47 patients having good results (Visik I or II). Several centres in Russia, have continued to employ pylorus preserving gastrectomy (Mazurik *et al* 1988) for peptic ulcers and benign gastric lesions with good results, and a recent report of long term follow-up (7-10 years) of these patients (Cherniakevich *et al* 1988) is very favorable. Recently, Yan *et al* (1991) from China, reported their experience with a variant of Maki's procedure in dogs and in 125 patients with peptic ulcer. They found no cases of dumping or gastric stasis in patients (10-36 months post-operatively), and normal gastric emptying in dogs, although their method of evaluation of gastric emptying was very crude and was based on radiographic timing of complete emptying of a barium meal from the stomach. With most of the case series to date reporting on the outcome of pylorus-preserving gastrectomy, the methods used in the follow-up assessment of symptoms and gastric emptying have been quite subjective and crude (lacked the use of established and tested symptom scoring systems), raising questions about the validity of their conclusions. Thus, these reports have failed to persuade surgeons in other countries of the merits of pylorus preservation in distal gastrectomy.

Pylorus preserving gastrectomy has also been used in the surgery of early gastric cancer. Kodama & Koyama (1991), recently published their results in 11 patients with early gastric cancer confined to the middle third of the stomach in whom there were no postoperative complaints based on short-term follow-up after pylorus-preserving gastrectomy. Their study of lymph drainage by activated carbon particles had shown that there was little lymph flow towards the supra pyloric lymph node (left behind in this procedure) from the middle third of the stomach, thus allowing for an effective and safe anti-cancer operation.

Clearly, if physiological rationale and clinical advantages of pylorus preserving gastrectomy can be established, this operation should replace the current techniques of distal gastrectomy which were first employed by Billroth (1881) almost a century ago.

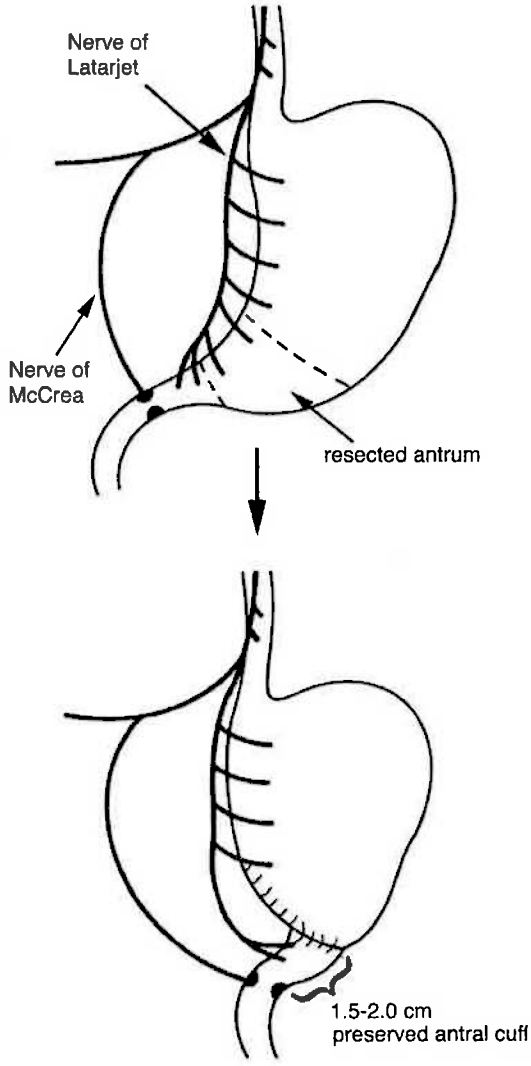


Figure 10.5.2: A Schematic drawing of pylorus preserving distal gastrectomy described by Maki *et al*, 1967.

Chapter 11

Objectives of this thesis

The initial goal of my studies was to devise effective surgical operations for the treatment of complicated peptic ulcer disease and gastric malignancy which avoided the gastric emptying problems identified by the previous literature review. However, it became apparent early on that there were a number of physiological questions with regard to the mechanics and control of gastric emptying which needed to be addressed first, before studies on the effects of surgery could be effectively undertaken.

The work presented in this thesis therefore evolved as follows: studies were done on some aspects of gastric motor mechanisms and their control, which are involved in normal emptying of ingesta from the stomach, and later analysis were made of the changes in normal pattern of gastric motor function and emptying produced by therapeutic gastric surgeries. Finally, I proposed and partially tested a novel method of maintaining near normal patterns of gastric emptying following distal gastrectomy.

11.1 PRIMARY RESEARCH QUESTIONS

The following questions were addressed in this thesis, not necessarily in the order presented here.

1. Does the human pylorus act as a physiological sphincter regulating the flow of ingesta between the stomach and duodenum? If so, what are the manometric motor patterns associated with the pyloric "braking" action.
2. Following a meal, how does a distended stomach "pump" ingesta out? Is lumen occlusion necessary for effective pumping?
3. Does antral contraction play a role in emptying of liquids from the stomach?
4. What is the effect of posture on gastric distribution and emptying of meals?
5. What role do antral enteric neural pathways play in regulating antral and pyloric motor function and gastric emptying?
6. Following a fatty meal, are cholecystokinin-dependent mechanisms important in regulating the rate of delivery of ingesta into the proximal intestine? If so, what are the sites of its action?
7. What changes in gastric and pyloric motor function are responsible for disturbances in the normal pattern of gastric emptying following highly selective vagotomy, truncal vagotomy and pyloroplasty, and distal gastrectomy?
8. Can the pylorus generate pyloric tone or develop isolated pyloric contractions after pyloroplasty?
9. Are there any compensatory changes in distal antral motility following highly selective vagotomy?
10. Can a one centimeter bridge of muscle preserve adequate intramural neural connections after antral transection to allow for the maintenance of normal patterns of antropyloric motility and gastric emptying?
11. Is it feasible to preserve a muscle bridge between proximal and distal resection margins following pylorus preserving distal gastrectomy?

Section B

Common Methodologies Used

Chapter 12

Introduction to the Methods

The studies in Sections C to G were performed on humans and pigs. The pigs were used for studies which involved experimental surgery, and measurements which could not be performed in humans. The studies were designed, whenever possible, to give concurrent measurements of gastric motor function, transpyloric flow (pigs only), and gastric emptying.

In humans, antropyloroduodenal motility was measured with sleeve/sidehole manometry, gastric emptying with a radionuclide technique, and gastric wall movement with videofluoroscopy.

In pigs, intraluminal antropyloroduodenal pressures were measured with sleeve/sidehole manometry, changes in gastric wall tension with strain gauges, gastric wall movement by videofluoroscopy, gastric emptying by a radionuclide technique, and transpyloric flow by duodenal drainage technique.

Different combinations of the various measurement techniques were used in different studies according to the specific question being examined. The methods used are all established and validated techniques (Heddle 1988, Fone 1990, Treacy 1991). Variations in some methods were required due to particular demands of some studies, and will be discussed in the appropriate chapters. In this section, techniques used to measure

antropyloroduodenal motility, gastric emptying and transpyloric flow will be described. Details of the techniques of videofluoroscopy and strain gauge recordings will be given in the appropriate chapters.

12.1 USE OF HEALTHY VOLUNTEERS AND PATIENTS

Healthy volunteers were recruited from the University of Flinders and University of South Australia. Each volunteer was assessed prior to the studies to exclude anyone with a present or past history of significant dyspepsia, peptic ulcer or gastrointestinal disease. Smokers, and subjects with a history of upper gastrointestinal surgery or those taking any form of medication were excluded. Females who were pregnant, and subjects who had radiation exposure over the preceding year were excluded from studies involving fluoroscopy or radionuclides.

Patient volunteers were recruited from the Departments of Surgery at the Royal Adelaide, Queen Elizabeth Hospitals and Flinders Medical Centre. Three groups of post-surgical patients were recruited (see Chapter 21). All patients were under 70 years of age and were at least one year past their surgery. Smokers, and patients with significant cardiac or pulmonary disease who could not tolerate the study, and those on medications which could interfere with gastrointestinal motility were excluded.

Both the healthy and patient volunteers were fully informed of all aspects of the experimental protocols and were provided with written information, detailing the procedures to be used, as well as potential risks from pharmaceuticals or radiation, where relevant. All volunteers signed a consent form prior to starting the experiments. With patient volunteers, their respective physicians were contacted and permission obtained prior to commencement of the studies. Study protocols were separately

submitted to, and approved by, the Human Ethics Committees of the University of Adelaide and the Royal Adelaide and Queen Elizabeth Hospitals and Flinders Medical Centre.

12.2 USE OF THE KANGAROO ISLAND PIG AS AN ANIMAL MODEL

This pig model, based on a locally bred strain of mini-pig, has previously been established and validated by Landers *et al* (1986) and Treacy *et al* (1990). The weight gain characteristics of Kangaroo Island pigs make them suitable for this type of study. After an initial growth spurt over 4-5 months when they reach a weight of 25-30 kg, weight gain temporarily slows down and the pigs maintain a manageable weight of about 35-50 kg for 3-6 months (McIntosh & Pointon 1981). The animals used in these studies were bred in the Waite Institute of the University of Adelaide. The pigs were disease free and highly trainable (as compared to commercially available pigs), which made them suitable for chronic studies.

The anatomy of the stomach and gastroduodenal junction, and the physiology of the gastrointestinal tract of the pig have been previously documented (Torgerson 1942, Gregory *et al* 1987 &1989 &1990, Treacy et al 1990, Treacy 1991). The dog is the animal most used for these types of studies, but as use of dogs for chronic studies is not possible in South Australia, the pig provided the best alternative.

All animal studies were submitted to and approved by the Animal Ethics Committees of the University of Adelaide and the Institute of Medical and Veterinary Science.

12.2.1 Training of Pigs

Pigs were housed in the Institute of Medical and Veterinary Science. Over a period of 2-3 months they were trained (from 2 month of age) to stand quietly in a loose fitting sling attached to a Pavlov stand for periods up to 120 minutes. They were first studied at 4-5 months of age.

As all studies were done without sedation, it was imperative that the animals stood quietly so as not to produce large pressure changes from straining which would obscure recordings. Pigs which were found to be difficult to train (1 in 5 pigs) were excluded and returned to the piggery.

Despite extensive training of the pigs, almost 40% of the studies conducted, had to be repeated as they were unsuitable for analysis. This was due to either excessive movement artifacts (>5% of the recording time), or not meeting the strict (TMPD) criteria for correct positioning of the catheter (Chapter 13).

12.2.2 Surgical preparation of the pigs

Under halothane/nitrous oxide anesthesia, each pig had two modified Thomas cannulae (Jones *et al* 1971) inserted, one in the stomach 15 cm proximal to the pylorus and the other in the duodenum 5 cm distal to the pylorus.

All surgery was carried out in a fully equipped operating theatre under full sterile technique. The animals received perioperative antibiotics (mixture of streptomycin and penicillin (Penstrep) 250 mg/kg IM od), which was continued for 5 days post op. Pain relief was provided by twice daily injections of Methadone *IM* at a dose of 0.25 mg/kg.

12.2.3 Study procedures in pigs

Most studies were conducted after a 6 week post-operative recovery period. Studies which were conducted earlier after operations, are specified in the appropriate chapter.

Pigs were fasted for 16 hours prior to each study. On the morning of the study, the stomach of the animal was washed out through the gastric cannula with water at body temperature, until the effluent was clear.

Animals stood in a loose fitting sling attached to a Pavlov stand. The manometric catheter was passed from the gastric cannula to the duodenal cannula by traction with a length of soft plastic tubing (3mm diameter) which between experiments connected the plugs of the two cannulae. A specially designed connector attached to the gastric cannula allowed instillation of liquids into the stomach without leakage around the manometric catheter.

A Foley catheter, with a central infusion port and an inflatable balloon 3 cm proximal to the tip, was inserted into the distal duodenum via the duodenal cannula . The Foley balloon was inflated with 5 ml of water. It has previously been shown that this volume of balloon distension in the duodenum, does not produce any significant change in the pattern of antropyloric motility and gastric emptying in this pig model (Treacy 1991). The Foley catheter was used to infuse different test solutions into the duodenum, at a site distal to its balloon.

A funnel attached to a collecting jar was fastened underneath the duodenal cannula for collection of the duodenal effluent (Figure 12.2.3). The collecting jar was placed on an electronic weighing machine for continuous recording of the weight of the duodenal effluent. A weak vacuum (50 mmHg) applied to the collecting jar ensured a prompt

delivery of the liquid draining through the funnel into the jar. An interface between the weighing machine and the polygraph recorder allowed the weight of the duodenal effluent to be recorded on the same chart paper as the manometric tracing (with a time delay of 0.5 sec). The recording of the weight of the effluent then, reflected the volume and timing of transpyloric flow of liquid.

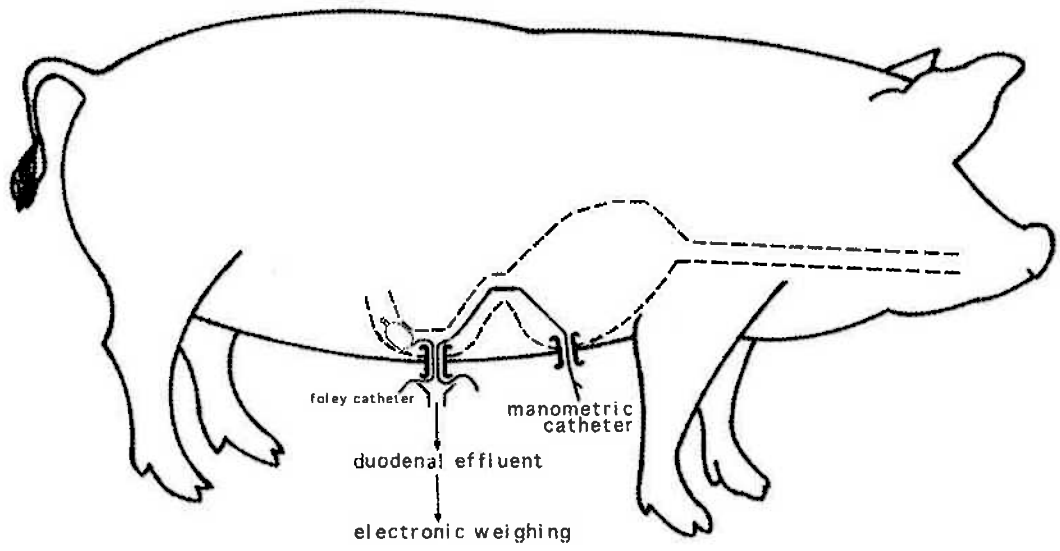


Figure 12.2.3: The schematic drawing of the recording methods used in pigs. Antropyloroduodenal motility is assessed with a sleeve/sidehole catheter. Gastric emptying and duodenal drainage is measured by continuous collection and weighing of the duodenal effluent, and quantifying the radioactivity of the collected specimens over time. The funnel under the duodenal cannula collects the duodenal effluent which is quickly suctioned into the collecting bottle over the electronic weighing scale. A Foley catheter in the distal duodenum is used to infuse solutions into the small intestine.

Chapter 13

Manometric Assembly and Equipment

Antral, pyloric, and duodenal intraluminal pressures, were measured in both humans and pigs with multiple lumen perfused catheters incorporating a sleeve sensor (Heddle *et al* 1988a, Treacy *et al* 1990). The sleeve device was first described by Dent (1976) for use in the measurement of lower oesophageal sphincter pressure, and later adapted for use in pyloric manometry (Heddle *et al* 1988a).

13.1 ADVANTAGES AND LIMITATIONS OF SLEEVE/SIDEHOLE MANOMETRY

Perfused sideholes have been shown to reflect intraluminal pressures accurately (Pope 1967, Dodds *et al* 1976, Valori *et al* 1986), but being point sensors, they are less suitable for accurate recording from a narrow mobile zone such as the pylorus (Aste *et al* 1979, Pandolfo *et al* 1979, Defilippi 1985). The ability of the sleeve to record pressures from any point along its length allows recordings to be made despite the movements of the catheter astride the pylorus, and is ideal for prolonged recording of pyloric pressures.

Contractions which do not occlude the lumen may produce little or no rise in intraluminal pressures (Mittal *et al* 1990), even though such contractions may be of mechanical significance. This is a major limitation of intraluminal manometry in corpus

and proximal antrum, where fluoroscopic studies (Carlson 1962, Carlson *et al* 1966) have shown that some contractions do not result in lumen occlusion.

The primary limitation of the sleeve derives from it protruding into both the antrum and duodenum, and consequently, because it records the highest pressure from anywhere along its length, a sleeve detected pressure rise may be due to changes of terminal antral, pyloric or proximal duodenal pressure. Thus, in order to correctly identify isolated pyloric pressure waves, the manometric data from sideholes positioned along the sleeve length need to be considered in conjunction with sleeve recorded pressures. Criteria have been established for such analysis (Heddle *et al*, 1988a, Treacy *et al* 1990). Compliance of the sleeve membrane is another limitation of the sleeve (Dent 1976). This compliance results in pressure rise rates which vary along the length of the sleeve; at the antral end, the sleeve responds to a pressure rise at a rate similar to the sideholes, but this rate drops as the pressure rise is applied more distally towards the duodenal end. However, it remains adequate for monitoring of pyloric and duodenal pressure waves (Heddle *et al* 1988a) which do not exhibit very rapid pressure rise, such as seen in upper oesophageal sphincter (Jacob *et al* 1989). In any case, these studies examined the pattern of antropyloroduodenal pressure waves, and were not affected by any limitation in determining the rate of pressure rise.

The presence of a manometric catheter across the pylorus might alter the pattern of antropyloroduodenal motility, but Fone *et al* (1991) reported no alteration in gastric emptying in a group of healthy volunteers who had undergone studies with and without a manometric assembly across the pylorus. It is, however, well established that pain or stress alters the pattern of antropyloric motility and gastric emptying (Fone *et al* 1990), and therefore, any study in which the human volunteers (verbal expression of

pain or stress) or the animals (based on behavioral change) were distressed was excluded from analysis.

13.2 DESIGN OF THE MANOMETRIC ASSEMBLY

The length of the sleeve sensor and the spacing of the sideholes was based on the maximum length of the high pressure zone at the pylorus. In humans, the length of the pyloric high pressure zone has been shown to be within 0.9 mm (Heddle *et al* 1988a), but in pigs, this was not well documented. Pylorus length was addressed in studies described in Chapter 15 . It was found that in the Kangaroo Island pigs weighing 35-50 kg, the maximum length of the pyloric high pressure zone is 1.8 mm.

13.2.1 Manometric assembly design for human studies

Figure 13.2.1 shows the spacing of the ten-lumen manometric assembly used for the human studies. It incorporated a 4.5 cm sleeve sensor and four sideholes (1.5 cm apart) along the full length of the sleeve. Four other sideholes, spaced at 1.5 cm intervals, were used to measure antral pressures, and an additional sidehole, 3 cm distal to the sleeve, recorded duodenal pressures. A series of small weights attached to its distal end aided transpyloric passage of the assembly.

13.2.2 Manometric assembly used in pig studies

The nine-lumen assembly used in the pig studies consisted of a 4 cm sleeve, with 2 cm sidehole spacing (figure 13.2.2). The catheter had 8 sideholes, three of these being spaced along the full length of the sleeve, three more proximal to the sleeve and two distal to the sleeve.

All human and pig catheters were designed and constructed by Professor John Dent.

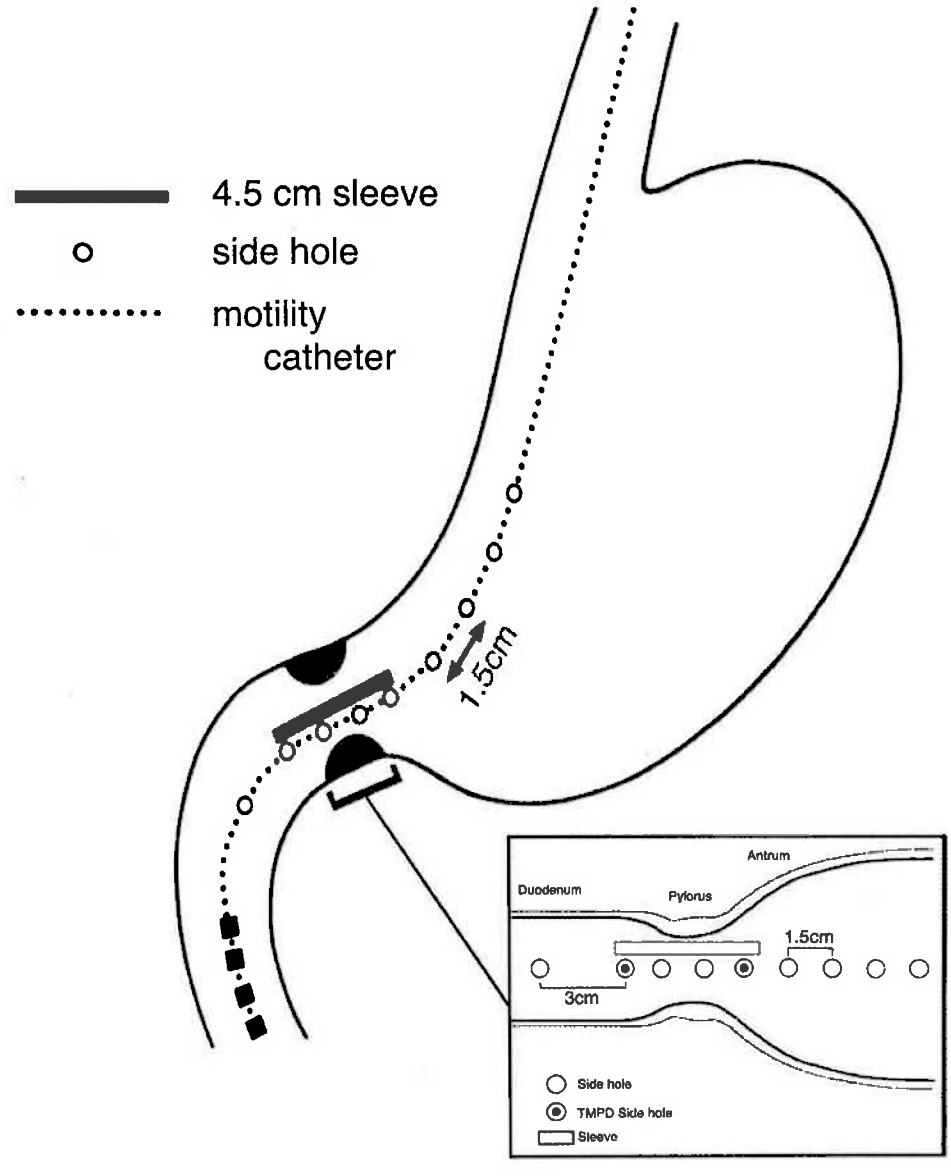


Figure 13.2.1: The position of the manometric assembly in the human studies with the 4.5cm sleeve astride the pylorus. The position and spacing of the sideholes in relation to the sleeve are shown.

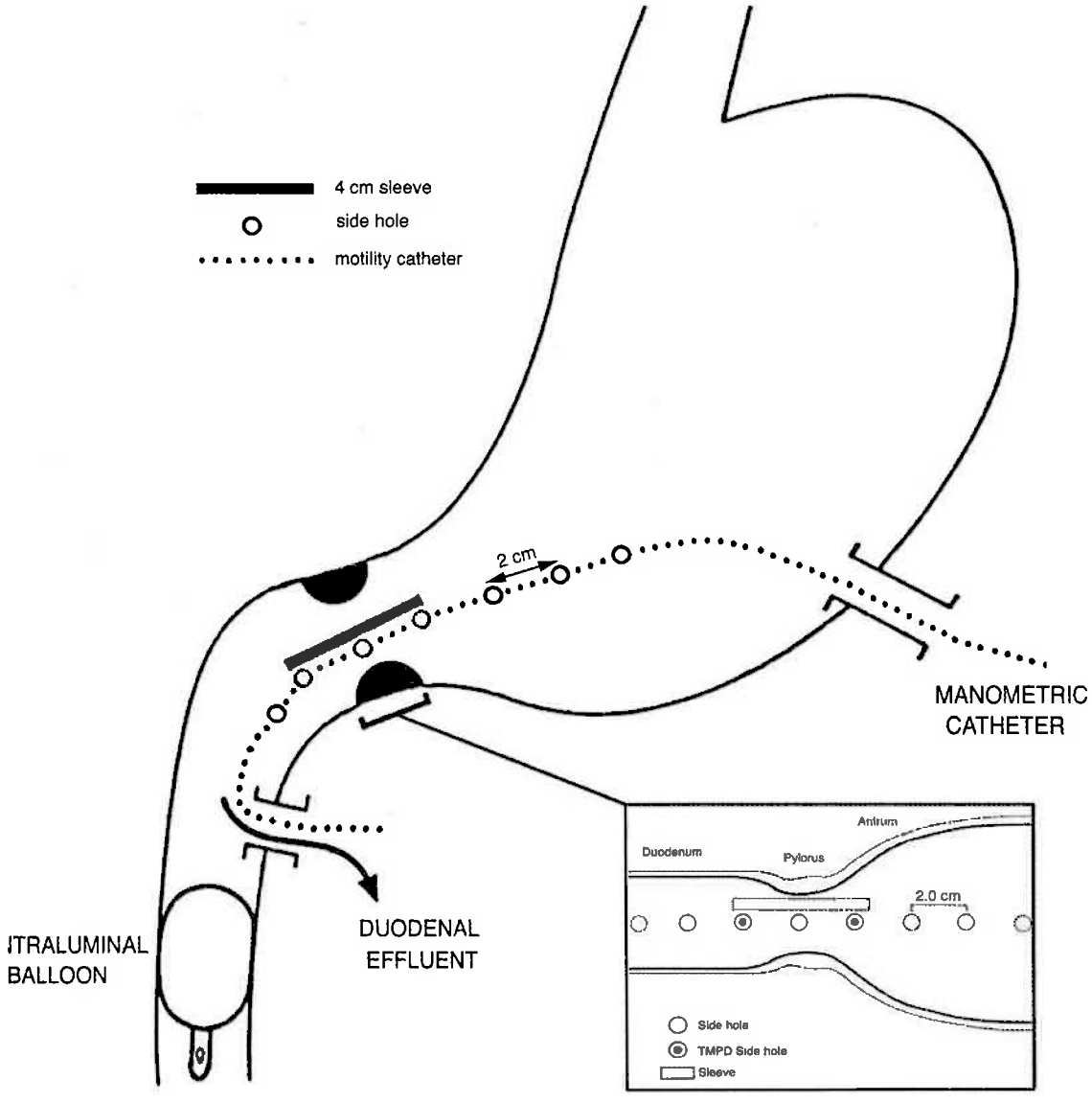


Figure 13.2.2: The position of the manometric assembly in the pig stomach. The catheter was passed between the gastric and duodenal cannula with the 4 cm sleeve positioned astride the pylorus. The position and spacing of the sideholes in relation to the sleeve are shown.

13.3 POSITIONING OF THE MANOMETRIC CATHETER

In both humans and pigs, the correct placement of the manometric catheter astride the pylorus was determined by measuring the transmucosal potential difference (TMPD) at either end of the sleeve. There is a difference in the transmucosal potential difference between the terminal antrum and the duodenum in both humans and pigs. The two sideholes at either end of the sleeve were perfused with saline instead of water and by using established techniques (Heddle *et al* 1988a, Treacy *et al* 1990), were used to record the potential difference of the mucosa of the terminal antrum and duodenum. The following TMPD criteria based on transpyloric potential difference gradient, were used for correct positioning of the manometric catheter:

In humans:

i) antral TMPD should be more negative than -20 mV

ii) duodenal TMPD should be more positive than -15 mV

iii) the difference between antral and duodenal TMPD should be at least 15 mV

In pigs:

i) antral TMPD should be more negative than -15 mV

ii) duodenal TMPD should be more positive than -5 mV

The TMPD measurements were recorded continuously on the chart recorder throughout each experiment, and the manometric assembly was withdrawn or advanced as necessary, to keep the sleeve astride the gastroduodenal TMPD gradient.

13.3.1 Intubation in humans

The volunteers were fasted overnight and were requested not to drink alcohol the night before the study. The manometric catheter was introduced transnasally, after the nostril and the throat had been anaesthetized with 10% lignocaine spray. The catheter was introduced until at least 20-30 cm of its length lay in the stomach. The subjects were then asked to lie in a right lateral position in bed. Entry into the duodenum normally occurred during propagated phase II and III activity of the interdigestive migrating motor cycle. Entry of the catheter into the duodenum was indicated by the pattern and rate of pressure waves recorded by the sleeve and sideholes distal to it and confirmed by TMPD measurement. The weights attached to the end of the catheter helped with the passage of the catheter across the pylorus, and probably helped to stabilize the catheter once it had passed through the pylorus, preventing slippage of the catheter.

13.3.2 Positioning of the catheter in pigs

The manometric catheter was passed between the gastric and duodenal cannulae with the aid of a plastic connecting tube. TMPD measurement was used to confirm the position of the catheter. Water tightness at the gastric cannula was maintained by a specially designed connector which also permitted instillation of liquids into the stomach.

13.4 OTHER ASPECTS OF THE MANOMETRIC AND RECORDING TECHNIQUE

Manometric channels were perfused with degassed water or saline at a constant rate of 0.3 ml/min by a low-compliance pneumohydraulic pump (Andorfer *et al* 1977), at a reservoir pressure of 50 KPa. The pressure rise rate of the sleeve sensor and sideholes at this perfusion pressure have been well documented (Heddle *et al* 1988a, Heddle 1988, Fone 1990). Pressures were measured by external transducers (Cobe model

01N4655, Lakewood, CO, USA), with output to a 12-channel polygraph (Grass model 7D, Grass Inc., Quincy, MA, USA). A chart speed of 100 mm/min and full scale calibration of either 0-100 mmHg or 0-50 mmHg were used.

The data from all studies were recorded on the polygraph paper. In addition, during all human studies and some animal studies, the outputs of the polygraph were digitized with an A/D card at a frequency of 10 Hz (NB Mio 16, National Instruments, Texas, USA), and the signals stored on disc in a Macintosh II ci, Apple Computer, with a purpose developed program based on Labview software program (National Instruments Corporation, Texas, USA).

13.5 ANALYSIS OF MANOMETRIC TRACINGS

Recordings were only analyzed when transmucosal potential difference criteria confirmed that the manometric assembly was correctly positioned across the pylorus (Heddle *et al* 1988a, Treacy *et al* 1990). Studies in which the sleeve was out of position for more than 5% of the study time, were discarded and repeated. Any resolvable pressure rise of less than 25 seconds in duration, which was not attributable to respiration, straining or changes of posture, was scored. These appeared as identical pressure rises in all antral, pyloric and duodenal channels. No threshold on amplitude was used. Pressure waves were then classified according to site, extent and their timing in relation to each other. Pressure waves recorded in two or more adjacent sideholes were judged to be associated if their onset of the major upstroke occurred less than 5 seconds (Heddle *et al* 1988a) before or after the other.

Pressure waves were classified as follows(Figure 13.5a):

Isolated pyloric pressure wave (IPPW): recorded by the sleeve ± only one pyloric sidehole along the sleeve, but not by antral or duodenal TMPD sideholes at either end of the sleeve.

Antropyloric pressure wave (APPW): recorded by the sleeve and at least the antral TMPD sidehole ± other antral sideholes. In human studies, pressure waves recorded by sleeve and both pyloric sideholes along the sleeve were also classified as antropyloric pressure wave, as they were too broad (two sideholes) to be classified as isolated pyloric pressure wave.

In some studies, antropyloric waves have been further divided to either long, when the antral component of the wave was greater than or equal to 6 cm, or short, when the antral component was less than 6 cm.

Pyloroduodenal pressure wave (PDPW): recorded by the sleeve and duodenal TMPD sidehole ± pyloric sidehole(s) along the sleeve ± distal duodenal sidehole, but not recorded by antral TMPD sidehole.

Antral common cavity pressure wave (antral CCPW): the concept of antral common cavity pressure wave will be introduced in Chapter 17. These are low amplitude pressure waves recorded simultaneously by all antral channels and represent phasic pressurization of the gastric cavity. The antral CCPWs are distinguished from pressure rises due to movement or straining, by the fact that they are only recorded by the antral sideholes (and occasionally the duodenal TMPD sidehole) and not by the most distal duodenal sideholes (Figure 13.5 b), suggesting that they are generated by motor activity in the stomach.

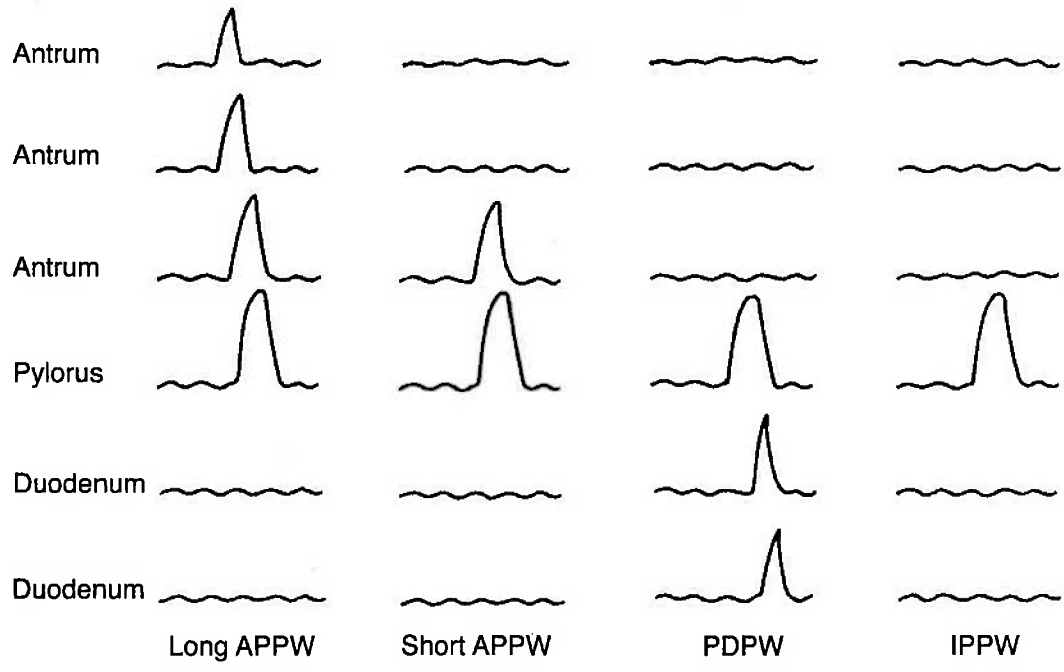


Figure 13.5a: Schematic diagram of an APPW (long & short), a PDPW, and an IPPW.

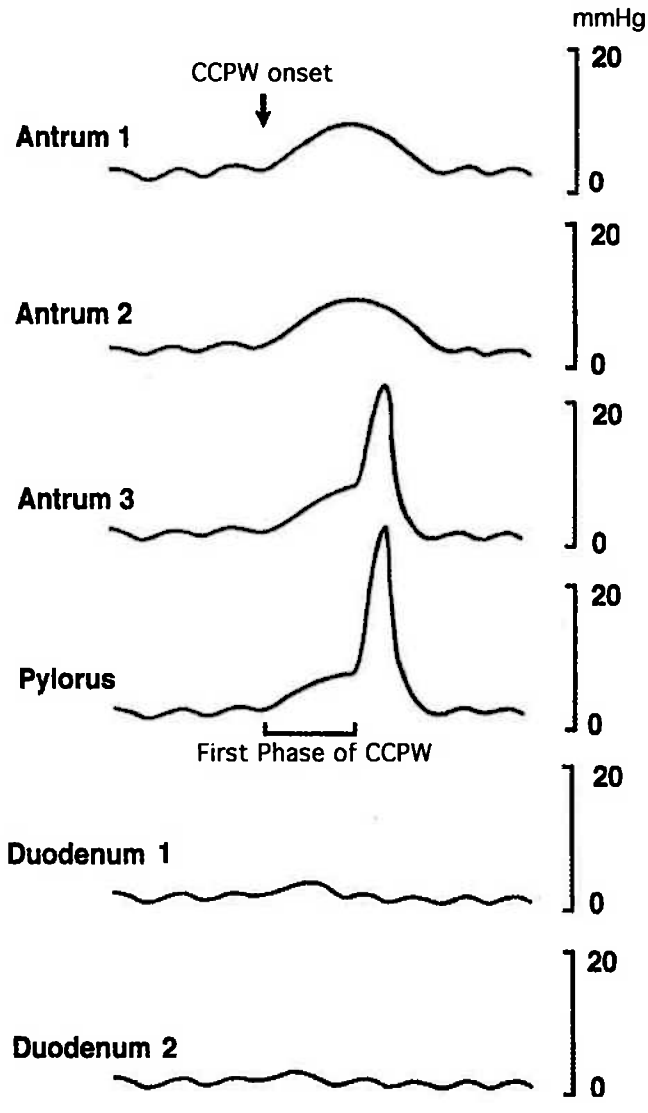


Figure 13.5b: Schematic diagram of an antral CCPW. The interval between the onset of the antral CCPW and pyloric pressure rise recorded by the sleeve is termed the "first phase of CCPW".

Chapter 14

Measurement of Gastric Emptying and Transpyloric Flow

In humans, gastric emptying was evaluated by labeling the meal with radionuclide markers prior to ingestion and then measuring the amount of radioactivity remaining in the stomach over time. In pigs, gastric emptying was assessed by gastric instillation of a radio-labeled meal, followed by measurement of the amount of radioactivity in the duodenal effluent.

In pigs, transpyloric flow was measured by continuous collection and weighing of effluent draining from the duodenal cannula.

14.1 RADIONUCLIDE GASTRIC EMPTYING TECHNIQUE IN HUMANS

Scintigraphic measurement of gastric emptying is a non-invasive, sensitive and reproducible means of quantitating gastric emptying in humans. This technique is considered to be the best available technique for measuring gastric emptying in humans (Meyer *et al* 1976, Collins *et al* 1983 & 1988, Horowitz & Akkermans 1989). It is also particularly suitable for studies combined with manometry. The technique also allows concurrent measurement of solid and liquid emptying by use of a dual isotope technique.

14.1.2 Acquisition

The subjects were positioned in front of a gamma camera (Nuclear Chicago Pho-Gamma 111 HP, Digital Equipment Corporation), and were given a meal labeled with either ^{113m}In or ^{99m}Tc or both (dual isotope used for a mixed liquid/solid meal). The gamma camera was linked to a computer (PDP 11/55) which allowed rapid determination of the distribution of radioactivity within the abdomen, and storage of scintigraphic images. Data were collected at frame rates of 30 seconds (liquid emptying) or 3 minutes (solid emptying). At the conclusion of the study, a lateral image was obtained for the required corrections for radionuclide gamma ray attenuation during analysis (Collins *et al* 1984). To this purpose, the subjects were positioned at right angles to the gamma camera, and given 150 ml drink of water labeled with 5 MBq of ^{99m}Tc. Data were collected every 5 seconds for a period of 30 seconds.

14.1.2 Analysis

From these computer-generated images, the stomach could be identified on a screen by its anatomical shape, around which a region of interest was drawn with a cursor, excluding the small intestine. Furthermore, proximal and distal gastric regions of interest were identified, enabling estimation of the regional distribution of the meal within the stomach (Collins *et al* 1988). For each image, counts were corrected for subject movement and radionuclide decay. As only a single camera was used for acquisition, correction factors derived from a lateral image of the stomach were used to minimize the error due to radionuclide gamma ray attenuation (Collins *et al* 1983).

14.1.3 Single isotope liquid emptying

This technique was used in the studies presented in Chapter 18, in which gastric emptying of 150 ml of normal saline was assessed in different postures, both before and after atropine. These studies involved measurement of the emptying of two separate test meals in the same experimental session. The second test meal was given after the first meal had emptied completely from the stomach. The drinks were always given at the start of phase I of a migrating motor cycle to control for possible effects of phase II or III contractions on emptying.

To avoid possible error from radionuclide emptied into overlapping small bowel or colon from the first test meal, the sequential measurements for the second drink were carried out using a different radionuclide marker. The radionuclide marker used for the first emptying test was ^{113m}In-DTPA and the marker for the second test was ^{99m}Tc-sulfur colloid. The radiation dose of both markers used was 20-24 MBq (0.5-0.6 mCi). Data were collected at a frame rate of 30 seconds for 45 minutes.

14.1.4 Dual isotope mixed liquid/solid gastric emptying

In these studies, the subjects were given a test meal of 100 g cooked ground beef containing chicken liver labeled *in vivo* on the morning of the experiment with around 40 MBq (1 mCi) ^{99m}Tc-sulphur colloid (Collins *et al* 1988, Houghton *et al* 1988a). The subjects were asked to eat the beef burger over 5 minutes and were then asked to drink 150 ml of 10% Dextrose labeled with 20-24 MBq ^{113m}In over 30 seconds.

For these studies, the subjects were seated on a stool with their arms on a table (Houghton *et al* 1988a). Data were collected continuously, frames being formed for 30 second periods for the first 30 minutes and then over every 3 minutes for another 150

minutes. At the conclusion of the study, a lateral image was again obtained, as described previously, and used to determine the necessary corrections.

14.1.5 Parameters used for assessment of gastric emptying

Liquid emptying

The following parameters were measured during liquid emptying in both single and dual isotope studies:

i) **Lag period**: the time taken for start of emptying into the duodenum.

ii) **Proximal T_{50}**: the time interval for 50% of the meal to leave proximal stomach.

iii) **Total T_{50}**: the time interval for 50% of the liquid meal to leave the whole stomach.

iv) **P/D_{30} Ratio**: the ratio of counts remaining in the proximal to the distal stomach at the time when 30% of the drink had emptied from the whole stomach (T_{30}). This was calculated as a measure of relative intra-gastric distribution of liquid in the stomach.

Solid emptying

The following parameters were assessed for emptying of solids:

i) **lag period**: the time taken for start of emptying of solids from the stomach into the duodenum.

ii) **Total T_{50}**: the time interval for 50% of the meal to leave the total stomach.

iii) **Proximal T_{50}**: the time interval for 50% of the meal to leave the proximal stomach.

iv) **Total R_{100}**: the percentage of meal retained in the total stomach after 100 minutes.

v) **Proximal R_{100}**: the percentage of meal retained in the proximal stomach after 100 minutes.

vi) **Total R_{170}**: the percentage of meal retained in the total stomach after 170 minutes.

14.2 MEASUREMENT OF GASTRIC EMPTYING IN PIGS

Studies of gastric emptying in pigs involved only non-nutrient liquids, specifically, normal saline. The influence of calorie content or osmolarity on gastric emptying was tested by infusion of different test solutions into the distal duodenum via a Foley catheter, distal to its balloon.

The liquid meal consisted of 1000 ml of normal saline labeled with 4 MBq (0.1 mCi) of ^{113m}In-DTPA. Prior to each study, a 1 ml sample was taken from the labeled meal which was used to determine the total counts instilled into the stomach of the pig. Drainage from the duodenal cannula was collected over 2.5 minute intervals, the volume noted and a sample stored for subsequent radio-isotopic counting. From this, the corrected volume of the radio-labeled meal emptied was calculated for each 2.5 minute interval, for the duration of the study (Treacy *et al* 1990).

Although the technique of duodenal drainage for measurement of gastric emptying has been employed and validated previously (Landers *et al* 1986, Treacy *et al* 1990), it has been suggested that an open duodenal or jejunal cannula or fistula will speed the gastric emptying of liquids by the order of 25-50% (Miller *et al* 1981, Morrison & Kelly 1987), by reducing the resistance to flow offered by the proximal small bowel.

In order to assess the impact of duodenal drainage on gastric emptying, we compared this technique with the standard dilutional assessment of gastric emptying (Hunt & Spurrell 1951). The studies are described in Chapter 16. We have found that measurement of gastric emptying by a duodenal drainage technique leads to a significantly more rapid emptying rate only in the first 5 minutes. This fact was considered when deriving any conclusions from our results.

14.3 MEASUREMENT OF TRANSPYLORIC FLOW IN PIGS

Transpyloric flow was assessed in the pigs by a duodenal drainage technique. This technique has previously been reported by other investigators (Landers *et al* 1986, Treacy *et al* 1990). Transpyloric flow was measured by the continuous collection and weighing of all effluent from the open duodenal cannula (Figure 14.3). A funnel tied over the arm of the cannula delivered effluent to a container into which its stem was plugged. The container was on an electronic weighing machine, the output of which was connected to one channel of the polygraph which had an automatic reset to zero when the weight of effluent reached 100 g. Thus, both the volume and rate of delivery of fluid to the container was recorded. Prompt delivery of fluid to the container was ensured by applying of a vacuum to the funnel. The length of the connecting tube between the funnel and the container caused a fixed delay of 0.5 seconds in recording outflow from the cannula. This delay was corrected for when data were analyzed.

14.3.1 Analysis of flow results

Transpyloric flow occurred either as a nonpulsatile low volume flow, or as short duration high volume pulses. Pulsatile flow was defined as occurring when there was an episode of flow which exceeded 0.5 ml/sec, and had a total volume of at least 4 ml over 8

seconds. Non-pulsatile flow was defined as any flow that did not fit within the above definition. The onset of pulsatile flow was determined visually as the point at which the flow rate exceeded 0.5 ml/sec, and the offset was taken as the point in time when the flow rate returned to < 0.5 ml/sec. The minimum volume of pulsatile flow was set at 4 ml, dictated by the fact that our measurement techniques did not have the accuracy to reliably identify flow pulses less than 4 ml.

Section C

Development and Evaluation of Methodologies

Chapter 15

Topography of the Pig Pylorus

15.1 INTRODUCTION

It was necessary to design a manometric assembly which could distinguish between isolated pyloric pressure waves and short antropyloric pressure waves. In order to do this, we had to first evaluate the functional rather than the anatomical length of the pig pylorus. This was done with methodologies described by Heddle *et al* (1988a) for determining the topography of pyloric pressures in humans.

15.2 METHODS

15.2.1 Animal preparation

Five pigs weighing 48- 55 kg (median 52kg) were studied. This was the maximum weight range that the pigs would reach during the studies conducted for this thesis, and so allowed us to assess the maximum possible length of the pyloric motor region. All pigs had gastric and duodenal cannulae, as described in Chapter 12, and were at least 6 weeks post-surgery when the studies were conducted. The pigs were fasted overnight, and had a gastric washout prior to each study (Chapter 12). The animals were unsedated and standing in a sling.

15.2.2 Manometric assembly

In order to assess the pyloric length, a manometric assembly (without a sleeve device) was used which had 10 sideholes spaced at regular 3mm intervals. The catheter was

perfused with water at 0.6 ml/min. Two central channels (5 and 6) were perfused with saline and used to record transmucosal potential difference (TMPD) as described in Chapter 13.

15.2.3 Study protocol

The manometric assembly was passed from the gastric to the duodenal cannula until all sideholes were external to the duodenal cannula. An infusion of 25% dextrose at 5 ml/min was commenced into the distal duodenum. This has been shown previously, to consistently induce regular isolated pyloric pressure waves in pigs, within 5-10 minutes of commencement (Treacy *et al* 1990). Fifteen minutes after the start of the infusion, the manometric catheter was pulled into the antrum in 3 mm steps, with 30 seconds between each pull. Pressure and TMPD tracings were recorded on the polygraph paper.

15.2.4 Analysis

By using the spacing between the sideholes and the distance of the pull-through, we were able to assess the maximum length of the active pyloric motor zone during stimulation of isolated pyloric pressure waves by intraduodenal dextrose.

In addition, the transmucosal potential difference values for the proximal duodenum, pyloric canal and terminal antrum were recorded.

15.3 RESULTS

All pigs exhibited isolated pyloric pressure waves with total abolition of antral pressure waves within 10 minutes of the start of the dextrose infusion.

15.3.1 Pyloric zone generating isolated pyloric pressure waves

The length of the pyloric zone which exhibited phasic contractions during the dextrose infusion varied from 0.9-1.8 mm with a median of 1.5 mm. The rates of isolated pyloric pressure waves measured for 5 minutes in each pig were similar with a median of 3.0 waves/minute (range of 2.8-3.5 waves/min)

15.3.2 TMPD recording

The table below gives the range and the median values for the TMPD recordings at the duodenal bulb, pyloric canal and terminal antrum.

	TMPD measurement in mV Median (range)
Terminal Antrum	**-16** (-15 to -22)
Pyloric Canal	**-8** (-7 to -11)
Proximal Duodenum	**-0.5** (0 to -5)

15.4 CONCLUSIONS

This study provided us with the information required to design an appropriate manometric assembly for use in the pig studies. Our results showed that the pyloric zone responsible for IPPWs was always less than 2 cm in length, therefore a sleeve sensor 4 cm long, with 3 sideholes spaced at either end of the sleeve and in its centre would allow us to differentiate reliably between isolated pyloric pressure waves and short segment antropyloric pressure waves (>2 cm).

Furthermore, the measurement of the TMPD in the duodenum, pylorus and terminal antrum helped us to formulate the TMPD criteria (Chapter 13) for the correct positioning of the sleeve across the pylorus.

Chapter 16

Validation of the Duodenal Drainage Technique for Measurement of Gastric Emptying

16.1 INTRODUCTION

Although the technique of duodenal drainage for measuring gastric emptying has been employed previously in the literature (Landers *et al* 1986, Treacy *et al* 1990), it has been suggested that an open duodenal or jejunal cannula or fistula will speed the gastric emptying of liquids by the order of 25-50% (Miller *et al* 1981, Morrison & Kelly 1987), by removal of the effect of resistance to flow from the proximal small bowel motor mechanisms.

In order to assess the impact of duodenal drainage on gastric emptying, we compared gastric emptying results, obtained by the duodenal drainage technique described in Chapter 14, with the standard dilution technique for measurement of gastric emptying described by Hunt & Spurrell (1951).

16.2 METHODS

In three pigs with gastric and duodenal cannula, the impact of duodenal drainage was assessed by measurement of gastric emptying using two techniques on separate days:

Technique 1: Standard duodenal drainage technique described in Chapter 14.

Technique 2: With the duodenal cannula closed, 5 ml samples of gastric contents were withdrawn from the gastric cannula every five minutes, and a 5 ml bolus of saline, containing a constant amount of ^{113m}In (around 1 MBq) was instilled into the stomach via the gastric cannula. One minute after each addition, a second 5 ml sample was taken from the gastric contents. This procedure was repeated every 5 minutes for 30 minutes after the meal. The amount of radiation in each sample was assessed by a gamma-counter (CompuGamma 1282, LKB Wallac, Finland) and was used to calculate the gastric residual volume for each 5 minute, using the formula described by Hunt & Spurrell (1951).

Gastric emptying was measured twice with each technique on separate days in each pig.

16.3 RESULTS

The isotopic dilution measurements of emptying showed that duodenal drainage altered the early emptying pattern. With the duodenal cannula open, emptying was 27% faster ($p<0.05$) in the first 5 minutes. After the first 10 minutes, the emptying rate was similar, regardless of whether the duodenal cannula was open or not (Figure 16.3).

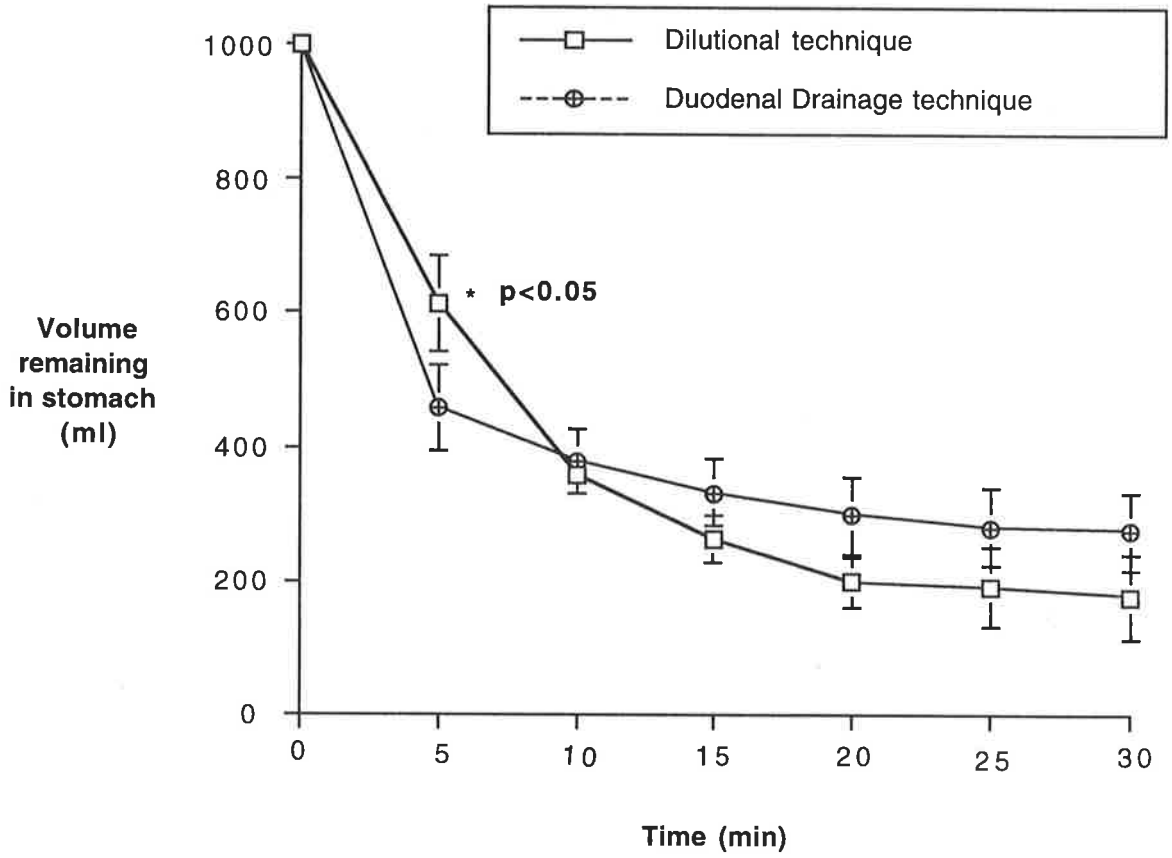


Figure 16.3: The emptying curves obtained by the duodenal drainage and the dilutional techniques.

16.4 CONCLUSIONS

We have shown that measurement of gastric emptying by the duodenal drainage technique leads to a more rapid emptying rate only in the first 5 minutes, and that the gastric emptying rates are comparable to those using the closed duodenal technique after the first ten minutes.

This effect should be considered during the interpretation of results obtained by the duodenal drainage technique. We do not, however, believe that the difference in the emptying rate caused by the duodenal drainage technique alters the physiological significance of our findings regarding the mechanics of emptying presented in future chapters.

Section D

Studies on The Mechanics of Gastric Emptying

Chapter 17

Mechanics of Transpyloric Flow and the Role of the Pylorus

17.1 CONCURRENT VIDEOFLUOROSCOPY AND MANOMETRY IN HEALTHY VOLUNTEERS

17.1.1 Introduction

The exact role of the pylorus in controlling gastric outflow has been controversial for years. There are conflicting data on patterns of pyloric motility during fasting and during delivery of acid, sugars, or lipids into the duodenum. Recent studies in humans, using sleeve manometry, have reported stimulation of localized pyloric tonic and phasic contractions after meals, and during intraduodenal infusion of nutrients (Heddle *et al* 1988b & 1988c, Houghton *et al* 1988a & 1988b), while earlier studies using less reliable techniques, had failed to show such responses (Valenzuela & Defilippi 1976, White *et al* 1981). The effect on gastric emptying and transpyloric flow of localized contractions at the pyloric zone in humans, is still unknown.

The goal of this study was to assess the transpyloric flow of liquid barium fluoroscopically during stimulation of tonic and phasic pyloric motor activity by intraduodenal infusion of lipids.

17.1.2 Methods

Subjects

Eight healthy male volunteers with a mean age of 26 (ranging from 19-42 yrs) were studied.

Measurement techniques

Antropyloroduodenal pressures were recorded with a 15-lumen manometric sleeve/sidehole assembly (Figure 17.1.2) incorporating a 4.5 cm sleeve sensor with a radio-opaque metal stiffner. The sideholes located at the upper margin of the sleeve and at 2.5 and 5 cm orad to this level, monitored antral pressures. The sideholes arrayed at 5 mm intervals within the sleeve length allowed assessment of the spatial patterns of pressure waves across the pylorus. Duodenal pressures were monitored from 3 sideholes 0, 2.5 and 5 cm aborad from the distal sleeve end. The two sideholes at either end of the sleeve were used to measure transpyloric TMPD gradient, for correct positioning of the sleeve, and the most distal duodenal sidehole was also used to infuse either saline or triglyceride emulsion into the duodenum.

The diameter of the pyloric canal and state of opening and closure of the pylorus was assessed concurrently by videofluoroscopy. These images were recorded (3/4 inch Sony videocassette) with subjects positioned in a prone, oblique position with the right side down, to allow viewing of the pylorus at right angles. Occasionally, subjects were positioned in a supine, oblique position for better fluoroscopic determination of the pyloric canal diameter. Fluoroscopic and manometric events were correlated in time by simultaneous recording of a superimposed image of the sleeve tracing onto the videotape of the fluoroscopic image (using a Hewlett-Packard signal mixer).

Study protocol

At the commencement of Phase I of the MMC cycle, normal saline was infused at 1 ml/min (4 subjects) or 3 ml/min (4 subjects) into the duodenum 5 cm distal to the sleeve, for 5 minutes. The subjects then swallowed a 50 to 100 ml bolus of diluted barium-sulfate suspension, and the transpyloric flow of this was observed fluoroscopically for the subsequent 30 minutes.

After a 10 minute recovery period, a triglyceride emulsion (Intralipid 10%) was infused into the duodenum at rates of 1 and 3 ml/min (4 subjects at each rate) for 5 minutes. A second bolus of barium was swallowed and the distal antrum and pylorus were examined fluoroscopically for 3 minutes.

Analysis of Data

Manometric tracings were analyzed for each 3 minute period of concurrent recordings. Mean basal pyloric pressure (pyloric tone), referenced to distal antral basal pressure, was determined for each 15 second period.

A sleeve detected pressure rise in absence of any discernible (10 mmHg) antral or duodenal pressure rise (± 2 sec), and recorded by two or less sideholes along the sleeve, was scored as an IPPW. When there was an antral pressure wave that had occurred within 2 seconds of the onset of the sleeve detected pressure rise, an APPW was scored.

The pyloric lumen was defined as open, closed or indeterminate for each of the 15 second periods in which mean basal pyloric tone was measured. If the lumen was open at any time during the 15 seconds, the period was defined as open.

A 2x2 table was constructed for correlation of pyloric opening or closure versus pyloric tone. Analysis of variance was used for statistical analysis of the relationship between pyloric tone and opening of pyloric lumen. A paired student's t-test was used for statistical validation of the response to intraduodenal lipid infusion compared to saline infusion.

17.1.3 Results

During intraduodenal saline infusion, the dominant motor pattern was an irregular occurrence of antropyloric pressure waves, and absence of pyloric tone and IPPWs (Figure 17.1.3a, Table 17.1.3a). By contrast, intraduodenal lipid infusion was associated with suppression of antral and duodenal contractions, and stimulation of pyloric tone and IPPWs (Figure 17.1.3b, Table 17.1.3a).

Table 17.1.3b summarizes the relationship of sleeve-recorded pyloric tone to the presence of a barium column across the pylorus for the two conditions studied. In 98.4% of the 15 second periods during which pyloric tone was greater than 2 mmHg, the pylorus was closed around the sleeve assembly. A barium column extended across the pylorus in 97.3% of the periods in which basal pyloric tone was less than or equal to 2 mmHg.

All IPPWs occurred when pyloric tone was present. Consequently, the pylorus was always closed just prior to the onset of each IPPW. There was **no** peristaltic pumping of barium by IPPWs.

In 7 of the 8 subjects, antropyloroduodenal pressure waves occurred when pyloric tone was absent. These waves occluded the lumen of the distal antrum as they advanced towards an already open pylorus. Pumping of barium was observed in advance of the lumen occluding contraction. The six APPWs that occurred in the subject in whom pyloric tone was present during intraduodenal saline infusion, also propelled barium across the pylorus.

The radiological outlines of the antropyloroduodenal segments were distinctly different during the two study conditions. During the triglyceride infusion, the antrum was globular, and because there was no emptying of barium into the duodenum, it was not necessary to refill the antrum with barium as recordings were made. There was a deep, static, lumen-occluding ring at the pylorus when pyloric tone and IPPWs were present (Figure 17.1.3c). This ring was approximately 1 cm long, as judged by comparison with the length of the spring wire which stiffened the sleeve. The appearance of the ring did not change during the IPPWs, indicating that tonic and phasic contractions occurred in an identical zone. The length of the pyloric lumen that was observed to be consistently occluded correlated well with manometry, as 89% (61/65) of all IPPWs recorded during fluoroscopy were seen in only one sidehole, indicating that the zone of localized pyloric contraction was usually equal to or less than 1 cm in length. In keeping with radiological appearances, pyloric tone was recorded from the same sideholes as IPPWs. The position of the sidehole that recorded pyloric tone and IPPWs was in accord with the position of the lumen-occluding pyloric ring on the manometric assembly, as judged fluoroscopically by reference to the sleeve spring wire stiffener.

During the intraduodenal saline infusion, the antrum emptied rapidly, and so required refilling with barium during the period of fluoroscopy. No discrete pyloric ring could be discerned (Figure 17.1.3d)

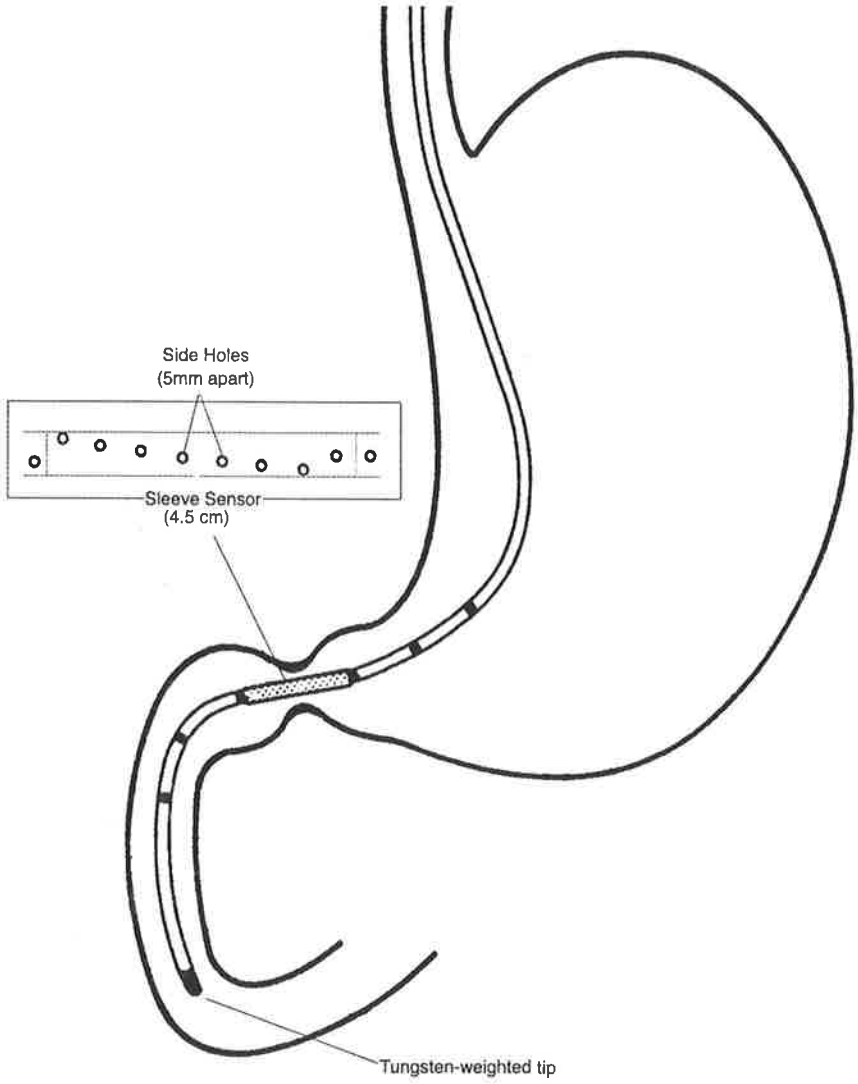


Figure 17.1.2: A schematic diagram of the manometric assembly used. The sideholes along the 4.5 cm-sleeve were 5 mm apart. The three antral and three duodenal sideholes were 2.5 cm apart.

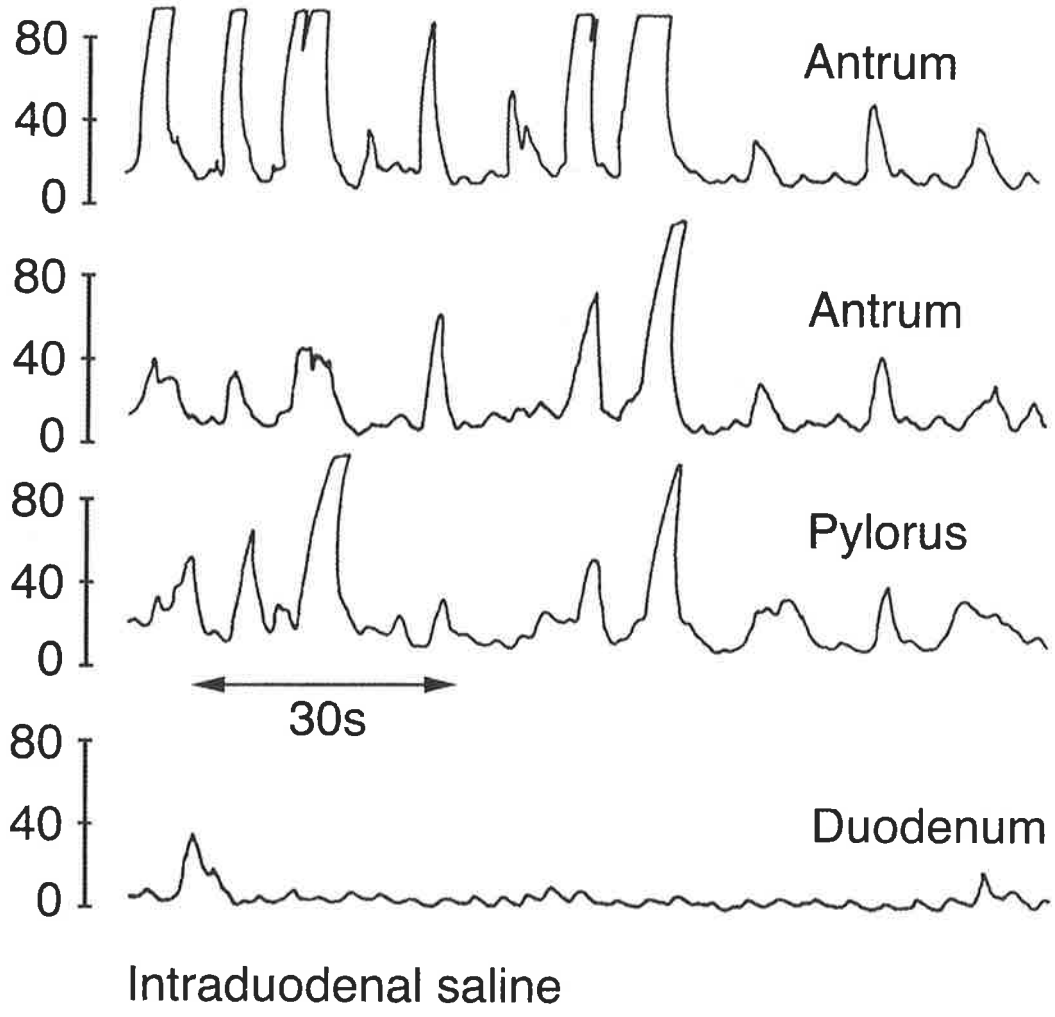


Figure 17.1.3a: Manometric tracing during intraduodenal infusion of saline demonstrating a mixed antropyloric pressure pattern and an almost absent pyloric tone.

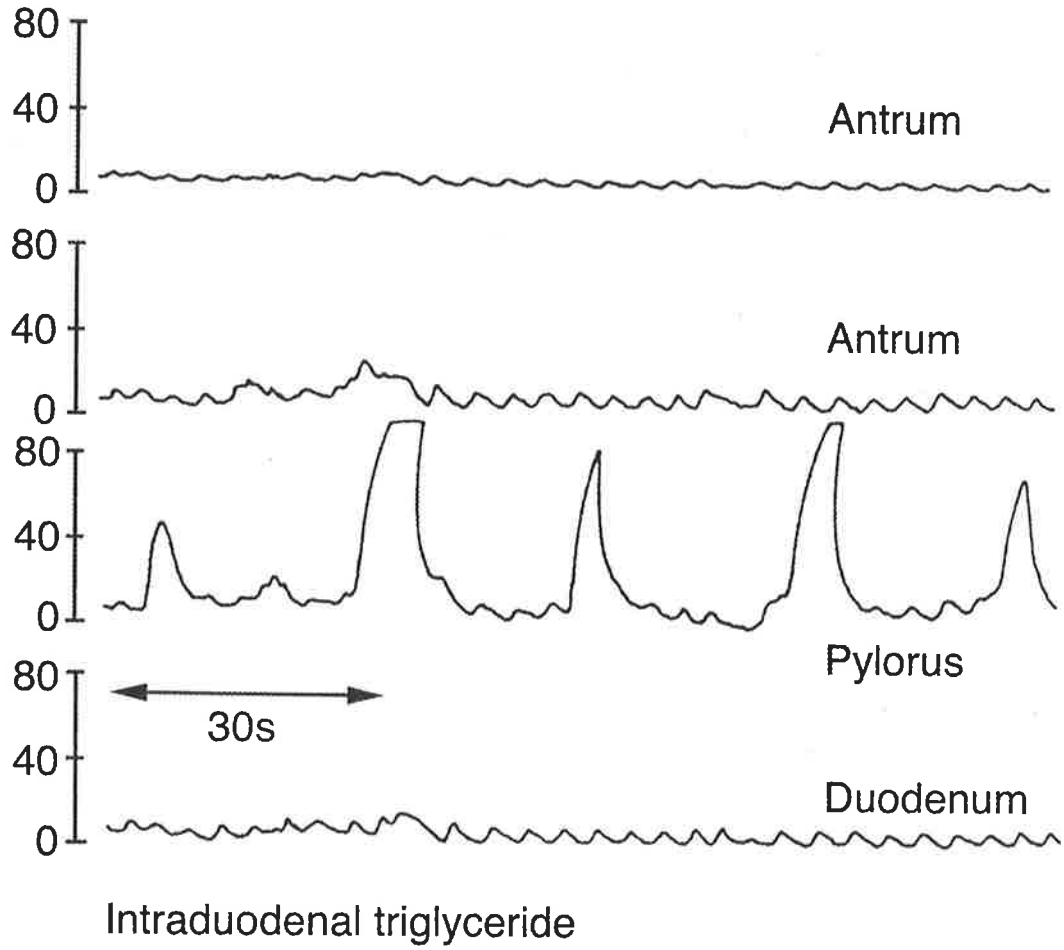


Figure 17.1.3b: Manometric tracing during intraduodenal infusion of lipids showing regular isolated pyloric pressure waves in association with an increase in pyloric tone.

Table 17.1.3a: Pyloric pressure patterns during duodenal infusion of normal saline or triglyceride emulsion.

Duodenal Infusate	**Saline**	**Triglyceride**	**p**
Pyloric tone (mmHg)	**0.33** ± 2.04	**6.56** ± 3.63	**<0.0001**
IPPWs (no/min)	**0.97** ± 0.39	**2.63** ± 0.73	**<0.002**

IPPW = isolated pyloric pressure wave

Values are given as mean ± SD

Table 17.1.3b: Relation between pyloric aperture and pyloric tone.

	Pyloric lumen	
Pyloric tone	**Closed**	**Open**
≤ 2 mmHg	**1** (1.6%)	**63** (98.4%)
> 2 mmHg	**72** (97.4%)	**2** (2.6%)

The values are the number of 15 second periods with each condition.

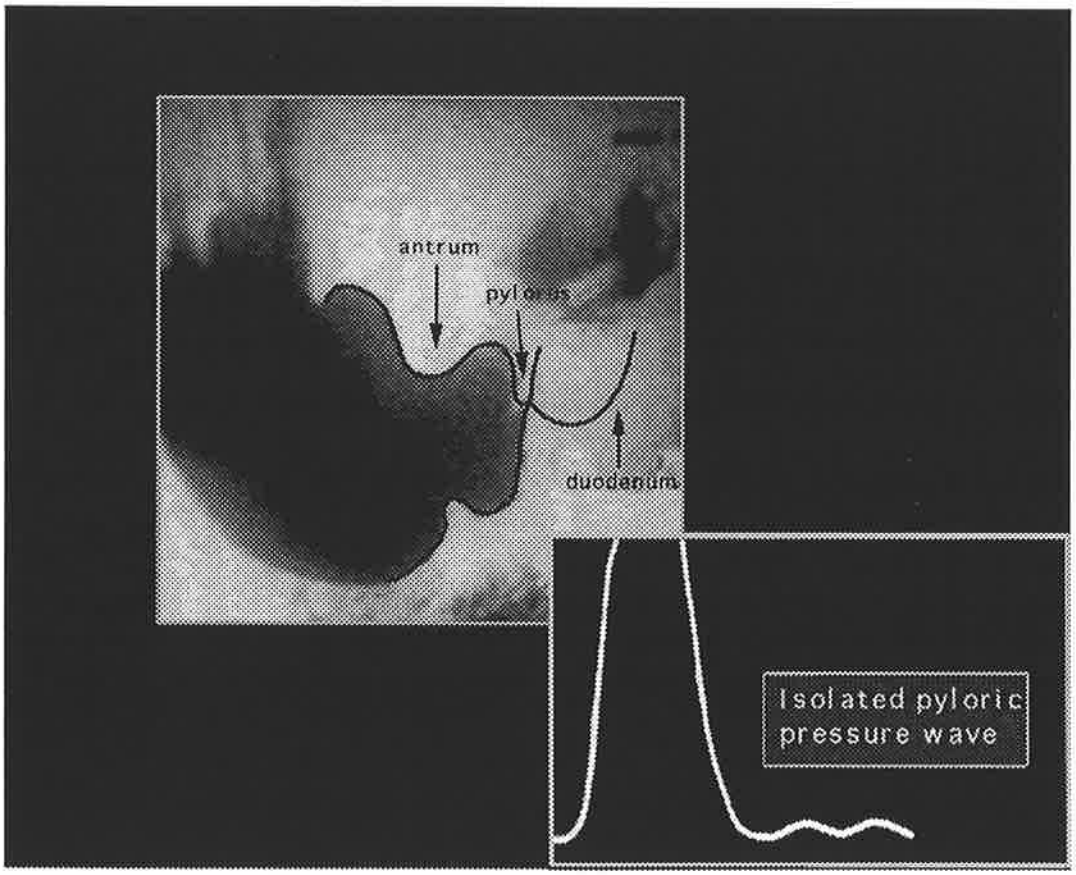


Figure 17.1.3c: During intraduodenal lipid infusion, when pyloric tone and IPPWs were present, a lumen-occlusive ring is visible at the pylorus, interrupting the flow of barium between the stomach and duodenum.

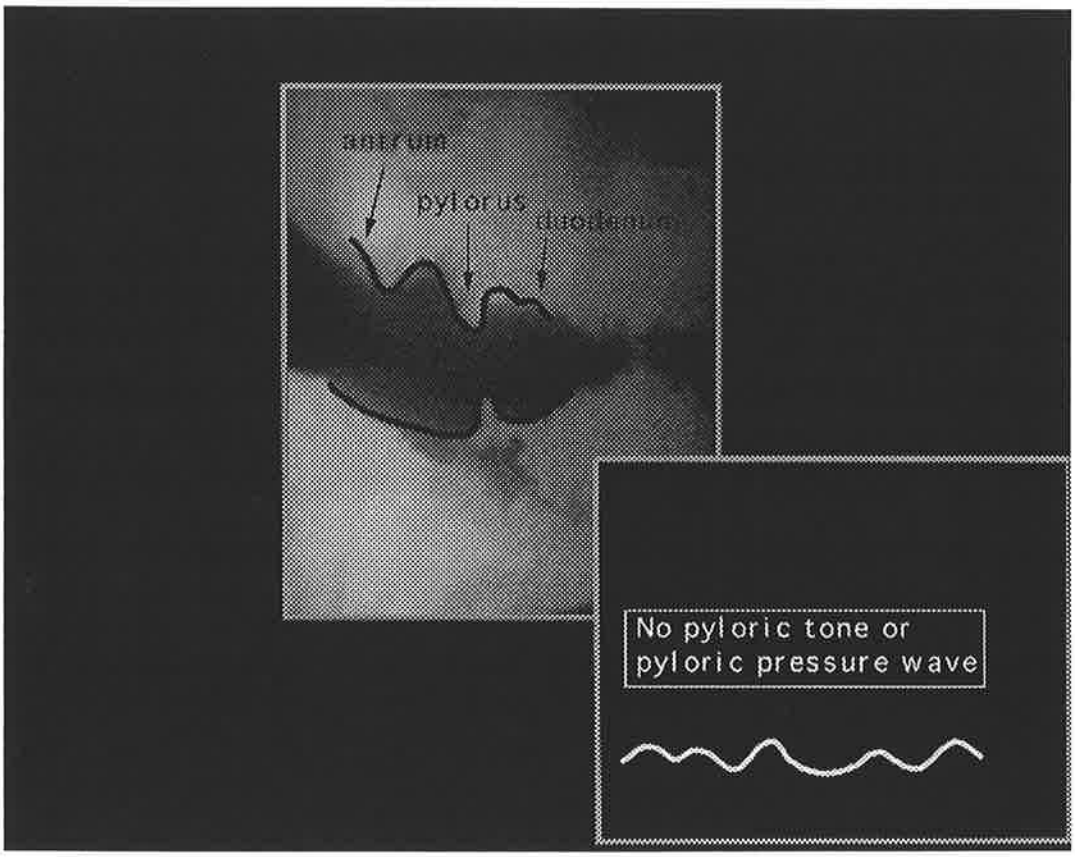


Figure 17.1.3d: The pyloric ring appears open during intraduodenal saline infusion with barium flowing freely between the stomach and the duodenum.

17.1.4 Discussion

These studies are the first in humans to examine the effect of isolated pyloric pressure waves and pyloric tone on transpyloric flow. The observations illustrate how profoundly intraduodenal stimuli can alter both antropyloroduodenal motility and the movement of luminal contents.

These observations define the functional significance of the pyloric motor mechanism, as a pyloric tone of greater than 2 mmHg above distal antral pressure occludes the pyloric lumen and prevents transpyloric flow. This effect presumably also relies on the suppression of antral contractions that was also produced by the intraduodenal lipid infusion. Studies of pyloric diameter in conscious dogs by Ehrlein (1988) have produced results consistent with those reported in the present study.

The mechanical significance of IPPWs remains unclear, as pyloric tone was always present when IPPWs occurred, and pyloric tone alone closed the pylorus. Our fluoroscopic and manometric data indicate that IPPWs are non-propagated contractions localized to the zone of the tonically contracted pylorus. The use of multiple manometric sampling points combined with simultaneous fluoroscopy shows clearly that IPPWs are distinct from the terminal antral contractions in humans (Smith *et al* 1957). It is possible that IPPWs occurring in the absence of pyloric tone (Heddle *et al* 1988a) may also obstruct transpyloric flow by "chopping" any transpyloric flow that might be occurring between IPPWs. Such an effect could produce a more graded braking of gastric emptying by the pylorus than could be produced by a pyloric tonic response.

Although the methods did not allow measurement of transpyloric flow, it was apparent that transpyloric flow occurred only when the pylorus was open, and was especially rapid (based on radiographic filling of the duodenum) just prior to lumen occlusion by antropyloroduodenal contractions. Similarly, pyloric closure consistently prevented transpyloric flow.

17.1.6 Conclusions

The pylorus has a significant role in slowing the gastric emptying of nutrient liquids. This mechanism should be considered as one among several that contributes to slowing of gastric emptying. The other mechanisms currently recognized are fundic relaxation, suppression of antral contractions and stimulation of duodenal resistance to flow.

17.2 CONCURRENT MEASUREMENT OF GASTRIC EMPTYING, TRANSPYLORIC FLOW AND MANOMETRY IN PIGS

17.2.1 Introduction

There has been a major emphasis on the primary role of tonic contraction of the gastric fundus in the control of liquid gastric emptying (Wilbur & Kelly 1973, Kelly 1981, Minami & McCallum 1984). This view is based on measurements of gastric emptying during barostatic control of fundic pressure, and comparison of emptying patterns before and after fundectomy (Wilbur *et al* 1974) and after proximal and distal vagotomy (Wilbur & Kelly 1973).

Pulsatile transpyloric flow accounts for the major component of gastric emptying (Klein 1926, Carlson *et al* 1966, King *et al* 1984 & 1988, Malbert & Ruckebusch 1991). It is difficult to envisage how proximal gastric tone could lead to this pattern of flow. Our hypothesis was that the intermittency of transpyloric flow observed during gastric emptying is due to intermittent rises in gastric pressure, rather than episodic opening and closure of the pylorus. To test this hypothesis, sleeve/sidehole manometry and transpyloric flow monitoring were used concurrently in conscious, trained pigs to correlate gastric, pyloric and duodenal pressures with the flow of gastric contents into the duodenum.

17.2.2 Methods

Studies were done on eight Kangaroo Island pigs (38 - 45 Kg) equipped with chronic gastric and duodenal cannulae.

Experimental procedure

Recordings of antropyloroduodenal motility and transpyloric flow were made concurrently for 30 minutes after the instillation of 1000 mls of saline into the stomach via the gastric cannula. The studies were performed twice in each pig. Animals were allowed 3-5 days rest between studies.

Recordings

Antropyloric pressures were recorded with an nine-lumen sleeve/sidehole catheter (Chapter 13). Transpyloric flow was determined by continuous collection and weighing of duodenal effluent (Chapter 14). Total and corrected gastric emptying were determined using the radionuclide technique (Chapter 14).

Statistical analysis

The values are given as means ± standard error of the mean. Statistical differences were assessed with one-way analysis of variance, and $p < 0.05$ was taken as significant.

17.2.3 Results

Gastric emptying measured by duodenal drainage

The volume of saline emptied in individual animals over 30 minutes ranged from 482 to 884 ml (627 ± 51.2 ml). During this period, pulsatile flow accounted for 71±3.5% of liquid emptying (430 ±51.0 ml) (Figure 17.2.3a). Most flow pulses (59%) occurred during the first 5 minutes of emptying. The number and volume of flow pulses dropped significantly after the first 5 minutes, but the duration of flow pulses remained the same (Table 17.2.3).

Temporal association of pulsatile flow with motor events

The onset of the rapid upstroke of the lumen-occlusive pressure wave recorded by the sleeve was used as the time reference point for correlations of motility with flow. The pattern of pulsatile flow was expressed by the collation of flow volumes every 2 seconds relative to this time reference. The onset of 68% of the flow pulses preceded the sleeve-detected lumen-occlusive pressure wave (Figure 17.2.3b). The 10 second interval prior to the sleeve-detected lumen-occlusive pressure wave accounted for 62% of the volume emptied by pulsatile flow from the stomach (Figure 17.2.3c).

The factors that determined onset of pulsatile emptying were therefore analyzed further, as presented below:

Antral Common Cavity Pressure Waves

The onset of 58% of the flow pulses occurred during a distinctive component of the antral pressure wave associated with gastric contraction. This was a prolonged 4-15 mmHg pressure wave which had an identical amplitude and pattern in all antral manometric channels (Figure 13.5b, page 80). This component of the antral pressure wave was called the common cavity pressure wave (CCPW), because its pattern indicated that the entire lumen of the antrum/stomach was being pressurized as a single cavity (Chapter 13). A second, briefer component of the antral pressure wave usually terminated the CCPW component. Antral CCPW associated pulses accounted for 66% of pulsatile liquid emptying over 30 minutes (Figures 17.2.3d).

There were 13.3±1.53 antral CCPWs in the 30 minutes following the liquid meal, 76% of which were associated with pulsatile transpyloric flow (Figure 17.3.3a, page 136). A

second component of lumen-occlusive antropyloric or pyloroduodenal pressure waves, terminated 93% of antral CCPWs in the terminal antrum and pylorus.

In 96% of the antral CCPWs, onset of the pressure wave was recorded by antral side holes up to 12 seconds prior to the sleeve-detected pressure rise (mean: 7.9 ± 0.6 sec) (Figure 17.2.3e). The antral CCPWs, however, persisted in the antrum beyond the time of onset of distal antral or pyloric lumen occlusion. Accordingly, the pressure waves recorded from the gastric regions that developed lumen occlusion consisted of a first phase, in which there was communication with the main gastric cavity, and then a pressure wave unique in pattern to that recording site. Transpyloric flow was only noted during this first phase of antral CCPW before pyloric lumen occlusion abruptly stopped flow (Figure 13.5b, page 80; Figure 17.3.3a, page 136).

Volume of flow pulses associated with gastric contractions

Gastric contractions associated with CCPWs had a mean pulse volume of 29.1 ± 2.31 ml, significantly higher than the flow pulses associated with antropyloric contractions which were not preceded by CCPWs (mean 11.9±1.2 ml) (Figure 17.2.3d). Furthermore, only 20% of the contractions of this second type were associated with any flow pulse.

In the first 5 minutes after the saline meal, when most antral CCPWs occurred, there was no correlation between the volume of flow pulses and the total duration ($r=0.16$) or maximum amplitude ($r=0.12$) of antral CCPWs. There was, however, a linear relationship ($p<0.01$, $r=0.72$) between flow pulse volume and the duration of the "first phase" of antral CCPW (Figure 13.5b, page 80; Figure 17.3.3a, page 136); that is, the time from onset of the antral CCPW to occurrence of the sleeve-detected lumen-

occlusive pressure wave. When this first phase was less than 3 seconds, pulsatile flow either did not occur or was of very small volume (Table 17.2.3b).

Flow patterns of pulsatile emptying

The flow pulses all had a similar pattern, with flow peaking abruptly within the first 2 seconds and then subsequently falling off less rapidly. The highest peak flows occurred in the pulses that had the longest flow (first phase of CCPW) intervals ($p<0.05$) (Figure 17.2.3f).

Effect of intra-gastric volume on pulsatile emptying and pressure patterns

In order to assess the influence of intra-gastric volume on pressure and flow patterns, comparisons were made between the periods during which the first and second 330 ml of the instilled saline were emptying. Table 17.2.3c summarizes this comparison. When compared to the second third, the first third of emptying had many more episodes of pulsatile flow and gastric CCPWs per unit time, and mean flow pulse volume was over three times greater.

Non-pulsatile emptying

Over the full 30 minute observation period, the mean non-pulsatile transpyloric flow was 7.3 ± 0.8 ml/min and accounted for 31% of observed liquid emptying. Non-pulsatile flow decreased slightly over time, but this decrease did not reach statistical significance ($p=0.07$) (Figure 17.2.3a). Non-pulsatile flow occurred between episodes of gastric CCPW, phasic antropyloric and isolated pyloric pressure waves, and was not associated with a measurable transpyloric pressure gradient.

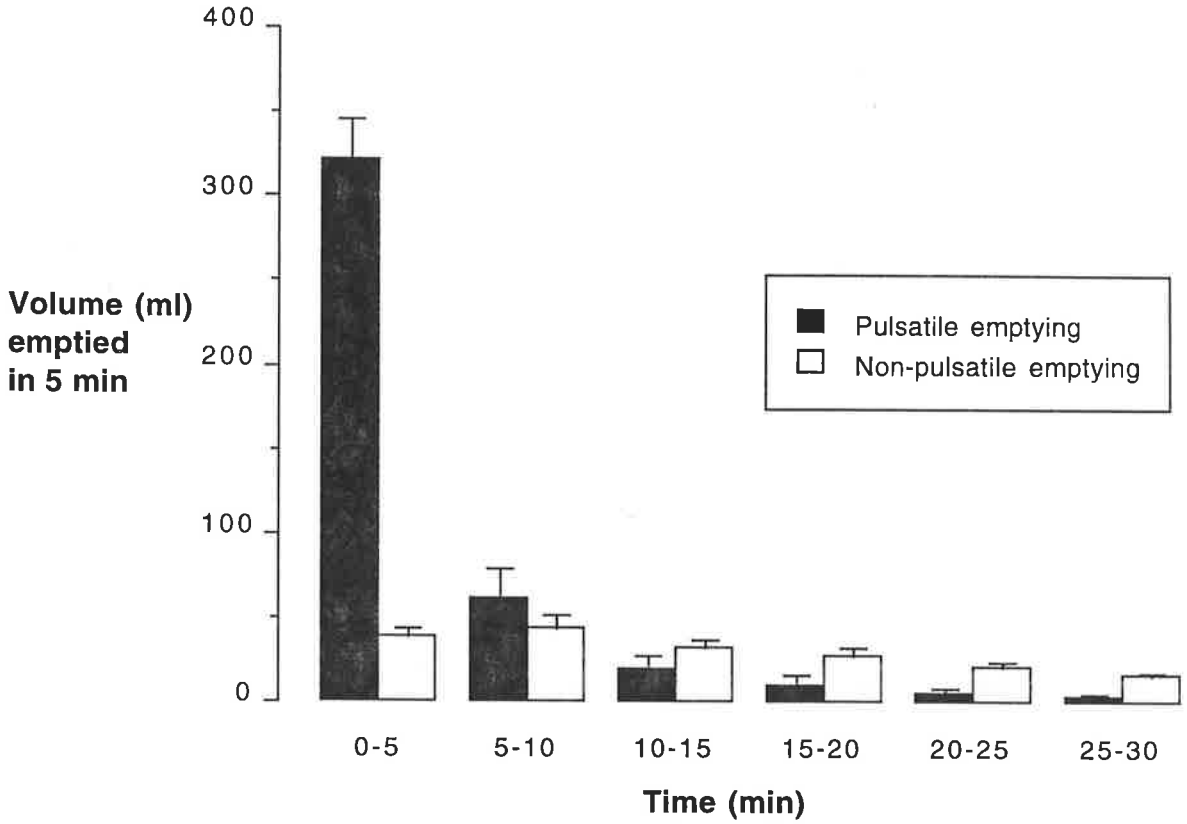


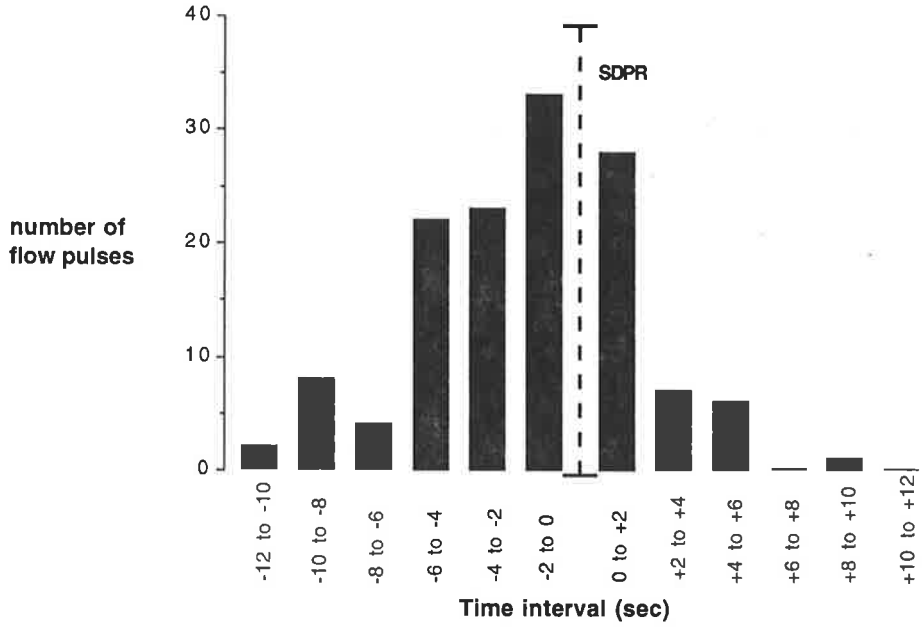
Figure 17.2.3a: Volume of liquid emptying in pulsatile and non-pulsatile fashion in the first 30 minutes after a test meal consisting of 1000 ml of saline.

Table 17.2.3: Characteristics of flow pulses during the first 10 minutes after the test meal of 1000 ml of saline.

	0-5 min	5-10 min
Duration of flow pulses (sec)	5.6 ± 0.58	5.7 ± 0.49
Volume of flow pulses (ml)	24.2 ± 3.14	14.4 ± 1.72*
Number of flow pulses per 5 min	12.0 ± 0.44	3.8 ± 0.71*

Values are given as mean ± SE, * $p<0.01$.

17.2.3b: Time of onset of flow pulses



17.2.3c: Volume of pulsatile flow

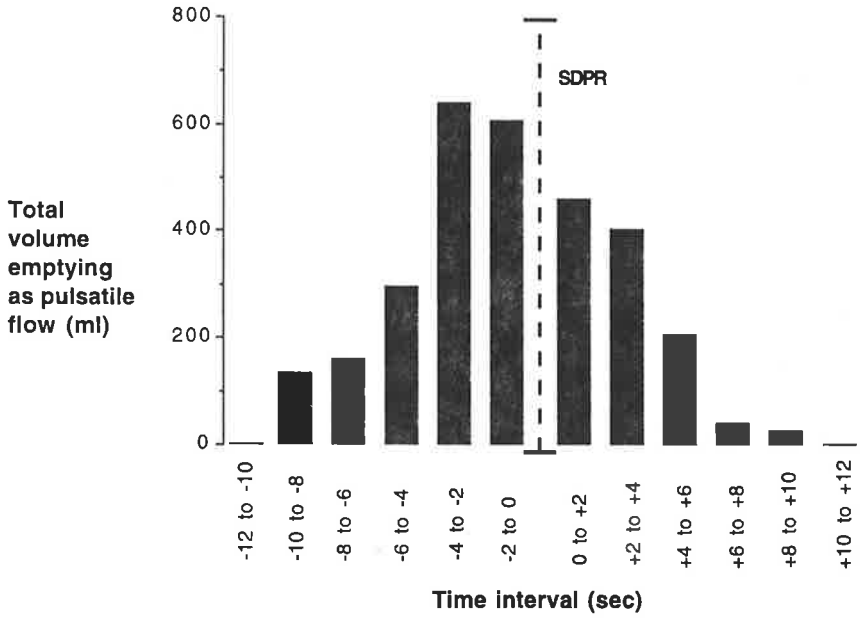


Figure 17.2.3 b&c: Analysis of timing of onset of transpyloric flow pulses (17.2.3b), and total volume of pulsatile emptying (all studies) (17.2.3c), in relation to sleeve detected pressure rise (SDPR) indicated by the dotted line.

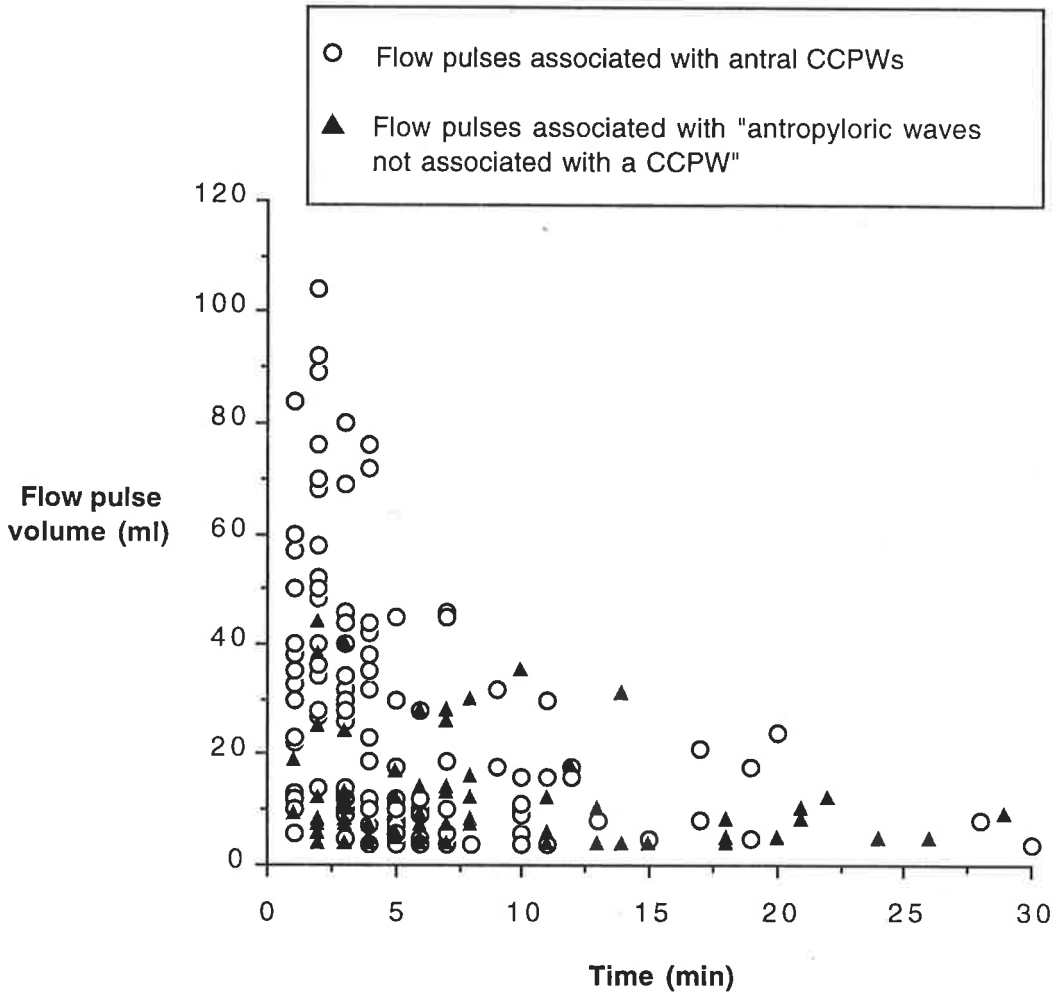


Figure 17.2.3d: Comparison of volume of flow pulses associated with antral CCPW, or antropyloric pressure waves (not associated with a CCPW), and their relation to the time of instillation of saline meal.

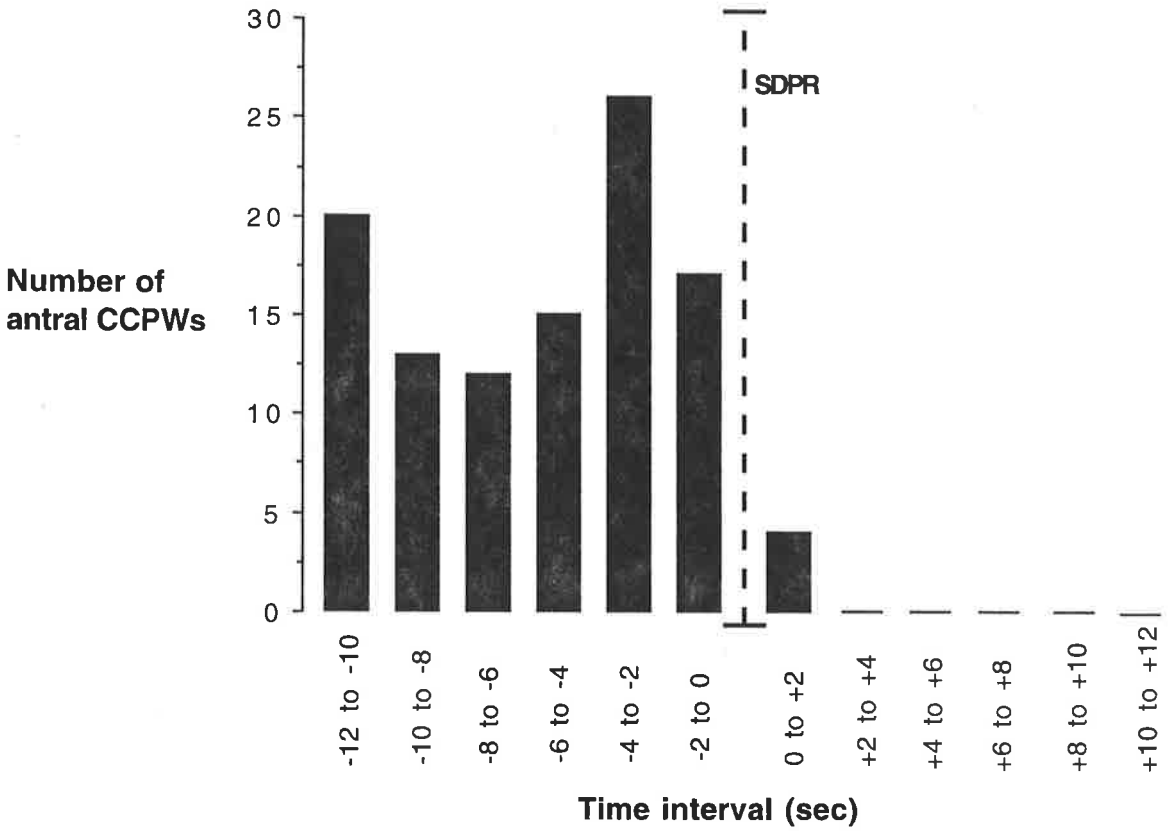


Figure 17.2.3e: Timing of onset of all recorded antral common cavity waves (from 8 studies) in relation to sleeve detected pressure rise (SDPR), indicated by the dotted line.

Table 17.2.3b: Relationship of the duration of the first phase of antral CCPWs to the volume of pulsatile flow in the first 5 minutes. The first phase is the interval between the onset of the CCPW and the onset of the sleeve-detected lumen-occlusive pressure wave.

	Duration of first phase of CCPW	
	≤ 3 sec	**> 3 sec**
Total number of CCPW	49	84
Duration of "first phase" of CCPW (sec)	1.7 ± 0.16	11.2 ± 0.53*
Volume of flow pulse per CCPW (ml)	2.8 ± 0.56	33.0 ± 2.53*

Values are given as mean ± SE, * $p<0.01$.

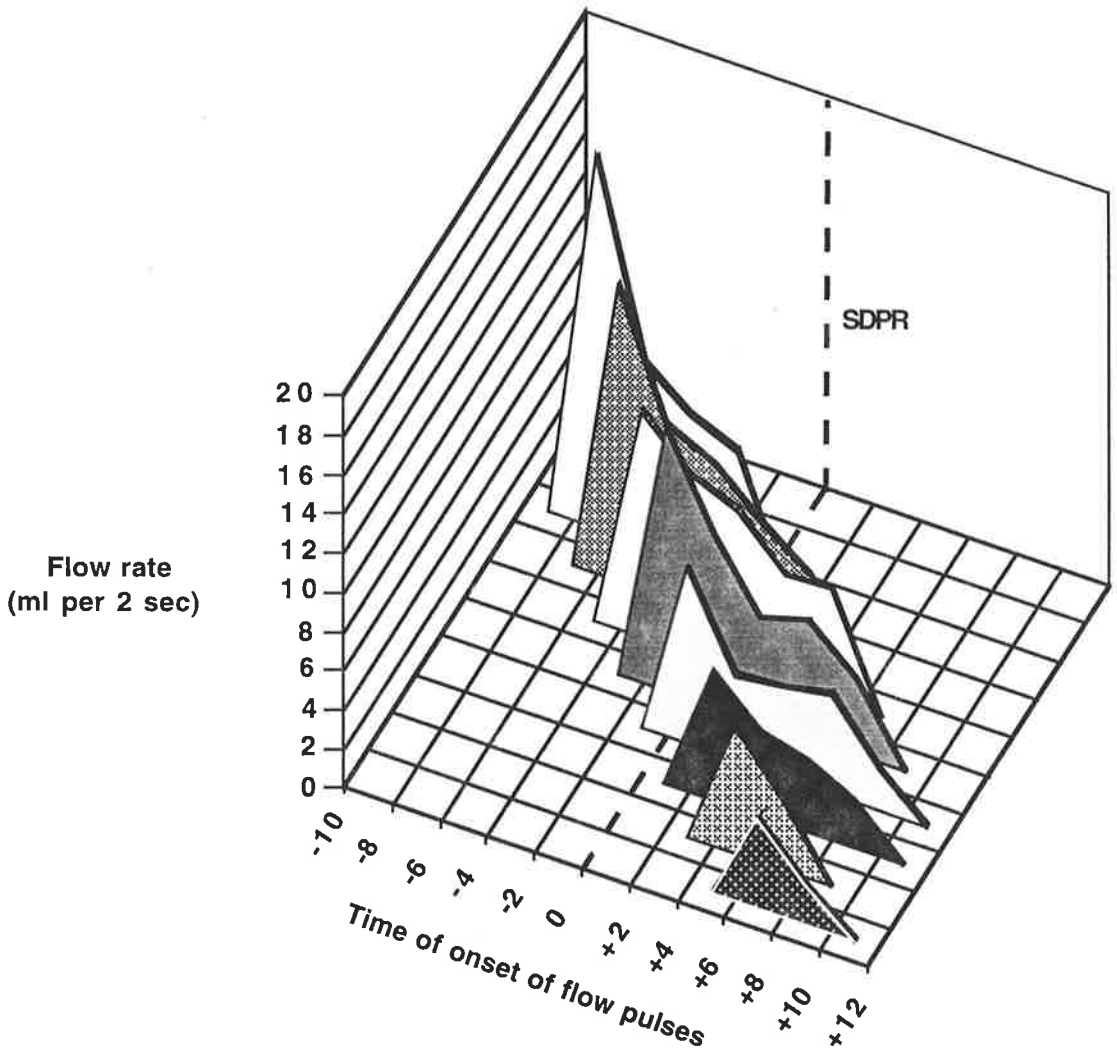


Figure 17.2.3f: Characteristics of flow pulses associated with antral CCPWs in relation to their timing of onset, referenced to sleeve detected pressure rise (SDPR).

Table 17.2.3c: Relationship of motor events and transpyloric flow to intragastric volume. Values are given for the two time intervals, during first and second third emptying.

	first third emptying	**second third emptying**
duration of the emptying for each third (min)	4.7 ± 0.47	21.7 ± 1.6*
number of flow pulses	11.4 ± 1.1	7.4 ± 2.0
flow pulse volume (ml)	30.3 ± 3.2	9.6 ± 1.7*
number of antral CCPWs	7.1 ± 0.7	6.2 ± 1.4
number of antropyloric pressure waves	7.4 ± 0.8	20.4 ± 4.3*

Values are given as mean ± SE, * $p<0.05$.

17.2.4 Discussion

The measurement approaches used have allowed novel and precise temporal correlation of transpyloric flow with intraluminal pressures. This correlation has revealed a previously unrecognized mode of gastric pumping: sustained, phasic pressurization of the entire antrum, and thus of the gastric cavity, produced possibly by an advancing non-lumen-occlusive gastric contraction. This relatively long-lasting elevation of intra-gastric pressure produces an hydraulically significant transpyloric pressure gradient, which is apparently sufficient to cause relatively high volume pulsatile flow in the absence of gastric luminal closure. This pattern of pumping has some similarities with cardiac ejection even though only a portion of the gastric musculature is contracting at any particular moment.

The manometric pattern of the antral common cavity wave has probably not been noted previously by others because of its relatively small amplitude and plateau pattern, when compared to the sharp up-stroke and high peak values of antral pressure waves associated with lumen occlusion. Attention has focused previously on lumen-occlusive pressure waves (Treacy *et al* 1990, Malbert & Ruckebusch 1991) in the belief that they are the sole mechanism responsible for pumping through progressive lumen occlusion along the antrum, akin to the well defined mode of pumping by oesophageal body peristalsis. At least in the circumstances of the studies described in this chapter, tensioning of the entire gastric wall and pressurization of the entire gastric cavity was more important than lumen-occlusive pumping.

There was substantial variation in the volume of pulsatile flow associated with CCPWs. Our analysis shows that the highest pulse volumes occurred with CCPWs that had the

longest intervals between their onset and the occurrence of distal antral/pyloric lumen occlusion. The mechanical basis of prolonged antral CCPWs requires radiological evaluation. It is likely that such CCPWs would occur when the stomach is filled and when non-lumen-occlusive gastric contractions are relatively forceful, and so cause major constriction high in the stomach. Our more extensive data with manometry alone showed no relationship of the transpyloric pulse volume to the maximum pressure of the antral CCPW. This finding initially seems somewhat contradictory to the concept of non lumen-occlusive pumping. Possibly though, the pressure generated by a non lumen-occlusive contraction in a fluid distended stomach depends not only on the force generated by the contraction, but also on the resistance to flow provided by the pylorus and proximal duodenum. We did not measure these variables, as manometry does not recognize variations in pyloric ring diameter, short of closure, which could influence the resistance to transpyloric flow driven by the low pressure seen in antral CCPWs. Variations in pyloric ring diameter have been reported in dogs with studies that used the inductographic method for monitoring of pyloric diameter (Ehrlein 1988).

Earlier studies have suggested an important role for the pylorus in the control of gastric outflow (Chapter 17.1). Intestinal infusion of nutrients is associated with isolated pyloric contraction and retardation of transpyloric flow (Heddle *et al* 1988b &1988c, Chapter 17.1). However, very little is known of the regulatory influence of the pylorus on gastric outflow of ingesta during conditions of emptying. The manometric technique used has allowed correlation of the relationship of the timing of pyloric closure to the antral CCPW. The findings are consistent with those of Carlson *et al* (1966) in unanaesthetized dogs, who found that the timing of pyloric closure varies in relation to antral contraction. Carlson's estimates of flow pulse volumes by fluoroscopy of radio-opaque content were crude, but they support the concept that variation of the timing of

pyloric closure in relation to non lumen-occlusive antral contraction is a key determinant of the degree of propulsion and retropulsion during any individual contraction.

The conclusions of this study depend heavily on the accuracy of the timing of transpyloric flow. The method used for duodenal drainage was designed to give as accurate an indication as possible of the timing of flow into the proximal duodenum by the use of a carefully sited catheter, and a suction system. Prior studies have evaluated the time delay of this system by direct, accurately timed delivery of known amounts of liquid into the proximal duodenum and observation of the flow registration by the collection system (Treacy *et al* 1990). The fixed time delay factored into our measurements was derived in this way and showed little variation with repeated testing of simulated pulsatile emptying into the proximal duodenum. Thus, it is reasonable to believe that the timing of flow was recorded with an accuracy of about 0.5 seconds. This accuracy allows us to be confident that the episodes of pulsatile flow were indeed related to times when gastric CCPWs were occurring in the stomach, given the duration of those waves.

Care is needed in the analysis of the relatively low amplitude antral CCPWs. Pressures must be recorded concurrently, preferably from at least 2 points in the duodenum, as this makes it possible to distinguish antral CCPWs from low amplitude increases of intra-abdominal pressure produced by sustained slight straining. Such straining elevates both duodenal and gastric pressures symmetrically. The very proximal duodenum is not the ideal point for monitoring of intra-abdominal pressure under these experimental conditions, as very high volume pulsatile flow appeared, at times, to pressurize the duodenal bulb to the gastric cavity pressure during antral CCPWs. A more

distal duodenal side-hole is preferable, or possibly a rectal catheter, as an independent indicator of intraperitoneal pressure.

The analysis of pressure and flow required a time reference point in relation to the gastric contraction cycle. Because lumen occlusion occurred most often at the pylorus as a result of gastric contraction, we elected to use the sleeve-recorded onset of pyloric lumen occlusion as the reference point. This should not be taken to imply that we considered this a fixed point in the gastric contraction sequence. There is a second consideration about the use of the sleeve detected pressure rise as the time reference. This pressure rise can be generated by a contraction anywhere along the sleeve span - that is, in the last centimetre or so of the distal antrum, the pylorus itself, or the proximal duodenum (Heddle *et al* 1988a). The degree of inaccuracy that would have resulted from this is relatively unimportant, given the long time scale over which flow and antral CCPWs occurred.

The experiments were done in the absence of any significant duodenal distension or duodenal nutrient stimulation. Such stimuli produce substantial alteration in the patterning and vigor of antropyloric contraction. Correlation of intra-gastric pressure, transpyloric flow and wall motion are highly desirable and can be achieved with the use of concurrent videofluoroscopy (Chapter 17.3).

17.2.6 Conclusions

This study demonstrates that the primary method of gastric pumping in a fluid-distended stomach is by pressurization of the gastric cavity, recorded manometrically as common cavity waves. The mechanical generation of antral CCPW needs further investigation.

17.3 CONCURRENT MEASUREMENT OF WALL MOTION, MANOMETRY AND FLOW

17.3.1 Introduction

In order to establish the gastric contractile pattern responsible for generating antral CCPWs, we measured either wall motion by fluoroscopy, or wall tension by strain gauges, concurrently with gastric pressure and transpyloric flow monitoring.

17.3.2 Methods

Concurrent manometry and videofluoroscopy

In three pigs, antropyloroduodenal pressures were measured after instillation of 1000 ml of dilute barium concurrently with the videofluoroscopic recording of gastric contractile activity. While standing in the sling, the pigs were elevated 1 meter off the ground with a hydraulic jack so that the C-arm of the X-ray machine (Siemens, Germany) fitted around the animal in the horizontal plane. After instillation of a mixture of 900 ml saline and 100 ml liquid barium, stomach images were recorded on videotape (AG-6500-A, Matsushita Electric Industrial Co. Ltd., Osaka, Japan) at 25 frames per second. Recordings were started immediately after the instillation of a saline/barium mixture and continued for 6 minutes. The x-ray tube was then allowed to cool for two minutes and the stomach was screened for a further 6 minutes.

A video-timer (Biomedical Engineering, Royal Adelaide Hospital) synchronized the videofluoroscopic images and the manometric recording, enabling precise temporal correlation between images and pressures. Images were analyzed by a radiologist, who

was blinded to the manometric and flow data. The site of origin, timing and propagation of each gastric wall motion were scored.

Concurrent manometry and strain gauge recording

In three other Kangaroo Island pigs (35 - 41 Kg), 3 strain gauges were sutured to the serosa of the stomach; on the fundus, corpus and antrum (Figure 17.3.2), at the same time as implantation of gastric and duodenal cannulae. The long axis of the strain gauges was at right angles to the circular muscle layer. The leads of the strain gauges were exteriorised through a subcutaneous tunnel between the shoulders of each animal.

Concurrent measurements of gastric emptying, transpyloric flow and wall tension were carried out after the 6 week recovery period.

The miniature Wheatstone bridge curved strain gauge transducers (Micromeasurements, USA) (Ruckebusch & Brady 1982), were used to record phasic motor activity of the fundus, corpus and antrum. The strain gauges were activated by external half bridge completion within the polygraph amplification module. The strain gauges were calibrated before implantation using the procedure of Gill *et al* (1990). This calibration was stored in the memory of the computer used for data acquisition.

Outputs of the polygraph from manometric and strain gauge channels were recorded on the polygraph chart paper and also digitized and stored on disc in a computer (Chapter 13).

Complex wave forms from the strain gauge signals, which were recorded within the same baseline elevation, were considered as clustered. Manometric and strain gauge

recordings were considered to be from the same region on the basis of estimates of the spacing of the sideholes relative to the position of the sleeve relative to the pylorus. These estimates were related to the distance of implanted strain gauge from the pylorus, as determined at the time of implantation.

17.3.3 Results

Concurrent manometry and videofluoroscopy

The stomach and pylorus were observed radiologically in full during 14 antral CCPWs in three pigs, over a total observation time of 36 minutes. All of the gastric CCPWs were associated with contractions which produced a ring of constriction in the gastric outline, which propagated from the corpus into and along the antrum. This ring of contraction became lumen-occlusive only at the distal antrum and pylorus. In another 17 CCPWs recorded during fluoroscopy, animal movement and the limitations of the fluoroscopic equipment resulted in incomplete imaging of gastric wall motion. In all of these incompletely imaged events, the CCPW was also temporally associated with clear constriction of the gastric wall by a propagated contraction (Figure 17.3.3a). Delivery of contrast to the duodenum was visualized during all 14 completely imaged antral CCPWs, as the indentation propagated down the stomach from the corpus to the pylorus. Transpyloric flow was seen to cease when the pylorus closed, in close temporal association with the upstroke of the sleeve-detected lumen-occlusive pressure wave.

Fluoroscopy showed a second distinct pattern of gastric contraction. This originated in the mid or distal antrum as a lumen-occlusive contraction, which then propagated to the pylorus. Twenty-four such contractions were observed. All of these were associated with phasic pressure waves which also indicated occurrence of lumen occlusion since they had

differing shapes and amplitudes at each antral and pyloric side-hole. None of these antropyloric contractions were associated with a prior antral CCPW of the pattern described above, in either the antrum or the main gastric cavity, above the highest point of lumen occlusion.

Correlation of wall tension and intraluminal pressure

At both body and antral level, the strain gauges indicated either a monophasic tensing of the gastric wall, or a cluster of up to 3 closely associated changes in tension (Figure 17.3.3b). Not all strain gauge recorded clusters were, however, associated with manometric pressure waves or transpyloric flow (Table 17.3.3). In the first 15 minutes, 87% of strain gauge recorded wall motions were associated with manometric CCPWs and 95% were associated with transpyloric flow. During the second 15 minutes, however, when the volume of saline in the stomach was much less, only 23% of strain gauge clusters were associated with CCPWs and 35% associated with flow. The number of undulations of the baseline tension per cluster remained the same throughout the study (2.2±0.19 in the first 15 minutes *versus* 2.4±0.20 in the second 15 minutes).

Sensitivity of Manometry

In the first 15 minutes, comparison of strain gauge and manometric recording in over 50 waves showed an almost perfect relationship between gastric CCPWs and episodes of wall motion recorded by the corpus strain gauge. Time independent representation of force (strain gauge) *versus* pressure changes (manometry) forms a hysteresis suggesting a different detection speed between strain gauge and manometry (Figure 17.3.3c). The onset of wall motion was first recorded by the strain gauge; hence the first half of the ascending part of the hysteresis curve was horizontal. Once the contraction was detected by manometry, there was a good correlation (r=0.67) between

manometry and strain gauge recordings. In the antrum, peak values were recorded first by strain gauge and then 1.2 (±1.1) seconds after, by manometry. The descending arm of the hysteresis curve was a symmetrical image of the ascending part.

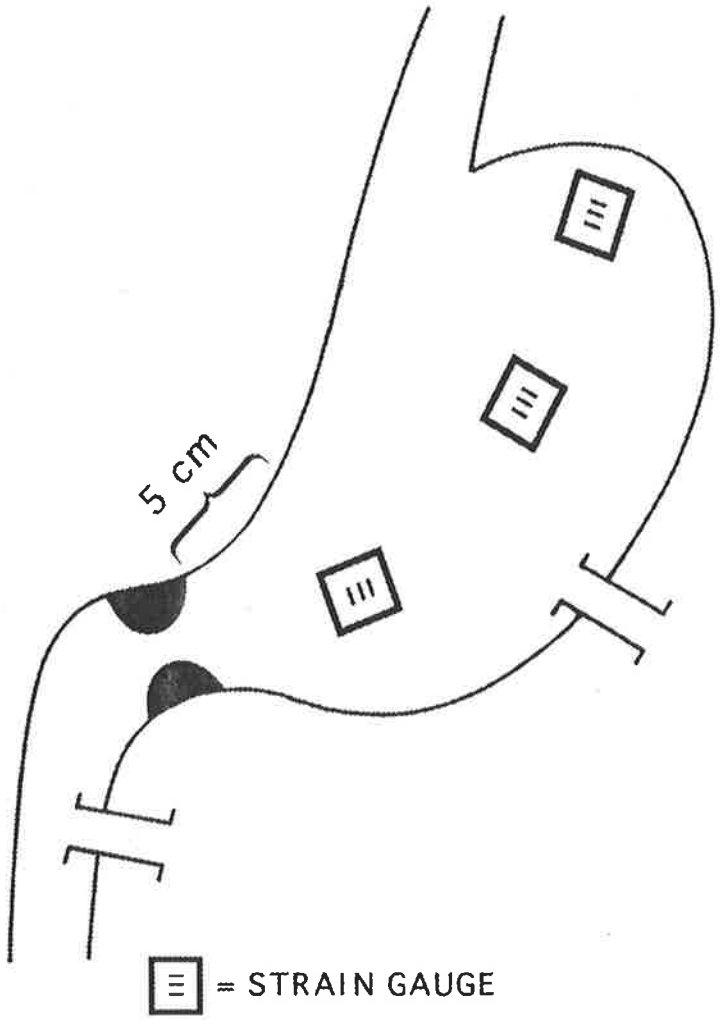


Figure 17.3.2: Location of strain gauges on the stomach of the Kangaroo Island pigs. The strain gauges were 10-12 cm apart and the most distal strain gauge was 5 cm proximal to the pylorus.

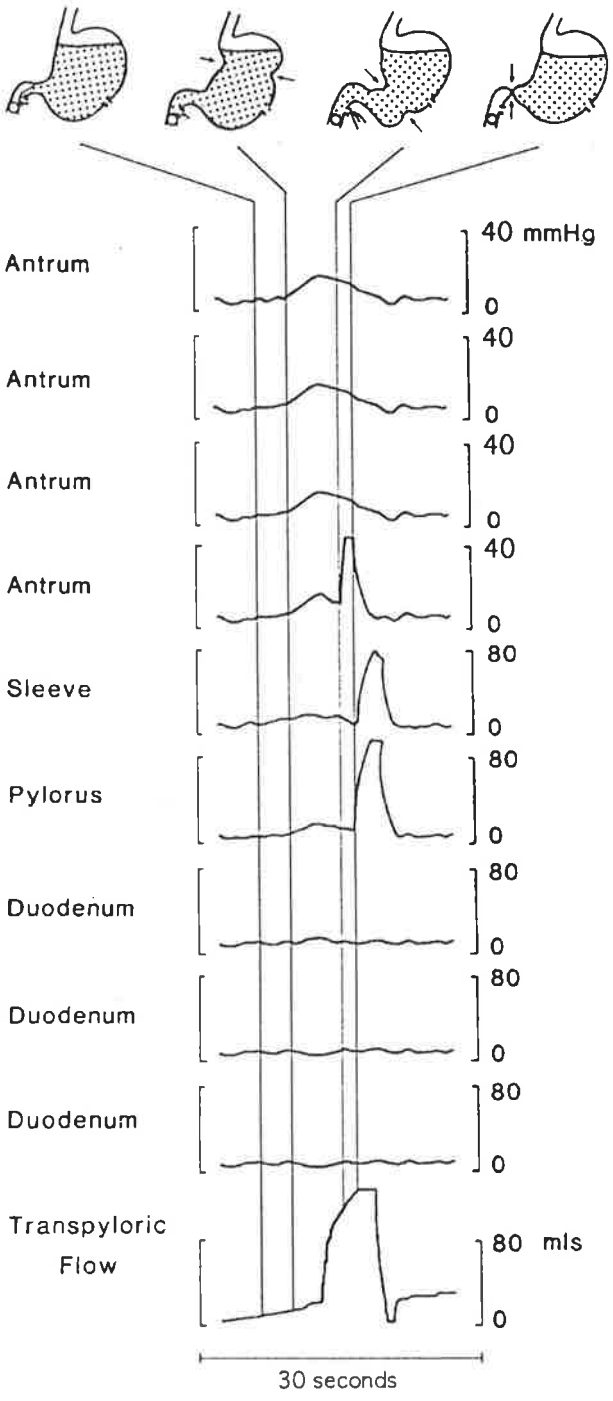


Figure 17.3.3a: Manometric recording of antral CCPW in association with constriction of the gastric wall recorded radiologically.

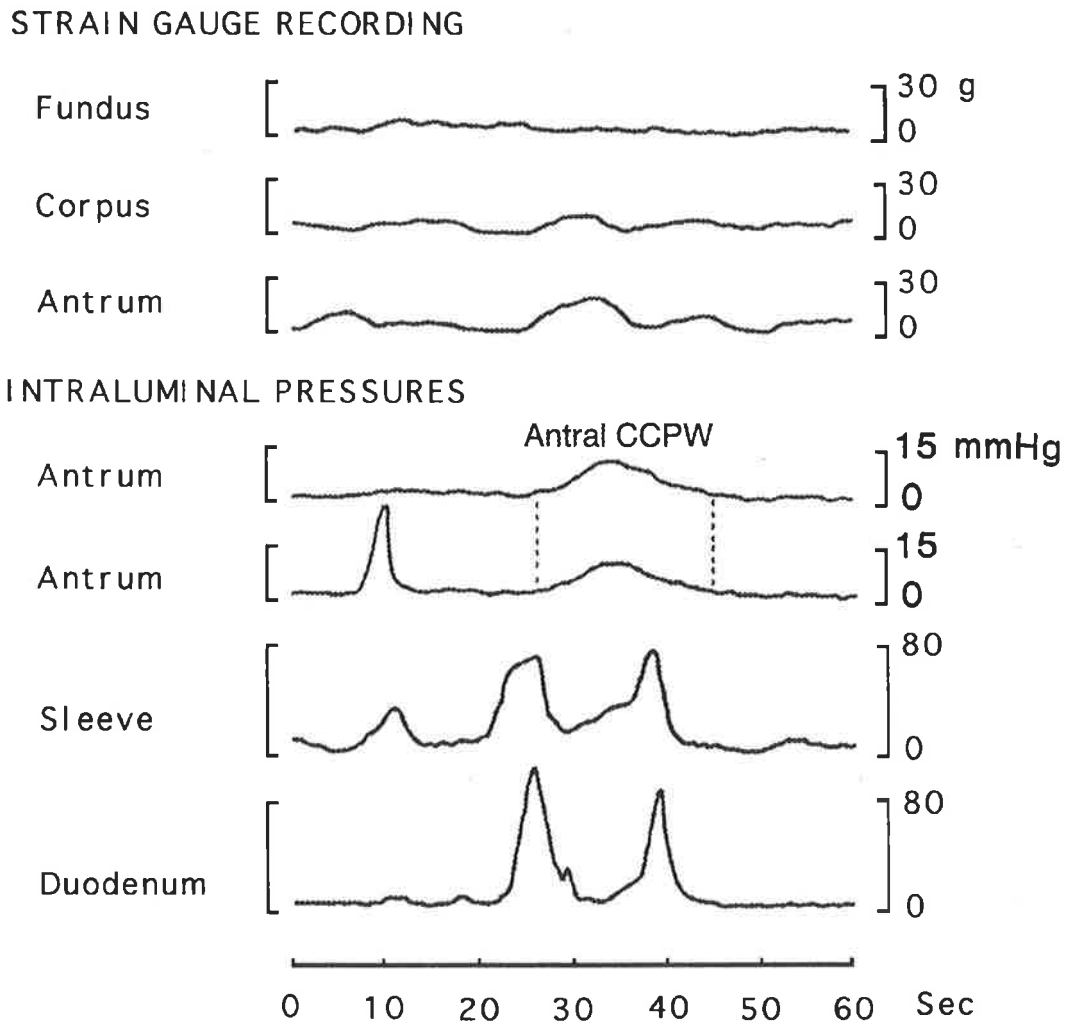


Figure 17.3.3b: The strain gauge recording of an antral CCPW produced by non-lumen occlusive contraction of the stomach.

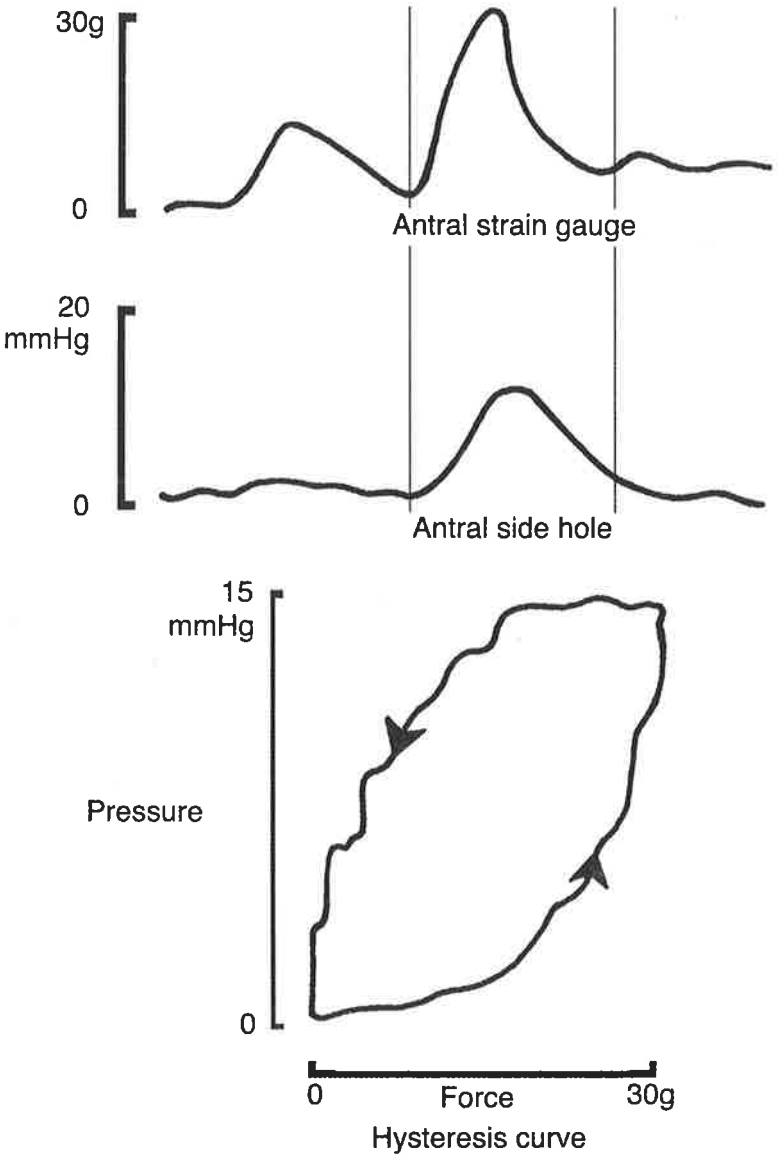


Figure 17.3.3c: Hysteresis in force (strain gauge recordings) versus pressure changes (manometric assessments).

Table 17.3.3: Comparison of strain gauge and manometry in detection of contractions at the corpus area.

	0 - 15 min	**15 - 30 min**
number of clusters per 15 min (Strain gauge)	**13.2** ± 2.21	**7.5** ± 2.3*
number of antral CCPWs per 15 min (Manometry)	**11.5** ± 2.66	**1.7** ± 1.75*

Values are given as mean ± SE, * $p<0.05$

17.3.4 Discussion

Our observation of the consistent relationship of pulsatile transpyloric flow to the subtle but characteristic pressure pattern of the antral CCPW focused our attention on mechanical events in the stomach around this time. The fluoroscopic studies established that antral CCPWs only occurred when the gastric cavity was being indented by a non lumen-occlusive contraction wave as it passed towards the distal antrum. Fluoroscopy also differentiated between contractions which produced antral CCPWs, starting in the gastric body or upper antrum, and shorter antropyloric contractions which did not produce antral CCPWs. These contractions originated in the mid or distal antrum, consistent with strain gauge data.

The concept of pressurization of a fluid-filled cavity by a non lumen-occlusive propagated contraction has been illustrated in studies on the oesophageal body by Mittal *et al* (1990). With fluid in the oesophagus, and the distal oesophagus obstructed, oesophageal body common cavity pressure waves occurred when an advancing oesophageal body peristaltic contraction failed to occlude the lumen. This model aids understanding of what appears initially to be a paradox - that is, generation of a synchronous, identical pressure pattern within the lumen by a truly peristaltic contraction. In the case of the stomach, this is a normal mode of functioning. Awareness of this will allow more effective interpretation of gastric motor function through intraluminal pressure recordings.

The stroke volume of non-lumen-occlusive pumping is not limited to the volume that is trapped distal to a lumen-occlusive contraction traveling aborad, and therefore, it has the capacity to expel large volume pulses from the stomach, as shown in the last series

of studies (Chapter 17.2). The analysis of the impact of gastric volume shows that this method of pumping is most important at relatively high gastric volumes. Presumably a greater degree of gastric filling gives greater potential for phasic pressurization of the entire gastric lumen by a propagating, constricting contraction. It should be noted though, that this mechanism of gastric pumping occurs well within the normally encountered physiological range of gastric volume seen in pigs, since we have observed that pigs will readily drink volumes in excess of one liter within a very short time interval.

The fluoroscopic observations made concurrently with manometry, were limited in scope by major technical factors. Most importantly, we had access only to a mobile x-ray unit, and correct positioning of the pigs relative to the C-arm of the x-ray machine required them to be elevated in their frames with a hydraulic jack. The need to study the animals when conscious also limited the scope of the imaging. However, the observations that were made were sufficient to determine the relationships among gastric wall motion, gastric lumen occlusion by contraction and transpyloric flow.

17.3.5 Conclusions

This study demonstrated that manometry can record pressure events caused by non-lumen occlusive gastric contractions. However, it should be emphasized that in the stomach, manometry does not measure wall motion and thus the use of incorrect terminology (like 'contraction') in describing manometric events should be avoided. The ability of manometry to register non-lumen occlusive contractions as pressure waves is dependent on the transmission of intraluminal pressures to the sideholes/sleeve by a fluid medium. Therefore, its accuracy in detecting changes in wall motion of the corpus and proximal antrum when the stomach is almost empty, is poor. Fluoroscopy or strain

gauges are better suited than manometry to assess the gastric wall motion (tension) in the corpus and proximal antrum under these conditions.

Chapter 18

Influence of Posture on Gastric Distribution, Motility and Emptying

18.1 INTRODUCTION

In considering gastric emptying of non-nutrient liquids, the importance of gravity in relation to active "pumping" and "braking" mechanisms has not been clarified. It has been suggested that the effects of gravity on gastric emptying are "passive" - being influenced by gastric configuration (Jonderko 1987) and affecting the pressure gradient across the gastroduodenal junction as a result of redistribution of ingesta from the proximal to the distal stomach, rather than related to changes in gastric motility (Hunt *et al* 1965, Moore *et al* 1988).

Atropine inhibits antral contractions (Cattau *et al* 1984, Harada *et al* 1981), reduces fundic tone (Harada *et al* 1981) and slows gastric emptying (Chernish *et al* 1978, Rashid *et al* 1990), and also abolishes the stimulatory effect of intraduodenal nutrients on pyloric motility (Fone *et al* 1989, Fraser *et al* 1992). Evaluation of the effects of posture on gastric emptying, both before and after atropine, could therefore clarify the mechanisms by which gravity affects gastric emptying. In particular, it could determine whether modifications in posture are associated with alterations in active gastric "pumping" or "braking" mechanisms, or changes in intra-gastric distribution.

The aim of the current study was to examine the effects of posture on intra-gastric distribution and antropyloroduodenal motor function after ingestion of a non-nutrient drink, both before and after administration of atropine.

18.2 METHODS

18.2.1 Subjects

Studies were performed in 7 healthy volunteers (four women : three men) with a median age of 21 years (range 18 -28).

18.2.2 Experimental Procedure

Concurrent measurements of antropyloroduodenal manometry and gastric emptying were performed in each subject on two separate days, one with the subject sitting and the other while in the left lateral decubitus position. In each position, 150 ml radio-labeled saline (0.9 M) was consumed within 30 seconds. After all the saline had emptied from the stomach (75-150 min after the first drink), a further drink of 150 ml radio-labeled saline (0.9 M) was given. Each subject was asked to stand for 30 min prior to ingestion of the second drink which was consumed 5 minutes after intravenous atropine sulphate (4 mcg/kg) had been given as a bolus into an antecubital vein. Gastric emptying was again monitored for 30 minutes after the second drink. Pulse rates were measured every 5 minutes, before and after atropine. Both drinks were ingested during phase I of the MMC cycle (Houghton *et al* 1988b), and the order of the study days was randomized.

Manometry

Antropyloroduodenal motility was measured with a ten-lumen sleeve/sidehole manometric catheter using techniques described in Chapter 13.

Measurement of gastric emptying

Measurement of gastric emptying was carried out using previously described techniques (Chapter 14). The first drink was labeled with 20-24 MBq of ^{113m}In diethylenetriamine penta-acetic acid (DTPA), and the second with 20-24 MBq of ^{99m}Tc sulphur colloid. Counts were taken at 30 second intervals and stored on computer for later analysis.

18.2.3 Data Analysis

Manometric Tracings

Pressure waves were scored if their amplitude was greater than or equal to 10 mmHg (Heddle *et al* 1988a). As in all studies, a minimum of 13% of the liquid remained in the stomach at 30 minutes after the first drink. Over the 30 minute period immediately following consumption of each drink, the following were calculated:

i. number of pressure waves subdivided according to their pattern

ii. mean basal pyloric pressure (pyloric tone) in relation to basal antral pressure, for each minute (Heddle *et al* 1988a)

Gastric distribution and emptying

From the emptying curves, the following parameters (Chapter 14) were derived for subsequent statistical analysis:

i. lag phase

ii. the 50% emptying times for the proximal (proximal T_{50}) and total (total T_{50}) stomach

iii. the time for 30% of the liquid to empty from the total stomach (T_{30})

iv. the relative intragastric distribution of liquid between proximal and distal stomach at the time when 30% of the liquid had emptied.

Statistical analysis

Data are expressed as median values and interquartile ranges, and were evaluated using the Wilcoxon signed rank test. A p-value of less than 0.05 was considered statistically significant in all analyses.

18.3 RESULTS

All subjects tolerated the study well. After atropine, there was an increase of 5.5 (range: 4.0 - 7.0) beats/min in heart rate which lasted for 5-10 minutes. No volunteer reported dryness of mouth or blurring of vision after atropine.

Before atropine

In the sitting position, the lag phase, the proximal T_{50}, and total T_{50} were all significantly less than in the left lateral position ($p<0.05$) (Table 18.3a). At 30 minutes, 31% (range: 13-61) of the liquid meal remained in the stomach. The relative intragastric distribution of liquid between proximal and distal stomach at the time when 30% of the liquid had emptied was not significantly different between sitting and decubitus positions.

There were significantly more long antropyloric ($p<0.05$) and isolated pyloric pressure waves ($p<0.05$) in the sitting position than in the left lateral position (Table 18.3b). The total number of antropyloric waves was also greater in the sitting position, but this

difference did not quite achieve statistical significance ($p=0.07$). Pyloric tone was also higher ($p<0.01$) in the sitting position.

After atropine

Atropine slowed total stomach emptying in both postures ($p<0.05$) (Table 18.3a), but did not affect relative intragastric distribution. After atropine, gastric emptying was still faster ($p<0.05$) in the sitting than in the decubitus position.

In the sitting position the number of antropyloric pressure waves ($p<0.05$), long antropyloric pressure waves ($p<0.05$) and pyloric tone ($p<0.01$) decreased after atropine (Table 18.3b). The mean decrease in the number of isolated pyloric pressure waves was not statistically significant. In the decubitus position, atropine had no effect on the number of pressure waves or pyloric tone (Table 18.3b). After atropine, there was no difference in antral or pyloric motility between the two postures.

Table 18.3a: Gastric emptying in sitting and left lateral positions, before and after atropine. Data are given as median values (and inter quartile ranges) for 30 min.

	lag period (min)	proximal T_{50} (min)	total T_{50} (min)	P/D ratio at T_{30}
sitting	**0.5**	**1.0**	**14.0**	**0.7**
	(0.12-2.0)	(0.5-1.0)	(11.5-18.7)	(0.3-0.8)
sitting + atropine	**0.5**	**1.0**	**18.0 #**	**0.4**
	(0-1.3)	(0.6-2.0)	(13.5-63.7)	(0.2-0.6)
lying	**7.0 ***	**4.0***	**28.0 ***	**0.4**
	(4.6-10.5)	(1.2-9.5)	(19.7-45.5)	(0.3-0.6)
lying + atropine	**3.0**	**5.0**	**35.0 #**	**0.5**
	(2.0-3.7)	(2.2-8.7)	(34.0-55.5)	(0.3-0.5)

* $p<0.05$ compared with sitting, # $p<0.05$ compared to before atropine

Table 18.3b: Number of antropyloric (APPW) and localized pyloric (IPPW) pressure waves and the pyloric tone for first 30 minutes after each drink in the sitting and left lateral positions, before and after atropine. Data are given as median values (and inter quartile ranges) for 30 min.

	total APPWs no/30min	**long APPWs** no/30min	**IPPWs** no/30min	**pyloric tone** (mmHg)
sitting	**10.0** (6.7-11.7)	**3.0** (2.0-4.7)	**36.0** (27.0-52.7)	**4.0** (1.5-7.0)
sitting + atropine	**0 #** (0-4.2)	**0 #** (0-0)	**19.0** (13.5-54.5)	**2.5 #** (1.5-4.0)
lying	**4.0** (2.2-11.7)	**0 *** (0-0.7)	**17.0 *** (8.2-20.0)	**3.0 *** (1.0-5.0)
lying + atropine	**4.0** (0.5-9.7)	**1.0** (0.2-1.0)	**20.0** (12.5-37.5)	**2.0** (0.5-6.0)

* $p<0.05$ compared with sitting, # $p<0.05$ compared to before atropine

18.4 DISCUSSION

This study adds to the knowledge of the mechanics of emptying of non-nutrient liquids from the stomach. In particular, it has demonstrated for the first time that the effects of gravity on gastric emptying are associated with significant modifications in antropyloric motility.

It has been suggested that the effects of posture on gastric emptying of non-nutrient liquids are secondary to passive changes in intragastric meal distribution, rather than changes in gastric motility (Burn-Murdoch *et al* 1980). We observed that the faster emptying of saline in the sitting position was associated with increases in the number of long antropyloric and isolated pyloric pressure waves and pyloric tone. Long, antropyloric pressure waves appear to be important in gastric expulsion of liquids, while isolated pyloric pressure waves and pyloric tone prevent transpyloric flow (Chapter 17, Treacy *et al* 1992). These observations support the concept that gastric mechanical activity does not simply control intragastric distribution or outflow, but is itself influenced by them. It may be expected that changes in gastric configuration also interact with gravity in determining intragastric distribution. The previous observations that posture influences the rate of intragastric distribution of liquids (Burn-Murdoch *et al* 1980) is not unexpected. It seems probable that these effects are primarily due to gravity rather than changes in gastric motility, particularly as the postural effect on intragastric distribution was not altered by atropine, which reduces gastric tone (Harada *et al* 1980). The fact that the ratio between proximal and distal counts did not change in different postures, despite the more rapid emptying in sitting position, suggests that as the liquid meal is redistributed from the proximal to distal stomach, it stimulates gastric "pumping" mechnaisms which propel the distally added

fraction out of the stomach, thus maintaining a relatively constant ratio between the portions of the meal present in the proximal and distal stomach.

Previous studies in humans (Oberle *et al* 1990, Rees *et al* 1979a) and dogs (Gleysteen & Gohlke 1979) indicate that ingestion of non-nutrient liquids in volumes less than 200 ml, does not alter the fasting pattern of gastric motility. However, we have shown that despite giving the saline drinks during phase I of the migrating motor complex, 150 ml of saline stimulated antropyloric pressure waves, particularly in the sitting position. The greater stimulation of antral pumping mechanisms in the sitting position could be a response to earlier and greater antral distension caused by position-dependent redistribution of the gastric content.

As would be expected, atropine inhibited motor activity of the antrum, and slowed gastric emptying in both postures (Cattau *et al* 1983, Chernish *et al* 1978, Harada *et al* 1981, Rashid *et al* 1990). However, even after atropine, liquid emptying was faster in the sitting position when compared to the left lateral position, despite the absence of any differences in antropyloroduodenal motility between the two postures after atropine. While it is possible that the effects of atropine on proximal gastric tone are modified by posture, these observations support the concept that gravity, per se, also influences emptying of liquid from the stomach. Our study design cannot exclude an "order effect," *i.e.* atropine was, by necessity, always given before the second drink. The possibility of such an effect occurring appears unlikely.

We did not predict the increased number of isolated pyloric pressure waves and higher basal pyloric tone observed during conditions of rapid gastric emptying in the sitting position. Previous studies have shown that isolated pyloric pressure waves and an

increase in pyloric tone result in closure of the pyloric lumen and retardation of transpyloric flow (Chapter 17.1). It is likely that the increased frequency of isolated pyloric pressure waves and the higher basal tone observed, resulted from stimulation of small intestinal mechanoreceptors (Edelbroek *et al* 1994) to prevent overdistension of the duodenum, which would occur as a result of excessive transpyloric flow. This concept is supported by previous studies demonstrating that distension of the duodenum stimulates isolated pyloric pressure waves and increases pyloric tone in both animals (Treacy 1991) and humans (Edelbroek *et al* 1994). The effects of posture on gastric emptying of non-nutrient liquids would, therefore, likely be greater if it were not for this control mechanism. The observations in this study are likely to apply to more normal "meals" *i.e.* solids and nutrient liquids and larger volumes, but the influence of gravity is likely to be modified by the triggering of other control mechanisms.

18.5 CONCLUSIONS

The faster emptying of non-nutrient liquids in different postures is not simply due to the action of gravity. Posture may influence the rate of intragastric distribution of a liquid meal, which in turn effects gastric motility and emptying of the meal.

Section E

Studies on Control of Gastric Motility and Emptying

Chapter 19

Effect of Division of Intramural Nerves on Antropyloric Motility, Transpyloric Flow and Gastric Emptying

19.1 INTRODUCTION

Propagated, non-lumen-occlusive gastric contractions are major contributors to pulsatile transpyloric flow in a fluid distended stomach. The volume of pulsatile gastric outflow associated with gastric contractions is related to normal variation of the interval between the onset of the low amplitude gastric common cavity pressure wave (CCPW), produced by the non-lumen-occlusive phase of a gastric contraction sequence, and the onset of the lumen-occlusive pyloric pressure wave associated with the same contraction sequence (Chapter 17.3).

The relationship of flow patterns of the gastric content to the timing of closure of the pylorus relative to contraction of the antrum, has received limited attention (Cannon 1898, Carlson *et al* 1966, Treacy *et al* 1990). In particular, the mechanism(s) which modulate(s) variation in the relative timings of antral CCPWs and gastric contraction-induced pyloric lumen occlusion is unknown; intramural neural pathways are the most plausible mechanism. The existence of descending inhibitory intramural pathways between the antrum and the duodenum has been demonstrated by antral transection in anaesthetized dogs (Allescher *et al* 1988). The physiological roles of these pathways

remain to be evaluated, but these could include modulation of the timing of pyloric contractions relative to the antrum.

Ascending, excitatory intramural pathways between the duodenum and the pylorus have also been demonstrated (Allescher *et al* 1988). It has been postulated that these pathways are important in the stimulation of pyloric motor function by nutrients within the duodenum. Duodenal nutrient receptors also inhibit antral and fundic motor activity (Azpiroz & Malagelada 1986, Heddle *et al* 1988b & 1988c, Treacy *et al* 1990) suggesting the possibility that antral intramural nerves may play a role in the duodenal regulation of gastric motor activity.

This study was designed to investigate two proposed physiological roles for antral intramural nerves: i) the control of pulsatile gastric emptying by modulation of the timing of pyloric closure, and ii) the suppression of antral motility by duodenal nutrient receptors.

19.2 METHODS

19.2.1 Surgical preparation

Five Kangaroo Island pigs (40 - 45 Kg) underwent studies before and after antral transection. The first set of studies, conducted prior to transection, was done after a recovery period of 6 weeks following the insertion of cannulae. The animals then underwent a second operation, 10-12 weeks after their initial preparation. This involved the complete transection of the antrum, 2 cm proximal to the pylorus, with re-anastomosis, in an end-to-end fashion, using single layer interrupted 2-0 Vicryl sutures and without resection of any gastric tissue. The second set of studies, post-transection, were done after a further 6 week recovery period.

19.2.2 Experimental procedure and recordings

Details of the experimental protocol and recording techniques for concurrent measurements of antropyloric pressures, transpyloric flow and gastric emptying, after instillation of 1000 ml of saline into the stomach, have been described (Chapters 13 & 14).

Each pig underwent two sets of studies before and after antral transection. The protocol was identical in the two sets of studies, except that the 5 ml/minute intraduodenal infusion was normal saline in one set of studies and 25% dextrose in the other. The order of study of the different duodenal infusates was randomized.

19.2.3 Data analysis

Analysis of transpyloric flow and manometric pressure waves followed previously described criteria (Chapters 13 & 14).

19.2.4 Statistical analysis

The values are given as means ± S.E. of the mean. One-way analysis of variance was used to compare the group means; differences were considered significant if $p < 0.05$.

19.3 RESULTS

19.3.1 Intraduodenal infusion of saline

Gastric emptying

Compared to pre-transection, antral transection was associated with a significant reduction in the percentage of saline meal which emptied over 30 minutes (36% post-transection versus 62% before transection, $p<0.05$). The time patterns of emptying are shown in Figures 19.3.1a and 19.3.1b. Post-transection, the volume of flow pulses was reduced by more than half (8.6±0.4 compared with 18.7±1.5 pre-transection, $p<0.05$). However, transection produced no significant effect on the number of flow pulses recorded over 30 minutes (24.4±3.2 pre-transection compared to 22.0±4.0 post-transection). Thus, the reduced volume of transpyloric flow pulses (Figure 19.3.1b) accounted for the observed reduced emptying, since non-pulsatile emptying was not significantly changed by antral transection (Figure 19.3.1c).

Changes in gastric and pyloric motility and the impact on emptying

Transection did not alter the number of antral CCPWs (Table 19.3.1a). Notably though, transection was associated with a significantly shorter duration of the first phase of CCPWs (Figure 19.3.1d). This alteration was associated with a reduced volume of the flow pulses associated with antral CCPWs. These results are presented in Table 19.3.1a.

The shorter interval between CCPW onset and occlusion of the pyloric lumen was not associated with any changes in the total duration of CCPWs in the upper antrum, above the region in which contraction sequences resulted in lumen occlusion (15.8± 0.4 seconds pre-transection compared to 14.4 ± 0.4 seconds post-transection). Thus, the effect of the transection was to move the timing of pyloric closure within an unchanged pattern of occurrence of antral CCPWs.

Transection was also associated with a decrease in the number of non CCPW-related distal antropyloric pressure waves ($p<0.05$), and an increase in the number of isolated pyloric pressure waves, ($p< 0.05$) (Figure 19.3.1e). The number of flow pulses that occurred independently of CCPWs was unchanged after transection. The mean volume of CCPW independent flow pulses was numerically smaller post-transection; this reduction approached statistical significance ($p=0.07$) (Table 19.3.1b).

19.3.2 Intraduodenal infusion of 25% dextrose

Antral transection had no effect on the potent retardation of emptying associated with intraduodenal infusion of dextrose (Figure 19.3.2), with the majority (97% and 96%) of the meal still remaining in the stomach after 30 minutes pre and post-transection respectively.

Transection also did not alter the dextrose-induced stimulation of IPPWs (2.6±0.12 compared with 2.5±0.38 pre-transection). The dextrose-induced abolition of antropyloric pressure waves and antral CCPWs was also unaffected by transection.

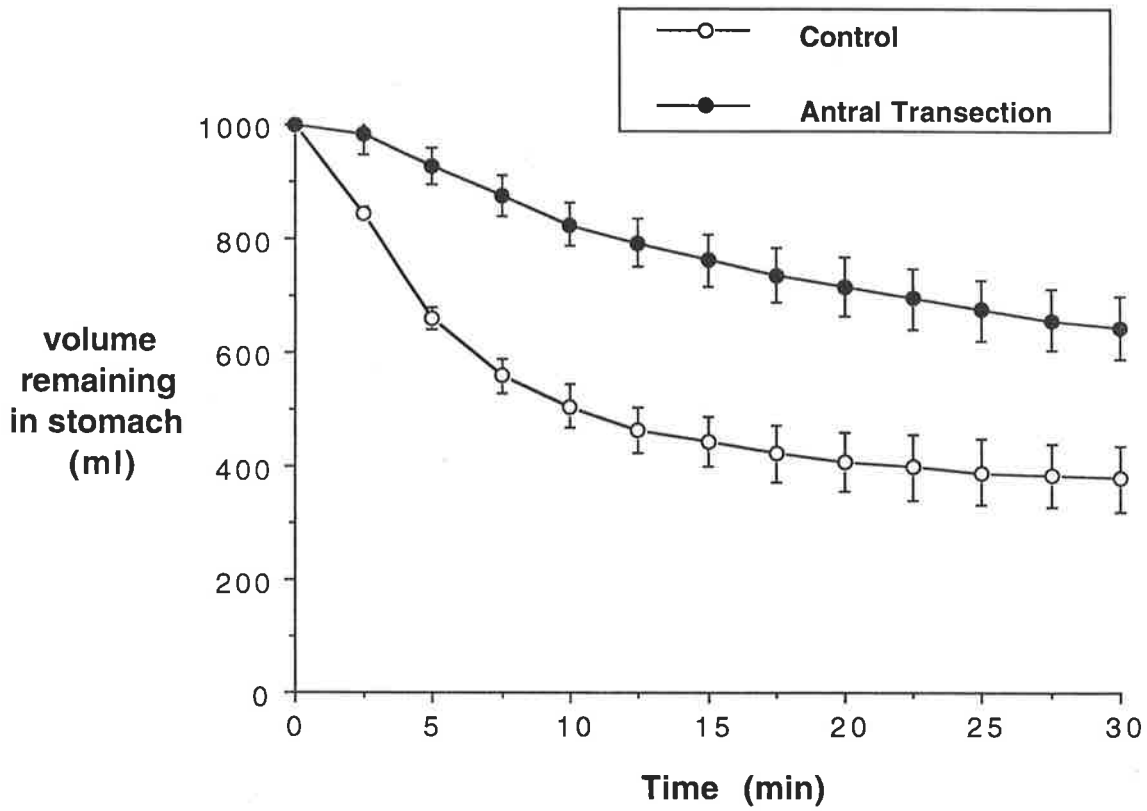
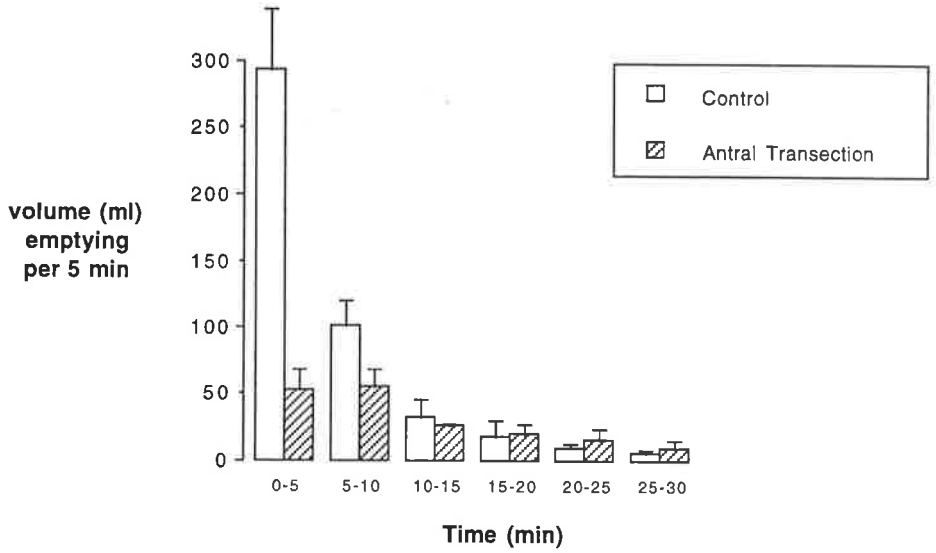


Figure 19.3.1a: Gastric emptying of one litre of saline before and after antral transection, with intraduodenal infusion of saline.

19.3.1a: Pulsatile Emptying



19.3.1b: Non pulsatile Emptying

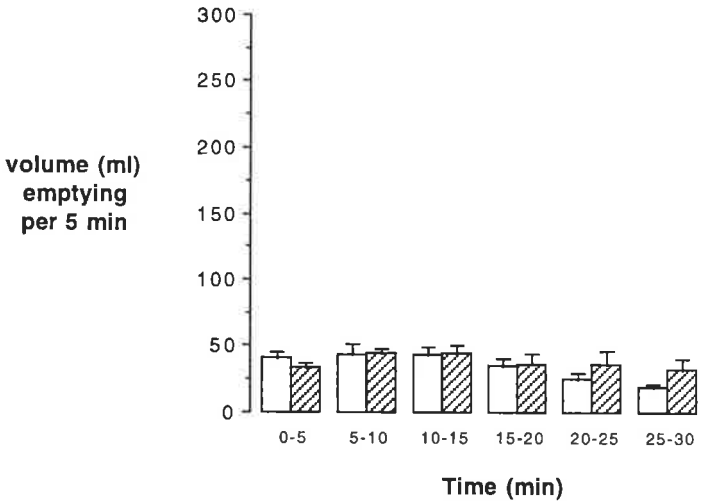


Figure 19.3.1b&c: Volume of pulsatile (19.3.1b), and non pulsatile (19.3.1c) gastric emptying for the first 30 minutes after instillation of one litre of normal saline into the stomach.

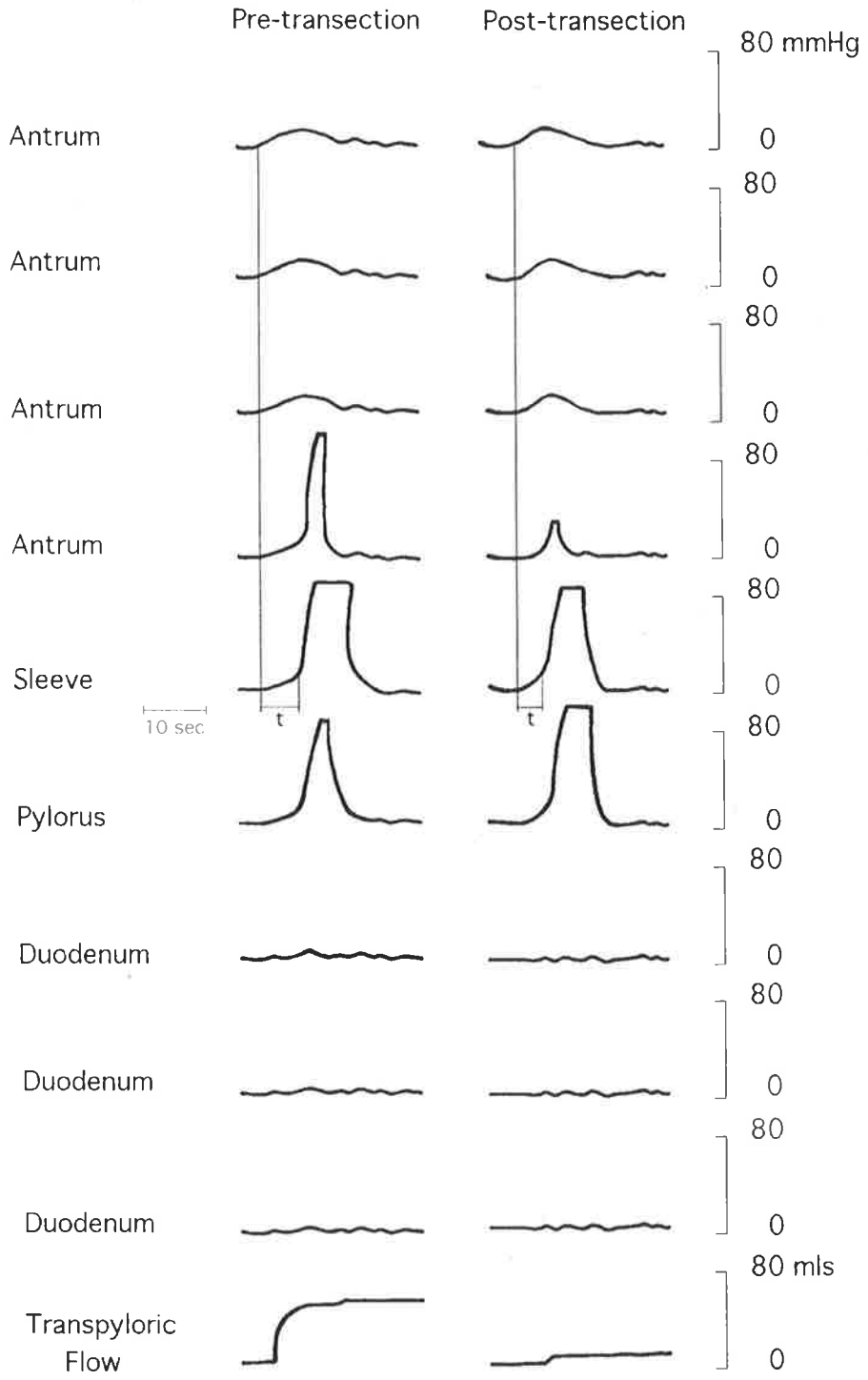


Figure 19.3.1d: Manometric presentation of an antral common cavity wave recoreded before and 6 weeks after antral transection. There is considerable shortening of the first phase of CCPW **(t)** post-transection, with a resultant drop in pulsatile flow.

Table 19.3.1a: Summary of antral CCPWs and the attendant flow pulses before and after antral transection

	Control	Antral Transection
number of CCPW/pig/30min	**14** ± 1.3	**16** ± 3.4
duration of CCPW (sec)	**15.8** ± 0.4	**14.4** ± 0.4
duration of first phase of CCPW (sec)	**7.9** ± 0.6	**3.2** ± 0.3*
volume of flow pulse/CCPW (ml)	**25.9** ± 2.7	**9.0** ± 0.6*

Values are given as mean ± S.E, * indicates a statistical difference ($p < 0.05$)

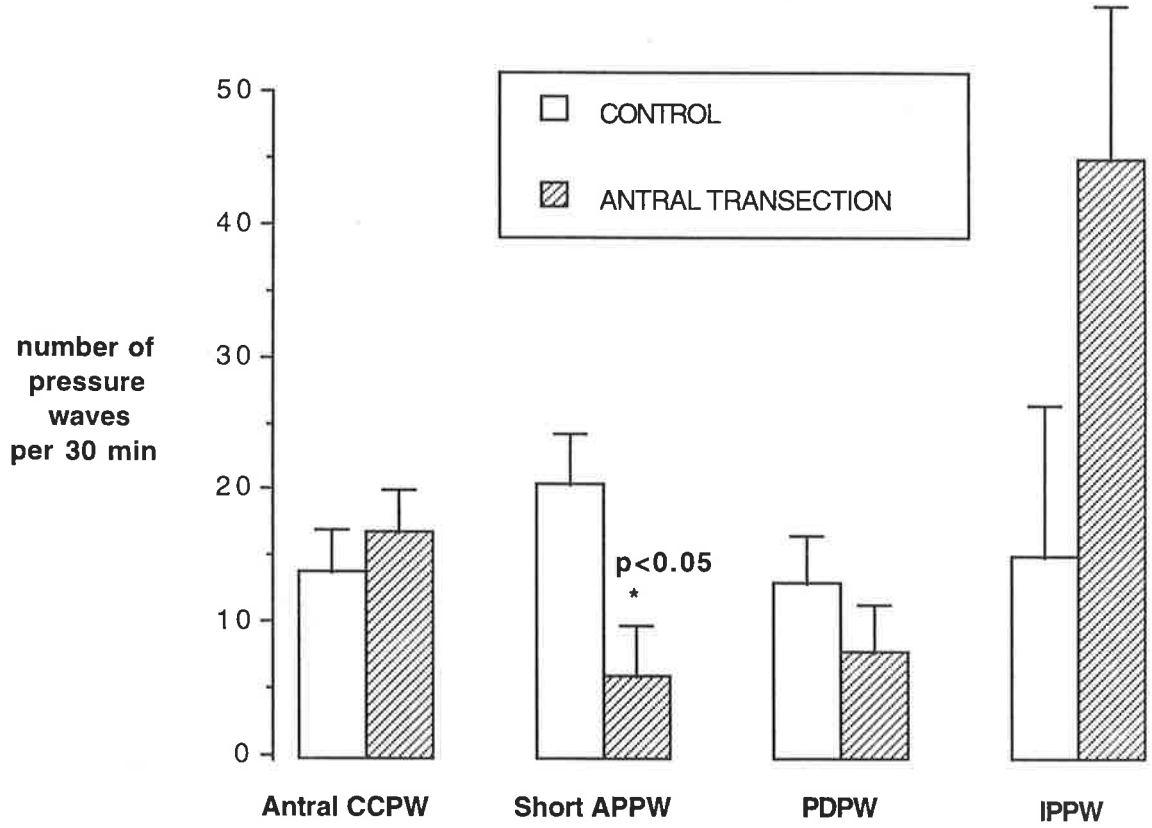


Figure 19.3.1e: Frequency of different pressure waves for the first 30 minutes during emptying of the saline meal.

Table 19.3.1b: Non CCPW-associated flow pulse parameters before and after antral transection

non CCPW-associated flow pulses	**Control**	**Antral Transection**
number/pig/30 min	**12.4**±3.8	**14**±3.6
volume of flow pulses (ml)	**11.9**±1.2	**8.5**±0.5

Values are given as mean ± S.E, no significant difference detected.

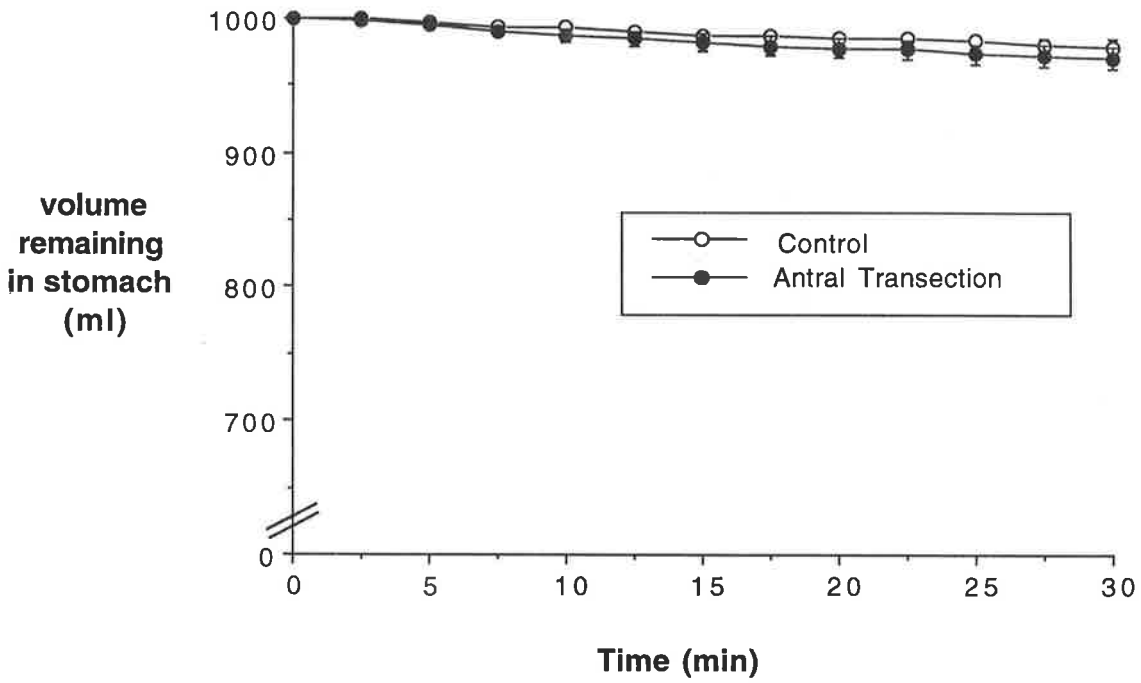


Figure 19.3.2: Gastric emptying of one litre of saline before and after antral transection during intraduodenal infusion of 25% dextrose.

19.4 DISCUSSION

These data indicate that antral intramural pathways have a substantial influence on the timing of the onset of pyloric lumen occlusion, relative to the onset of antral common cavity pressure waves. Concurrent measurements of transpyloric flow have demonstrated that the shortening of this interval, which we have termed the first phase of CCPW, is associated with substantial reduction of the volume of individual pulses of transpyloric flow. There is a resultant reduction of total pulsatile emptying to less than half of the control value. These studies have also explored the physiological importance of ascending intramural pathways to the antrum, and have shown that duodenal nutrient-induced suppression of antral motility persists, despite division of ascending intramural pathways from the duodenum. This shows that other pathways are involved in the major changes of gastric motility produced by duodenal nutrients.

With motility and gastric outflow recorded concurrently, antropyloric contractions were shown to have a very close temporal association to pulses of outflow. This study has shown that, although pulses of emptying are associated with phasic contractions, not all such contractions cause gastric outflow. The volume of flow pulses and the time interval between them varied substantially. This implies that the mechanics of individual antropyloric contractions varies considerably, presumably under the influence of gastric motor control mechanisms. Neural mechanisms are the most likely control; acute physiological studies have revealed the existence of several intrinsic and extrinsic neural mechanisms that have potent effects on gastric motility (Allescher *et al* 1988). The present study is one of the few that has investigated the physiological contribution of one of these demonstrated mechanisms, intramural nerve pathways. The data show that division of these neural pathways just above the pylorus has potent effects on the timing

of pyloric contraction relative to gastric body/antral contraction, more than halving the interval between pressurization of the antral cavity by non-lumen occlusive contraction and pyloric closure. The concurrent monitoring of gastric outflow has demonstrated the potent reduction of pulsatile outflow which occurred as a result of this intervention.

It is not a new concept that there is substantial variation in the timing of pyloric closure relative to more proximal gastric contraction (Cannon 1898, Carlson *et al* 1966), but attention has shifted from study of this variable to other aspects of gastric motor function. The methods used in the present study allowed us to correlate motor events to transpyloric flow relatively precisely. Our findings emphasize the importance of evaluating the temporal relationships among contractions and occurrence of lumen occlusion among different sites in the stomach. It appears likely that the variability of mechanical outcome of individual phasic gastric contractions depends on normal variation of these relationships.

It is unlikely that the effects on the timing of pyloric closure reported in the present study could be due to any factor other than division of intramural neural pathways. Our method of transection ensured that vagal supply to the pylorus was preserved. In acute studies in dogs, it was demonstrated that descending inhibitory neural pathways travel to the pylorus via both intramural pathways in the antrum and via the vagus (Allescher *et al* 1988). Electrical field stimulation of intramural nerves in the mid-antrum was shown to inhibit pyloric contraction. Allescher *et al* (1988) showed that these pathways traveled intramurally, as antral transection distal to the field stimulating electrodes abolished the inhibitory effects on the pylorus. Given our results, it appears that intramural pathways are of major importance in controlling the timing of pyloric closure. Our studies did not address the factors that generate and control the inhibitory

signals that travel to the pylorus via the antral intramural pathways. Candidate mechanisms include indirect effects from vagal inputs entering the gastric wall at a higher level and influencing the intrinsic nervous system, and the modulatory influences of gastric intramural sensory mechanisms and their connections. Such sensory mechanisms include mechanoreceptors, and possibly mucosal afferent receptors and motor programs present within the enteric nervous system.

Out of necessity, the experimental approach oversimplified the control systems that are normally active during emptying. In order to be able to interpret the influence of antral intramural nerves, we standardized conditions in the small intestine, thus minimizing the potent modulatory influences of intestinal feedback mechanisms (Gregory *et al* 1989, Treacy *et al* 1990 & 1992). Accordingly, the volume loading of the small intestine was controlled for by constant infusion of normal saline into the distal duodenum beyond the duodenal cannula. Normal saline was chosen to avoid production of feedback effects on the stomach from the small intestine due to osmotic or caloric stimulation (Gregory *et al* 1989, Treacy *et al* 1990 & 1992). Therefore, the described observations relate solely to gastric functioning in the absence of any nutrient or osmotic stimulus to the distal duodenum and small intestine. Future studies are needed to explore the interaction of selective sectioning of nervous pathways involved in the control of gastric motility and emptying, not only during emptying of non-nutrient material, but also during normal digestion and absorption.

This study was also designed to test the effects of interrupting ascending neural pathways from the duodenum to the antrum. Many studies have shown that small intestinal nutrient receptors have a potent inhibitory effect on antral motor function (Heddle *et al* 1988b & 1988c, Treacy *et al* 1990). There is evidence for mediation of these effects

both via vagal neural pathways as well as through hormone release (Mei 1983, Allescher 1990). There is also evidence for involvement of ascending neural pathways from the duodenum to the pylorus (Treacy *et al* 1992). The finding in the present study that antral transection had no detectable influence on the inhibition of antral motility by small intestinal nutrient loading, suggests that ascending intramural neural pathways are relatively unimportant in the mediation of this effect. This conclusion needs to be qualified, since it is possible that potent effects of antral transection on inhibiting antral feedback might have been revealed with lower rates of nutrient delivery to the small intestine. Unfortunately, it was not feasible to undertake dose response studies in the present series of experiments.

Advances in the understanding of normal and disordered gastric emptying have been hampered by inadequate understanding of gastric mechanics and the way that control mechanisms modulate them. Most correlations of gastric motility with gastric emptying have not attempted to separate the different patterns of sequencing of lumen-occlusion due to gastric contractions, despite the knowledge that some gastric contractions expel little, if any, of the gastric content. Our findings suggest that substantially more progress will be made if recording methods are used that are capable of recognizing differing mechanical patterns of phasic gastric contraction, and analysis of contractions is based on concurrent second to second monitoring of transpyloric flow. These approaches will allow better evaluation of the modulation of the mechanics of individual sequences of gastric contractions, and exploration of underlying control mechanisms. Better understanding of delayed gastric emptying is likely to result from the recognition of the possibility that defective control of the sequencing of pyloric lumen occlusion may be a cause of abnormal emptying in its own right. This possibility does not of course,

exclude the likelihood that slow emptying also results from defects in triggering gastric contraction sequences and impairment of gastric muscle contractile function.

19.4 CONCLUSIONS

In pigs, descending antral intramural neural pathways play an important role in controlling transpyloric flow, by regulating the timing of pyloric closure in relation to the associated gastric contraction. Antral intramural nerves are not essential for the inhibition of antral motor function by duodenal osmoreceptors during high rates of small intestinal glucose delivery.

Chapter 20

Role of CCK Mechanisms in Control of Gastric Motility and Emptying

20.1 INTRODUCTION

There is considerable evidence that cholecystokinin (CCK), which is released in response to ingestion of nutrient meals containing fat or protein, is important in the regulation of postprandial gastric motility and gastric emptying. Intravenous infusions of exogenous CCK analogues (CCK_8 or CCK_{33}) slow gastric emptying, decrease proximal gastric tone and antral contractions, and stimulate pyloric contraction. The specific CCK receptor antagonist, loxiglumide, has been reported to accelerate gastric emptying of liquid and solid test meals in humans, although its effects on gastric and pyloric motility is still not determined.

The aim of this study was to evaluate the role of a CCK dependent-mechanism in the effects of intraduodenal fat infusion on gastric motility and gastric emptying.

20.2 METHODS

20.2.1 Animal preparation

A combination of sleeve/sidehole manometry and transpyloric flow measurement was used to evaluate the effect of loxiglumide on the changes in antropyloric motility and gastric emptying associated with intraduodenal fat infusion.

Studies were done in four pigs (40-45 kg) equipped with chronic gastric and duodenal cannulae. Venous access was obtained via a silastic intravenous cannula, which was inserted into the jugular vein and brought out at the back of the animal through a subcutaneous tunnel. The intravenous cannula was flushed daily with a solution of heparinized saline (10 ml of 100 units/ml) to maintain its patency.

20.2.2 Experimental protocol

Either normal saline or oleic acid soap (13.9 g/l, 0.12 kcal/ml) was initially infused into the distal duodenum via the Foley catheter at 5 ml/min, and continued until the end of the study. Fifteen minutes after the commencement of the intraduodenal infusion, 1000 ml of labeled saline was instilled into the stomach. Recordings of antropyloroduodenal motility and transpyloric flow and gastric emptying were made for 20 minutes after instillation of saline into the stomach.

Each pig underwent three studies separated by 2 days. The studies were done in randomized order and were completed twice in each pig.

Study 1: intraduodenal infusion of saline (control)

Study 2: intraduodenal infusion of oleic acid

Study 3: intraduodenal infusion of oleic acid with intravenous loxiglumide.

Intravenous loxiglumide (Rotta Research Laboratories, Monza, Italy) was given initially as a bolus of 30 mg/kg over 10 minutes, starting 15 minutes before intraduodenal infusion of oleic acid, followed by an intravenous infusion of 10 mg/kg/hr for the remainder of the study. Loxiglumide infusion was prepared by dissolving the drug in sterile saline at a concentration of 2 grams per litre.

20.2.3 Recordings and analysis

Antropyloroduodenal pressure waves, transpyloric flow and gastric emptying were measured and analyzed according to previously described techniques (Chapters 13 & 14).

20.2.4 Statistical analysis

Data are shown as mean values ± S.E.M. Repeated-measures ANOVA was used to assess underlying variation between the three test conditions, and the Newman-Keuls test was used to determine critical values indicating significant differences among the three conditions (corrected alpha levels were 0.05).

20.3 RESULTS

The catheter was positioned correctly, according to predefined criteria for the transmucosal potential difference (Treacy et al, 1983), for more than 98% of the recording time. The loxiglumide was well tolerated by the animals without any apparent untoward effect.

20.3.1 Gastric emptying and transpyloric flow

With intraduodenal infusion of saline (control), total liquid emptying over 20 minutes ranged between 353-761 ml with a mean of 57.1±6.8 % emptying. Of the total emptying, 82±1.1% occurred as pulsatile transpyloric flow and the remainder as nonpulsatile flow (Table 20.3.1).

Oleic acid infusion versus saline infusion

Infusion of oleic acid into the duodenum was associated with marked retardation ($p<0.05$) of gastric emptying, when compared to the intraduodenal saline infusion

(Figure 20.3.1). Only 4.2±0.5 % of the saline emptied from the stomach during intraduodenal oleic acid infusion. The slower gastric emptying was associated with reductions in both the number ($p<0.05$) and volume ($p<0.05$) of transpyloric flow pulses (Table 20.3.1).

There was a significant reduction in the non-pulsatile emptying rate with oleic acid infusion compared to saline (Table 20.3.1). However, during oleic acid infusion, nonpulsatile emptying was the principle pattern of transpyloric flow, accounting for 98.1±1.6% of the emptying observed compared to 17.8±1.1% during saline infusion.

Effect of intravenous loxiglumide

Intravenous loxiglumide prevented the retardation of gastric emptying produced by oleic acid (Figure 20.3.1) so that emptying became comparable to that seen during intraduodenal infusion with saline. After loxiglumide and during intraduodenal oleic acid infusion, both the volume and number of flow pulses were greater ($p<0.05$), when compared to intraduodenal oleic acid alone. The volume of flow pulses was also greater after loxiglumide than intraduodenal saline ($p<0.05$). Nonpulsatile transpyloric flow during oleic acid infusion was also increased by pre-medication with loxiglumide ($p<0.05$), reaching similar volumes to that during intraduodenal saline infusion. Table 20.3.1 shows these results.

20.3.2 Gastric and pyloric motility

Oleic acid infusion versus saline infusion

Infusion of the oleic acid was associated with stimulation of isolated pyloric pressure waves (IPPWs) ($p<0.05$) and reductions in the number of gastric CCPWs ($p<0.05$),

antropyloric (APPW) ($p<0.05$) and pyloroduodenal (PDPW) pressure waves ($p<0.05$) when compared to intraduodenal saline (Table 20.3.2).

Effect of intravenous loxiglumide

During loxiglumide infusion, there was a reduction in the number of IPPWs ($p<0.05$) and an increase in the number of gastric CCPWS ($p<0.05$) and antropyloric waves ($p<0.05$), when compared to oleic acid alone (Table 20.3.2). When compared to intraduodenal saline, there were fewer gastric CCPWS ($p<0.05$) after loxiglumide, but no difference in the number of APPWs, IPPWs and PDPW waves (Table 20.3.2).

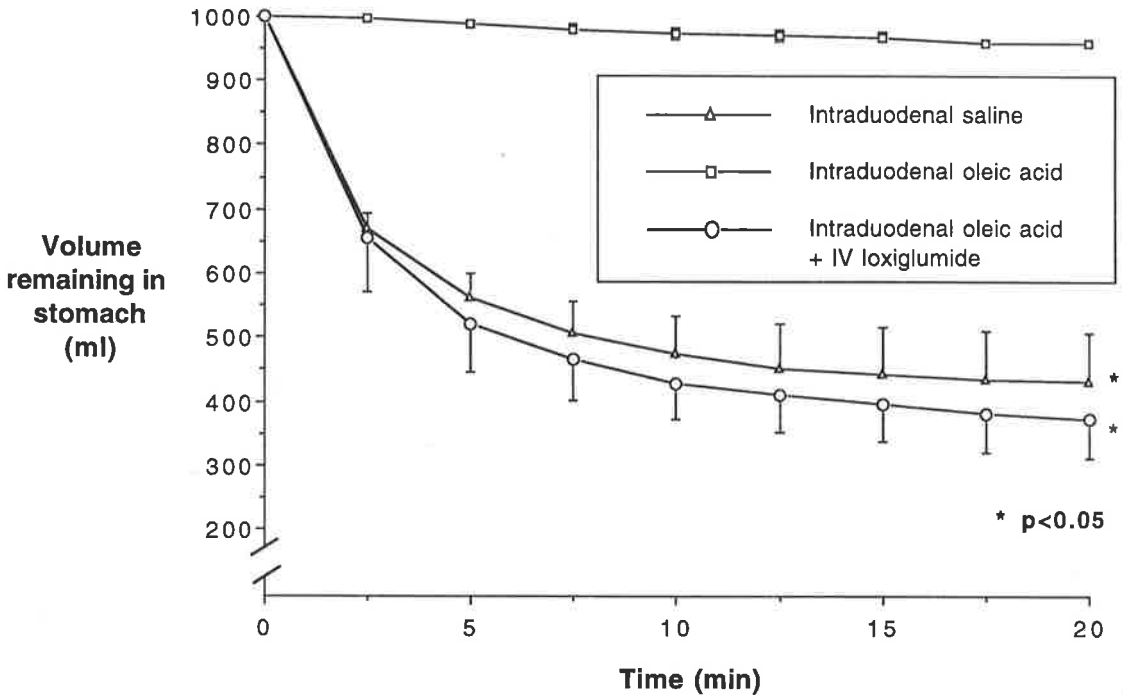


Figure 20.3.1: Effect of oleic acid and loxiglumide on gastric emptying of 1000 ml of normal saline.

Table 20.3.1: Values for overall emptying of saline meal, and the number and volume of flow pulses in the three test conditions.

values per 20 min	**intraduodenal saline**	**intraduodenal oleic acid**	**intraduodenal oleic acid+IV loxiglumide**
amount of meal emptied (%)	**57.1**±6.8	**4.2**±0.5*	**62.8**±6.1#
volume of pulsatile emptying (ml)	**468.7**±69.2	**1.0**±1.0*	**493.2**±67.5#
volume of non-pulsatile emptying (ml)	**101.6**±8.7	**41.2**±6.4*	**134.6**±6.8#
number of flow pulses	**15.8**±1.4	**0.5**±0.3*	**13.0**±1.3#
volume of flow pulses (m l)	**29.0**±2.4	**4.0**±0.0*	**37.3**±3.4* #

mean ± SE, * p<0.01 cf intraduodenal saline, # p<0.01 cf intraduodenal oleic acid.

Table 20.3.2: Number of different pressure waves under the three test conditions.

values per 20 min	**intraduodenal saline**	**intraduodenal oleic acid**	**intraduodenal oleic acid+IV loxiglumide**
antropyloric pressure waves	**23.7**±2.9	**1.1**±0.5*	**22.0**±5.5#
isolated pyloric pressure waves	**12.8**±2.8	**38.0**±5.9*	**17.6**±2.4#
antral common cavity waves	**14.5**±1.9	**1.0**±0.4*	**7.5**±0.4*#
pyloroduodenal pressure waves	**9.8**±1.9	**0.8**±0.6*	**7.0**±1.7#

mean ± SE, * $p<0.05$ cf intraduodenal saline, # $p<0.05$ cf intraduodenal oleic acid.

20.4 DISCUSSION

The results of our study indicate that the effects of intraduodenal oleic acid on gastric emptying and antropyloric motility in the pig are mediated by CCK-dependent mechanisms.

It has been suggested that cholecystokinin is an important mediator of the changes in gastric motility and emptying associated with ingestion of fatty meals (Chapter 6). The CCK antagonists, loxiglumide and L364,718 (later termed MK-329) prevent the retardation of gastric emptying by exogenous CCK infusion (Fried *et al* 1991b) and accelerate the emptying of meals containing fat, protein or glucose in humans (Fried *et al* 1991b, Ricci Maccarini *et al* 1991) and animals (Green *et al* 1988, Forester *et al* 1990). The effect of these competitive CCK antagonists have been shown to be dose dependent (Malesci *et al* 1990). Furthermore, pre-medication with these antagonists may be necessary for them to be effective (Lloyd *et al* 1992). The dose of loxiglumide used in our study has been shown to increase gastric emptying of fat-containing meals in dogs (Niederau *et al* 1991) and humans (Ricci Maccarini *et al* 1991, Schmidt *et al* 1991). Infusion of loxiglumide was started 15 minutes before the intraduodenal infusion of oleic acid in an attempt to ensure reliable blockade of peripheral CCK receptors. The effects of loxiglumide appear to be specific on the CCK mechanisms, as gastric emptying of meals that do not release CCK, such as saline (Green *et al* 1988) or guar (Fried *et al* 1991b) is not affected by loxiglumide and other specific CCK antagonists .

Intraduodenal infusion of oleic acid inhibited antral motility, stimulated localized pyloric contractions with associated near total abolition of pulsatile transpyloric flow

and a decrease in non-pulsatile flow. Administration of loxiglumide essentially reversed these changes, strongly supporting the hypothesis that endogenous CCK has a major role in mediating the effects of intraduodenal oleic acid on antropyloric motility and gastric emptying in pigs.

Our results are consistent with previous observations that report that exogenous CCK_8 inhibits antral and stimulates pyloric motor activity (Fraser *et al* 1993, Isenberg & Csendes 1972, Phaosawasdi & Fisher 1982).

In this study, loxiglumide resulted in patterns of motility and transpyloric flow which were similar to those observed with intraduodenal saline, but there were some differences. The greater volume of non-pulsatile emptying with loxiglumide compared to saline, may reflect a reduction in gastric outlet resistance, an increase in proximal gastric tone, or both of these. However, it should be recognized that, in view of the small number of experiments, the significance of these minor differences is uncertain. Studies in Chapter 17, have demonstrated that pulsatile transpyloric flow of liquids in pigs is related to propagated contractions of the stomach, originating in the corpus. These contractions are registered manometrically as common cavity pressure rises within a distended stomach. The sensitivity of manometry to record these low amplitude pressure ramps is related to intragastric volume, as well as distal resistance. The diminished number of gastric CCPWs recorded after loxiglumide in comparison to intraduodenal saline is somewhat surprising, but may reflect the technical difficulties in recording these pressure waves because of a reduction in distal resistance.

The mechanism by which CCK influences gastric and pyloric motor function is unclear. Based on results obtained in rats, Forester *et al* (1990) suggested that the initial site of

action of CCK on the corpus and antrum is on primary afferent neurons that are also gastric mechanoreceptors, and that this causes activation of an inhibitory vago-vagal reflex pathway, which leads to relaxation of the body of the stomach. This theory was supported by the observation that atropine completely abolished the CCK effect on antral smooth muscle, and the fact that CCK infusion led to gastric hypomotility rather than increased motility, which is the expected effect of direct action of CCK on antral smooth muscle.

20.5 CONCLUSIONS

In pigs, CCK pathways are important in the retardation of gastric emptying induced by delivery of fats into the small intestine. This is an important physiological control which can be blocked by use of a specific CCK antagonist. This may have important clinical implications in the treatment of patients with idiopathic gastroparesis.

Section F

Effect of Therapeutic Gastric Surgery on Stomach Motility and Emptying

Chapter 21

Pattern of Antropyloroduodenal Motor Activity during Gastric Emptying of a Mixed Meal after Therapeutic Gastric Operations

21.1 INTRODUCTION

Gastric surgical procedures which involve resection, denervation or division of muscle lead to major disturbances in gastric emptying of solids and liquids and can be associated with unwanted symptoms such as dumping or bloating. Although studies have shown the patterns of gastric emptying following various gastric surgical procedures, limited direct comparison has been made between changes in gastric emptying and gastric motor function. This study investigated the changes in antropyloroduodenal motor activity which may contribute to changes in the normal pattern of gastric distribution and emptying seen after three common anti-ulcer procedures.

21.2 METHODS

21.2.1 Subjects

Four groups of patients and volunteers were studied:

Group 1: Seven healthy volunteers **(CONTROL)** (2 female : 5 male, with mean age of 24 , range: 21-30) with no previous history of gastrointestinal symptoms.

Group 2: Six patients (2 female: 4 male, with mean age of 43, range: 20-58) who had undergone Highly Selective Vagotomy **(HSV)** for peptic ulcer disease, at least 1 year prior to study (mean: 3.8 years, range: 2-6 yrs).

Group 3: Six patients (all male with mean age of 57, range: 33-67) who had undergone Truncal Vagotomy and Pyloroplasty **(TV&P)** for peptic ulcer disease, at least 1 year prior to the study (mean: 2 years, range: 1-7 yrs).

Group 4: Five patients (3 female: 2 male, with mean age of 47, range 31-58) who had undergone Truncal Vagotomy and Antrectomy **(TV&A)** for peptic ulcer disease, with either Billroth I or Billroth II reconstruction at least 1 year prior to the study (mean: 4 years, range: 2-5 yrs).

Recruitment of patient volunteers for groups 2,3 and 4 was extremely difficult, as many patients refused to take part in the studies which took an average of eight hours to complete and involved nasal passage of the manometric catheter. As a result, the proposed goal of 10 patients for each group could not be realized.

21.2.2 Study protocol

Antropyloroduodenal motility was measured with a 10-lumen sleeve/sidehole catheter, for 3 hours, during emptying of 100g of ^{99m}Tc-labeled beef and 150ml of ^{113m}In-labeled dextrose (10%) drink.

21.2.3 Recordings and data analysis

The measurement and analysis of gastric emptying and antropyloroduodenal manometry followed previously described techniques (Chapters 13 & 14). The positioning of the

manometric catheter across the pylorus was more difficult and often took longer in HSV and TV&P patients. Studies in two HSV patients and three TV&P patients had to be aborted as the positioning took too long (>5 hours) and the patients were unable to continue.

Symptoms ascribable to abnormal gastric motor function, such as dizziness or bloating, were recorded.

21.2.4 Statistical analysis

Values are given as median and interquartile ranges. A Mann-Whitney U test was used to compare the data between the three surgical groups and the controls (healthy volunteers).

21.3 RESULTS

21.3.1 Gastric emptying

Liquid drink

The half emptying times of the dextrose drink are given in table 21.3.1a. Those were significantly faster in the HSV ($p=0.04$) and TV&P ($p=0.003$) groups as compared to the controls. The median Total T_{50} for the liquid drink in the TV&A group was extremely variable, and not significantly different from controls ($p=0.2$). There was no significant difference in proximal gastric emptying and overall retention at 170 minutes among the four groups (Table 21.3.1a).

Solid meal

There was a shortening (p=0.05) of the lag phase in the TV&P group as compared to controls, while the lag phase in the other two surgical groups was not significantly different from controls. Solid gastric emptying, measured as percent retention at 100 minutes, was faster in the TV&P group as compared to controls (p=0.04), but the percent retention at 170 minutes did not differ from control subjects (p=0.2) (Table 21.3.1b). The percent retention at 170 minutes in the HSV and TV&A groups was not statistically different from controls (Table 21.3.1b).

21.3.2 Antropyloric motility

Manometrically, the only difference between the four groups was the reduced number of antropyloric pressure waves observed in the TV&P and TV&A groups which only reached statistical significance in the TV&A group (p=0.04) (Table 21.3.2). Patients with TV&A in whom the distal antrum and pylorus had been removed did not exhibit IPPWs, but the rate of IPPWs in the other two surgical groups was not significantly different from the controls, including TV&P patients in whom the pylorus had been surgically altered. There were no significant difference in the extent of APPWs observed in the four groups.

Table 21.3.1a: Emptying of liquids in healthy volunteers and patients with HSV, TV&P and TV&A.

	Proximal stomach T_{50} (min)	Total stomach T_{50} (min)	Total Stomach % Retention at 170 minutes
Healthy	**1.0** (0.5-4.5)	**22.0** (22.0-53.0)	**7.0** (3.0-7.5)
HSV	**2.0** (0.0-3.0)	**14.5*** (12.0-19.0)	**9.5** (7.8-11.3)
TV&P	**1.5** (1.0-4.0)	**6.3*** (4.1-13.6)	**6.0** (2.0-8.5)
TV&A	**1.5** (0.0-3.0)	**15.5** (1.8-37.0)	**9.0** (5.5-11.5)

Values shown are median (interquartile ranges). HSV: highly selective vagotomy; TV&P: truncal vagotomy and pyloroplasty; TV&A: truncal vagotomy and antrectomy. *$p<0.05$ using the Mann-Whitney U test.

Table 21.3.1b: Emptying of solids in healthy volunteers, and patients with HSV, TV&P and TV&A.

	Lag period	Proximal Stomach T_{50}	Proximal stomach % retention at 170 min	Total Stomach % retention at 100 min	Total Stomach % retention at 170 min
Healthy controls	**60.0** (35.8-76.4)	**52.0** (14.8-84.3)	**4.5** (1.0-15.0)	**71.5** (44.0-94.5)	**25.0** (3.0-26.0)
HSV	**60.0** (53.0-80.0)	**59.0** (38.0-76.0)	**5.0** (2.0-19.3)	**73.0** (70.0-88.0)	**33.5** (17.8-59.5)
TV&P	**29.0*** (14.0-48.5)	**26.5** (5.8-54.0)	**2.3*** (2.0-3.6)	**35.0*** (15.0-51.5)	**8.5** (2.2-10.5)
TV&A	**39.0** (9.5-119.5)	#	#	**64.0** (24.0-87.5)	**39.0** (6.5-91.0)

Values shown are median (interquartile ranges). HSV: highly selective vagotomy; TV&P: truncal vagotomy and pyloroplasty; TV&A: truncal vagotomy and antrectomy. *$p<0.05$ using the Mann-Whitney U test. # signifies an inadequate sample size.

Table 21.3.2: Number of pressure waves per minute for 180 minute duration of study in the four groups.

	IPPW *per minute*	**APPW** *per minute*	**PDPW** *per minute*
Healthy	**0.47**	**0.79**	**0.15**
	(0.18-0.68)	(0.47-1.01)	(0.08-0.64)
HSV	**0.34**	**0.78**	**0.33**
	(0.21-0.64)	(0.29-0.76)	(0.11-0.59)
TV&P	**0.65**	**0.59**	**0.41**
	(0.11-0.65)	(0.45-0.82)	(0.21-0.50)
TV&A		**0.12***	**0.64**
		(0.04-0.57)	(0.27-0.64)

Values shown are median (interquartile ranges) for 180 minutes. IPPW: isolated pyloric pressure wave; APPW: antropyloric pressure wave; PDPW: pyloroduodenal pressure wave; HSV: highly selective vagotomy; TV&P: truncal vagotomy and pyloroplasty; TV&A: truncal vagotomy and antrectomy.

*$P<0.05$ using the Mann-Whitney U test.

21.4 DISCUSSION

Due to time limitations and difficulty in recruitment of patient volunteers, the initial goal of 10 subjects in each group could not be realized. The small size of the study groups limits the scope of the correlations that can be made between disturbance in patterns of emptying and loss of different gastric motor mechanisms, but the data obtained do support some of our earlier observations in pigs and on healthy volunteers.

As expected, patients with highly selective vagotomy and truncal vagotomy and pyloroplasty exhibited faster liquid emptying. This is believed to be a result of vagal denervation of the proximal stomach with resultant increase in gastric tone. Concurrent measurement of gastric tone could not be made during this study due to technical limitations of recording techniques available. A second series of experiments is required to measure gastric tone in these patients.

Loss of the pyloric control mechanism may also contribute to the faster rate of liquid emptying observed in TV&P group. The increased speed by which liquids empty from the stomach is believed to be the primary cause of dumping syndrome in post-surgical patients. None of our patients however, experienced symptoms of dumping after the test meal. This may be, in part, due to the relatively small volume and low sugar concentration (Kaushik *et al* 1982) of the liquid drink used.

The patients with truncal vagotomy and distal gastrectomy exhibited a wide variation in the rate of liquid emptying. This is consistent with findings of other investigators (Wittebol *et al* 1988), and may be due to a different compensatory response to the loss of several control mechanisms, namely, increased gastric tone due to vagotomy, reduced

gastric pumping due to antrectomy and vagotomy, and loss of the pyloric control mechanism. A larger volume of liquids may have produced a different result.

Truncal vagotomy and pyloroplasty was associated with a shorter lag phase and faster emptying of solids as compared to the other three groups. Loss of the pyloric "braking" mechanism may be an important contributory factor, although the number of isolated pyloric pressure waves was not significantly different from the controls. It remains to be established how effective isolated pyloric pressures waves are in resisting transpyloric flow after pyloroplasty.

The TV&A subjects, which would also be expected to possess higher gastric tone due to truncal vagotomy, and in whom the pyloric mechanism is totally removed, did not exhibit a faster rate of solid emptying than the control subjects. This may be due to loss of the antral pumping mechanism. We have previously (Chapter 7.3) shown that the corpus of the stomach is also capable of generating phasic contractions which can propel food out of stomach. But, in patients with TV&A, this mechanism could not compensate adequately for the loss of the antrum, with reduced number of propagated gastric waves being observed as compared to the patients with TV&P. It is possible, however, that the sensitivity of the manometric assembly to measure non-lumen occlusive phasic contractions in the corpus may have been affected by the presence of a mixed meal in the stomach. The propagated pressure waves recorded in the gastric remnant of TV&A patients were scored as APPWs, although to be technically correct, they should have been called differently.

The patients with highly selective vagotomy demonstrated emptying parameters which resembled controls values more closely than the other two surgical groups. A relative

preservation of antropyloric motor activity that closely resembled the controls, may be a primary reason for this.

Posture and gravity will be expected to have a major role in the rate of gastric emptying in patients with TV&P and TV&A, in whom the pyloric "braking" mechanism has been altered or removed. This effect was not examined in this study, but warrants future evaluation.

21.5 CONCLUSIONS

The stomach functions as a complex pump. Its function can be altered by various surgical procedures. Of the three surgical procedures studied, highly selective vagotomy is associated with the least disturbance in antropyloric motor function and exhibits the least amount of disturbance in gastric emptying patterns. This is likely the primary factor in the smaller incidence of postoperative symptoms of dumping or bloating reported in various series (Goligher 1978, Jamieson 1983). This procedure should be considered as the operation of choice in treatment of patients with peptic ulcer disease, even though the recurrence rate of ulcers in this group is reported by some series (Jamieson 1983) to be higher than the other two groups.

Chapter 22

Gastric and Pyloric Motor Response to Intraduodenal Lipid Infusion after Vagotomy and Pyloroplasty

22.1 INTRODUCTION

Infusion of lipids into the duodenum is associated with stimulation of isolated pyloric pressure waves and pyloric tone, suppression of phasic antral contractions, a reduction in proximal gastric tone, and retardation of gastric emptying (Chapter 7.1, Heddle *et al* 1988c, Azpiroz & Malagelada 1986). The rapid emptying of nutrient liquids observed after vagotomy and pyloroplasty, which can lead to dumping syndrome, may be, in part, due to loss of pyloric control mechanism which is capable of contributing to the regulation of the rate of delivery of nutrients into the small intestine. The aim of this study was to evaluate whether the intraduodenal infusion of lipids could stimulate isolated pyloric contractions in patients with TV&P, and whether the pylorus is capable of providing any resistance to flow of ingesta across it during liquid emptying, following pyloroplasty.

22.2 METHODS

22.2.1 Subjects

Five male patients between ages of 33 and 67 yrs, who had had vagotomy and pyloroplasty at least 1 year (range: 1-7 yrs) prior to the time of study.

22.2.2 Study protocol

Gastric emptying of a 150ml ^{113m}In-labeled 10% dextrose drink was measured, in a sitting position, both before (control period) and during duodenal infusion of 10% Intralipid (1.5 ml/min). Concurrent measurements of antropyloroduodenal pressures were made with a 10-lumen sleeve/sidehole catheter.

The two drinks were given at least 3 hours apart, ensuring that the first drink had completely emptied from the stomach and the proximal small bowel before the ingestion of second drink. The duodenal infusion of Intralipid was commenced 15 minutes prior to the ingestion of the second drink.

22.2.3 Recordings and data analysis

The measurement and analysis of gastric emptying and manometry followed previously described techniques (Chapters 13 & 14). The same radio-label was used in both drinks as the length of time between drinks ensured complete evacuation of the first drink from the stomach and proximal intestine. There were no problems with radiolabelling of overlapping bowel from the first drink, during testing of the second.

The pyloric tone was averaged for the first 30 minutes after each meal. The numbers of the different pressure waves were also counted over the same time intervals.

22.2.4 Statistical analysis

Values are given as medians and interquartile ranges. Wilcoxon signed rank test was used to compare the data between the two conditions.

22.3 RESULTS

Intraduodenal infusion of lipid was associated with stimulation of isolated pyloric pressure waves but not pyloric tone (Table 22.3). It also caused suppression of antral pressure waves, although this did not reach statistical significance ($p=0.07$).

Despite stimulation of IPPWs during lipid infusion, the rate of liquid emptying was not altered from the control period (Table 22.3).

Table 22.3 Manometric and emptying parameters before (control) and after lipid infusion.

	CONTROL	LIPID INFUSION
T_{50} liquid emptying (min)	6.2 (5-13)	6.2 (2-17)
Pyloric tone (mmHg)	0.5 (0-2.1)	0.3 (0-2.5)
Isolated pyloric pressure waves /30 min	1 (0-5)	17.5* (6-18)
Antropyloric pressure waves/30 min	13.5 (6-22)	5 (4-32)

Values are given as medians (inter quartile range), * $p<0.05$.

22.4 DISCUSSION

These results suggest that stimulation of isolated pyloric pressure waves by duodenal chemoreceptors is not mediated *via* the vagus nerve, and is probably primarily *via* the intrinsic intramural pathways (Treacy *et al* 1992), and the humoral mechanisms (Chapter 6 & 20). Failure of development of pyloric tone during lipid infusion may be caused by the deformity of the pylorus due to pyloroplasty, and may be partly responsible for the failure of lipid infusion to retard the emptying of liquids in these patients. Furthermore, despite the stimulation of IPPWs by intraduodenal lipids, no retardation of liquid emptying was observed in the TV&P patients. This suggests that either IPPWs without pyloric tone are not obstructive to transpyloric flow, or that pyloroplasty disturbs the effectiveness of IPPW in breaking the flow of ingesta across the pylorus.

Partial suppression of antral motility by lipid infusion suggests that other mechanisms, in addition to vagal pathways, are involved in this important regulatory mechanism. Studies in Chapter 20 have shown that CCK pathways are one such important mechanism.

22.5 CONCLUSIONS

Truncal vagotomy and pyloroplasty is associated with some loss of intestinal feedback control of gastric emptying, and loss of pyloric "braking" mechanism. Thus, in these patients, the emptying of liquids (nutrient & non-nutrient) from the stomach, will be expected to be faster under conditions where posture favours emptying.

Chapter 23

Antral Compensation after Highly Selective Vagotomy

23.1 INTRODUCTION

Highly selective vagotomy (HSV), in which the innervation of the distal antrum and the pylorus is preserved, is associated with a near normal pattern of solid gastric emptying (Chapter 10). This may be in part due to compensatory mechanisms which overcome the loss of pumping function of the corpus and proximal antrum. Increased fundic tone due to the loss of vagal innervation may be one mechanism. Another could be a change in antral motor patterns.

In this study, we investigated whether patients who have had HSV have changes in distal antral motility which could compensate for the loss of proximal motor mechanisms.

23.2 METHODS

23.2.1 Subjects

Studies were done in four healthy volunteers between ages of 21 and 30 (mean age 24 years) and four patients between ages of 20 and 67 (mean age 42 years) who had had HSV for ulcer disease at least one year prior to study.

23.2.2 Study protocol

Antropyloroduodenal motility was measured with a 10-lumen sleeve/sidehole catheter, for 3 hours, during emptying of 100g of ^{99m}Tc-labeled beef and 150ml ^{113m}In-labeled dextrose (10%) drink, in a sitting position.

23.2.3 Recordings and data analysis

The measurement and analysis of gastric emptying followed previously described techniques (Chapters 13 & 14). The manometric data, in addition to being recorded by the polygraph were also recorded on-line by a computer (Chapter 13). The computer program was used to analyze the amplitude and duration of pressure waves observed in the proximal antrum (6 cm proximal to the pylorus), distal antrum (2 cm proximal to the pylorus), and the pylorus (sleeve detected). Only pressure waves with an amplitude of 10 mmHg or greater were analysed.

23.2.4 Statistical analysis

Values are given as mean ± standard error of the mean. A one-way analysis of variance was used to compare the data between the two groups.

23.3 RESULTS

23.3.1 Gastric emptying

The patients with HSV demonstrated a more rapid liquid emptying ($p<0.05$) than the controls (Figure 23.3), but solid emptying was similar in the two groups (Figure 23.3).

23.3.2 Frequency of pressure waves

In the HSV patients the numbers of antral pressure waves in the proximal and distal antrum were significantly ($p<0.05$) less than the control group (Table 23.3). The frequency of pyloric pressure waves was higher ($p<0.01$) than proximal or distal antral pressure waves in both groups, and not significantly different between the two groups.

23.3.3 Amplitude of pressure waves

In the HSV group, in comparison to the controls, the amplitude of pressure waves were significantly ($p<0.05$) lower in the proximal antrum, but significantly ($p<0.05$) higher in the distal antrum (Table 23.3). The mean amplitude of the few pressure waves recorded in the proximal antrum was higher than the mean amplitude of pressure waves recorded by the sleeve, in both groups.

23.3.4 Duration of pressure waves

Duration of pressure waves followed the same trend as the amplitude (Table 23.3), with the HSV patients exhibiting a shorter duration proximal antral and longer duration distal antral pressure waves, in comparison to the controls. The duration of pyloric (sleeve detected) pressure waves was longer than antral pressure waves in either group.

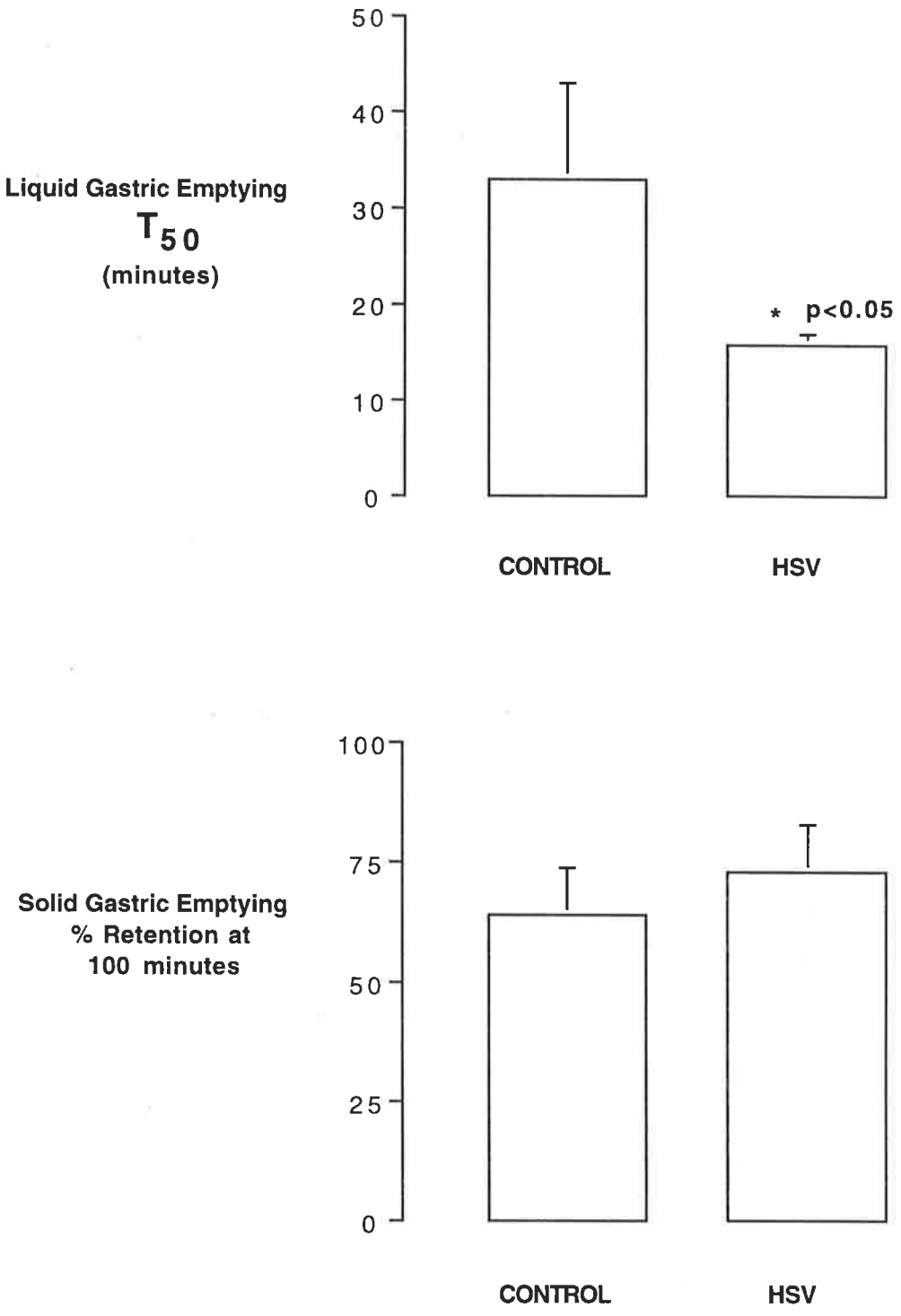


Figure 23.3: Liquid and solid emptying in patients with HSV, and the control group.

Table 23.3: Frequency, amplitude and duration of proximal antral, distal antral and pyloric pressure waves over the 3 hour duration of study.

		Proximal Antrum	Distal Antrum	Pylorus
Frequency	*CONTROL*	1.9±1.0†	16.8±2.6†	39.6±3.4
(per hour)	*HSV*	0.6±0.4†*	9.0±1.5†*	43.8±4.0
Amplitude	*CONTROL*	30.1±3.0†	19.2±1.1	13.3±1.7
(mm Hg)	*HSV*	22.2±1.5†*	24.8±3.1†*	14.7±0.7
Duration	*CONTROL*	2.0±0.3†	1.0±0.02†	2.7±0.13
(sec)	*HSV*	1.1±0.06†*	2.4±0.3*	2.8±0.2

Values shown are mean ± SE, *$p<0.05$ compared to control, † $p<0.05$ compared with pylorus.

23.4 DISCUSSION

The observed changes in liquid emptying are consistent with earlier results (Chapter 21). This study used a computer analysis of all contractions recorded in the two antral sideholes (2 & 6 cm proximal to the sleeve) and the sleeve sensor (pyloric). We analyzed all pressure waves recorded by these channels irrespective of whether they were isolated pressure waves or part of a sequence *i.e.* an APPW or PDPW.

The reduced number of antral pressure waves observed in the HSV group may suggest that antral motility is disturbed after this procedure. However, in an earlier study, where patterns of antropyloric pressure waves were scored, HSV was found not to be associated with any significant change in the number of propagated antropyloric pressure waves during emptying of a mixed solid/liquid meal, in comparison to healthy volunteers (Chapter 21).

The observed reduction in the number of antral pressure waves in the proximal antrum was expected, but the similar finding in the distal antrum was not. It is generally believed that preservation of distal antral innervation in HSV, helps to maintain the motor function of the distal antrum (Hould *et al* 1994). These results, if confirmed with a larger sample size, may suggest that denervation of the proximal stomach will also significantly effect the motor activity of the distal antrum, despite maintaining its direct vagal input.

The decrease in amplitude and duration of proximal antral pressure waves in comparison to controls, supports the hypothesis than proximal vagal denervation disturbs proximal antral motility in HSV patients. The effect of an increase in amplitude and duration of

distal antral contraction is not known. It is possible that such changes may be compensatory, and associated with more effective "pumping" of ingesta across the pylorus, by the distal antrum.

There were more frequent pressure waves recorded by the sleeve than any of the antral sideholes. This is not surprising as the sleeve would record any pressure rise related to APPWs, IPPWs, or PDPWs. The lower amplitude of pressure waves recorded by the sleeve in comparison to proximal antral sidehole may be related to two factors: i- a difference between the sleeve and sideholes in recording the pressure wave amplitude, ii- the fact that the number of pressure waves recorded by the sleeve was more than proximal antral sidehole by a factor of 20-40 times, thus the few pressure waves recorded in the proximal antrum may have had to been of considerable amplitude to achieve lumen occlusion and be recorded.

It is widely recognized that the pyloric pressure waves tend to be of longer duration than antral or duodenal pressure waves (Heddle *et al* 1988a). The mechanical significance of this is not known, but it is postulated that this will allow for a more effective arrest of transpyloric flow when the pylorus contracts.

23.5 CONCLUSIONS

The relatively small number of subjects studied does not allow us to reach firm conclusions, but even as a pilot data, the results suggest that after highly selective vagotomy, some changes in the amplitude and duration of distal antral contractions is observed. These changes may partially compensate for the loss of proximal and distal gastric motor mechanisms after proximal gastric denervation.

Section G

Design of Pylorus Preserving Gastric Surgery

Chapter 24

Use of a Muscle Bridge to Maintain Intramural Connections after Antral Transection

24.1 INTRODUCTION

Preservation of the pylorus has been proposed as a means of minimizing the disturbance in the normal pattern of gastric emptying which follows distal gastrectomy (Maki *et al* 1967, Cherniakevich & Ettinger 1988). Pylorus-preserving gastrectomy, however, has failed to gain popularity among surgeons due to concerns that poor pyloric function that may occur after such surgery may lead to gastric retention (Isono & Kelly 1979, Griffith 1974).

In an earlier study, we have shown that the time interval between pyloric contraction and the preceding gastric contraction is a major determinant of the volume of attendant pulses of transpyloric flow (Chapter 17). Division of antral intramural nerves, which occurs during a gastrectomy, alters this timing and leads to a delay in gastric emptying (Holle *et al* 1994). Following the complete interruption of antral intramural nerves, the pylorus closes early in relation to the associated gastric contraction and thus reduces the volume of attendant pulsatile flow (Chapter 19). As a result of these findings, we sought to test whether preservation of a limited pathway for descending intramural signals would preserve the coordination of pyloric motility and thus, reduce the disturbance of gastric emptying. A muscle bridge has previously been used in the ileum to preserve intramural connections (Collin *et al* 1979). Our aim was to determine if

preservation of a 1 cm wide bridge of muscle in the antrum could maintain the intramural signals between the transected portions of the antrum.

24.2 METHODS

24.2.1 Surgical preparation of pigs

Ten Kangaroo Island pigs (40 - 45 kg), with chronic gastric and duodenal cannulae were used.

The pre-transection studies (control) were performed after a recovery period of six weeks following the insertion of cannulae. The animals then underwent a second operation 10-12 weeks after their initial preparation. In five pigs (Group 1), the antrum was completely transected 2 cm proximal to the pylorus and re-anastomosed, in an end-to-end fashion, using single layer interrupted 2-0 Vicryl sutures (Ethicon, USA) and without resection of any gastric tissue. In the second group of five pigs (Group 2) the antral transection was kept incomplete by leaving a 1 cm bridge of muscle intact. Post-transection studies were done after a minimum recovery period of six weeks.

24.2.2 Experimental procedure

Recordings of antropyloroduodenal motility and transpyloric flow were made concurrently for 30 minutes after instillation of 1000 mls of saline into the stomach via the gastric cannula.

24.2.3 Recordings and data analysis

The recording techniques and the analysis followed previously described methods (Chapters 13 & 14).

24.2.4 Statistical analysis

The values are given as means ± S.E. of the mean. The differences between the groups were compared using ANOVA; differences were considered significant if $p<0.05$.

24.3 RESULTS

24.3.1 Gastric emptying

In Group 1 animals, antral transection was associated with marked retardation of gastric emptying (Figure 24.3.1). By contrast, subtotal antral transection did not alter emptying when compared to pre-transection studies.

24.3.2 Pulsatile transpyloric flow

Total antral transection was associated with significant reduction in the volume of transpyloric flow pulses but the number of pulses did not alter (Table 24.3.2). In the subtotal transection animals, transpyloric flow pulses remained at pre-transection levels.

24.3.3 Manometry

In both groups, the transection of the antrum did not alter the number of antral CCPWs (Figure 24.3.3a), but the interval between the onset of the CCPWs and pyloric closure was significantly shortened after total antral transection (Figure 24.3.3a). There was no change in the duration of the first phase of CCPW after subtotal antral transection.

In both groups, antral transection was associated with a significant reduction in the number of short APPWs ($p<0.05$) (Figure 24.3.3b). An increase in the number of IPPWs was seen in both groups but did not reach statistical significance (Figure 24.3.3b). The number of PDPWs remained unchanged after transection in both groups (Figure 24.3.3b).

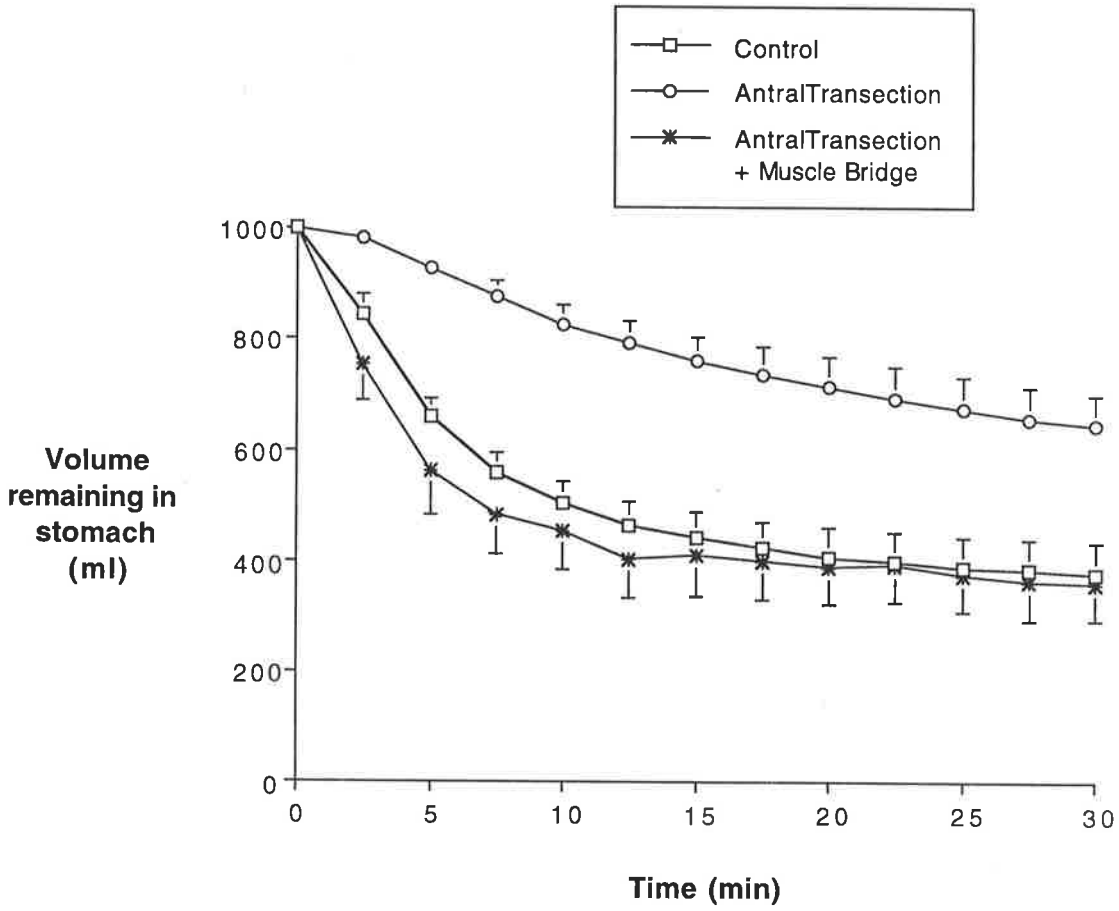


Figure 24.3.1: Gastric emptying of 1000 ml of saline during the first 30 minutes.

Table 24.3.2: Volume and number of transpyloric flow pulses

	control	antral transection	antral transection + muscle bridge
number of flow pulses /30 min	24.4±3.2	22.0±4.0	22.3±2.7
volume of flow pulses (ml)	18.7±1.5*	8.6±0.4	21.2±1.1*

Values are given as mean ± SE, * $p<0.05$ compared to antral transection

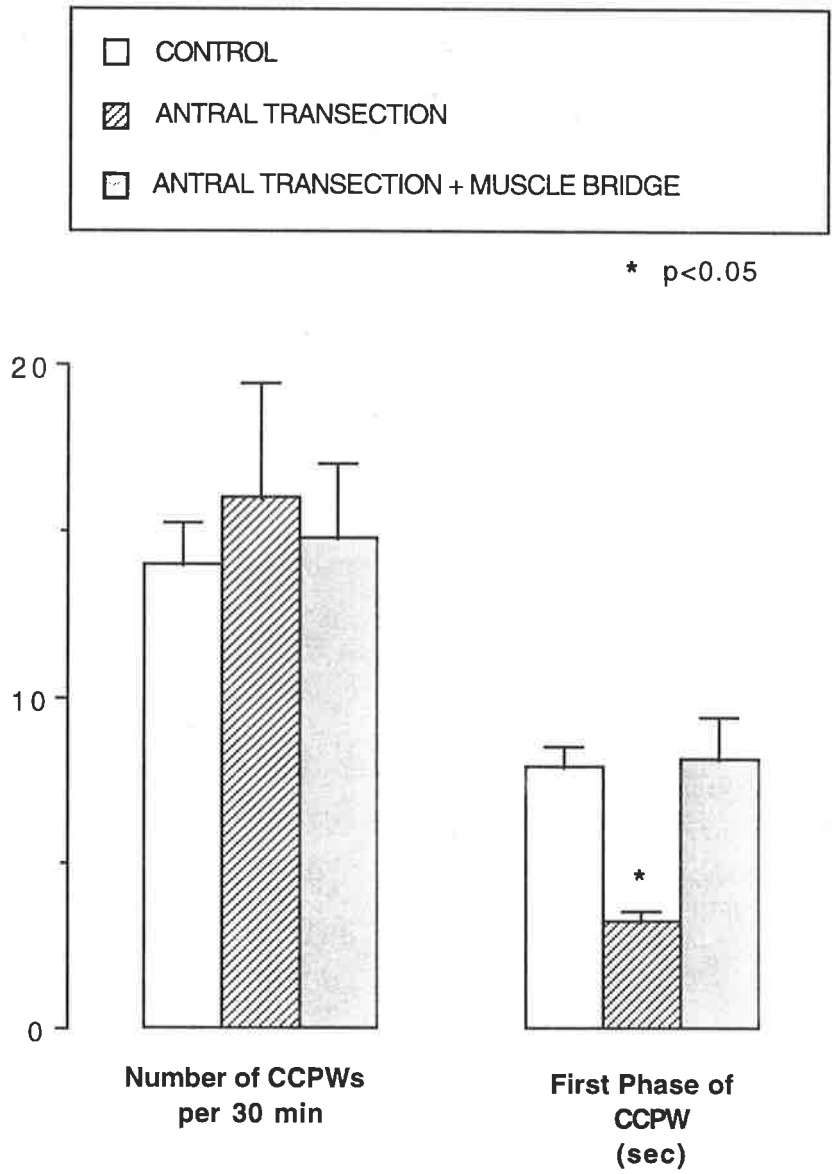


Figure 24.3.3a: The frequency of antral CCPWs and the duration of the "first phase" of CCPWs in the three groups.

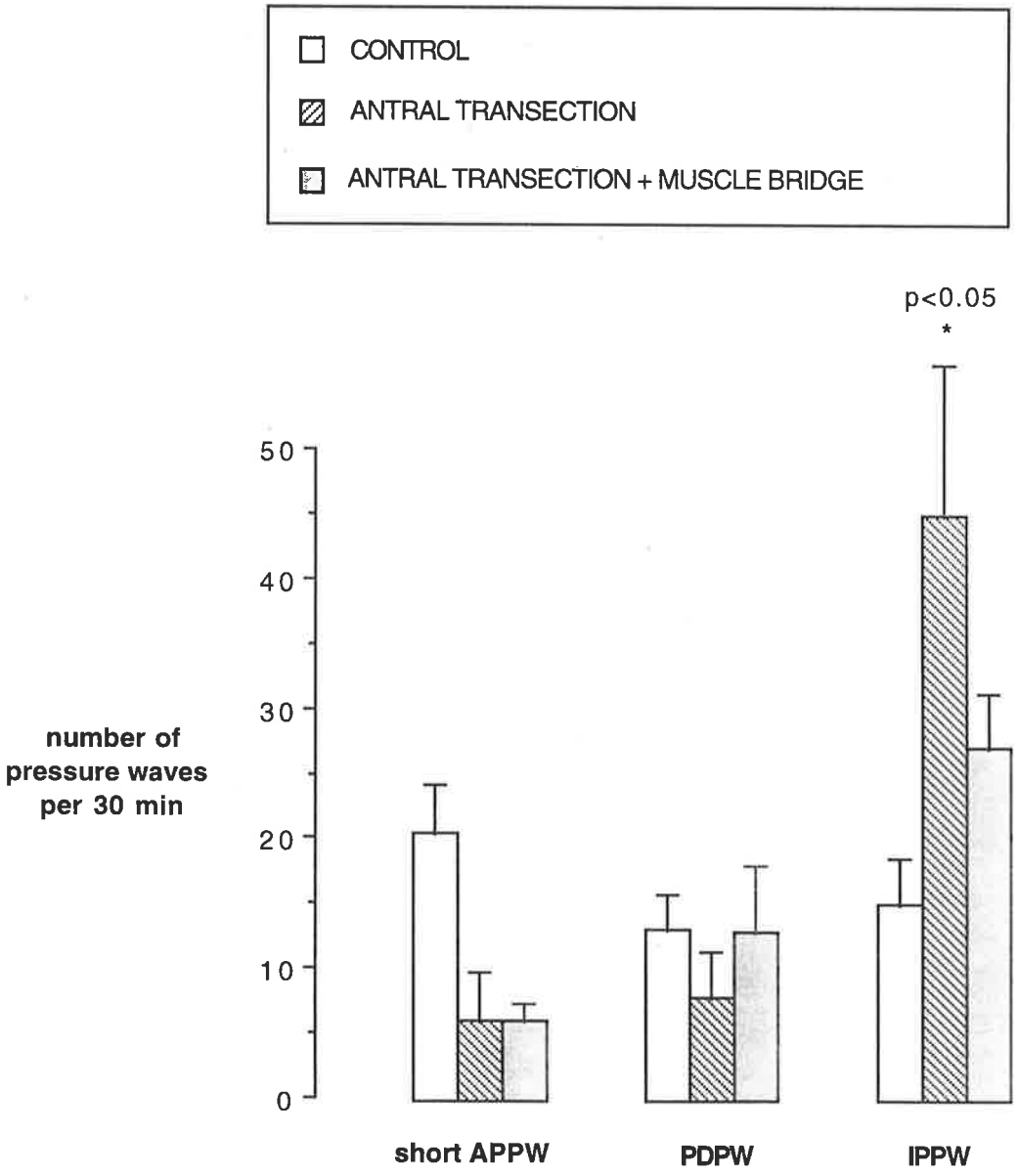


Figure 24.3.3b: The frequency of non-CCPW pressure waves.

24.4 DISCUSSION

We have shown that a one centimetre bridge of muscle maintains enough intramural neural connections to preserve the normal relation between timing of antral and pyloric lumen occlusion during a propagated antropyloric contractile sequence. The preservation of this timing is associated with the maintenance of a normal pattern of pulsatile emptying of gastric contents, even after antral transection. This has important implications to pylorus preservation in distal gastrectomy, which has been associated with delayed gastric emptying (Griffith 1974, Isono & Kelly 1978). The study did not, however, test the impact of antral resection combined with preservation of a muscle bridge.

Studies of antral transection (Holle *et al* 1994, Chapter 19) have suggested that control signals in the antral wall are important for normal coordination of pyloric closure with an associated antral contraction. Previous evidence (Collin *et al* 1979) that a muscle bridge is capable of maintaining important intramural signals in the ileum led us to test the hypothesis that a small muscle bridge can act as a cable, preserving intramural neural connections between the pylorus and antrum after transecting the antrum, and allowing the preservation of important physiological signals during gastric emptying. Our data strongly supports this hypothesis.

Although the muscle bridge did not prevent the disruption of the localized distal antropyloric contractions associated with antral transection, this did not have any significant effect on the overall pattern of gastric emptying.

While it would have been ideal to study the animals after subtotal transection and then again after division of the muscle bridge to complete the transection, this was not

practical because of the local scarring following antral transection which would have made the second surgical procedure more difficult and the results subject to bias.

Effective propagation of a gastric contraction to the antrum and the pylorus requires resumption of muscle-to-muscle transmission of electrical control activity (ECA) across the transection site (Hinder & Kelly 1977). Once this has been established, the neural connections are necessary to modulate the timing of pyloric closure relative to the stereotyped electrical control activity.

24.5 CONCLUSIONS

Preservation of the control of timing of pyloric lumen occlusion by use of a muscle bridge is associated with preservation of normal pyloric control of gastric emptying after antral transection. This appears to be a promising strategy for pylorus-preserving distal gastrectomy. Further studies are required to test the effectiveness of a muscle bridge in maintaining normal patterns of gastric emptying following antral resection and/or vagotomy.

Chapter 25

Future Directions in Pylorus Preserving Gastrectomy

The study in the previous chapter suggests that the use of a muscle bridge may allow the surgeon to maintain an important connection between the antrum and the pylorus. This would allow preservation of the timing of pyloric closure in relation to proximal gastric contractions. This should theoretically reduce the likelihood of gastric stasis following a pylorus-preserving gastrectomy, while at the same time, maintain all the advantages of preserving the pyloric sphincter mechanism.

25.1 DISTAL GASTRECTOMY WITH PRESERVATION OF A MUSCLE BRIDGE

The theoretical possibility of maintaining a muscle bridge during a distal gastrectomy was evaluated in one pig.

25.1.1 Surgical technique

Figure 25.1.1 shows the technique used. After full mobilization of the greater curvature of the stomach, a bridge of muscle, 5 cm long and 1 cm wide, was maintained on the lesser curvature, while the distal third of the stomach down to 2 cm proximal to the pylorus was resected. The vessels and nerves entering the muscle bridge on the lesser curvature side were maintained. The mucosa over the muscle bridge was excised. The reconstruction of the proximal and distal resective margins was relatively simple, with

the muscle bridge forming part of the distal margin being anastomosed to the proximal margin using a single layer Vicryl (2-0) suture (Ethicon, USA).

25.1.2 Results

The pig survived the surgery well and was started on oral liquids the day after the surgery. The animal progressed to a regular diet by day three, and showed no vomiting or intolerance to the food. The animal was not equipped with gastric and duodenal cannulae for manometric and emptying studies. It was observed for 3 weeks and showed no untoward effects from the surgery.

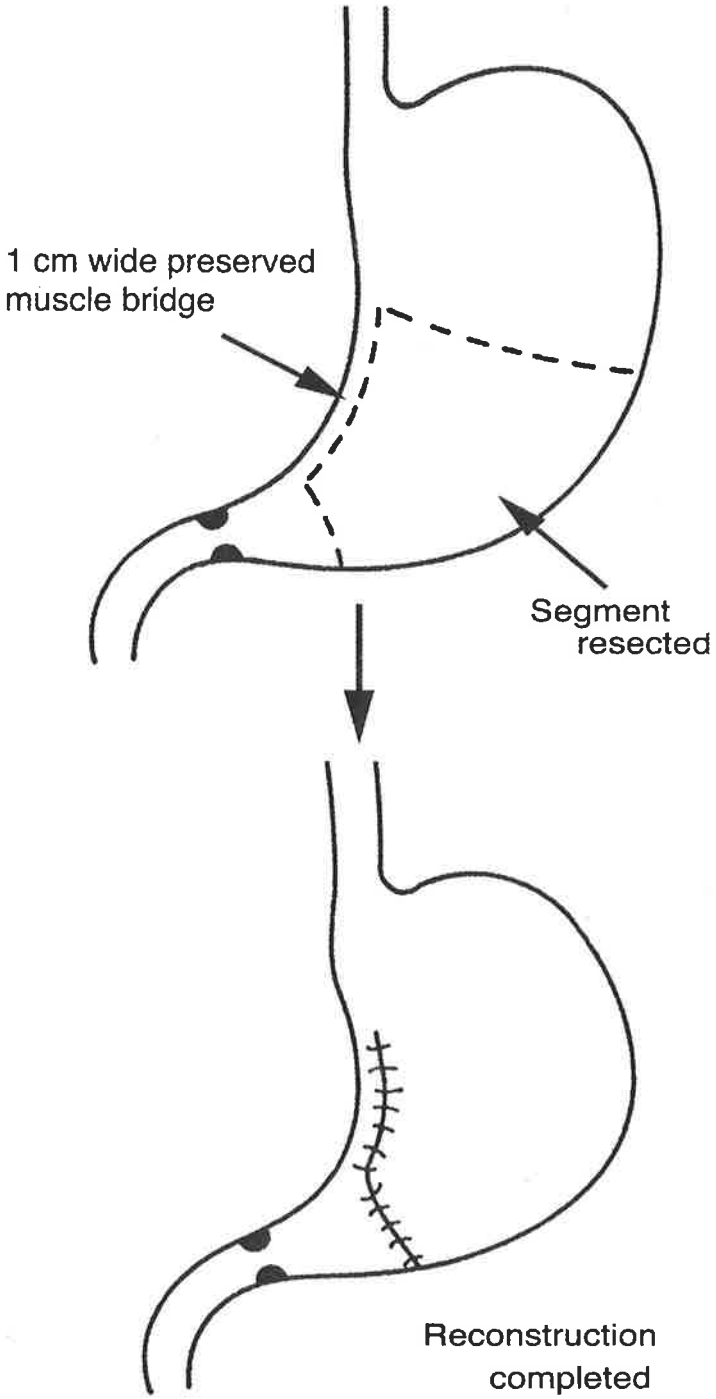


Figure 25.1.1: Pylorus preserving distal gastrectomy with preservation of a muscle bridge

25.1.3 Discussion

This limited experience suggests that preservation of a muscle bridge during distal gastrectomy is a viable option. Further studies are required to assess whether a muscle bridge provides added benefits to standard pylorus-preserving gastrectomy. Also, a maximum functional length for a muscle bridge needs to be defined. However, there is no theoretical reason why a longer bridge of muscle should not continue to work in the same manner.

The surgical procedure described in this chapter is ideal for the resection of benign gastric lesions on the greater curvature side of the antrum. The same operation may be performed for a lesser curvature lesion with preservation of a muscle bridge on the greater curvature, but this may be technically more difficult.

Chapter 26

Summary and Conclusions

The work presented in this thesis has led to the following conclusions:

1 - The pylorus acts as a true physiological sphincter and is important in the regulation of emptying of ingesta from the stomach. It is capable of motor activity distinct from that of the adjoining antrum and duodenum. An increase in pyloric tone, with or without development of isolated pyloric pressure waves, provides an increased resistance to the flow across the pylorus, and thus retards gastric emptying. Isolated pyloric pressure waves are also observed under conditions of emptying and may serve to regulate the rate of duodenal filling.

2 - Emptying of liquids and liquefied solids from the stomach occurs predominantly as pulses of flow associated with propagated contractions of the corpus and antrum, which may or may not achieve lumen-occlusion. In a fluid-distended stomach, an apparently distinct patterning of the propagated gastric contractions causes a pressurization of the gastric cavity, with a resultant flow of ingesta across the pylorus into the duodenum, while the pylorus is open. The variable time delay between the onset a propagated gastric contraction and ensuing pyloric contraction/closure, determines the

volume of transpyloric flow pulses. Variation of this timing may be a mechanism of importance in the normal physiological control of the volume of pulsatile gastric outflow. We postulate that, in the early stages following ingestion of a mixed meal (solid lag phase), the timing of pyloric closure in relation to gastric contractions may be shorter, thus limiting the amount of ingesta propelled out of the stomach (mainly liquids) and causing the retropulsion of the remainder which may help 'grind' the solid component. Later, the time interval between onset of gastric contraction and pyloric closure may be lengthened to allow larger volumes of ingesta to leave the stomach. The antral transection studies described in this thesis indicate that this timing is regulated, in part, by descending antral intramural nerves.

3 - Studies described in this thesis confirm the importance of feedback signals (neural and humoral) from the small intestine in regulation of gastric and pyloric motor function during the fed state. The experiments with a blocker of cholecystokinin indicates that this is important in regulating gastric motor function and emptying after ingestion of a meal containing fats. Ascending intramural neural pathways from the duodenum have been shown to play a role in the regulation of pyloric motor function, but they do not play a major role in the regulation of antral motility after a meal.

4 - Posture influences gastric emptying through changes in gastric motility. Our data suggests that gravity may influence the rate of distribution of a meal within the stomach, in various body positions. This, in turn, effects the gastric motor mechanisms responsible for expelling the meal. Thus, emptying is more rapid in positions were gravity favours distal emptying as compared to lying in a position where gravity works in the opposite direction to transpyloric flow.

5 - Therapeutic gastric surgery alters the normal patterns of gastric emptying by disturbing gastric and/or pyloric motor mechanisms:

i - Truncal vagotomy and pyloroplasty, in which the pyloric mechanism is disabled and the stomach and other abdominal viscera are denervated, was shown to be associated with reduced antral motility, and loss of pyloric "braking" mechanism. As a result, these patients demonstrate a rapid liquid emptying (predisposing to dumping and/or diarrhoea) and a variable rate of solid emptying (predisposing to bloating).

ii - Highly selective vagotomy, in which the innervation of the antrum and pylorus is maintained, is associated with near normal patterns of gastric emptying. Maintaining this innervation helps to preserve the frequency of propagated antropyloric pressure waves, but the motility of the proximal and distal antrum is partially disturbed. There are, however, compensatory changes observed that may offset these disturbances.

iii - Distal gastrectomy, in which the antral and pyloric motor mechanisms are removed, is associated with rapid emptying of liquids and variable emptying of solids. The presence of phasic motor activity in the gastric remnant, suggests that some gastric "pumping" action is preserved.

6 - Pylorus preservation may diminish the disturbance in rate of liquid gastric emptying that is observed after distal gastrectomy, and thus prevent the occurrence of symptoms of dumping and diarrhoea. Use of a one centimeter bridge of muscle during pylorus preservation was shown to be capable of maintaining adequate intramural

neural connections to maintain a near normal functioning of the pylorus after antral transection. Preserving a bridge of muscle during pylorus preserving distal gastrectomy is technically feasible.

6 - These conclusions on mechanics and control of gastric emptying and the effect of therapeutic gastric surgeries can be used to provide general guidelines for gastrointestinal surgeons:

i - Avoid surgical denervation or resection of the stomach whenever possible. If resection is therapeutically indicated, minimize the extent of resection and denervation of the stomach within the limits necessary to achieve the therapeutic goals.

ii - If vagal denervation of the stomach is necessary to reduce acid output, then highly selective vagotomy is the procedure of choice.

iii - In resection of the distal stomach, consider preserving the pyloric mechanism, if possible. Use of a muscle bridge may provide additional physiological benefits if it is possible to construct within the limits of resection.

7 - Future studies are necessary to explore the physiological and clinical merits of pylorus preserving gastrectomy with the use of a muscle bridge. In addition, further studies to explore the mechanics of gastric distribution, grinding, sieving and emptying, the relative role of the fundus, and the importance of different neurotransmitters (NO) and enterogastrones (GLP-1) involved in the control of gastric emptying are planned.

Appendix

Published Work Based on Experiments Described in this Thesis

A.1 PAPERS PUBLISHED

1. Tougas G, Anvari M, Richards D, Dent J, Somers S, Stevenson G (1992): Relation of pyloric motility to pyloric opening and closure. *Gut* 33(4), 466-471.

2. Anvari M, Jamieson GG (1992): Surgical applications of the function of the pylorus. *Annual Surgery* 24(1), 181-194 .

3. Anvari M, Malbert CH, Horowitz M, Jamieson GG (1994): Loxiglumide abolishes the effects of intraduodenal oleic acid on gastric motility and emptying in the pig. *Neurogastroenterology and Motility* 6:181-187.

4. Dent J, Sun WM, Anvari M (1994): Modulation of the pumping function of gastric body and antropyloric contractions. *Digestive Diseases and Sciences (suppl)* 39 (12):28S-31S.

5. Anvari M, Horowitz M, Fraser R, Maddox M, Myers J, Dent J, Jamieson GG (1995): Effects of posture and atropine on gastric distribution and antropyloroduodenal motility during gastric emptying of non-nutrient liquids. *American Journal of Physiology* 268 (Gastrointest Liver Physiol 31): G868-G871.

6. Anvari M, Dent J, Jamieson GG (1995): Mechanics of pulsatile transpyloric flow. *Journal of Physiology* (London) 488 (1): 193-202.

7. Anvari M, Dent J, Yu P, Jamieson GG (1995): Role of antral intramural pathways in control of gastric emptying. *Journal of Physiology* (London) 488 (1): 203-209.

A.2 PAPERS SUBMITTED

1. Anvari M, Dent J, Malbert CH, Jamieson GG: Preservation of gastric emptying following gastric surgery by use of a muscle bridge. *American Journal of Surgery.*

A.3 PAPERS TO BE SUBMITTED

1. Anvari M, Horowitz M, Maddox M, Myers J, Dent J, Jamieson GG: Pyloric motor function in fed state in patients with truncal vagotomy and pyloroplasty.

2. Anvari M, Malbert CH, Dent J, Jamieson GG: Comparison of strain gauge and intraluminal manometry in detection of non-lumen occlusive gastric contractions.

A.4 PUBLISHED ABSTRACTS

1. Anvari M, Dent J, Fraser R, Maddox M, Taylor M, Horowitz M, Jamieson GG (1991): Influence of posture on gastric motility, distribution and emptying of a non-nutrient liquid meal. *Gastroenterology* 100 (5): A415.

2. Anvari M, Dent J, Fraser R, Maddox M, Taylor M, Horowitz M, Jamieson GG (1991): Effect of atropine on antropyloric motility and gastric distribution and emptying of non-nutrient liquid meal. *Gastroenterology* 100 (5): A415.

3. Anvari M, Riddell P, Taylor M, Dent J, Jamieson GG (1991): Antral transection perturbs antropyloroduodenal coordination and slows gastric emptying. *Gastroenterology* 100 (5): A416.

4. Anvari M, Yu P, Dent J, Jamieson GG (1991): Role of intramural neural pathways in duodenal inhibition of liquid gastric emptying. *Gastroenterology* 100 (5): A416.

5. Anvari M, Riddell P, Taylor M, Dent J, Jamieson GG (1991): Origin and mechanical effect of broad gastric pressure waves during liquid emptying in pigs. *Gastroenterology* 100 (5): A416.

6. Anvari M, Malbert CH, Dent J, Jamieson GG (1992): Manometric correlates of gastric wall motion. Gastroenterology 102 (4): A418.

7. Anvari M, Malbert CH, Taylor M, Sgro R, Horowitz M, Jamieson GG (1992): Loxiglumide abolishes the effects of intraduodenal oleic acid on gastric motility and emptying. Gatroenterology 102 (4): A418.

8. Anvari M, Taylor M, Sgro R, Jamieson GG (1992): Antropyloroduodenal manometry; functional correlates of different wave patterns. *Gastroenterology* 102 (4): A 418.

9. Anvari M, Malbert CH, Edelbroek M, Myers J, Dent J, Jamieson GG (1992): Antral compensation after proximal gastric vagotomy. *Gastroenterology* 102 (4): A418.

10. Anvari M, Myers J, Horowitz M, Dent J, Jamieson GG (1993): Pattern of antropyloroduodenal motor activity after vagotomy and pyloroplasty in fed state. *Gastroenterology* 104 (4): A471.

11. Anvari M, Myers J, Horowitz M, Dent J, Jamieson GG (1993): Gastric and Pyloric motor response to intraduodenal lipid infusion after vagotomy and pyloroplasty. *Gastroenterology* 104 (4): A471.

12. Anvari M, Malbert CH, Dent J, Jamieson GG (1993): Preservation of antral intramural pathways by use of a muscle bridge. Gastroenterology 104 (4) A471.

Bibliography

Allescher HD, Dent J, Daniel EE, Fox JET, Kostalanska F. (1988): Extrinsic and intrinsic neural control of pyloric sphincter pressure in the dog. *Journal of Physiology (London),* 401:17-38.

Allescher HD, Daniel EE, Fox JET, Kostalanska F, Rovati LA. (1989): Effect of the novel cholecystokinin receptor antagonist CR-1392 on cholecystokinin-induced antroduodenal and pyloric motor activity *in vivo. Journal of Pharmacology and Experimental Therapeutics* 251(3):1134-1141.

Allescher HD. (1990): Extrinsic nerves and hormones. In: Van Nueten JM, Schuurkes JAJ, Akkermans LMA. (Eds) *Gastro-pyloro-doudenal Coordination.* Petersfield, Wrightson Biomedical Publishing. pp. 97-126.

Andersson S, Grossman MI. (1965): Profile of pH, pressure, and potential difference at gastroduodenal junction in man. *Gastroenterology* 49:364-371.

Andrews PLR, Morgan KG, Go VLW, Szurszewski JH. (1980): Reflex excitation of antral motility induced by gastric distension in the ferret. *Journal of Physiology (London)* 298:79-84.

Anuras S, Cooke AR, Christensen J. (1974): An inhibitory innervation at the gastroduodenal junction. *Journal of Clinical Investigation* 54:529-535.

Arndorfer RC, Stef JJ, Dodds WJ, Lineham JH, Hogan WJ. (1977): Improved infusion system for intraluminal oesophageal manometry. *Gastroenterology* 73:23-27.

Aste H, Pandolfo N, Pugliese V, Nebiacolombo C. (1979): Prolonged endoscopic and manometric observations of the pylorus. *Scandinavian Journal of Gastroenterology* 14 (Supplement 54):72-77.

Atkinson M, Edwards DAW, Honour AJ, Rowlands EN. (1957): Comparison of cardiac and pyloric sphincters. A manometric study. *Lancet* ii:918-922.

Aylett P. (1962): Gastric emptying and change of blood glucose level as affected by glucagon and insulin. *Clinical Science* 22:171-178.

Azpiroz F, Malagelada JR. (1985a): Physiological variations in canine gastric tone measured by an electronic barostat. *American Journal of Physiology* 248:G229-G237.

Azpiroz F, Malagelada J-R. (1985b) : Intestinal control of gastric tone. *American Journal of Physiology* 249(12):G501-G509.

Azpiroz F, Malagelada J-R. (1986): Vagally medicated gastric relaxation induced by intestinal nutrients in the dog. *American Journal of Physiology* 251(14):G727-G735.

Azpiroz F, Malagelada JR. (1987): Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis. *Gastroenterology* 92:934-943.

Barajas-Lopez C, Berezin I, Daniel EE, Huizinga JD. (1989): Pacemaker activity recorded in interstitial cells of Cahal of the gastrointestinal tract. *American Journal of Physiol*ogy 257(26):C830-C835.

Beaumont W. (1833): *Experiments and observations on the gastric juice and the physiology of digestion.* F.P. Allen, Plattsburg.

Becker JM, Kelly KA. (1983): Implications for vagotomy. In: Carter DC. (Ed) *Peptic Ulcer Disease. Clinical Surgery International.* Churchill Livingstone, London. pp. 77-89.

Behar J, Biacani P, Zabinski P. (1979): Characterization of feline gastroduodenal junction by neural and hormonal stimulation. *American Journal of Physiology* 236(5):E45-E51.

Berger (1969): Studies on the gastric emptying mechanism. *Acta Chirurgica Scandinavica. (Suppl),* 404:1-51.

Bertiger G, Reynolds JC, Ouyang A, Cohen S. (1987): Properties of the feline pyloric sphincter *in vitro*. *Gastroenterology* 92:67-92.

Billroth T. (1881): Offenes Schreiben an Herrn Dr. L. Wittelshofer. *Wien Med Wochenschr* 31:161.

Boeckxstaens GE, Pelckmans PA, Bult H, De Man JG, Herman AG,Van Maercke YM. (1990): Non-adrenergic non-cholinergic relaxation mediated by nitric oxide in the canine ileocolonic junction. *European Journal of Pharmacology* 190(1-2):239-246.

Bortoff A, Davis RS. (1968): Myogenic transmission of antral slow waves across the gastroduodenal junction in situ. *American Journal of Physiology* 215:889-897.

Bortolotti M, Sanavio C, Sansone G, Labo G. (1975): Modifications in human gastric motility induced by secretin and by glucagon. *Rendiconti di Gastroenterologia* 7:240.

Brener W, Hendrix TR, McHugh PR. (1983): Regulation of the gastric emptying of glucose. *Gastroenterology* 85:76-82.

Brink BM, Schlegel JF, Code CF. (1965): The pressure profile of the gastroduodenal junctional zone in dogs. *Gut* 6:163-171.

Brough WA, Taylor TV, Torrance HB. (1984): The surgical factors influencing duodenogastric reflux. *British Journal of Surgery* 71:770-773.

Buhner S, Ehrlein HJ, Thoma G, Schumpelick V. (1988): Effects of nutrients on gastrointestinal motility and gastric emptying after Billroth 1 Gastrectomy in dogs. *Digestive Diseases and Sciences* 33(7):784-794.

Burn-Murdock R, Fisher MA, Hunt JN. (1980): Does lying on the right side increase the rate of gastric emptying? *Journal of Physiology (London)* 302:395-398.

Bury V, Boev K. (1979): Studies on the transmembrane ion currents in the smooth-muscle cells of the gastric fundus. *Experimentia* 36:216-217.

Calabuig R, Carrio I, Mones J, Puig La Calle J, Viladell F. (1988): Gastric emptying after truncal vagotomy and pyloroplasty. *Scandinavian Journal of Gastroenterology* 23(6):659-664.

Cannon WB. (1898): The movements of the stomach studied by means of Roentgen Rays. *American Journal of Physiology* 1:359-382.

Cannon WB, Lieb CW. (1911): The receptive relaxation of the stomach. *American Journal of Physiology* 29:267-273.

Carlson HC. (1962): *Motor Action of the gastroduodenal junctional zone: a cineradiographic, pressure and electric study.* PhD Thesis. University of Minnesota.

Carlson HC, Code CF, Nelson RA. (1966): Motor action of the canine gastroduodenal junction: A cineradiographic, pressure and electric study. *American Journal of Digestive Diseases* 11:155-176.

Cattau E, Artnak E, Castell D, and Meyer G. (1983): Efficacy of atropine as an endoscopic premedication. *Gastrointest Endosc* 29:285-288.

Cherniakevich SA, Ettinger AP. (1988): Gastric and duodenal motor functions in the late period after pylorus preserving resection. *Klinicheshaia Khirurgiia* 8:13-16.

Chernish SM, Brunelle RR, Rosenak BD, Ahmadzai S. (1978): Comparison of the effects of glucagon and atropine sulfate on gastric emptying. *American Journal of Gastroenterology* 70:581-586.

Christinck F, Jury J, Cayabyab F, Daniel EE. (1991): Nitric oxide may be the final mediator of nonadrenergic, noncholinergic inhibitory junction potentials in the gut. *Canadian Journal of Physiology and Pharmacology* 69:1448-1458.

Christofides ND, Modlin IM, Fitzpatrick ML, Bloom SR. (1979): Effect of motilin on the rate of gastric emptying and gut hormone release during breakfast. *Gastroenterology* 76:903-907.

Christofides ND, Lang R, Fitzpatrick ML, McGregor G, Bloom SR. (1981): Effect of motilin on the gastric emptying of glucose and fat in humans. *Gastroenterology* 80:456-460.

Clarke RJ, Alexander-Williams J, (1973): The effect of preserving antral innervation and of a pyloroplasty on gastric emptying after vagotomy in man. *Gut* 14:300-307.

Code CF, Carlson HC. (1968): Motor activity of the stomach. In: Code CF, Heidel WF (Eds). *Handbook of Physiology*, Section 6, Volume 4: Alimentary Canal. American Physiological Society, Washington. pp. 1903-1916.

Code CF, Szurszewski JH, Kelly KA, Smith IB. (1968): A concept of control of gastrointestinal motility. In: Code CF, Heidel WF. (Eds). *Handbook of Physiology, Section 6, Volume 5: Alimentary Canal.* American Physiological Society, Washington, D.C. pp. 2881-2896.

Code CF, Marlett JA. (1975): The interdigestive and myoelectric complex of the stomach and small bowel of dogs. *Journal of Physiology* 246:289-309.

Collins PJ, Horowitz M, Cook DJ, Harding PE, Shearman DJC. (1983): Gastric emptying in normal subjects- a reproducible technique using a single scintillation camera and computer system. *Gut* 24:1117-1125.

Collins PJ, Horowitz M, Shearman JC, Chatterton BE. (1984): Correction for tissue attenuation in radionuclide gastric emptying studies: a comparison of a lateral image method and a geometric mean method. *The British Journal Of Radiology* 57:689-695.

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

Collins PJ, Horowitz M, Maddox A, Myers JC, Chatterton BE. (1991): Increased meal size is associated with more rapid gastric emptying. *Australian and New Zealand Journal of Medicine* 21 (4):632.

Colmer MR, Owen GM, Shields R. (1973): Pattern of gastric emptying after vagotomy and pyloroplasty. *British Medical Journal* 2:448-450.

Cooke AR, Chyasta TE, Weisbrodt NW. (1972): Effect of pentagastrin on emptying and electrical and motor activity of the dog stomach. *American Journal of Physiology* 223:934-938.

Cooke AR. (1974): Duodenal acidification: role of first part of duodenum in gastric emptying and secretion in dogs. *Gastroenterology* 67:85-92.

Cooke AR. (1975): Control of gastric emptying and motility. *Gastroenterology* 68:804-816.

Cooke AR. (1977): Localization of receptors inhibiting gastric emptying in the gut. *Gastroenterology* 72:875-880.

Corazziari E, Ricci R, Biliotti D. (1990): Oral administration of loxiglumide (CCK antagonist) inhibits postprandial gallbladder contraction without affecting gastric emptying. *Digestive Diseases and Sciences* 35(1):50-54.

Costa M, Furness JB. (1982): Nervous control of intestinal motility. In: Bertaccini G. (Ed) *Mediators and Drugs in Gastrointestinal Motility.* Springer-Verlag, New York. pp. 279-382.

Cowley DJ, Vernon P, Jones T. (1972): Gastric emptying of solid meals after truncal vagotomy and pyloroplasty in human subjects. *Gut* 13:176-181.

Daniel EE. (1965): Electrical and contractile responses of the pyloric region to adrenergic and cholinergic drugs. *Canadian Journal of Physiology and Pharmacology* 44:951-979.

Daniel EE, Irwin J. (1971): Electrical activity of the stomach and upper intestine. *American Journal of Digestive Diseases* 16(7):602-610.

Daniel EE, Jury J, Robotham KH, (1986): Receptors for neurotransmitters in opossum oesophagus muscularis mucosa. *British Journal of Pharmacology* 88(3):707-14.

Daniel EE, Collins SM, Fox JET, Huizinga JD. (1989a): Pharmacology of drugs acting on gastrointestinal motility. In: Schultz S. (Ed), *Handbook of Physiology-The Gastrointestinal System I,* The American Physiological Society, Waverly Press, Baltimore, Maryland. pp 715-758.

Daniel EE, Collins SM, Fox JET, Huizinga JD. (1989b): Pharmacology of neuroendocrine peptides. In: Schultz S. (Ed), *Handbook of Physiology-The Gastrointestinal System I,* The American Physiological Society, Waverly Press, Baltimore, Maryland. pp 759-816.

Daniel EE, Huizinga JD, Berezin I. (1990): Introduction to ionic basis of electrical behaviour. Origin and characteristics of gastrointestinal pacemakers. (Review). *Progress in Clinical & Biological Research.* 327:205-218.

Daniel EE, Allescher HD. (1990): Structure of the pyloric region. In: Van Nueten JM, Schuurkes JAJ, Akkermans LM. (Eds) *Gastro-pyloro-doudenal Coordination.* Wrightson Biomedical Publishing Ltd., Petersfield, pp. 19-34.

Debas HT, Farooq O, Grossman MI. (1975): Inhibition of gastric emptying is a physiological action of cholecystokinin. *Gastroenterology* 68:1211-1217.

Defilippi CC. (1985): Continuous recording of pyloric sphincter pressure in dogs. Relationship to migratory motor complex. *Digestive Diseases and Sciences.* 30:669-674.

Dent J. (1976): A new technique for continuous sphincter pressure measurement. *Gastroenterology* 71:263-267.

De Ponti F, Azpiroz F, Malagelada JR. (1987): Reflex gastric relaxation in response to distension of the duodenum. *American Journal of Physiology* 252(15):G595-G601.

Dodds WJ. (1976): Instrumentation and methods for intraluminal oesophageal manometry. *Archives of Internal Medicine* 136:515-523.

Dooley CP and Valenzuela JE. (1988): Antropyloroduodenal activity during gastric emptying of liquid meals in humans. *American Journal of Physiology* 255(18):G93-G98.

Dozois RR, Kelly KA. (1971) Effect of a gastrin pentapeptide on canine gastric emptying of liquids. *American Journal of Physiology* 221(1):113-7.

Dozois RR, Kelly KA, Code CF. (1971): Effect of distal antrectomy on gastric emptying of liquid and solids. *Gastroenterology* 61:675-681.

Dragstedt LR, Harper PV, Jr, Tovee EB, Woodward ER. (1947): Section of the vagus nerves to the stomach in the treatment of peptic ulcer. *Annals of Surgery* 126:687.

Duthie HK, Kwong NK, Brown BH, Whitacker GE. (1971): Pacesetter potential of the human gastroduodenal junction. *Gut* 12:250-256.

Duthie HL, Brown BH, Robertson-Dunn B, Kwong NK, Whittaker GE, Waterfall W. (1972) Electrical activity in the gastroduodenal area--slow waves in the proximal duodenum. A comparison of man and dog. *American Journal of Digestive Diseases* 17: 344-51.

Edelbroek M, Horowitz M, Dent J, Sun W, Malbert C, Smout A, and Akkermans L. (1994): Effects of duodenal distension on fasting and postprandial antropyloroduodenal motility in humans. *Gastroenterology* 106(3):583-592.

Edin R, Ahlman H, Kewenter J. (1979): The vagal control of the feline pyloric sphincter. *Acta Physiologica Scandinavica* 107(2): 169-174.

Edin R, Lunberg J, Tenenius L, Dahlstrom A, Hokfelt T, Kewenter J, Ahlman H. (1980): Evidence for vagal and encephalinergic neural control of the feline pylorus and the stomach. *Gastroenterology* 78:492-497.

Ehrlein HJ, Prove J, Schweiker W. (1980): The function of the pyloric sphincter for regulating gastric emptying and for preventing reflux in dogs. In: Christensen J. (Ed) *Gastrointestinal Motility* Raven Press, New York. pp. 177-184.

Ehrlein HJ, Hiesinger E. (1982): Computer analysis of mechanical activity of gastroduodenal junction in unanaesthetized dogs. *Quarterly Journal of Experimental Physiology* 67(1):17-29.

Ehrlein HJ, Buhner S, Thoma G, Schemann M, Keinke O, Tsiamitas C, Schumpelick V. (1987): Gastric emptying after roux-y and Billroth-1 gastrectomy depends on viscosity of meal and contractile patterns of small intestine in dogs. *Digestive Diseases and Sciences* 32 (5):529-537.

Ehrlein HJ, Thoma G, Keinke O, Tsiamitas C, Schumpelick. (1987): Effects of nutrients on gastrointestinal motility and gastric emptying after distal gastrectomy with roux-y gastrojejunostomy in dogs. *Digestive Diseases and Sciences* 32 (5) 538-546.

Ehrlein HJ. (1988): Motility of the pyloric sphincter studied by the inductograph method in conscious dogs. *American Journal of Physiology* 254:G650-G657.

Ehrlein HJ, Wulschke S, Sahyoun H. (1989a): Computer analysis of orally propagated contractions in canine small intestine after Billroth-II gastrectomy. *Digestive Diseases and Sciences* 34 (8):1257-1264.

Ehrlein HJ, Wulschke S, Thoma G, Schumpelick V. (1989b): Gastrointestinal motility and gastric emptying after Billroth II gastrectomy in dogs. *Digestive Diseases and Sciences* 34 (8):1199-1210.

Elfvin LG, Lindh B. (1982): A study of the extrinsic innervation of the guinea pig pylorus with the horseradish perioxidase tracing technique. *Journal of Comparative Neurology* 208:317-324.

El-Sharkawy TY, Morgan KG, Szurszewski JH. (1978): Intracellular electrical of canine and human gastric smooth muscle. *Journal of Physiology (London)* 279:291-307.

El-Sharkawy TY, Szurszewski JH. (1978): Modulation of canine antral circular smooth muscle by acetylcholine, non-adrenalin and pentagastrin. *Journal of Physiology (London)* 279:309-320.

Faxen A, Berger T, Kewenter J, Kock NG. (1977): Gastric emptying after different surgical procedures for duodenal ulcer. *Scandinavian Journal of Gastroenterology* 12: 983-987.

Fisher RS, Cohen S. (1973): Physiological characteristics of the human pyloric sphincter. *Gastroenterology* 64:67-75.

Fisher RS, Lipshutz W, Cohen S. (1973): The hormonal regulation of pyloric sphincter function. *Journal of Clinical Investigation* 52:1289-96.

Fitch A, Neri M, Camilleri M, Kelly KA, Phillips SF. (1990): Stasis syndromes following gastric surgery: clinical and motility features of 60 symptomatic patients. *Journal of Clinical Gastroenterology* 12(5):505-512.

Flynn PJ, Longmire WP Jr. (1960): Subtotal gastrectomy with pyloric sphincter preservation. *Surgical Forum* 10:185.

Fone D, Horowitz M, Dent J, Read N, and Heddle R. (1989): Pyloric motor response to intraduodenal dextrose involves muscarinic mechanisms. *Gastroenterology* 97:83-90.

Fone DR, Horowitz M, Maddox A, Akkermans LM, Read NW, Dent J. (1990): Gastroduodenal motility during the delayed gastric emptying induced by cold stress. *Gastroenterology* 98(5):Pt 1: 1155-1161.

Fone DR, Horowitz M, Heddle R, Maddox AF, Collins PJ, Read NW, Dent J. (1991): Comparative effects of duodenal and ileal intubation on gastric emptying and postprandial antral, pyloric and doudenal motility. *Scandinavian Journal of Gastroenterology* 26(1):16-22.

Fone DR. (1990): Studies of the function of the human pylorus and its role in the regulation of gastric emptying. *Doctor of Medicine Thesis*, University of Adelaide.

Forester ER, Green T, Elliot M, Bremner A, Dockray GJ. (1990): Gastric emptying in rats: role of afferent neurons and cholecystokinin. *American Journal of Physiology* 258(21):G552-G556.

Fox DA, Epstein ML, Bass P. (1983): Surfactants actively ablate enteric neurons of the rat jejunum. *Journal of Pharmacology and Experimental Therapeutics* 227:538-544.

Fox JE. Motilin--an update. [Review] (1984) *Life Sciences* 35(7):695-706.

Fraser R, Fone D, Heddle R, Horowitz M, and Dent J. Pyloric motor response to intraduodenal lipid is sustained and atropine sensitive. (1992) *Journal of Gastroenterology and Hepatology* 7:563-568.

Fraser R, Fone D, Horowitz M, Dent J. (1993): Cholecystokinin stimulates phasic and tonic pyloric motility in healthy humans. *Gut* 34:33-37.

Fried M, Erlacher U, Schwizer W. (1991a): Role of cholecystokinin in gastric emptying and pancreatic enzyme secretion in humans. *Gastroenterology* 101:503-411.

Fried M, Schwizer W, Beglinger C, Keller U, Jansen JB, Lamers CB. (1991b): Physiological role of cholecystokinin on postprandial insulin secretion and gastric meal emptying in man. Studies with the cholecystokinin receptor antagonist loxiglumide. *Diabetologia* 34:721-726.

Gabella G. (1972): Innervation of the intestinal muscular coat. *Journal of Neurocytology* 1:341-362.

Gabella G. (1987): Structure of muscle and nerves in the gastrointestinal tract. In: Johnson LR. (Ed) *Physiology of the Gastrointestinal Tract,* 2nd Edition, Volume 1. Raven Press, New York. pp. 335-382.

Gaffney PR, Gleeson DJ, Hall JW, Brady MP. (1987): The manometric findings at the human pylorus. The evidence against the presence of a tonic sphincter. *Scandinavian Journal of Gastroenterology* 22:525-532.

Gill RC, Kellow JE, Browning C, Wingate DL. (1990): The use of intraluminal strain gauges for recording ambulant small bowel motility. *American Journal of Physiology* 258: G610-G615.

Gillespie JS. (1982): Non-adrenergic Non-cholinergic inhibitory control of gastrointestinal motility. In: Wienbeck M. (Ed) *Motility of the Digestive Tract.* Raven Press, New York. pp. 51-66.

Gillis RA, Quest JA, Paganini FD, Norman WP. (1989): Neural control of motility. In: Schultz S. (Ed), *Handbook of Physiology-The Gastrointestinal System I,* The American Physiological Society, Waverly Press, Baltimore, Maryland. 621-683.

Gleysteen JJ, Gohlke EG. (1979): The antrum can control gastric emptying of liquid meals. *Journal of Surgical Research* 26:381-391.

Gleysteen JJ, Sarna SK, Myrvik AL. (1988): Truncal vagotomy as a possible potentiator of gastric atony. *American Journal of Surgery* 155:199-205.

Goligher JC. (1970): The comparative results of different operations in the elective treatment of duodenal ulcer. *British Journal of Surgery* 57:780.

Goligher JC, Hill GL, Kenny TE, Nutter E. (1978): Proximal gastric vagotomy without drainage for doudenal ulcer: results after 5-8 years. *British Journal of Surgery* 65:145-151.

Gough MJ, Humphrey CS, Giles GR. (1981): Does osmotic control of gastric emptying persist after truncal vagotomy? *British Journal of Surgery* 68:77-80.

Green T, Diamaline R, Peikin DS, Dockray J. (1988): Action of the cholecystokinin antagonist L364,718 on gastric emptying in the rat. *American Journal of Physiology* 255:G685-G689.

Gregory PC, McFadyen, Rayner DV. (1987): The influence of gastrointestinal infusions of glucose on the regulation of food intake in pigs. *Quarterly Journal of Experimental Physiology* 72:525-535.

Gregory PC, McFadyen M, Rayner DV. (1989): Control of gastric emptying in the pig: influence of duodenal infusions of glucose and emulsified fat. *Quarterly Journal of Experimental Physiology* 74: 109-119.

Gregory PC, McFadyen M, Rayner DV. (1990): Pattern of gastric emptying in the pig: relation to feeding. *British Journal of Nutrition* 64(1):45-58.

Griffith CA. (1974): Selective vagotomy plus suprapyloric antrectomy with and without pylorotomy for duodenal ulcer. *Annals of Surgery* 179(4):516-518.

Grundy D, Scratcherd T. (1982): A splanco-vagal component of the inhibition of gastric motility by distension of the intestines. In: Wienbeck M. (Ed) *Motility of the Digestive Tract,* Raven Press, New York. pp. 39-43.

Grundy D, Scratcherd T. (1984): Sensory afferents from the gastrointestinal tract. In: Schultz S. (Ed) *Handbook of Physiology - The Gastrointestinal System I.* American Physiological Society, Bethesda. pp. 593-620.

Grundy D. (1988): Vagal control of gastrointestinal function. *Bailliere's Clinical Gastroenterology.* 2:23-43.

Grundy D, Scratcherd T. (1989): Sensory afferents from the gastrointestinal tract. In: Schultz S. (Ed), *Handbook of Physiology-The Gastrointestinal System I,* The American Physiological Society, Waverly Press, Baltimore, Maryland. pp. 593-620.

Gulsrud PO, Taylor IL, Wats HD,Cohen MB, Elashoff J, Meyer JH. (1980): How gastric emptying of carbohydrate affects glucose tolerance and symptoms after truncal vagotomy with pyloroplasty. *Gastroenterology* 78:1463-1471.

Gustafsson LE, Wiklund CU, Wiklund NP, Persson MG, Moncada S. (1990): Modulation of autonomic neuroeffector transmission by nitric oxide in guinea pig ileum. *Biochemical & Biophysical Research Communications* 173(1):106-110.

Hall KE, El-Sharkawy TY, Diamant NE. (1986): Vagal control of canine postprandial upper gastrointestinal motility. *American Journal of Physiology* 250(13):G501-G510.

Hall W, Read R. (1970): Effect of vagotomy on gastric emptying. *American Journal of Digestive Diseases* 15 (12):1047-1053.

Hara Y, Kubota M, Szurszewski JH. (1986): Electrophysiology of the smooth muscle of the small intestine of some mammals. *Journal of Physiology (London),* 372:501-520.

Harada M, Mayuzumi K, Yano S. (1981): Peripheral and central effects of atropine and chlorpromazine on gastric motility and ulceration in stressed rats. *Journal of Pharmacobio-Dynamics* 4:309-316.

Hata F, Ishii T, Kanada A,Yamano N, Kataoka T, Takeuchi T, Yagasaki O. (1990): Essential role of nitric oxide in descending inhibition in the rat proximal colon. *Biochemical & Biophysical Research Communications* 172(3):1400-406.

Heddle R. (1988): *Pyloric Motility - Measurement, Control and Function.* Doctor of Medicine Thesis. University of Adelaide.

Heddle R, Dent J, Toouli J, Read NW. (1988a): Topography and measurement of pyloric pressure waves and tones in humans. *American Journal of Physiology* 255(18):G490-G497.

Heddle R, Fone D, Dent J, Horowitz M. (1988b): Stimulation of pyloric motility by intra-douodenal dextrose in normal subjects. *Gut* 29:1349-1357.

Heddle R, Dent J, Read NW, Houghton LA, Toouli J, Horowitz M, Maddern GJ, Downton J. (1988c): Antropyloroduodenal motor responses to intraduodenal lipid infusion in healthy volunteers. *American Journal of Physiology* 254(17):G671-G679.

Heddle R, Collins PJ, Dent J, Horowitz M, Read NW, Chatterton B, Houghton LA. (1989): Motor mechanisms associated with slowing of the gastric emptying of a solid meal by an intraduodenal lipid infusion. *Journal of Gastroenterology and Hepatology* 4:437-447.

Hennessy TPJ, Whelton MJ, Brady MP. (1974): The place of pylorus preserving gastrectomy in the treatment of duodenal ulcer. *British Journal of Surgery* 61:844-846.

Hinder RA, Kelly KA. (1977): Human gastric pacesetter potential: Site of origin, spread, and response to gastric transection and proximal gastric vagotomy. *American Journal of Surgery* 133:29-33.

Hinder RA, Bremner CG. (1978): Relative role of pyloroplasty size, truncal vagotomy, and milk meal volume in canine gastric emptying. *Digestive Diseases* 23 (3):210-216.

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

Hoffman HH, Schnitzlein HN. (1969): The number of vagus nerves in man. *Anatomical Record* 139:429-435.

Holle GE, Steinbach E, Forth W. (1994): Intrinsic corporoantropyloric coordination of motility and gastric emptying. *American Journal of Physiology* 266:G255-G262.

Horowitz M, Maddern GJ, Chatterton BE, Collins PJ, Harding PE, Shearman DJC. (1984): Changes in gastric emptying rates with age. *Clinical Science* 67:213-218.

Horowitz M, Harding PE, Maddox A, Maddern GJ, Collins PJ, Chatterton BE, Wishart J, Shearman DJC. (1986): Gastric and oesophageal emptying in insulin-dependent diabetes mellitus. *Journal of Gastroenterology and Hepatology* 1:97-113.

Horowitz M, Akkermans LMA. (1989): Scintigraphic Measurement of Gastric Emptying In: Read NW. (Ed): *Gastrointestinal motility-which test?*, Wrightson Biomedical Publishing Ltd, Petersfield pp73-92.

Horowitz M, Harding PE, Maddox AF, Wishart JM, Akkermans LMA, Chatterton BE, Shearman DJC. (1989): Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 32:151-159.

Houghton LA, Read NW, Heddle R, Maddern GJ, Downton J, Toouli J, Dent J. (1988a): Relationship of the motor activity of the antrum, pylorus and duodenum to gastric emptying of a solid-liquid mixed meal. *Gastroenterology* 94:1285-1291.

Houghton LA, Read NW, Heddle R, Maddern GJ, Downton J, Toouli J, Dent J. (1988b): Motor activity of the gastric antrum, pylorus, and duodenum under fasting conditions and after a liquid meal. *Gastroenterology* 94:1276-1284.

Hould FS, Cullen JJ, Kelly KA. (1994): Influence of proximal gastric vagotomy on canine motility and emptying. Surgery 116(1): 83-89.

Howlett PJ, Sheiner HJ, Barber DC, Ward HS, Perez-Avila CA, Duthie HL. (1976): Gastric emptying in control subjects and patients with doudenal ulcer before and after vagotomy. *Gut* 17:542-550.

Humphrey CS, Johnson D, Walker BE, Pulvertaft CN, Goligher JC. (1972): Incidence of dumping after truncal and selective vagotomy with pyloroplasty and highly selective vagotomy without drainage procedure. *British Medical Journal* 3:785-788.

Hunt JN, Spurrell WR. (1951): The pattern of emptying of the human stomach. *Journal of Physiology* 113:157-168.

Hunt JN. (1956): Some properties of an alimentary osmoreceptor mechanism. *Journal of Physiology* 132:267-288.

Hunt JN. (1963): The duodenal regulation of gastric emptying. *Gastroenterology* 45:149-156.

Hunt JN, Knox MT, Oginski A. (1965): The effect of gravity on gastric emptying with various test meals. *Journal of Physiology* 178:92-97.

Hunt JN, Knox MT. (1972): The slowing of gastric emptying by four strong and three weak acids. *Journal of Physiology* 222:187-208.

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

Hunt JN, Smith JL, Jiang CL. (1985): Effect of meal volume and energy density on the gastric emptying of carbohydrates. *Gastroenterology* 89:1326-1330.

Hutson WR, Roehrkasse RL, Wald A. (1989): Influence of gender and menopause on gastric emptying and motility. *Gastroenterology* 96:11-7.

Isenberg JI, Csendes A. (1972): Effect of octapeptide of cholecystokinin on canine pyloric pressure. *American Journal of Physiology* 222:428-431.

Isono K, Kelly KA. (1979): Proximal gastric vagotomy and suprapyloric antrectomy. *Archives of Surgery* 114:623-627.

Jacob P, Kahrilas PJ, Logemann JA, Shah V, Ha T. (1989): Upper oesophageal sphincter opening and modulation during swallowing. *Gastroenterology* 97(6):1469-1478.

Jacobs F, Akkermans LMA, Yoe OH, Hoekstra A, Wittebol P. (1982): A radioisotopic method to quantiify the function of fundus, antrum, and their contractile activity in gastric emptying of a semi solid and solid meal. In: Wienbeck M. (Ed) *Motility of the Digestive Tract.* New York, Raven Press. pp.233-240.

Jahnberg T, Martinsen J, Hulten L, Fasth S. (1975): Dynamic gastric response to expansion before and after vagotomy. *Scandinavian Journal of Gastroenterology* 10:593-598.

Jamieson GG. (1983): Operations available for duodenal ulcer: an overview. In: Carter DC. (Ed) *Peptic Ulcer Disease. Clinical Surgery International.* Churchill Livingstone, London. pp. 90-103.

Jansson G. (1969): Extrinsic nerve control of gastric motility. An experimental study in the cat. *Acta Physiologica Scandinavia* (Supplement) 326:1-42.

Jennewin HM, Hummelt H, Siewert R, Waldeck F. (1975): The motor stimulating effect of natural motilin on the lower oesophageal sphincter, fundus, antrum and duodenum in dogs. *Digestion* 13:246-250.

Jonderko K. (1987): Radionuclide studies on gastric evacuatory function in health and in the duodenal ulcer disease. 1. Types of solid meal distribution within the stomach and their relation to gastric emptying. *Nuclear Medicine Communications* 8:671-680.

Jones RS, Yee TK, Michielsen CE. (1971): A modified Thomas cannula for gastric and intestinal fistulas. *Journal of Applied Physiology* 30:427-428.

Kalbasi H, Hudson FR, Herring A, Moss S, Glass HI, Spencer J. (1975): Gastric emptying following vagotomy and antrectomy and proximal gastric vagotomy. *Gut* 16(7): 509-513.

Kaushik SP, Ralphs DNL, Hobsley M, (1982): Gastric emptying and dumping after proximal gastric vagotomy. *American Journal of Gastroenterology* 77(6):363-366.

Keinke O, Ehrlein HJ. (1983): Effect of oleic acid on canine gastroduodenal motility, pyloric diameter and gastric emptying . *Quarterly Journal of Experimental Physiology* 68:675-686.

Kelly KA, Code CF. (1969): Effect of transthoracic vagotomy on canine gastric electrical activity. *Gastroenterology* 57:51-58.

Kelly KA, Code CF, Elveback LR. (1969): Patterns of canine gastric electric activity. *American Journal of Physiology* 217:461-470.

Kelly KA. (1981): Motility of the stomach and gastrodoudenal junction. In: Johnson LR. (Ed) *Physiology of the Gastrointestinal Tract.* Raven Press, New York. pp 393-410.

Killen DA, Symbas PN. (1962): Effect of preservation of the pyloric sphincter during antrectomy on postoperative gastric emptying. *American Journal of Surgery* 104:836-842.

King PM, Adam RD, Pryde A, McDicken WN, Heading RC. (1984): Relationship of human antralduodenal motility and transpyloric fluid movement: non-invasive observations with real-time ultrasound. *Gut* 25:1384-1391.

King PM, Pryde A, Heading RC. (1988): Effect of alterations in test meal composition on episodic transpyloric fluid movement in humans. *Digestive Diseases and Sciences* 33(12):1537-1543.

Kleibeuker JH, Beekhuis H, Jansen JBM, Piers DA. (1988a): Cholecystokinin is a physiological hormone mediator of fat-induced inhibition of gastric emptying in man. *European Journal of Clinical Investigation* 18:173-177.

Kleibeuker JH, Beekhuis H, Piers DA, Schaffalitzky de Muckadell OB. (1988b): Retardation of gastric emptying of solid food by secretin. *Gastroenterology* 94:122-126.

Klein E. (1926): The origin and character of gastric peristalis. *Archives of Surgery* 12:571-582.

Kodama M, Koyama K. (1991): Indications for pylorus preserving gastrectomy for early gastric cancer located in the middle third of the stomach. *World Journal of Surgery* 15:628-634.

Kuwahara A, Ozawa K, Yanaihara N. (1986): Effects of cholecystokinin-octapeptide on gastric motility of anaesthetised dogs. *American Journal of Physiology* 252(14):G678-G681.

Landers BR, DevittPG, Jamieson GG. (1986): The pig as an animal model for the study of liquid gastric emptying. *Australian New Zealand Journal of Surgery* 56:265.

Latarjet A. (1922): Resection des nerfs de l'estomac. *Bulletin de L'Acadamie Nationale de Medecine* (Paris) 87:681.

Lavigne ME, Wiley ZD, Martin P, Way LW, Meyer JH, Sleisenger MH, MacGregor IL. (1979): Gastric, pancreatic, and bilary secretion and the role of gastric emptying after parietal cell vagotomy. *American Journal of Surgery* 138:644-657.

Lawaetz O, Aritas Y, Brown NJG, Ralphs DNL, Sjontoft E. (1982): Distrubution of a liquid meal within the stomach and gastric empying after vagotomy and drainage operations. *Gut* 23:683-691.

Lee KY, Chang TM, Chey WY, (1983): Effect of rabbit antimotilin serum on myoelectric activity and plasma motilin concentration in fasting dogs. *American Journal of Physiology* 245:G547-653.

Lerman SH, Mason GR, Bathon EM, Ormsbee HS. (1981): Pyloric motor response to sympathetic nerve stimulation in dogs. *Surgery* 89:460-465.

Liddle RA, Morita E, Conrad C, Williams J. (1986): Regulation of gastric emptying in humans by cholecystokinin. *Journal of Clinical Investigation* 77:992-996.

Liddle RA, Gertz BJ, Kanayma S. (1989): Effects of a novel cholecystokinin antagonist MK-329, on gallbladder contraction and gastric emptying in humans. *Journal of Clinical Investigation* 84:1220-1225.

Lin HC, Doty JE, Reedy TJ, Meyer JH. (1989): Inhibition of gastric emptying by glucose depends on length of intestine exposed to nutrient. *American Journal of Physiology* 256(19): G404-G411.

Lin HC, Doty JE, Reedy TJ, Meyer JH. (1990a): Inhibition of gastric emptying by sodium oleate depends on length of intestine exposed to nutrient. *American Journal of Physiology* 259(22): G1031-G1036.

Lin HC, Doty JE, Reedy TJ, Meyer JH. (1990b): Inhibition of gastric emptying by acids depends on pH, titratable acidity, and length of intestine exposed to acid. *American Journal of Physiology* 259(22): G1025-G1030.

Lind JF, Schlegel JF, Code CF. (1961): Motility of the gastric fundus. *American Journal of Physiology* 201:197-202.

Lipshutz W, Cohen S. (1972): Interaction of gastrin I and secretin on gastrointestinal circular muscle. *American Journal of Physiology* 222(3):775-781.

Lloyd KCK, Maxwel V, Kovacs TOG, Miller J, Walsh JH. (1992): Cholecystokinin receptor antagonist MK-329 blocks intestinal fat-induced inhibition of meal stimulated gastric acid secretion. *Gastroenterology* 102:131-138.

Lopez Y, Fioramonti J, Beuno L. (1991): Central and peripheral control of postprandial pyloric motility by endogenous opiates and cholecystokinin in dogs. *Gastroenterology* 101:1249-1255.

Ludtke F, Golenhofen C, Kohne C. (1988): Direct effects of cholecystokinin on human gastric motility. *Digestion* 39:210-218.

MacGregor IL, Gueller R, Watts HD, Meyer JH. (1976): The effect of acute hyperglycemia on gastric emptying in man. *Gastroenterology* 70(2): 190-196.

MacGregor IL, Martin P, Meyer JH. (1977a): Gastric emptying of solid food in normal man and after subtotal gastrectomy and truncal vagotomy with pyloroplasty. *Gastroenterology* 72:206-211.

MacGregor IL, Parene J, Meyer JH. (1977b): Gastric emptying of liquid meals and pancreatic and bilary secretion after subtotal gastrectomy or truncal vagotomy and pyloroplasty in man. *Gastroenterology* 72:195-205.

Maki T, Shiratori T, Hatafuku T, Sugawara K. (1967): Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. *Surgery* 61:838-845.

Malbert CH, Ruckebush Y. (1991): Relationships between pressure and flow across the gastroduodenal junction in dogs. *American Journal of Physiology* 260(23): G1-G5.

Malesci A, De Fazio C, Festorazzi S. (1990): Effect of loxiglumide on gallbladder contractile response to cerulein and food in humans. *Gastroenterology* 98:1307-1310.

Martinson J, Muren A. (1963): Excitatory and inhibitory effects of vagas stimulation on gastric motility in the cat. *Acta Physiologica Scandinavia* 57:309-316.

Mayer EA, Thomson JB, Jehn D, Reedy T, Elashoff J, Meyer JH. (1982): Gastric emptying and sieving of solid food and pancreatic and bilary secretions after solid meals in patients with truncal vagotomy and antrectomy. *Gastroenterology* 83:184-192.

Mayer EA, Thomson JB, Jehn D, Reedy T, Elashoff J, Deveny C, Meyer JH. (1984): Gastric emptying and sieving of solid food and pancreatic and bilary secretions after solid meals in patients with nonresective ulcer surgery. *Gastroenterology* 87:1264-1271.

Mazurik MF, Demianiuk DG, Mazurik SM, Rudy MA, Gilenko IA. (1988): Variants of pylorus preserving resection in gastric peptic ulcer. *Klinicheskaia Khirugiia* 8:34-36.

McCrea ED. (1924):The abdominal distribution of the vagus. *Journal of Anatomy* 59:18-40.

McHugh PR, Moran TH. (1979): Calories and gastric emptying: a regulatory capacity with implications for feeding. *American Journal of Physiology* 236:R254-R260.

McHugh PR, Moran TH. (1986): The stomach, cholecystokinin, and satiety. *Federation Proceedings* 45:1384-1390.

McIntosh GH, Pointon A. (1981): The Kangaroo Island strain of pig in biomedical research. *Australian Veterinary Journal* 57:182-185.

McKelvey STD. (1970): Gastric incontinence and post-vagotomy diarrhoea. *British Journal of Surgery* 57(10):741-747.

Mearin F, Azpiroz F, Malagelada JR. (1987): Pyloric contribution to antroduodenal resistance to flow in the conscious dog. *American Journal of Physiology* 253(16):G72-G78.

Meeroff JC, Go LW, Phillips SF. (1975): Control of gastric emptying by osmolarity of duodenal contents in man. *Gastroenterology* 68:1144-1151.

Mei N. (1983): Recent studies on intestinal vagal afferent innervation. Functional implications. *Journal of the Autonomic Nervous System* 9:199-206.

Meyer BM, Werth BA, Beglinger C, Hildebrand P, Jansen JB, Zach D, Rovati LC, Stalder GA. (1989): Role of cholecystokinin in regulation of gastrointestinal motor functions. *Lancet*: 2(8653):12-15.

Meyer JH, MacGregor IL, Gueller R, Martin P,Camalieri R. (1976): 99m-Tc tagged chicken liver as a marker of solid food in the human stomach. *American Journal of Digestive Diseases* 21:296-304.

Meyer JH, Thomson JB, Cohen MB, Schadchehr A, Mandiola SA. (1979): Sieving of solid food by the canine stomach and sieving after gastric surgery. *Gastroenterology* 76:804-813.

Meyer JH, Ohashi H, Jehmn D, Thomson JB. (1981): Size of liver particles emptied from the human stomach. *Gastroenterology* 89:1489-1496.

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

Meyer JH. (1987): Motility of the stomach and gastroduodenal junction. In: Johnson LR. (Ed) *Physiology of the Gastrointestinal Tract*, Second Edition, Raven Press, New York. pp. 613-629.

Miedema BW, Kelly KA. (1991): The Roux operation for postgastrectomy syndromes. *American Journal of Surgery* 161(2):256-261.

Miller J, Kauffman G, Elashoff J, Ohashi H, Carter D, Meyer JH. (1981): Search for resistances controlling gastric emptying of liquid meals. *American Journal of Physiology* 241(4):G403-G415.

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

Miolan JP, Roman C. (1975): Mechanisms of the inhibitory effects of glucagon on gastric motility. In: Vantrappen G. (Ed) *Vth International Symposium on Gastrointestinal Motility*. Typoff, Herentals. pp. 70-75.

Mittal RK, Junlong R, McCallum RW, Shaffer Jr, HR, Sluss J. (1990): Modulation of feline oesophageal contractions by bolus volume and outflow obstruction. *American Journal of Physiology* 258(21): G208-G215.

Moore JG, Christian PE, Coleman RE. (1981): Gastric emptying of varying meal weight and composition in man. Evaluation by dual liquid- and solid-phase isotopic method. *Digestive Diseases and Sciences*, 26(1):16-22.

Moore JG, Christian PE, Brown JA, Brophy C, Datz F, Taylor A, Alazraki N. (1984): Influence of meal weight and caloric content on gastric emptying of meals in man. *Digestive Diseases and Sciences* 29:513-519 .

Moore JG, Dubois A, Christian PE, Elgin D, Alazraki N, (1986): Evidence for a midgastric transverse band in humans. *Gastroenterology* 91:540-545.

Moore JG, Datz FL, Christian PE, Greenberg E, Alazraki N. (1988): Effect of body posture on radionuclide measurements of gastric emptying. *Digestive Diseases and Sciences*. 33 (12):1592-1595.

Moore JG, Datz FL, Christian PE. (1990): Exercise increases solid meal gastric emptying in men. *Digestive Diseases and Sciences* 35 (4):428-432 .

Moran TH, McHugh PR. (1982): Cholecystokinin supresses food intake by inhibiting gastric emptying. *American Journal of Physiology* 243:R491-R497.

Morgan KG, Muir TC, Szurszewski JH. (1981): The electrical basis for contraction and relaxation in canine fundal smooth muscle. *Journal of Physiology (London)* 311:475-488.

Morrison PD, Kelly KA. (1987): Influence of a jejunal fistula on gastric emptying. *European Surgical Research* 19:241-245.

Morrison P, Miedema BW, Kohler L, Kelly KA. (1990): Electrical dysrhythmias in the Roux jejunal limb: cause and treatment. *American Journal of Surgery* 160(3): 252-256.

Mroz C, Kelly KA. (1977): The role of the extrinsic antral nerves in the regulation of gastric emptying. *Surgery, Gynecology and Obstetrics* 145:369-377.

Nelson TS, Kohatsu S. (1971): The stomach as a pump. *Rendiconti di Gastroenterologia* 3:65-70, 1971.

Niederau C, Karaus M. Effects of CCK receptor blockade on intestinal motor activity in conscious dogs. (1991) *American Journal of Physiology* 260(23):G315-G24.

Norman WP, Pagani FD, Ormsbee HS, Kasbekar DK, Gillis RA. (1985): Use of horseradish peroxidase to identify hindbrain sites that influence gastric motility in the cat. *Gastroenterology* 88:701-705.

Oberle R, Chen T, Lloyd C, Barnett J, Owyang C, Meyer J, Amidon G. (1990): The influence of the interdigestive migrating myoelectric complex on the gastric emptying of liquids. *Gastroenterology* 99:1275-1282.

Okike N, Kelly KA. (1977) Vagotomy impairs pentagastrin-induced relaxation of canine gastric fundus. *American Journal of Physiology* 232:E504-509.

Ormsbee HS, Bass P. (1976): Gastroduodenal motor gradients in the dog after pyloroplasty. *American Journal of Physiology* 230:389-397.

Pandolfo N, Bortolottii M, Nebiacolombo C, Labo G, Mattioli F. (1979): Prolonged manometric study of the gastroduodenal junction in man. *Digestion.* 19:86-92.

Parr NJ, Grime S, Brownless S, Critchley M, Baxter JN, Mackie CR. (1988a): Relationship between gastric emptying of liquid and postvagotomy diarrhoea. *British Journal of Surgery* 175:279-282.

Parr NJ, Grime S, Critchley M, Baxter JN, Mackie CR. (1988b): Mechanisms governing the biphasic pattern of gastric emptying after truncal vagotomy and pyloroplasty. *Gut* 29:1253-1257.

Phaosawasdi K, Fisher R. (1982): Hormonal effects on the pylorus. *American Journal of Physiology* 243(6):G330-G335.

Pope CE. (1967): A dynamic test of sphincter strength: its applicaiton to the lower esophageal spincter. *Gastroenterology* 52(5):779-786.

Prensky AL. (1976): Migraine and migrainous variants in pediatric patients. *Pediatric Clinics of North America.* 23:461-471.

Publicover NG, Sanders KM. (1985): Myogenic regulation of propagation in gastric smooth muscle. *American Journal of Physiology* 248:G512-G520.

Quigley JP, Read MR, Radzow KH, Meschan I, Werle JM. (1942): The effect of hydrochloric acid on the pyloric sphincter, the adjacent portions of the digestive tract and on the process of gastric evacuation. *American Journal of Physiology* 137:153-159.

Ralphs DNL, Thomson JPS, Haynes S, Lawson-Smith C, Hobsley M, Le Quesne LP. (1978): The relationship between the rate of gastric emptying and the dumping syndrome. *British Journal of Surgery* 65:637-641.

Rashid M, Bateman D. (1990): Effect of intravenous atropine on gastric emptying, paracetamol absorption, salivary flow and heart rate in young and fit elderly volunteers. *British Journal of Clinical Pharmacology* 30:25-34.

Rees WDW, Go VLW, Malagelada J-R. (1979a): Simultaneous measurements of antroduodenal motility, gastric emptying, and duodenogastric reflux in man. *Gut* 20:963-97.

Rees WDW, Go VLW, Malagelada J-R. (1979b): Antroduodenal motor responses to solid-liquid and homogenised meals. *Gastroenterology* 76:1438-1442.

Reynolds JC, Ouyang A, Cohen S. (1985): Opiate nerves mediate feline pyloric response to intraduodenal amino acids. *American Journal of Physiology* 248(11):G307-G312.

Rhodes J, Goodall P, Apsimon HT. (1966): Mechanics of gastroduodenal emptying. A study of gastric and duodenal emptying with miniature balloons and intestinal glass electrodes. *Gut* 7(5):515-20.

Ricci Maccarini L, Ghidini C, Stanghellini V. (1991): Loxiglumide prevents the effects of dietary fats on gastric motility in humans. *Gastroenterology* 100:A487 (Abstract).

Roman C, Gonella J. (1981): Extrinsic control of digestive tract motility. In: Johnson LR. (Ed),*Physiology of the Gastrointestinal Tract.* Raven Press, New York. pp. 289-334.

Ruckebusch Y, Brady JC. (1982): Recording and analysis of electrical and mechanical activity of the gastrointestinal tract. In: Titchen DA. (Ed) *Techniques in Digestive Physiology* County Care, Ireland. Elsevier Biomedical. pp. 209/1-28.

Ruckebush Y, Malbert CH. (1986): Physiological characteristics of ovine pyloric sphincter. *American Journal of Physiology* 251(14):G804-G814.

Ruppin H, Domschke W, Wunsch E, Jaeger E, Demling L. (1975): Effects of 13-nle-motilin on the electrical and mechanical activity of the isolated perfused canine stomach and duodenum. *Gut* 17:362-370.

Sakamoto T, Guo Y-S, Thompson JC. (1987): Motility: Gut and Biliary. In: Thompson JC, Greeley GH, Rayford PL, Townsend CM. (Eds) *Gastrointestinal Endocrinology* McGraw Hill, New York, pp 123-136.

Sanders K, Publicover NG. (1988): Electrophysiology of the gastric musculature. In: Schultz S. (Ed) *"Handbook of Physiology-The Gastrointestinal System I"*, The American Physiological Society, Waverly Press, Baltimore, Maryland, pp 187-216.

Sarna SK, Daniel EE. (1973): Electrical stimulation of gastric electrical control activity. *American Journal of Physiology* 325(1):125-131.

Sarna SK, Daniel EE. (1975): Vagal control of gastric electrical control activity and motility. *Gastroenterology* 68(2):301-308.

Sarna SK, Kitai R, Muniappan K, Marzio L, Daniel EE, Waterfall WE. (1978): Gastroduodenal co-ordination: a computer analysis. In: Duthie HL. (Ed) *Gastrointestinal Motility in Health and Disease*, MTP, Lancaster, pp. 271-274.

Schmidt WE, Creutzfeldt W, Schleser A, Choudhury AR, Nustede R, Hocker M, Nitsche R, Sostmann H, Rovati LC, Folsch UR. (1991): Role of CCK in regulation of pancreaticobiliary functions and GI motility in humans: effects of loxiglumide. *American Journal of Physiology* 260:G197-G206.

Schultzberg M, Hokfelt T, Nilsson G, Terenius L, Rehlfeld JL, Brown M, Elde R, Goldstein M, Said S. (1980): Distribution of peptide and catecholamine-containing neurones in the gastrointestinal tract of rat and guinea pig: immunohistochemical studies with antisera to substance P, vasoactive intestinal polypeptide, enkephalins, somatostatin, gastrin-cholecystokinin, neurotensin and dopamine-hydroxylase. *Neuroscience* 5:689-744.

Schulze-Delrieu K, Brown CK. (1985): Emptying of saline meals from the cat stomach as a function of pyloric resistance. *American Journal of Physiology* 249(6 Pt 1):G725-G732.

Schuurkes JAJ, Charbon GA. (1978): Motility and hemodynamics of the canine gastrointestinal tract. Stimulation by pentagastrin, cholecystokinin and vasopressin. *Archives Internationales de Pharmocodynamie et de Therapie* 236:214-227.

Shahidullah M, Kennedy TL, Parks TG. (1975): The vagus, the brake, and gastric emptying. *Gut* 16:331-336.

Sheiner HJ, Quinlan MF, Thompson IJ. (1980): Gastric motility and emptying in normal and post-vagotomy subjects. *Gut* 21:753-759.

Skandalakis JE, Gray SW, Soria RE, Sorg JL, Rowe SL. (1980): Distribution of the vagus nerve to the stomach. *American Surgeon* 46:130-139.

Smith AWM, Code CF, Schlegel JF. (1957): Simultaneous cineradiographic and kymographic studies of human gastric antral motility. *Journal of Applied Physiology* 11:12-16.

Smith GP, Gibbs J. (1979): Postprandial satiety. In: Sprague JM, Epstein AN. (Eds) *Progress in psychobiology and physiological psychology.* Volume 8, New York: Academic, pp. 179-242.

Smout AJPM, Akkermans LMA, Roelofs JMM, Pasma FG, Oei HY, Wittebol P. (1987): Gastric emptying and postprandial symptoms after Billroth-II resection. *Surgery* 101(1):27-34.

Spencer MP, Sarr MG, Hakin NS, Soper NJ. (1989): Interdigestive gastric motility patterns: The role of vagal and nonvagal extrinsic innervation. *Surgery* 106:185-194.

Springfield AC, Weddle CO, Ormsbee HS, Barreras RF, Bass P. (1974): Influence of truncal vagotomy on canine gastric emptying of liquids. *American Journal of Surgery* 128:678-682.

Staadas JO, Aune S. (1970): Intragastric pressure/volume relationship before and after vagotomy. *Acta Chirurgica Scandinavica* 136:611-615.

Staadas JO. (1975): Intragastric pressure/volume relationship before and after proximal gastric vagotomy. *Scandinavian Journal of Gastroenterology* 10:129-134.

Stark ME, Bauer AJ, Szurszewski JH. (1991) Effect of nitric oxide on circular muscle of the canine small intestine. *Journal of Physiology* 444:743-61.

Strunz UT, Code CF, Grossman MI. (1979): Effect of gastrin on electrical activity of antrum and duodenum in dogs. *Proceedings of the Society for Experimental Biology and Medicine* 161:25-27.

Szurszewski JH. (1969): A migrating electric complex of the canine small intestine. *American Journal of Physiology* 217:1757-1763.

Szurszewski JH. (1975): Mechanism of action of pentagastrin and acetylcholine on the longitudinal muscle of the canine antrum. *Journal of Physiology (London)* 252:335-361.

Szurszewski JH. (1985): Motions of Alexis St. Martin's stomach. *Federation Proceedings* 44:2894-2896.

Szurszewski JH. (1987): Electrical basis for gastrointestinal motility. In: Johnson LR. (Ed) *Physiology of the Gastrointestinal Tract.* Second Edition, Raven Press , New York. pp. 383-422.

Telford GL, Mir SS, Mason GR, Ormsbee HS. (1979): Neural control of the canine pylorus. *American Journal of Surgery* 137:92-98.

Thomas JE. (1957): Mechanics and regulation of gastric emptying. *Physiology Review* 37:453-474.

Thompson JC, Wiener I. (1984) Evaluation of surgical treatment of duodenal ulcer: short- and long-term effects. [Review] *Clinics in Gastroenterology* 13:569-600.

Thuneberg L. (1982): Interstitial cells of Cajal: Intestinal pacemaker cells? In: Beck F, Hild W, van Limbrorgh J, Ortmann R, Pauly JE, Schiebler TH. (Eds) *Advances in Anatomy, Embryology and Cell Biology.* Volume 71, Springerverlag, Berlin. pp 1-130.

Thuneberg L. (1989): Interstitial cells of Cahal. In: Schultz S. (Ed) *Handbook of Physiology-The Gastrointestinal System I.* The American Physiological Society, Waverly Press, Baltimore, Maryland. pp. 349-386.

Toda N, Baba H, Okamura T. (1990): Role of nitric oxide in non-adrenergic, non-cholinergic nerve-mediated relaxation in dog duodenal longitudinal muscle strips. *Japanese Journal of Pharmacology* 53:281-284.

Torgensen J. (1942): The muscular build and movements of the stomach. *Acta Radiologica* 45 (suppl):1-191.

Tottrup A, Svane D, Forman A. (1991): Nitric oxide mediating NANC inhibition in opossum lower oesophageal sphincter. *American Journal of Physiology* 260:G385-389.

Tougas G, Bovell KT, Collins SM, Dent J, Hunt RH. (1990): The effect of naloxone on lipid-induced pyloric motor response in humans. *Gastroenterology* 99:930-934.

Treacy PJ, Jamieson GJ, Dent J. (1988): The effect of pyloric excision on gastric emptying of a digestible solid in the pig. (Abstract) *Journal of Gastroenterology and Hepatology* 3 (Supplement 1):21.

Treacy PJ, Jamieson GG, Dent J. (1990): Pyloric motor function during emptying of a liquid meal from the stomach in the conscious pig. *Journal of Physiology* 422:523-538.

Treacy PJ. (1991): *Pyloric motor function in the control of gastric emptying.* Doctor of Medicine Thesis. University of Adelaide.

Treacy PJ, Jamieson GG, Dent J, Devitt PG, Heddle R. (1992): Duodenal intramural nerves in control of pyloric motility and gastric emptying. *American Journal of Physiology* 263:G1-5

Valenzuela JE. (1976): Effects of intestinal hormones and peptides on intragastric pressure in dogs. *Gastroenterology* 71:766-769.

Valenzuela JE, Defilippi C. (1976): Pyloric-sphincter studies in peptic-ulcer patients. Pylorus in peptic ulcer. *Digestive Diseases* 21:229-232.

Valenzuela JE, Defilippi C, Csendes A, (1976): Manometric studies on the human pyloric sphincter. Effect of cigarette smoking, metoclopramide and atropine. *Gastroenterology* 70 (4):481-483.

Valenzuela JE, Defilippi C. (1981): Inhibition of gastric emptying in humans by secretin, the octapeptide of cholecystokinin, and intraduodenal fat. *Gastroenterology* 81(5):898-902.

Valori RM, Collins SM, Daniel EE, Reddy SN, Shannon S, Jury J. (1986): Comparison of methodologies for the measurement of antroduodenal motor activity in the dog. *Gastroenterology.* 91:546-553.

Van Nueten JM, Schuurkes JA. (1984): Studies on the role of dopamine and dopamine blockers in gastroduodenal motility. *Scandinavian Journal of Gastroenterology* 96:89-99.

Vizi SE, Bertraccini M, Impicciatore M, Knoll J. (1973): Evidence that acetylcholine released by gastrin and related polypeptides contributes to their effect on gastroduodenal motility. *Gastroenterology* 64:268-277.

Walsh JD. (1987): Gastrointestinal Hormones. In: Johnson LR. (Ed) *Physiology of the Gastrointestinal Tract* (2nd Edition): Raven Press, New York. pp. 181-253.

Weber J, Kohatsu S. (1970): Pacemaker localization and electrical conduction patterns in the canine stomach. *Gastroenterology* 59:717-726.

Weinberg JA, Stempein SJ, Movius HJ *et al.* (1956): Vagotomy and pyloroplasty in the treatment of duodenal ulcer. *American Journal of Surgery* 92:202.

Wepfer. (1697): *Historia Cicutae Aquatica*. Basel, p 152.

White CM, Poxon V, Alexander-Williams J. (1981): A study of motility of normal human gastroduodenal region. *Digestive Diseases and Sciences* 26:609-617.

White CM, Poxon V, Alexander-Williams J. (1984): The importance of the distal stomach in gastric emptying of liquids in man. *Surgical Gastroenterology* 3:13-20.

Wilbur BG, Kelly KA. (1973): Effect of proximal gastric, complete gastric, and truncal vagotomy on canine gastric electric activity, motility, and emptying. *Annals of Surgery* 178 (3):295-303.

Wilbur BG, Kelly KA, Code CF. (1974): Effect of gastric fundectomy on canine gastric electrical and motor activity. *American Journal of Physiology* 226:1445-1449.

Williams NS, Miller J, Elashoff J, Meyer JH. (1986): Canine resistances to gastric emptying of liquid nutrients after ulcer surgery. *Digestive Diseases and Sciences* 31(3):273-280.

Williams PL, Warwick R, Dyson M, Bannister LH. (1989): Gastric structure. In: Williams PL. (Ed) *Grays Anatomy* (37th Edition), Churchill Livingstone, Edinburgh. pp. 1350-1351.

Wingate DL, Ruppin H, Green WE, Thompson HH, Domschke W, Wunsch E, Demling L, Ritchie HD. (1976): Motilin-induced electrical activity in the canine gastrointestinal tract. *Scandinavian Journal of Gastroenterology (Suppl)* 39:111-118.

Wittebol P, Haarman HJTM, Hoekstra A, Smout AJPM, Akkermans LMA. (1988): Gastric emptying after gastric surgery. *Digest of Surgery* :491-496.

Wood JR, Camilleri M, Low PA, Malagelada JR. (1985): Brainstem tumor presenting as an upper gut motility disorder. *Gastroenterology* 89:1411-1414.

Wood JD. (1990): Neural mechanisms of gastro-duodenal co-ordination. In: Van Nueten JM, Schuurkes JAJ, Akkermans LMA. (Eds) *Gastro-pyloro-duodenal Coordination.* Wrightson Biomedical Publishing Ltd. pp. 35-66.

Yamagishi T, Debas H. (1978): Cholecystokinin inhibits gastric emptying by acting on both proximal stomach and pylorus. *American Journal of Physiology* 234:E375-E378.

Yamamoto T, Satomi H, Ise H, Takahashi K. (1977): Evidence of the dual innervation of the cat stomach by the vagal dorsal motor and medial solitary nuclei as demonstrated by the horseradish peroxidase method. *Brain Research* 122:125-131.

Yan C, Zhou H, Ma X, Zhang C. (1991): Pylorus and antroseromuscular flap-preserving gastrectomy-a new type of reconstruction after subtotal gastrectomy for treatment of gastroduodenal ulcer: clinical and experimental study. *Surgery* 109(6):756-760.