THE MEASUREMENT OF PROXIMAL, DISTAL AND TOTAL STOMACH EMPTYING RATES USING RADIONUCLIDE METHODS

A thesis submitted for the degree of Master of Science

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DEDICATION

To my wife Ginette
and our children Danielle and Mark

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SUMMARY

In this thesis, the development of a radionuclide method for the measurement of proximal, distal and total stomach emptying rates is outlined. The technique enables the simultaneous measurement of both solid and liquid emptying using a single scintillation camera/computer system. The standard solid meal comprises 100g of ground beef containing invivo-labelled ^{99m}Tc-chicken-liver and 150 ml of dextrose containing ^{113m}In-DTPA.

The potential sources of error in the measurement of gastric emptying using radionuclide methods are discussed. In normal subjects, variations in tissue attenuation caused by the changing depth of radionuclide within the stomach accounted for large errors in the measurement of gastric emptying. A new technique for correction of attenuation, which uses factors derived from a lateral image of the stomach, is described. The method was validated in phantom and human studies. The reproducibility of the method was assessed and the day-to-day variation in gastric emptying was not significant for any measured parameter.

Intragastric distribution and emptying were assessed in normal subjects using a new method for defining proximal and distal stomach - this method utilises a proximal stomach 'reservoir' area, seen immediately after ingestion of solids, to define the proximal stomach region. Redistribution of solid from proximal to distal stomach was a significant component of the delay in emptying (lag period) in most subjects. Considerable intersubject variability in the rate of redistribution was also observed.

In a study with combined manometry, gastric emptying of solid was slowed by duodenal lipid infusion. This slowing was associated with (1) suppression of antral and proximal duodenal motility, (2) stimulation of isolated pyloric pressure waves (IPPWs) and (3) redistribution of food from the distal to the proximal stomach.

The effect of alterations in the calorie content of a meal on gastric motility and emptying was also assessed. Liquids redistributed rapidly within the stomach and emptied after a minimal lag period. Dextrose delayed liquid emptying when compared with saline - this delay was associated with (1) increased retention of liquid in the distal stomach, (2) an increase in IPPWs and (3) suppression of antral waves. Solid emptying was slower than liquid emptying and was characterised by a lag period, followed by approximately linear emptying. Dextrose delayed gastric emptying of solids by increasing proximal stomach retention and increasing the lag period.

In conclusion, the new technique described in this thesis is reproducible and sensitive to physiological changes, and can be used, not only for routine clinical studies, but also for experimental investigation of the mechanisms of gastric emptying in normal and pathological subjects.

Declaration of Authorship

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any University; and to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

I also consent to the thesis being made available for photocopying and loan.

Peter Collins

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With the following exceptions, I am wholly responsible for the development of the radionuclide methods described in this thesis. I developed the algorithms, wrote the computer programs and performed and analysed most of the studies. The experiments described in section II were joint collaborative works performed with Dr Horowitz, who has used the radionuclide method, for total stomach measurement, in a variety of clinical problems in his thesis. The manometric methods described in section III were developed by Dr Heddle, Dr Houghton, Professor Read and Dr Dent. Dr Heddle has used the duodenal lipid experiment data in his thesis. I acknowledge with gratitude Dr Bronte Gabb from the University of Adelaide for assistance with the statistical analysis.

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SECTION I
LITERATURE REVIEW

CHAPTER 1 THE PHYSIOLOGY OF GASTRIC EMPTYING

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CHAPTER 1
THE PHYSIOLOGY OF GASTRIC EMPTYING

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1.1 INTRODUCTION

The role that the stomach plays in the digestive process is twofold. Firstly, its secretions aid in the digestion, or breaking down of food, and secondly, it is responsible for the controlled delivery of nutrients to the small intestine, where they are absorbed into the blood. In its latter role, the stomach serves as a reservoir, enabling the body to ingest large meals, which can subsequently be fed to the small intestine at a rate which favours optimal absorption.

This chapter will focus on those aspects of stomach physiology that are primary to our understanding of how the stomach empties food - whether this is in the form of digestible solid, non-digestible solid or liquid. Consequently, the emphasis will be on motor, as distinct from secretory, events.

There have been a number of comprehensive review articles in the area of gastric motility - these include articles by Sheiner (1975), Heading (1980, 1987), Kelly (1981), Malmud (1982), Minami and McCallum (1984) and Meyer (1987).

1.2 FUNCTIONAL ANATOMY OF THE GASTROINTESTINAL TRACT

(i) Gastric musculature

The stomach contains three layers of visceral muscular fibres - longitudinal, circular and oblique. The longitudinal muscles, which are outermost, consist of two sets. One set, which is continuous with the longitudinal fibres of the oesophagus, passes along the lesser curvature and ends in the proximal pyloric region. The other set extends down the greater curvature of the stomach, with the more superficial fibres passing on to the duodenum. The deeper fibres turn in and intermingle with the fibres of the pylorus. The longitudinal muscles, across the anterior and posterior surfaces, are only very thin.

The circular muscles, internal to the longitudinal muscles, are continuous throughout the stomach, gradually increasing in thickness as they extend into the distal stomach, where they are the predominant muscle structure in the terminal antrum and pylorus. The fibres are continuous with the oesophagus, but are separated from the duodenum by connective tissue.

The oblique muscle fibres, which are innermost, start at the cardiac notch and sweep downwards over the anterior and posterior surfaces of the stomach. In the proximal stomach, they run parallel to the lesser curvature, gradually assuming a more transverse direction as they move down the stomach and, in the distal stomach, they blend in with the circular muscle.

(ii) Innervation of the gastrointestinal tract

The peripheral nervous system (ie. outside the central nervous system (CNS) of the brain and the spinal cord) can be viewed as three separate functional groups - the somatic, the autonomic (visceral) and the enteric nervous systems. Most of the gastrointestinal tract (and in particular the stomach) is innervated by fibres of the autonomic and enteric nervous systems.

a. <u>The enteric nervous system</u>

The enteric (intrinsic) nervous system consists of a number of distinct networks, or plexuses, that are distributed within the walls of the gastrointestinal tract and which function as integrated units. The two main plexuses are the myenteric plexus, which is situated between the longitudinal and circular muscle layers, and the submucosal plexus, which lies between the circular muscle and the mucosa. These two networks extend without discontinuities from the oesophageus to the anal canal. Neural connections exist between the two plexuses as well as with the mucosa, the muscle and the autonomic nervous system.

Sensory receptors (mechano-, chemo- or thermoreceptors) generate signals in the form of action potentials, which travel on afferent fibres to the plexus. For example, mechanosensitive endings are present in the gastric wall and are " activated by spontaneous, or vagally induced contractions and also by distention or compression of the stomach" (Roman and Gonella, 1987). Excitatory, or inhibitory signals, are then sent along efferent fibres to the appropriate effector systems (musculature, secretory or absorptive epithelium, blood vessels or endocrine cells). These reflex actions, located entirely in the enteric nervous system , are termed short loop reflexes. The system is not just a series of individual reflexes, as the interneuron connections can form pattern generating circuitry for the automatic control of repetitive cyclic motor phenomena (for example, the cyclic contractions of muscles of the antrum during digestion).

It can be seen therefore that the enteric nervous system is not, as previously thought, a simple relay distribution centre for autonomic nerves, but "an independent integrative system with structural and functional properties analogous to the CNS" (Wood, 1987). It can initiate and coordinate gastrointestinal activities - input from the autonomic nervous system (extrinsic nerves) is such as to modulate, rather than control, the enteric nervous system

b. <u>The autonomic nervous system</u>

Modulation of enteric nervous control can occur directly from signals from the CNS, or from long loop reflexes - these reflexes travel over afferent fibres from sensory receptors in the GIT, or from neurons of the enteric plexuses (Gabella, 1987), to the CNS and return along parasympathetic or sympathetic pathways. Peptides may be involved, at least in part, as neurotransmitters in the transmission of these reflexes - VIP, gastrin/cholecystokinin, substance P and somatostatin have been proposed (Hokfelt, 1979).

Parasympathetic: Efferent fibres of the parasympathetic system, which originate in the lower medulla oblongata, are carried by the vagus nerve to the stomach, small intestine and proximal large intestine. Another branch ,the sacral parasympathetic, originates in the spinal cord at the level of S1-S3 and supplies the large intestine (colon).

The preganglionic vagal fibres (cholinergic), which terminate on neurons in the enteric nervous system, are of two types - stimulation of some fibres has an excitatory effect on gastric function, while stimulation of others has an inhibitory effect (Roman and Gonella, 1987). With regard to the inhibitory effects of extrinsic nerves on stomach muscle function, relaxation is thought to occur through the action of preganglionic cholinergic fibres which synapse on inhibitory fibres (non cholinergic, non adrenergic) of the enteric nervous system. Vasoactive intestinal peptide (VIP) and ATP have been proposed as possible neurotransmitters in this inhibitory action (Baumgarten ,1982). The postganglionic excitatory fibres, which contract smooth muscle in the gastrointestinal tract, are cholinergic.

Sympathetic: Preganglionic sympathetic fibres, which are cholinergic, arise from neurons in the spinal cord (T5 to L2-3), pass through the sympathetic chain and synapse with neurons in the prevertebral ganglia (coeliac, superior mesenteric and inferior mesenteric). Postganglionic sympathetic efferent fibres, which innervate the stomach and proximal small intestine, are mainly from the coeliac ganglion - these fibres, which are adrenergic, pass along branches of the coeliac artery. The chief effect of stimulation of these efferent fibres is inhibition of stomach function (Roman and Gonella, 1987). Most postganglionic adrenergic axons synapse with enteric neurons and consequently have an indirect effect on gastric motility.

In summary, neural control of the gastrointestinal tract, and in particular the stomach, occurs in two distinct nervous systems. The primary level involves afferent and efferent pathways which are entirely within the enteric nervous system and results in coordinated gastrointestinal activity. The other level (autonomic nervous system) involves connections between the plexuses and the prevertebral ganglia or the CNS (spinal cord and medulla). This system acts to modulate activity at the primary, intrinsic level.

1.3 GASTROINTESTINAL PEPTIDES

Peptides, which are small proteins, are known to play an active role in the function of the gastrointestinal tract. The sphere of influence of these chemical messengers, which are released as a direct, or indirect consequence of the ingestion of food, is wide and varied. They are involved in regulating the secretion and absorption of water and electrolytes, the growth of the stomach, small intestine and pancreas, the release of other peptides, as well as influencing gastrointestinal motility (Johnson, 1985).

(i) Site of release and mode of action

Some GIT peptides are classical ***hormones*** - they are released from endocrine cells, travel in the general circulation and can influence gastrointestinal function at a site considerably removed from their point of origin. There are four known gastrointestinal hormones - secretin, gastrin, cholecystokinin (CCK) and gastric inhibitory peptide (GIP). Some of the actions of these hormones are as follows. Secretin, the first hormone named, is released from the duodenal mucosa by hydrochloric acid and stimulates pancreatic bicarbonate and fluid secretion. Gastrin stimulates gastric acid secretion in response to protein meals, while GIP, as its name implies, inhibits gastric secretions. GIP, which is released from intestinal mucosa by fat and glucose in the meal, also stimulates insulin release. CCK, a potent stimulator of gallbladder contraction, is released by the action of fatty acid on small bowel receptors. Hormones may also stimulate or inhibit the release of other hormones - for example, secretin can inhibit the release of gastrin from the stomach.

A number of other peptides may have hormonal action - these include pancreatic polypeptide, motilin, enteroglucagon, neurotensin, substance P, neuropeptide Y and peptide YY.

Peptides are also found in nerve endings and may act as ***neurotransmitters***. There are a number of peptides which are thought to act as neurotransmitters (Wattchow et al, 1988). Vasoactive intestinal peptide (VIP) is contained in the nerves of the gut and is thought to mediate relaxation of gastrointestinal smooth muscle. Gastrin releasing peptide (GRP), which is found in the nerves of the gastric mucosa, is thought to be the neurotransmitter in the vagal release of gastrin. The pentapeptides, leu- and met-enkephalin, are found in the nerves supplying smooth muscle and mucosa of the gastrointestinal tract. These neurotransmitters are thought to activate opiate receptors on circular smooth muscle and stimulate contractions - both peptides cause contraction of the pylorus and the lower oesophageal and ileocaecal sphincters.

Other peptides which may act as neurotransmitters include substance P, neuropeptide Y, and somatostatin.

Some peptides which are released from endocrine cells, do not travel in the bloodstream, but interact with receptors close to the point of release. As these local chemical messengers, referred to as ***paracrines***, may also stimulate hormone release, their effect is not necessarily limited to the place of origin. Somatostatin, found in gastric and duodenal mucosa and in the pancreas, is thought to function as a paracrine. It has been shown to inhibit the release of all gut hormones.

(ii) Problems associated with the study of GIT peptides

There are a number of problem areas in the study of gastrointestinal peptides (Bloom and Polak, 1978). The endocrine cells that contain gastrointestinal hormones are not clustered together, as with the glandular endocrine system, but are dispersed among the epithelial cells. Extirpation of a single cell type is not possible and tissue samples contain many different hormones as well as proteins and other peptides which interfere with the analysis.

Gastrointestinal peptides may have similar chemical structures and consequently, overlapping physiological responses. Gastrin and CCK are closely related (the five carboxy-terminal amino acids are identical), while secretin, glucagon, GIP and VIP also have common amino acid sequences. This has hindered the development of tests for specific hormones in test samples (for example, CCK levels in the presence of gastrin). Although target cells have an affinity for a particular peptide, these cells do respond, in a reduced way, to a large range of other peptides. Thus many hormones are known to stimulate a particular effector system (for example, antral contraction), but it is difficult to assess whether they have an effect at physiological concentrations.

Paracrines and neurotransmitters have very short path lengths and there are no easy techniques for measuring the small quantities that are produced in the intercellular fluid. However, the recent availability of specific inhibitors (antagonists) is aiding the study of these chemical agents. For example, the use of specific H2 receptor blocking agents has demonstrated that histamine does act in physiological concentrations to control the release of gastric acid. The development of peptide antagonists, such as the recently introduced CCK antagonist (Pendleton et al, 1987), will provide researchers with a powerful tool for studying the role of peptides in gastrointestinal physiology.

Finally, a peptide can fill more than one role - for example, CCK, a known hormone, is also found in nerve endings and may serve as a local chemical messenger (neurotransmitter or paracrine).

(iii) Effect on gastric emptying

After ingestion of a nutrient meal a number of intestinal hormones are released into the general circulation and are thought to influence gastric motility. For example, gastric emptying is slowed by apparently physiological concentrations of cholecystokinin (Debas et al, 1975, Liddle et al, 1986), secretin (Kleibeuker et al, 1988), peptide YY (Pappas et al, 1986), gastric inhibitory polypeptide (Brown et al, 1975) and glucagon (Phaosawasdi and Fisher, 1982).

1.4 MOTOR EVENTS ASSOCIATED WITH GASTRIC EMPTYING

The stomach can be considered as two separate motor regions - a proximal region comprising the fundus and approximately one third of the body, or corpus, while the distal stomach comprises the remaining corpus, the antrum and the pylorus (Kelly, 1980). The proximal stomach exhibits mainly slow sustained contractions, which move stomach contents into the distal region. The distal stomach generates aborally propagated peristaltic contractions, which start high in the distal stomach and sweep downwards to the pylorus, carrying some of the contents through into the duodenum. The motor events responsible for gastric emptying will now be described in detail.

(i) The proximal stomach

The motor pattern of the proximal stomach is mainly one of slow, strong contractions (tonic contractions), on which are superimposed rapid (phasic) events, which are nonpropagating. The tonic contractions last 1 to 3 minutes and have an amplitude of 10 to 50 cm of water, while the phasic contractions are weaker (5 to 15 cm of water) and last between 10 and 15 seconds.

On ingestion of food, the proximal stomach can distend enabling large amounts to be eaten wihout major changes in intragastric pressure. Even before the food bolus reaches the stomach, the proximal stomach temporarily relaxes - this is termed "receptive" relaxation and is vagally mediated (Cannon and Lieb, 1911). This is followed by a more prolonged "adaptive" relaxation ,often termed accommodation. Mechanoreceptors within the gastric muscle, which respond to stretch, enable this adaptive relaxation response. Accommodation is severely compromised by proximal vagotomy (Wilbur and Kelly, 1973) and relaxation of the proximal stomach is thought to be mediated by preganglionic vagal fibres acting on noncholinergic, nonadrenergic inhibitory fibres of the enteric nervous system (Azpiroz and Malagelada, 1986).

(ii) The distal stomach

A major motor difference between the proximal and distal stomach is the ability of the distal stomach to produce peristaltic contractions. These are circular rings of contraction that sweep distally through the stomach. The basis for these contractions are electrical events called pacesetter potentials (slow waves, electrical control activity, basic electric rhythm), which occur in the longitudinal smooth muscle cells.[o] The inherent frequency of occurrence of slow waves progressively declines from the orad corpus to the pylorus. However, the fastest beating area, called the gastric pacemaker, drives or entrains the more distal regions to its own frequency (approximately 3 cycles/minute in humans). The location of the pacemaker is at the junction of the proximal and distal stomach, on the greater curvature (Kelly and Code, 1971).

Slow waves propagate as a ring, increasing in velocity as they approach the pylorus. For contractions to occur during a slow wave ,another electrical phenomenon called an action potential (spike potentials, burst potentials, or electrical response activity) must occur. These rapid electrical spikes, when superimposed on the slow wave, initiate muscle contraction and hence sweeping peristaltic activity. The greater the amplitude and duration of the burst of action potentials, the stronger the contractions (Kelly et al, 1969). The site at which peristaltic waves

[o] Pacesetter potentials are myogenic, as they originate and transmit along muscle. They can be modified by intrinsic, or extrinsic nerves.

begin is a function of the "tone" of the distal gastric wall and of the magnitude of the intragastric pressure. The greater the intragastric pressure, the more distal the site at which the peristaltic wave begins, as "the contracting circumference, having to meet a greater distending force, is moved to a region where the muscles are stronger and in a smaller ring" (Cannon, 1911). Although gastric slow waves occur without the involvement of nerves, the enteric nervous system is necessary for the occurrence and co-ordination of peristaltic waves. Extrinsic nerves (parasympathetic and sympathetic) act to modulate these basic motor events in the antrum. Afferent nerves, responsive to mechanical and chemical perturbations are present in the distal stomach and influence emptying (Kelly, 1981).

There is still some controversy concerning the motor patterns in the pylorus, or gastroduodenal junction. It has been known for some years that the pylorus can contract as part of an integrated contraction involving the terminal antrum and proximal duodenum (Carlson et al, 1966, Code 1970, Ehrlein and Hiesinger, 1982), but recent work has also suggested that under certain conditions it may be capable of independent phasic and tonic contractions in the absence of associated contractions in the antrum or duodenal cap (White et al, 1983, Houghton et al, 1988, Heddle et al, 1988b, Fone et al, 1989). Phasic contractions, apparently confined to a narrow zone of phasically active pylorus, have been called isolated pyloric pressure waves (IPPWs) (Houghton et al, 1988, Heddle et al, 1988b).

The integrated behaviour of the antrum, pylorus and duodenum, as well as independent pyloric activity, are probably under myogenic control (Schuurkes and VanNeuten, 1984, Bertiger et al, 1987). The pylorus has excitatory (vagal) and inhibitory (vagal and sympathetic) nerve fibres, which serve to modulate pyloric function.

1.5 EMPTYING PATTERNS OF THE STOMACH

The stomach has the ability to discriminate between the various components of a meal (namely liquids, digestible solids and non-digestible solids) and empty them at different rates into the duodenum. Hinder and Kelly (1977) demonstrated in dogs that liquids are emptied rapidly, digestible solids are emptied more slowly and large non-digestible solids (greater than 7 mm) are retained within the stomach for a considerable period.

The underlying motor mechanisms involved in gastric emptying are still poorly defined. This is due to (i) problems in measurement and (ii) lack of concurrent assessment of emptying and motility (for example, using combined radionuclide and manometric techniques)

One model that has been proposed to explain the way that the stomach handles meals of different consistencies is called the Two Component Model (Kelly, 1980). This model assigns the major role in the emptying of liquids and solids to the proximal and distal stomach respectively. However, there is increasing evidence for a more complex multicomponent model of gastric emptying (Meyer 1987), with various mechanisms involved in the close regulation of gastric emptying.

(i) Gastric emptying of liquids

Isotonic solutions are observed to empty from the stomach in an exponential fashion, with the rate being dependent on the pressure gradient across the gastroduodenal junction. Intragastric pressure, which is largely controlled by proximal stomach tone, is probably a major contributing factor to this pressure gradient. Proximal stomach vagotomy, which impairs adaptive relaxation, increases intragastric pressure and increases the rate of gastric emptying of liquids (Wilbur and Kelly, 1973). Barostat experiments, in which intragastric pressure can be modified, show a linear relationship between pressure and the rate of gastric emptying (Strunz and Grossman, 1978).

Although the distal stomach probably plays a minor role in the emptying of isotonic saline solutions (Dozois et al, 1971), there is increasing evidence that it has a significant role to play in the emptying of nutrient liquids (Miller et al, 1981, White et al, 1983, Heddle et al, 1988c).

Miller et al (1981) ,using barostats to control the gastro-duodenal pressure gradient in the dog, found that even at zero pressure gradient , there was a significant flow rate (18 to 25 ml/minute) from the stomach. They showed that with infusion of glucose, fat or acid (all known intestinal inhibitors of antral peristalsis) in the intestine, the flow rate from the stomach was reduced.

There is increasing evidence to support the view that the pylorus acts to control transpyloric flow of nutrient liquids. Miller et al (1981) found that the inhibitory effects of intestinal fat, or acid on gastro-duodenal flow, was abolished after pyloric myotomy. Intragastric infusion of lipid (White et al, 1983), and intraduodenal infusion of lipid (Heddle et al, 1988a) and dextrose (Heddle et al, 1988c, Fone et al, 1989) has been shown to increase phasic and tonic pyloric contractions.

Besides influencing the rate of gastric emptying via a feedback mechanism (neural and/or hormonal pathways), the proximal duodenum may also act to obstruct flow of nutrients from the stomach by increasing the resitance to flow with non propogating contractile events (Thomas, 1957, Williams et al, 1986).

The emptying pattern for nutrient liquids is not a single exponential - there is an initial early emptying phase of 5-10 minutes duration, followed by a slower phase, which becomes progressively more linear, with increasing concentrations of nutrients (Meyer, 1987).

(ii) Gastric emptying of digestible solids

The distal stomach plays a major role in the emptying of digestible solid food from the stomach. During peristalsis, the solid and liquid food is propelled towards the pylorus, which starts to close, allowing only small solid particles less than 1 mm diameter (Meyer et al, 1979, 1981) to pass into the duodenum with the liquid. Particles larger than 1 mm are compressed during the terminal antral contraction with resulting retrograde movement into the corpus. This sequence of propulsion, grinding and retropulsion that occurs in the antrum, has the effect of thoroughly mixing the remaining solid food with gastric juice and breaking down the particles (trituration) into a size where they can be cleared from the stomach. With the total closure of the pylorus and terminal antrum, the proximal duodenum contracts to propel its contents distally.

The pylorus probably has a major role to play in restricting flow back into the stomach (duodeno-gastric reflux). It may also have a role to play, independent of the antrum and duodenum, in the regulation of solid emptying. In two recent experiments, the reduction in gastric emptying of a solid meal, as a result of stress (Fone et al, 1990a), or terminal ileum lipid infusion (Fone et al, 1990b), was associated with a significant increase in isolated pyloric pressure waves.

It is evident that gastric emptying of solids involves precise co-ordination of the motor events of the distal stomach, pylorus and proximal duodenum. This co-ordination in the distal stomach is a major factor in the selective handling of solids and liquids in the stomach (solid/liquid discrimination). Severing the vagus nerve reduces antral contractions and impairs antral trituration (Kelly, 1980). Antrectomy hastens the emptying of solid food from the stomach in dogs, as larger than usual particles enter the duodenum with liquids (Meyer et al, 1979). Small particles of food require less trituration to reduce them to chyme and empty faster from the stomach than large particles. Thoroughly triturated solids empty at a rate similar to liquids (Hinder and Kelly, 1977)

The proximal stomach is thought to have a limited role to play in the emptying of solid food. In dogs (Wilbur and Kelly, 1973) and in humans (Sheiner el al, 1980) proximal vagotomy had minimal effect on the rate of emptying of solid food from the stomach.

Hunt (1983) argues that the pressure resistance in the duodenum has a major role to play in regulating emptying of solids - chyme cannot leave the stomach until the duodenal cap is empty. After myotomy of the first and second part of the duodenum in dogs, contractile activity is diminished and the rate of gastric emptying is increased (Bortolotti et al, 1981).

(iii) Gastric emptying of non-digestible solids

Small particles (less than 1 mm in size) of non-digestible solid are emptied from the stomach with digestible food (Malagelada et al, 1980a) while larger particles are retained in the stomach. These particles are emptied from the stomach during a sequence of motor events which occurs during the fasting state and is termed the migrating motor complex (MMC), or the interdigestive (fasting) myoelectric complex (Code and Marlett, 1975). This complex has 4 phases and cycles during the fasting state approximately every 2 hours. Phase 1 is a relatively inactive motor period, while in phase 2 there are a number of contractile events whose frequency gradually increases. The motor activity culminates in phase 3, which is of 5 to 15 minutes duration. In this phase, there are intense bursts of action potential which occur with every pacesetter potential (one every 20 seconds) and result in powerful peristaltic waves. These intense waves sweep down the entire antrum and any remaining large particles are swept from the stomach. Phase 4 is an intermediate phase between the intense activity of phase 3 and the inactive phase 1 of the next cycle. The control of this cyclic activity is not completely understood. The hormone motilin may be an important stimulus for phase 3 - nervous control, however, probably plays a minor role in generating MMCs as this activity persists after vagal and splanchnic section (Meyer, 1987).

The 'fasting' pattern of motor activity is unchanged with the ingestion of isotonic solutions such as isotonic saline (Malagelada, 1981), but reverts to a 'fed' pattern (vigorous contractions in the antrum and duodenum) on ingestion of solid, or liquid nutrients.

1.6 PHYSIOLOGICAL FACTORS WHICH INFLUENCE GASTRIC EMPTYING

In this section, physiological factors which relate to the subject under investigation, and which influence the rate of gastric emptying, are discussed.

(i) Gender

There are conflicting reports as to the effect of gender on gastric emptying. Some workers (McCallum et al, 1985, Shay et al, 1987, Horowitz et al, 1984) have found similar emptying rates between men and women - others have demonstrated gastric emptying rates for solids (Wright et al, 1983, Jonderko, 1987, Rao et al, 1987) and liquids and solids (Datz et al, 1987, Hutson et al, 1989) which are slower in women than in men. The disparate results may be due to a number of differences in methodology - for example, variations in the composition of the meal, the inclusion of obese or elderly subjects in the study, or the use of different imaging techniques (correction for attenuation etc.).

Horowitz and co-workers (1985) have reported that the normal menstrual cycle does not effect gastric emptying of solid and liquid meals. However, Hutson and colleagues (1989) found that premenopausal women, and postmenopausal women taking hormone replacement therapy, had slower emptying of solids than men, while the emptying rate of solids in postmenopausal women not on hormone replacement was similar to men.

In view of the above results, it is possible that there is a variable inhibitory effect of female hormones on gastric emptying.

(ii) Age

Kupfer et al (1985), using ultrasound techniques, found a faster initial (first 5 minutes) liquid gastric emptying rate in elderly subjects compared with young controls. However, recent studies using radionuclides have demonstrated retarded gastric emptying of the liquid component (Moore et al, 1983, Wegener et al, 1988) or both the solid and liquid component (Horowitz et al, 1984) of a mixed meal in elderly subjects. The changes with age are small (Horowitz et al, 1984) and are unlikely to be of clinical significance.

(iii) Exercise and stress

a. Physical

Cammack and co-workers (1982) have reported an increase in gastric emptying with mild to moderate exercise. This effect was not observed by Carrio and co-workers (1989); however, they did report a slower basal rate of emptying with sedentary subjects compared with long distance runners. Severe or violent exercise, delays gastric emptying (Ramsbottom and Hunt, 1974), possibly related to the release of endogenous opiates due to muscle activity (Read and Houghton, 1989)

Two stressors that act through the central nervous system have been shown to effect gastric emptying. Labyrinthine stimulation (ear irrigation with cold water), at subnauseant levels, markedly delayed emptying of a liquid meal (Thompson et al, 1982). Cold pain, induced by plunging the arm repeatedly into ice cold water, delays gastric emptying of both liquids (Thompson et al, 1983) and solids (Fone et al, 1990a). In the later study, Fone and colleagues reported an increase in isolated pyloric pressure waves and a decrease in antral motility , which are likely to be of importance in the delay mechanism.

b. Psychological stress

There is limited information on the effect of psychological stress on gastric emptying. Acoustic stress caused a transient delay in solid and liquid emptying in dogs (Gue et al, 1989). Cann and colleagues (1983) could not demonstrate any significant effect on gastric emptying of solids using prolonged mental stress (dichotomous listening test) in humans. However, in a recent publication, Roland and co-workers (1990) also used a dichotomous listening test to induce mild stress, and reported a significant inhibitory effect on gastric emptying. Unlike Cann and co-workers (1983), these workers used a meal consisting of only one homogeneously labelled component (pancake) - they also corrected for tissue attenuation, which is a potential source of error for the measurement of emptying rate (Tothill et al, 1978). It is possible therefore, that psychological stress may have an inhibitory effect on gastric emptying.

1.7 DRUGS AND GASTRIC EMPTYING

A number of ***medications*** are known to influence gastric motility - these include, opiates, anticholinergics, levodopa, beta-adrenergic agonists, tricyclic antidepressants, and, to a lesser degree, aluminium hydroxide antacids (McCallum et al, 1987)

The rate of gastric emptying of a solid meal is reduced with ***smoking*** (Nowak et al, 1987, Gritz et al, 1988). Miller and co-workers (1989) also reported a delay in emptying of solids, but found no effect of smoking on the liquid component of a mixed meal.

1.8 THE REGULATION OF GASTRIC EMPTYING

The stomach is a reservoir which passes nutrients to the small intestine at a controlled rate which aids the process of digestion and absorption. There are receptors (mechano-, thermo-, chemo-) within the stomach, small and large bowel, which are sensitive to the physical and chemical properties of the meal - these receptors activate feedback mechanisms which enhance, or limit, gastric emptying. For example, distention of the oesophageus or duodenum induces a vagally mediated relaxation of gastric tone (De Ponti et al, 1989), and rectal distention, at a level below that which causes discomfort, delays emptying of solid from the stomach (Youle and Read, 1984).

(i) Physical properties of the meal

The characteristics of the meal which act on the mechano- and thermoreceptors are now discussed.

a. Meal consistency

Gastric motility is dependent on the physical properties of the meal (whether liquid, semi-solid or solid), over and above its chemical composition, as is shown by the study of Rees and co-workers (1979) who observed that particulate food induced more antral phasic contractility than the same food as a homogenate.

Increasing the viscosity of a liquid meal decreases the emptying rate (Holt et al, 1979) - either due to a reduction in the amplitude of the peristaltic contraction (Prove and Ehrlein, 1982), or because the greater inertia of the viscous solution resists propulsive contractions (Read and Houghton, 1989).

The particle diameter, particle density and fluid viscosity also influence gastric emptying of solids - an effect due probably as much to hydrodynamic effects within the stomach, as to regulatory processes involving receptors (Meyer, 1987). The canine gastric emptying rate of spheres with a density of 1 (water), increased as sphere diameters decreased from 5 to 1 mm, whereas spheres with densities greater than, or less than water emptied more slowly than spheres of the same size with a density of 1 (Meyer et al, 1985). Similar results were obtained in man (Meyer et al, 1988a). Holt and co-workers (1982) found that liver given as small cubes emptied faster than larger cubes.

Meyer and co-workers (1986) using a mixed solid (containing ^{99m}Tc labelled liver and 3.2 mm plastic spheres) and liquid meal found that increasing the viscosity of the meal increased the rate of emptying of the spheres and increased the diameter of the liver particles emptied. They concluded that meal viscosity significantly affects solid/liquid discrimination ("gastric sieving"). Solid particles, which are suspended in viscous solutions, would resist segregation from fluids due to gravity and contractile forces and are more likely to exit from the stomach with the liquid (Meyer, 1987, Read and Houghton, 1989).

b. Meal size

For liquids, increasing the volume of the test meal results in faster absolute emptying rates (Hunt et al, 1985), most likely due to an increase in intragastric pressure. Similarly for solids, increasing the meal weight, while keeping the caloric content the same, increases the absolute emptying rate - this effect may be due to "activation of stretch or volume receptors which, in turn, may stimulate antral peristalsis" (Moore et al, 1984).

c. Meal temperature

Bateman (1982), using ultrasonic methods to study liquid emptying, noted that the initial emptying rate (first 5 minutes) was faster for cold liquids than those at body temperature. There was no difference in the subsequent rate between the two test meals. These results suggest that meal temperature effects adaptive relaxation mechanisms - an effect which diminishes as the liquid is warmed to body temperature.

McArthur and Feldman (1989), using aspiration techniques, found no difference in the rate of gastric emptying of hot ($58^{0}C$), warm (body temperature), or cold ($4^{0}C$) coffee meals. However, their method did not enable them to assess the early phase of emptying.

(ii) Chemical properties of the meal

Besides the physical nature of the meal (solid, liquid, etc.) its chemical nature also has an influence on gastric emptying. There are a number of receptors in the small intestine (in particular the duodenum) which respond to the chemical composition of the meal and act through poorly defined neural and/or hormonal pathways to delay gastric emptying. Meyer (1987) argues that most evidence favours the former pathway (for example, the inhibition of antral contractions by intraluminal fat is markedly reduced by truncal vagotomy (Thomas, 1957)), and the role of hormones is best described as "modulation rather than control" (Strunz, 1979).

a. Small bowel chemoreceptors

Nutrient specialization: The osmolarity of chyme has long been known to influence gastric emptying (Carnot and Chassevant, 1905). Hyper- or hypotonic solutions are emptied more slowly than those of physiological (extracellular fluid) tonicity. However, the osmolarity of the duodenal contents are not the only factor as "acid, fatty acids, carbohydrates, amino acids and peptides have special potencies above their osmotic activities" (Meyer, 1987). Acid receptors found in the proximal duodenum and jejunum act to slow gastric emptying - the higher the concentration, the greater the inhibitory effect. Fatty acids are potent inhibitors of gastric emptying, particularly medium chain fatty acids (Hunt and Knox, 1968). Carbohydrates and amino acids (except for L-trytophan, which has a separate effect) probably retard gastric emptying mainly through osmoreceptors.

Regional specialization: The mechanisms for regulating gastric emptying have a regional as well as nutrient specialization (Azpiroz and Malagelada, 1985). Although many of the receptors (for example, for acid, amino acid, lipid and hypertonic solutions) are found in the duodenum and upper jejunum, the distal small intestine may also have a role to play in regulating emptying (Welch et al, 1988, Jain et al, 1989).

b. Rate of transfer of calories to the duodenum

McHugh and Moran (1979) found in rhesus monkeys, that solutions of glucose, casein and medium chain triglycerides containing 0.5 kcal/ml, emptied from the stomach at a similar rate. Brener and co-workers (1983), using a liquid glucose meal in humans, found that calories were delivered to the duodenum at a constant rate of approximately 2 kcal/minute. Hunt (1983) argues that the rate of transfer to the duodenum is independent of the proportion of fat, carbohydrate and protein in the meal and puts forward the hypothesis that the regulation is achieved, not through energy receptors, but "through the osmotic effect and calcium binding of the products of digestion in the duodenum".

Most nutrients inhibit in a load dependent fashion, with the slowing of gastric emptying proportional to the amount of nutrient entering the bowel per minute (McHugh and Moran, 1979). Lin and co-workers (1989), who studied the inhibition of gastric emptying by glucose, postulate that the "load dependent gastric emptying results from the saturation of mucosal absorptive mechanisms, so that a longer length of bowel is exposed to unabsorbed nutrients as more nutrient enters the intestine".

In conclusion, the stomach acts in a complex way to deliver nutrients to the small intestine. Various sensors, both within and outside the stomach, monitor emptying and bring into play regulatory mechanisms (mechanical, neural and hormonal), which help nutrient delivery and hence optimize absorption of nutrients from the small bowel.

CHAPTER 2
EVALUATION OF GASTRIC EMPTYING USING RADIONUCLIDE METHODS

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2.3 Radionuclide methods

2.4 Radiopharmaceuticals

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- **(vi) Superposition of stomach and proximal small bowel**

2.9 Reproducibility of radionuclide methods

2.10 Parameters for the analysis of gastric emptying data

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2.1 INTRODUCTION

In this chapter, the radionuclide methods used for the measurement of gastric emptying are discussed in detail. However, before covering these techniques, a summary of the non-radionuclide methods that have been used to study gastric emptying is given.

2.2 NON-RADIONUCLIDE METHODS

(i) Intubation methods

A number of different intubation techniques have been described which enable measurement of gastric emptying. These use a nasogastric tube for instillation and aspiration of test solutions. The serial test meal method (Hunt and Spurrell, 1951) uses a nonabsorbable marker, such as phenol red, in a specific volume of the test solution. After a specified time interval, the entire gastric contents are aspirated and the amount of liquid meal emptied from the stomach, as well as the contribution from gastric secretions to the liquid volume, are determined. By repeating this procedure on several days, with the meal being removed at different intervals, the entire emptying curve can be constructed (assuming that gastric emptying is similar on different days).

A double sampling technique (George, 1968) overcomes the problem of repeated intubation and the time limitations of the serial test method. In this technique small samples of the test meal are aspirated from the stomach and replaced with a small volume of known, concentrated marker. With repeated sampling, the remaining gastric volume can be calculated at each sampling time interval. The amount of gastric secretion can also be calculated from the chloride concentration of the sample (Hunt, 1974).

Meeroff and colleagues (1973) introduced a more sophisticated method which employs both gastric and duodenal intubation. This method uses both gastric and duodenal markers and enables measurement, not only of gastric emptying, but also pancreatic and biliary secretions. This method has been adapted by Malagelada and co-workers (1976) to study solid food emptying. However, as this complex technique has a number of possible problems including, intubation of the duodenum, influences of the tube on the antroduodenal area, and difficulty in recovering all the marker from the duodenum (Sheiner, 1975), it has been used only in a limited research setting.

Intubation methods, although reliable and reproducible (Hunt and Spurrell, 1951), are invasive and except for the method of Malagelada and co-workers (1976), can only be used for the study of liquid emptying. They are too complicated for routine clinical use, but have a role to play in some research investigations.

(ii) Radiological methods.

The emptying of liquid barium sulphate, or solid meals impregnated with enteric-coated barium sulphate granules can be assessed with radiological techniques. However, as it is not possible to accurately determine the amount of barium in the stomach, these methods only effectively measure the time for total emptying and provide little information about the rate of emptying (Sheiner, 1975). The accuracy of the method in the study of solid emptying is also questionable, as barium may dissociate from the solid meal and empty with the liquid phase (Minami and McCallum, 1984). Finally, radiological studies are associated with a significant radiation exposure to the subject.

(iii) Ultrasound techniques

Gastric emptying of liquid meals can also be measured using non-invasive ultrasound methods (Bateman and Whittingham, 1982). The volume of the meal remaining in the stomach, at various time intervals after ingestion, is calculated by adding cross-sectional areas of a series of slices through the stomach. However, the gastric fundus is often difficult to visualize because of the presence of gas and also because of its relative inaccessibility behind the costal margin (Mamtora and Thompson, 1989). The method is time consuming and cannot be used for accurate measurement of the emptying rate of solid meals as solid particles reflect the sound beams. The technique may have a useful role to play in the study of mechanisms involved in transpyloric flow (King et al, 1984), but it appears to have limited use for the measurement of gastric emptying.

(iv) Applied Potential Tomography

Another non-invasive method that has been used to measure gastric emptying is Applied Potential Tomography (Avill et al, 1987). This technique measures changes in resistivity of gastric contents during emptying of a meal, using electrodes placed in a circular array around the trunk. The rate of gastric emptying of conducting (soup) and non-conducting (5% aqueous sucrose) liquids, as well as semi-solid (mashed potato) meals, have been assessed using this technique (Avill et al, 1987). The method, however, has a number of serious limitations. As gastric acid secretion may affect the measurements, acid blockers, such as cimetidine, need to be administered before the study. Correct positioning of the electrodes over the body of the stomach is also necessary for reliable measurement - this is difficult to achieve because of normal anatomical variability. Finally, Applied Potential Tomography measures gastric emptying over a band of approximately 8 cm, and the relationship between this measurement and emptying from the total stomach is uncertain. At its current state of development, the technique appears to have limited research use in the measurement of gastric emptying. However, as it does not involve the use of ionizing radiation, it may, together with ultrasound methods, find a clinical use in sequential studies with pregnant women and infants.

2.3 RADIONUCLIDE METHODS

Radionuclide methods were first introduced by Griffith and co-workers (1966), who used a scanning device to quantify the gastric emptying rate of a solid meal labelled with ^{51}Chromium. In the last two decades the advent of new radiopharmaceuticals and better instrumentation has resulted in the development of an accurate methodology for use both in a clinical and research setting.

Radionuclide methods offer a number of distinct advantages over other methods, such as intubation techniques. They are non invasive and have the capability of continuous assessment of gastric emptying rate. Unlike radiological methods, various components of a physiological meal (liquid, semi - solid, digestible and non - digestible solid) can be labelled separately with radionuclides and studied. Using dual labels, solid and liquid emptying can be measured simultaneously - this may be important in assessing various pathological states where the emptying of one, or both components may be abnormal.

In the following sections, the technical aspects of the measurement of gastric emptying using radionuclides are discussed - in particular, the methodological problems and the errors in measurement due to detector limitations.

2.4 RADIOPHARMACEUTICALS

A large number of radiopharmaceuticals have been used for the measurement of gastric emptying. The radiolabel should ideally be inexpensive, non-toxic, and non-adsorbable to stomach mucosa. As solids and liquids empty at different rates from the stomach (chapter 1.5), it is important that the label remain firmly bound to the food component under investigation for the duration of the study. Dissociation of the solid marker, which then empties with the liquid component and/or adherence of the liquid to solid particles can be a major source of error in the estimation of gastric emptying rates. However some markers, particularly those used in early studies of gastric emptying, are not precise with liquid markers adhering to solids and/or solid markers dissociating and emptying with the liquid (Heading et al, 1971, Meyer et al, 1976, Wright et al, 1981).

(i) Radionuclides

A number of factors need to be considered when selecting suitable radionuclides for use in scintigraphic studies. To minimise the radiation burden to the subject, the radionuclide should have no particulate emissions (alpha or beta rays) and the half life should be as short as possible (measured in hours), keeping in mind the study duration (1-3 hours). It should also have gamma-ray energies suitable for conventional imaging equipment (the scintillation camera). Of the radionuclides available, Technetium (^{99m}Tc) is the most widely used, as it has suitable physical characteristics (half life = 6 hours, Gamma ray energy = 140 kev), is available from widely used commercial generators (parent radionuclide = Molybdenum), and is relatively inexpensive. Other useful nuclides include Indium (^{111}In and ^{113m}In) and Iodine (^{121}I and ^{123}I). The radionuclides of iodine are produced by a cyclotron and may not be available to some investigators.

(ii) Radiolabels for liquid meals

Although liquid markers have been used in gastric emptying studies for many years (Bromster et al, 1968, Chaudhuri, 1974), some of the early markers were not satisfactory. For example, ^{131}I - human serum albumin (Bromster et al, 1968) dissociates in the duodenum and is absorbed into the body. As ^{131}I is a beta emitter it can only be administered in low doses, thus limiting its use for scintigraphic imaging.

The most commonly used markers are in the form of non-absorbable chelates, such as ^{111}In- or ^{113m}In-diethylenetriaminepentaacetic acid (DTPA) (Heading et al, 1971), or ^{99m}Tc-DTPA (Chaudhuri, 1974). However, even with these markers it is likely that in a mixed solid and liquid meal adherence of some of the liquid marker to solid food occurs (Grimes and Goddard, 1977, Moore et al, 1981, Wright et al, 1981, Corinaldesi et al, 1987).

(iii) Radiolabels for digestible solid meals

Many of the early markers used for labelling solids were weakly bound surface labels which readily dissociated and emptied with the liquid component of the meal (or gastric secretions) - (for example, ^{51}Cr, as used in the study of Griffith and co-workers (1966) - Meyer et al, 1976).

The problem of labelling digestible solids was first overcome by Meyer and co-workers (1976). These workers described the use of intracellularly labelled chicken liver, as a marker of solid food. This marker has a very high labelling efficiency and excellent stability, making it an ideal marker.

For those investigators who do not have ready access to live chickens a number of alternative solid labels, using ^{99m}Tc-sulphur colloid, are available. These include - surface labelled liver (McCallum et al, 1980, Christian et al, 1981), pureed meat (pate) (Christian et al, 1981) and egg (Kroop et al, 1979, Knight and Malmud, 1981). The labelling efficiency and stability of pate and surface labelled liver approaches that of invivo labelled liver (Christian et al, 1981, Corinaldesi et al, 1987). However, there are varying opinions as to the stability of labelled egg - discrepancies probably "due, at least in part, to methodological differences" (Corinaldesi et al, 1987). Velasco and co-workers (1982) reported excellent labelling stability for ^{99m}Tc labelled egg when tested in vitro in gastric juice (less than 3% of the label eluted from the solid after 90 minutes). Others, (Christian et al, 1983, Corinaldesi et al, 1987) have reported significant elution of label off the solid, and the accuracy of labelled egg for the study of gastric emptying of digestible solid food is questionable.

(iv) Radiolabels for non-digestible solids

As discussed previously (chapter 1.5(iii)) non-digestible solids, which are resistant to mechanical and chemical breakdown, are emptied from the stomach at a different rate to digestible solids. A number of labels have been used to study non-digestible solids- these include ^{99m}Tc sulphur colloid-filter paper (Heading et al, 1976), ^{131}I-cellulose (Carryer et al, 1982, Malagelada et al, 1980a) and ^{99m}Tc-bran (Sagar et al, 1983).

Markers for other food components (for example, a fat label, ^{75}Selenium-glycerol triether-butter, (Jian et al, 1982)) have also been described.

(v) Radiation dose

The radiation burden received by the subject during a gastric emptying study is dependent on the physical and biological properties of the radiolabel administered. The common radiopharaceuticals have short half lives (^{99m}Tc = 6 hours, ^{113m}In = 100 minutes), have no particulate emissions, are not absorbed into the blood and are administered in low doses (40-80 Megabequerel). Consequently, the whole body radiation dose to the subject is relatively low - it is less than fluoroscopic investigations of the abdomen (Siegel et al, 1983) - and is acceptable for single, or sequential studies.

2.5 INSTRUMENTATION

Although some of the initial studies (Bromster et al, 1968) used probes to measure gastric emptying, the difficulty with probe placement, a problem inherent with these fixed non imaging devices, seriously limited their usefulness. This problem was partially overcome with the use of the rectilinear scanner which produced, at regular time intervals, an image of the distribution of radioactivity in the gastrointestinal tract (Griffith et al, 1966, Heading et al, 1971, Coates et al, 1973). However, the relatively long time for the scanner to form an image (5-10 minutes) limited the temporal resolution of this device.

The scintillation, or gamma camera was first used for gastric emptying studies in 1970

(Harvey et al, 1970, Jones et al, 1970). The use of this static imaging device was a significant advancement as it enabled continuous imaging and when interfaced to a digital computer extensive data analysis could be performed. The computer has also been used to apply correction factors to overcome various limitations inherent in imaging devices (chapter 2.8).

Recently, single photon emission computer tomography (SPECT) systems have been used to study gastric emptying (Moore et al, 1986, Bailey et al, 1989). These devices accumulate data from multiple angles around the patient, and enable tomographic images to be reconstructed optionally in transaxial, coronal and sagittal planes. Additional quantitative information may be obtained from these images - for example, they give information regarding the location of the stomach within the abdominal cavity, and may enable more accurate correction for tissue attenuation.

However, the temporal resolution of the conventional single headed SPECT camera (of the order of 30 minutes), determined by the speed of rotation, limits the use of the device for accurate determination of gastric emptying. Dual and triple headed SPECT systems, with more acceptable temporal resolution (at least for solid emptying studies), are now commercially available, but these devices are very expensive and their use will be restricted to a limited research setting in the near future.

Bailey and co-workers (1989) used the mobility of a SPECT system, not for tomographic imaging, but to enable sequential anterior and posterior images of the stomach to be acquired as the camera rotated back and forth about the subject. These images enabled correction for attenuation using the geometric mean method (chapter 2.8(iv)).

2.6 METHODOLOGICAL PROBLEMS ASSOCIATED WITH THE ESTIMATION OF GASTRIC EMPTYING RATE

There are a number of methodological factors involved in radionuclide tests, which contribute to the variability in the measured rate of gastric emptying, and consequentially may limit the sensitivity, specificity and reproducibility of these methods. These relate to the physical properties of the test meal, and to the test procedure.

(i) Meal composition

The composition (physical and chemical), size and temperature of the meal effect the rate of gastric emptying (chapter 1.8), and it is essential that the test meal is standardised.

(ii) Intragastric dilution

Malagelada and co-workers (1979) showed that gastric secretions in response to a meal can, in some individuals, exceed 1000 ml of fluid in the first three hours post prandially. Consequently, the markers for liquid and solid (once they are liquified in the distal stomach) will be progressively diluted by an unknown amount of gastric secretions. Thus it is not possible to quantitate absolute emptying rates using external counting methods.

(iii) Subject position

Moore and colleagues (1988) reported a significant slowing of gastric emptying of solids in the lying position compared with the three other positions studied (sitting, standing or combined sitting and standing). The fastest emptying rate occured when the subject was allowed to sit, stand or walk around.

Liquids empty more rapidly when subjects lie on their right side compared with their left - an effect most likely due to gravity (Burn-Murdoch et al, 1980). The effect of gravity may be more pronounced in surgical patients, as the abnormally fast emptying rate of liquids, seen in the erect position after vagotomy and pyloroplasty, is not apparent in the supine position (Gulstrud et al, 1980).

(iv) Data acquisition rate

Although the scintillation camera enables gastric emptying to be monitored continuously, many investigators (Christian et al, 1980, Meyer et al, 1983, Goo et al, 1987, Hutson et al, 1989) have not utilised this capability. A number of investigators (Christian et al, 1980, Goo et al, 1987, Hutson et al, 1989) have used the method of geometric mean (chapter 2.8(iv)) to correct for tissue attenuation, but this limits the rate at which data can be acquired with a single scintillation camera, as frequent sequential anterior and posterior imaging is cumbersome.

With infrequent sampling, important information regarding the intragastric distribution of stomach contents, the lag period of solid emptying (Siegel et al, 1988) and the pattern of liquid emptying - in particular, with the rapid emptying seen after surgery (Heading et al, 1976) - may be lost.

(v) Time of day

The results of a recent study (Goo et al, 1987) indicate that solids consumed in the morning are emptied from the stomach more rapidly than at night - the emptying rate for liquids was not significantly different. Consequently, the time at which studies are performed should be standardised.

2.7 PHYSIOLOGICAL FACTORS AND GASTRIC EMPTYING

A number of physiological factors which relate to the subject under investigation (for example, gender, age, exercise and stress), may influence the rate of gastric emptying (chapter 1.6). In some investigations, the variables ,for example gender and age, may be controlled - in paired studies where the subject acts as his/her own control, or by the use of matched controls. Other variables, such as physical and mental stress, cannot be controlled and their effects should be minimised.

2.8 ERRORS IN THE MEASUREMENT OF GASTRIC EMPTYING RATE

In this section, the errors inherent in the measurement of gastric emptying using radionuclide techniques, and the methods used for correction, are discussed.

(i) Radionuclide decay

As gastric emptying tests usually extend over several hours, significant radionuclide decay (particularly with short half life radionuclides such as ^{113m}In = 100 min) will occur and correction factors must be applied.

(ii) Subject movement

Significant error in measurement of gastric emptying rate may occur due to movement of the subject relative to the detector (Glowniak and Wahl, 1985). Although some workers have taken this into consideration (Moore et al, 1981, Glowniak and Wahl, 1985), this source of error has largely been ignored. Glowniak and Wahl (1985) used a large region-of-interest to accommodate movement, but did not correct for it - other workers have used skin markers to align the scintigraphic images (Moore et al, 1981). The latter approach corrects for subject movement, but does not account for stomach movement within the abdominal cavity.

(iii) Compton scatter

When two radionuclides are used simultaneously (such as ^{113m}In-DTPA as a liquid marker together with ^{99m}Tc as a solid marker) correction for Compton scatter (down scatter) may be required. In the scatter process, some radiation from the higher energy radionuclide, scattered in the subject's tissues or in the collimator, reaches the detector as low energy photons indistinguishable from those emitted from the lower energy radionuclide. This error can be minimised by using relatively lower quantities of the higher energy radionuclide (Christian et al,

1980) or by applying correction factors (Tothill et al, 1978, Weiner et al, 1981).

(iv) Radionuclide gamma-ray attenuation

After meal consumption food may move anteriorly as it descends from the fundus to the antrum. Movement of food away from the posterior surface will result in a decrease in posterior counts (or increase in anterior counts) as the amount of tissue (attenuating medium) between the source and the detector changes. This will lead to an over-estimation in the rate of gastric emptying measured with a posteriorly positioned detector. Although some workers have stated that attenuation effects are minimal (Harding et al, 1979, Meyer et al, 1983, Van Deventer et al, 1983) others have noted significant errors due to tissue attenuation (Tothill et al, 1978, 1980, Christian et al, 1980).

Various methods have been proposed for attenuation correction. The use of the geometric mean of anterior and posterior data (Tothill et al, 1980, Christian et al, 1980) results in the most accurate correction for tissue attenuation - the main assumption being that the body structure is uniform. This technique necessitates either the use of a dual headed camera, or, if a single scintillation camera is used, frequent repositioning of the patient or camera throughout the study. Other workers (Meyer et al, 1983, VanDeventer et al, 1983) have used the peak-to-scatter ratio for attenuation correction. Images are acquired using the gamma energy photopeak window and also a scatter (lower energy) window. Attenuation correction factors, to account for the varying depth of tissue between the stomach and the detector, are derived from a phantom determined calibration curve. In a recent publication, Fahey and colleagues (1989) proposed the use of the uncorrected left anterior oblique projection as a simple technique for minimising errors due to tissue attenuation.

(v) Septal penetration

The collimator of the scintillation camera is designed to accept only those photons which are travelling perpendicular to the camera - the majority of the angled photons, both direct and scattered are stopped by the lead septae between the holes. However some photons may traverse the lead (septal penetration) and be registered in an area of the camera which may not correspond with the organ beneath it. This may result in an error in the estimation of the organ counts (for example, recording within the stomach region counts from contents of adjacent bowel). This problem can be more pronounced with the higher energy radionuclides, for example ^{113m}In (393kev). Some workers have applied correction factors based on phantom studies to account for septal penetration (Weiner et al, 1981, Van Deventer et al, 1983, Lawaetz and Dige-Petersen, 1989), but the magnitude of the error remains contentious and most workers have not used correction factors.

(vi) Superposition of stomach and proximal small intestine

In some subjects superposition of proximal small intestine and stomach may occur in the projections used for analysis (Delin et al, 1978, Lawaetz and Dige-Petersen, 1989). Counts originating from these overlapping areas will be registered as still within the stomach region of interest, resulting in an artificially high value of % retention for the stomach. The large bowel, in particular the transverse colon, fills considerably later and is less of a problem. Although Van Deventer and co-workers (1983) have suggested that the errors due to gut overlap are small, close inspection of all images of the study is necessary to ensure that those frames in which obvious superposition occurs are excluded from subsequent statistical analysis.

2.9 REPRODUCIBILITY OF RADIONUCLIDE METHODS

As discussed previously (chapter 2.6, 2.7, 2.8) there are several potential limitations and methodological problems which may reduce the specificity and sensitivity of radionuclide gastric emptying tests, and there have been a number of studies which have assessed the reproducibility of these methods (Chaudhuri, 1974, Scarpello et al, 1976, Heading et al, 1976, Sheiner et al, 1980, Brophy et al, 1986, Jonderko, 1990). In a recent publication, Jonderko (1990), who studied the reproducibility of gastric emptying of solids, reported a nonsignificant between-day variation. Others (Scarpello et al, 1976, Brophy et al, 1986), have shown significant inter- and intraindividual variations in the rate of gastric emptying, and it is possible that day-to-day variability may limit the application of radionuclide tests.

2.10 PARAMETERS FOR THE ANALYSIS OF GASTRIC EMPTYING DATA

With the combined use of computers and scintillation cameras the entire process of gastric emptying can be recorded and quantitated. However, many methods have been used for the analysis of the digitised data, which has made a direct comparison of results between various investigators difficult.

The most commonly used methods of expressing gastric emptying results are the half-emptying time (Heading et al, 1976) and the percentage retention of the meal at various time intervals (McCallum et al, 1981, Fahey et al, 1989).

Other methods have been employed which aim to characterise the entire emptying curve. One such method is that of Principal Component Analysis (Barber et al, 1974, Howlett et al, 1976). The method extracts a number of factors (principal components) which describe the emptying curve and which may be useful in the characterisation of various patient subgroups (Howlett et al, 1976). However, the method poses conceptual problems in relation to the physiological meaning of the factors, and, to my knowledge, no further studies using this method have been reported to date.

The pattern of gastric emptying has also been analysed by fitting mathematical functions; for example, the residual area method (Dugas et al, 1982) and the modified power exponential function method (Elashoff et al, 1982, Siegel et al, 1988). It is important that the mathematical function adequately describes the various patterns of emptying which can occur with liquids and solids (Siegel et al, 1988), and it is unclear at present which of the available mathematical models is the most appropriate (Elashoff, 1983).

A combination of half-emptying times and retention parameters at various time points (McCallum et al, 1981, Meyer et al, 1983, Moore et al, 1984) can be used to characterise the retention curves and is considered adequate for most statistical analysis.

2.11 METHODS USED TO ASSESS PROXIMAL AND DISTAL STOMACH FUNCTION

It has been postulated that the proximal and distal stomach have different functions for handling ingested food (Kelly, 1980) and radionuclide methods to assess intragastric distribution of liquid and solid meals have been developed (Barker et al, 1979, Sheiner et al, 1980, Moore et al, 1981, Jacobs et al, 1982, Lawaetz et al, 1982, Urbain et al, 1989). The methods used to define the proximal and distal subregions have not always been clearly defined - the technique that has been documented to date employs a mid gastric contraction band observed during the study (Sheiner et al, 1980, Moore et al, 1981, Urbain et al, 1989). This band is most readily seen after ingestion of large solid meals (Moore et al, 1986). Emptying curves can be generated for proximal and distal stomach and permit quantitative analysis of intragastric distribution.

Functional images have also been used to assess meal distribution patterns within the stomach (Rudzki et al, 1986, Jonderko et al, 1987). These are static images which represent some aspect of the dynamic sequence of the study - for example, each pixel may display the half emptying time for that part of the image. Rudzki and co-workers (1986) introduced a method, Regional Distribution of Emptying Index (RDEI), which produces two functional images - the +RDEI image highlights the areas of the stomach which have a net emptying pattern, and the -RDEI image, which has an accumulation pattern during the study. Unlike curve analysis of proximal and distal stomach subregions, which provide quantitative information, this method is essentially qualitative. Temporal information is also lost in the data reduction process. As the images have high spatial resolution (pixel by pixel), the method will be subject to error due to patient movement - movement which may be considerable during long acquisition studies with the subject erect.

The types of meal distribution patterns within the stomach have also been assessed using the proximal:distal stomach ratio (Jonderko, 1987). This method uses the ratio of the widths (maximum) of the proximal and distal stomach contours to arbitrarily characterise three stomach emptying patterns. The method, unlike regional curve analysis, does not provide quantitative information regarding emptying from the proximal and distal stomach - this method of categorisation, however, may provide useful additional information regarding intragastric distribution.

Antral contractile activity has also been assessed using radionuclide methods (Akkermans et al, 1980, Jacobs et al, 1982, Stracher et al, 1984). Data were collected for 3 minute periods at a rapid frame rate (1 frame every 1-3 seconds) at regular intervals (10-20 minutes) during the gastric emptying of a semi-solid meal. The authors used a number (3-6) of small adjacent regions of interest in the antrum to generate antral activity-time curves. From these curves the amplitude, frequency and propogation velocity of antral contractions were calculated. This method is unique in that it provides a non-invasive assessment of antral peristaltic activity and enables correlation between emptying and motility. However, using standard equipment, the method requires the administration of a larger than usual dose of radioactivity (74-185 MBq), which has restricted the use of this method in the study of normal volunteers. The use of specialised scintillation cameras with high sensitivity may be required to further pursue this potentially useful method.

In conclusion, the radionuclide gastric emptying study is a relatively new investigation which offers a number of distinct advantages over other methods. However, various technical factors relating to the test procedure and the instruments used, may limit the accuracy and reproducibility of this method, and various correction factors need to be applied.

This method for assessing gastric emptying also has the potential to provide information about the two functional areas of the stomach, namely the proximal and distal stomach.

SECTION II
TOTAL STOMACH MEASUREMENT

CHAPTER 3 METHODS

CHAPTER 4 RESULTS

CHAPTER 5 DISCUSSION

CHAPTER 3
METHODS

3.1 Phantom studies

- **(i) Compton scatter**
- **(ii) Attenuation coefficients**

3.2 Studies in control subjects

- **(i) General methods**
- **(ii) Reproducibility/effect of alterations in the caloric content of the liquid component on solid and liquid emptying**
- **(iii) Validation study : a comparison of lateral image method and geometric mean method**

In this section (chapters 3,4 and 5) the development and validation of a radionuclide method for the measurement of gastric emptying is outlined.

The computers used for the studies (PDP 11/34 or PDP 11/55) were from Digital Equipment Corporation (DEC). Commercially available Nuclear Medicine software (Gamma-11 (DEC)) was used together with application software written in Fortran by the author.

The scintillation, or gamma, cameras used in the studies were ; Nuclear Chicago Pho-Gamma 111 HP, Searle LFOV and Searle LEM. The two Searle gamma cameras allowed events from two radionuclides (for example, ^{99m}Tc and ^{113m}In) to be registered simultaneously in separate energy "windows" using pulse height analysis. For dual radionuclide studies, the older Nuclear Chicago camera used an electronic switching device, which enabled the single energy window to alternate between the ^{99m}Tc and ^{113m}In settings. For each of the three cameras, the energy window is centred over the photopeak for each radionuclide. The window width can be varied and is typically set at 20% (± 10% around the photopeak value).

The Gamma-camera/computer system formed a two dimensional (x,y) image of the spatial distribution of radioactivity within the camera field of view. Each image consisted of 4096 pixels - 64 columns (x co-ordinate) by 64 rows (y co-ordinate).

3.1 PHANTOM STUDIES

(i) Compton scatter

a. Studies with Nuclear Chicago Pho-Gamma 111 HP scintillation camera

A 250 ml conical flask containing 37 Megabecquerel (MBq) of ^{99m}Technetium (Tc) pertechnetate in 200 ml of water was positioned 6 cm from the high energy (400 kev) collimator surface in a water-bath and a 20 second image was taken in the ^{99m}Tc window (Image A): 18 MBq of ^{113m}Indium diethylenetriaminepentaacetic acid (^{113m}In-DTPA) was then added to the flask and 20 second images were taken in the ^{99m}Tc and ^{113m}In windows. A region-of-interest (ROI) obtained from image A was used for all three images. This was automatically selected based on a fixed isocount level relative to the maximum pixel value of the image (lower threshold). A lower threshold of 10% (LT10) was used. The increase in counts in the ^{99m}Tc window resulting from the addition of ^{113m}In was expressed as a percentage of the counts in the ^{113m}In window.

b. Studies with Searle LFOV scintillation camera

Two experiments, the effect of depth and the effect of window width, were performed using a Searle LFOV camera and a high energy collimator designed for use with ^{113m}In. A large glass vial containing 74 MBq of ^{113m}In-DTPA in 150 ml of water was imaged in a large (32x32x32 cm) perspex water bath. Two images were formed - one in the ^{113m}In window (source image) and the other in the ^{99m}Tc window (scatter image). For each image pair (^{113m}In and ^{99m}Tc images) of the studies, LT10 was used on the 9 point weighted smoothed (S9, Gamma 11 software) ^{113m}In image to define the ROI. Using this ROI, the downscatter fraction, equal to the ratio of counts in the scatter image (^{99m}Tc) to the counts in the source image (^{113m}In), was obtained.

Effect of depth: The ^{113m}In source was imaged in water for 2 minutes each at different distances from the scintillation camera, and the downscatter fraction (expressed as a percentage) determined for each position.

Effect of window width: The ^{113m}In source was imaged at a fixed distance (11 cm) in water from the scintillation camera using varying combinations of window widths for both the ^{113m}In (source) and ^{99m}Tc (scatter) windows. The downscatter fraction (%) was calculated for each window combination.

(ii) Attenuation coefficients

a. Single camera experiment

The acquisition system used was a Nuclear Chicago Pho-Gamma III HP camera with a PDP 11/34 computer. A point source of 37 MBq of ^{99m}Tc was counted at varying depths in a large water-bath placed on the collimator surface. The study was repeated with a source of ^{113m}In.

b. Two camera experiment

A 125 ml stopcock flask containing 30 MBq of ^{99m}Tc, was imaged at various positions in water with two opposed scintillation camera/computer systems. The camera/computer systems were a Searle LEM with a low energy all purpose (LEAP) collimator (camera 1) and a PDP 11/34 computer, and a Nuclear Chicago Pho-Gamma 111 HP with a 4000-hole low energy collimator (camera 2) and a PDP 11/55 computer. The scintillation cameras were separated by a distance of 32 cm. The source was imaged for 2 minutes each at varying positions between the cameras. The series of measurements was repeated and the average values were used to minimize positional errors. Regions-of-interest, automatically selected using lower thresholds 10% (LT10) or 18% (LT18) were used to collect two sets of data, which were corrected for radionuclide decay. The radionuclide attenuation coefficient for ^{99m}Tc (u) was estimated using linear least-squares analysis on the log counts versus distance curve from the data obtained from each camera. The geometric mean ($\sqrt{(C_a \times C_p)}$, where C_a = anterior counts, C_p = posterior counts) of the two-camera counts was also obtained.

3.2 STUDIES IN CONTROL SUBJECTS

(i) General methods

The general method described below will be referred to in subsequent discussions as the Lateral Image Method.

a. Preparation of solid marker and liquid marker

One gigabecquerel of ^{99m}Tc sulphur colloid (Tc-SC) was injected into a wing vein of a live chicken, as described by Meyer and co-workers (1976). After 20 minutes the chicken was killed and the liver removed. The amount of liver containing 37-55 MBq of ^{99m}Tc-Sc was mixed into 100g of ground beef and the resulting 'hamburger' cooked on a griller. The total calorie content of the solid meal (25 g protein, 21 g fat) was approximately 270 kcal (1.13 Mj). The liquid marker was 18-28 MBq of ^{113m}In-DTPA mixed in 150 ml of 10% dextrose. The effective whole body radiation dose was calculated to be approximately 2 millisieverts, which is acceptable for paired studies. The dosimetry calculation is shown in Appendix I.

b. Performance of test

The gastric emptying test was conducted after an overnight fast. The study was performed in the sitting position with the detector behind the subject (Fig 3.1). A cross-shaped marker containing ^{99m}Tc was taped to the subject's back to aid in correction for patient movement during the study. The subject ate the solid meal gradually over a five minute period and then drank the 150 ml of liquid containing ^{113m}In-DPTA. Data acquisition commenced at the beginning of food ingestion. At regular intervals (10 minutes for the first interval, 30 minutes for subsequent intervals), data collection was interrupted for 3-5 minutes to allow the subject to stand or sit away from the camera. Each study was continued for at least two hours.

c. Data acquisition

A scintillation camera (Nuclear Chicago Pho-Gamma 111 HP with a 400 keV parallel-hole collimator) interfaced to a computer was used for data collection. The energy window alternated regularly between that of ^{113m}In (393 keV) and ^{99m}Tc (140 keV), using the automatic switching device. During the first 10 postcibal minutes, the energy window alternated every 5 seconds. For subsequent data collection periods, the window alternated every 50 seconds. The switching device placed switching 'marks' in the list mode data stream, to allow subsequent reconstruction into frame mode images. At the end of data acquisition, 3.7 MBq of ^{99m}Tc-DTPA in 150 ml water was given orally and a one minute, left lateral image of the upper abdomen was taken.

Figure 3.1
Commencement of a gastric emptying study. The subject is seated in front of the scintillation camera. After data acquisition was initiated the subject ate the standard test meal.

d. Data analysis

Frame mode reconstruction: A computer program determined the location of the sequential switching 'marks' placed in the list mode data stream (Fig 3.2). For each segment of data between 'marks,' the x and y co-ordinates of the gamma events were read and a frame mode image (64x64 pixels) constructed. On completion of this program there were two separate data files for each data collection period - a file for radionuclide A (^{99m}Tc = solid label) and a file for radionuclide B (^{113m}In = liquid label)

Correction for patient movement: The dynamic studies were corrected for subject movement using the ^{99m}Tc skin marker data. For each of the data collection periods of ^{99m}Tc, a cumulative image was displayed on the computer monitor, and the x and y co-ordinates of the marker location specified with the aid of a joy stick. The computer program then searched automatically for the marker location for each frame within a 12 pixel square 'mask' area centered on the operator determined point (Fig 3.3). Column and row sums were formed inside the 'mask' area and the mid-point of the marker determined. This enabled each frame of the ^{99m}Tc study to be aligned to a single reference point. Each temporally related ^{113m}In image was moved the corresponding amount.

Downscatter correction: The solid study was corrected for ^{113m}In Compton scatter by subtracting, pixel by pixel, a proportion (21%, chapter 4.1(i)a) of the counts in the ^{113m}In image from its corresponding ^{99m}Tc image. Because the energy window alternated between the two radionuclide photopeaks, an image equal to the average of the two ^{113m}In images adjacent in time to the ^{99m}Tc image was used for this correction.

Attenuation correction factors: The lateral image acquired at the end of the study, was viewed on a colour monitor, and a ROI was drawn around the stomach (ROI B) using a joy-stick (fig 3.4). A single pixel ROI (A) marked the position of the posterior skin marker. The distance from the midpoint of the stomach to the collimator surface in cm (x_i) was calculated for each row of the 64x64 image, from the level of the fundus of the stomach to the pylorus (Fig 3.5a). Two sets of line (row) correction factors (F_i), one each for the solid and liquid phases of the study, were generated (F_i = exponential(ux_i)) using the appropriate attenuation coefficient u (^{99m}Tc = 0.14, ^{113m}In = 0.09, chapters 4.1(ii), 5.1(ii)a).

Generation of Activity-Time Curves: Using the computer display, a ROI was drawn to include the whole stomach, but excluding the small intestine. For each frame of the study, the total counts in the region of interest (C_T) was the sum of the individual line sums which had been corrected for tissue attenuation (C_iF_i) - that is,

$$C_T = \sum_{i=1}^{n} C_iF_i$$

(Fig 3.5b). The activity-time curves for the solid and liquid components of the meal (expressed as a percentage of total meal remaining within the stomach vs time) were corrected for radionuclide

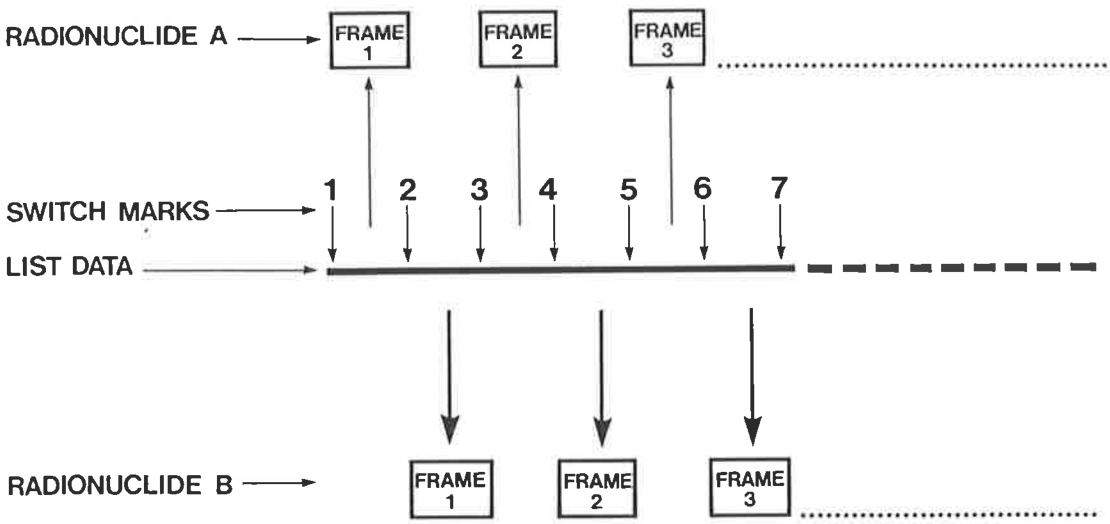


Figure 3.2

Reformatting list mode data files into two separate dynamic study files - one each for radionuclides A (^{99m}Tc = solid label) and B (^{113m}In = liquid label)

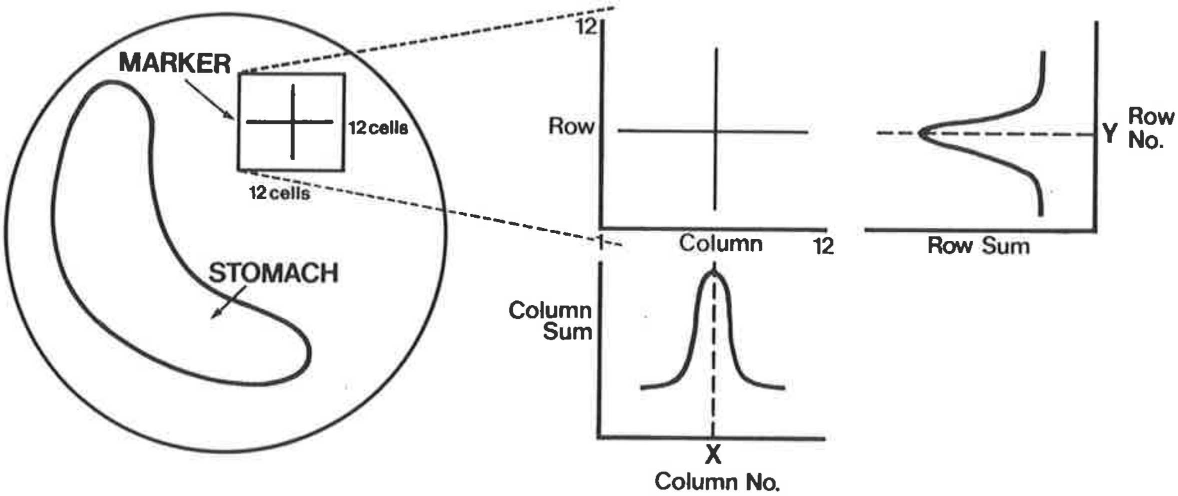


Figure 3.3

Correction for patient movement using a cross shaped ^{99m}Tc marker which is attached to the subject's back. For each frame of the dynamic study, row and column sums, formed in a 12x12 cell 'mask' area, are used to determine the x and y co-ordinates of the marker location.

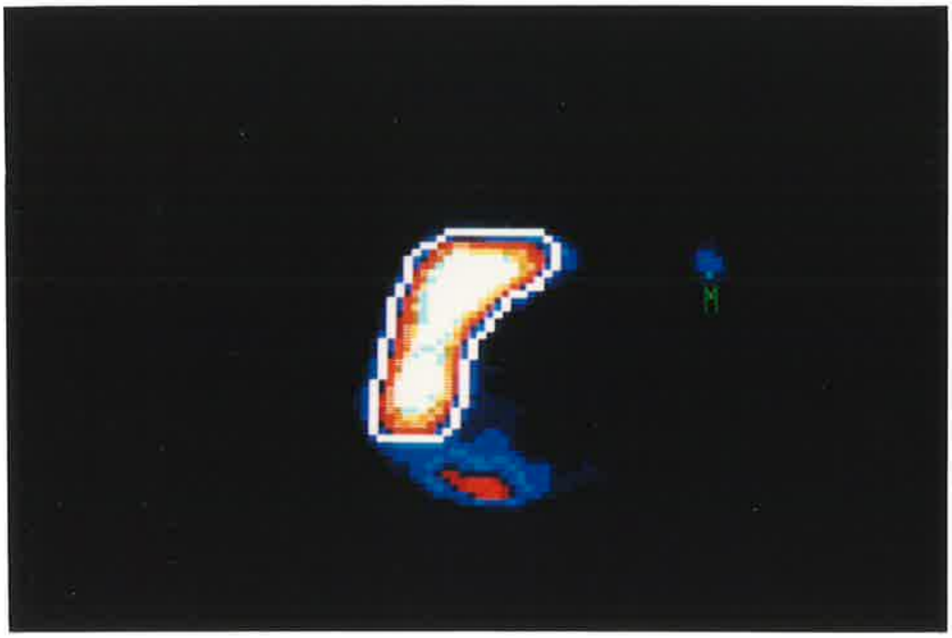


Figure 3.4

Left lateral image of the upper abdomen with the stomach region-of-interest outlined. The posterior edge of the subject is determined by the use of the skin marker (M).

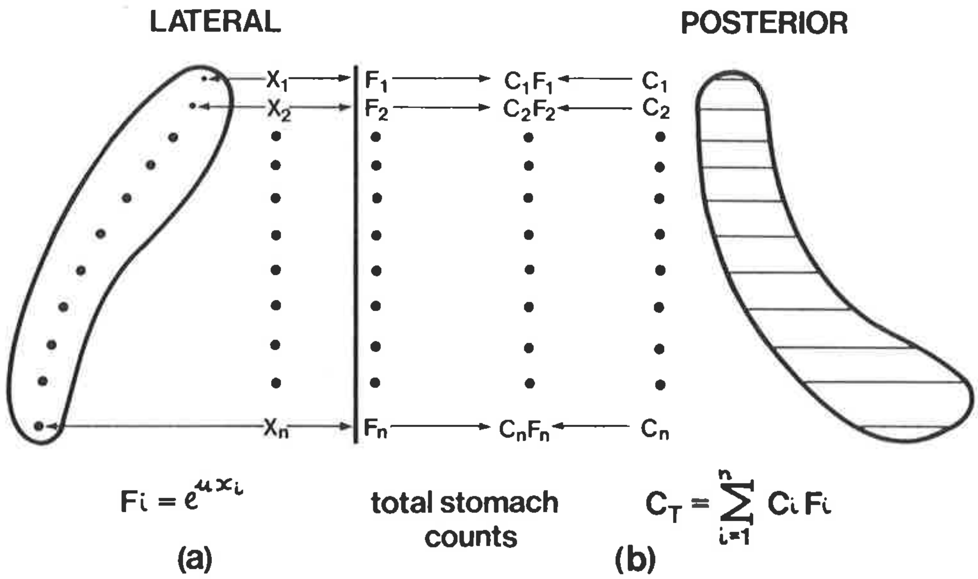


Figure 3.5

Correction for tissue attenuation using a lateral image of the stomach. (a) Generation of correction factors F_i = exponential (ux_i) where x_i is distance from mid-point of stomach to collimator surface and u is attenuation coefficient. (b) Formation of the total stomach counts

$$C_T = \sum_{i=1}^{n} C_i F_i$$

where C_i is sum, and F_i the attenuation correction factor for line i.

decay (using half times: ^{99m}Tc = 360 minutes, ^{113m}In = 100 minutes), and printed. The value for 100% retention of the meal was derived from the mean count rate achieved in the first 20 minutes after the meal completion. Various parameters were derived from these activity-time curves.

(ii) Reproducibility/effect of alterations in the caloric content of the liquid component on solid and liquid emptying

a. Subjects/Groups

Twenty four subjects, all non-smokers, on no medication and with no gastro-intestinal disease, were studied. Informed consent was obtained and the study was approved by the Research Review Committee of the Royal Adelaide Hospital.

Group A comprised eleven subjects (seven men, four women) who received solid and water. In group B, seven subjects (five men, two women) were given solid and 10% dextrose, and in group C, six subjects (five men, one woman) received solid and 25% dextrose.

The mean age in each group was similar: group A, 32 years (range 25-64 years) ; group B, 31 years (27-39 years); group C, 30 years (27-37 years). All subjects were within 20% of their ideal weight (mean ± SEM: 72 ± 3 kg, 70 ± 6 kg, 73 ± 5 kg, respectively).

The study was repeated within seven days in nine of group A, five of group B, and five of group C subjects to assess reproducibility.

b. Acquisition/Data analysis

The method of data acquisition and analysis has been described previously (chapter 3.2(i)). From the generated activity-time curves, a number of emptying parameters were obtained. For the solid component these parameters were: the lag period before onset of emptying, the time for 50% emptying (T_{50}) and the average linear emptying rate (expressed as %/minute). The linear emptying rate was calculated by linear least squares analysis, using the data points which followed the lag period. For the liquid component, the T_{50} and the amount of tracer remaining at 10 minutes after ingestion were obtained.

c. Statistical methods

Data were analysed using Student's t test and linear regression analysis. The reproducibility of the technique was analysed using analysis of variance.

(iii) Validation study : a comparison of lateral image method and geometric mean method

a. Subjects

Five normal subjects (4 male, 1 female; median age 31 years (range 28-35); mean body weight 68kg (range 55-83)) participated in the study after informed consent had been obtained. All were non-smokers, on no medication and had no gastro-intestinal disease. The study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital.

b. Data aquisition

The general method of data acquistion was described previously (chapter 3.2(i)). In this study the subject was seated between two gamma cameras (Nuclear Chicago Pho-Gamma III HP and Searle LEM) (Fig 3.6). Only the solid meal (chapter 3.2(i)a) was used and data were collected in frame mode at the rate of one frame per 2 minutes for at least two hours.

c. Data analysis

The method of attenuation correction has been described earlier (chapter 3.2(i)d). The line correction factors calculated from the lateral image were applied to data obtained from the posterior detector.

The posterior images were corrected for movement using the ^{99m}Tc skin marker - each temporally related anterior image was moved the corresponding amount. Separate ROI for the posterior and anterior images, identified on the computer display, were used to generate activity-time curves. Four curves, corrected for radionuclide decay, were printed for each of the five studies. These curves were of data obtained from (a) the anterior detector; (b) the posterior detector; (c) the posterior detector corrected for attenuation using the lateral image and (d) the geometric mean of anterior and posterior detectors. The activity-time curves were expressed as a percentage of the total meal remaining within the stomach versus time.

The following parameters were derived from these curves: the lag period, the T_{50} and the average rate of linear emptying in % minute^{-1}. The duration of the lag period was determined by the intercept of the linear emptying phase with the 100% retention value. An estimation of the lag period was also obtained by visual inspection of the images - the visual lag period (VLP) (Camilleri et al, 1985). This was derived from the frame at which activity was first seen in the duodenum.

Using the lateral view, the distances (in cm) of the middle of the proximal and distal stomach from the posterior detector were recorded to assess the magnitude of the difference in each subject.

Figure 3.6

Commencement of the invivo validation study. The subject is seated between two scintillation cameras. Data collected from the anterior and posterior projections are used to form the geometric mean, for comparison with the posterior data corrected for attenuation using the Lateral Image Method.

CHAPTER 4
RESULTS

4.1 Phantom studies

- **(i) Compton scatter**
- **(ii) Attenuation coefficients**

4.2 Studies in normal controls

- **(i) Correction for tissue attenuation using Lateral Image Method**
- **(ii) Lateral Image Method versus Geometric Mean Method**
- **(iii) Reproducibility**
- **(iv) Assessment of the effects of alteration of the caloric content of the liquid component of a mixed solid/liquid meal**

4.1 PHANTOM STUDIES

(i) Compton scatter

a. Studies with Nuclear Chicago Pho-Gamma 111 HP camera

The fraction of counts in the ^{113m}In window that scattered into the ^{99m}Tc window was 21%

b. Studies with Searle LFOV camera

Effect of depth: The fraction of ^{113m}In which scattered into the ^{99m}Tc window increased as the amount of scatter medium (water) between the source and detector increased (Table 4.1).

Table 4.1
Effect of distance in water on the percentage of ^{113m}In counts scattered into the ^{99m}Tc window

Distance (cm)	5	7	9	11	13	15	17	19	21
Downscatter (%)	55	59	62	65	68	70	72	75	74

Table 4.2
Effect of window width on the percentage of ^{113m}In counts scattered into the ^{99m}Tc window

Tc window* (%)	In window* (%)	Downscatter (%)
20	30	59
17.5	30	51
15	30	43
12.5	30	35
10	30	27
20	20	65
17.5	20	56
15	20	47
12.5	20	38
10	20	30

* window width is expressed as a percentage of the peak energy value

Effect of window width: Increasing the ^{99m}Tc window and/or decreasing the ^{113m}In window increased the downscatter fraction as recorded by the scintillation camera (Table 4.2).

(ii) Attenuation coefficients

a. Single camera experiment

The attenuation coefficients in tissue equivalent medium (water) were u=0.12 cm^{-1} for ^{99m}Tc (140 keV) and u=0.09 cm^{-1} for ^{113m}In (393 keV).

b. Two camera experiment

For each of the two cameras there was an exponential relationship between the count rate and the distance of the source in water from the detector. Table 4.3 gives the values of u obtained from this data.

The effect of source position between the two cameras on the geometric mean value is illustrated in Figure 4.1. The maximum variation from the mean geometric value was -4.3% for lower threshold 10% and -3% for lower threshold 18%.

Table 4.3
Values of the attenuation coefficient for ^{99m}Tc obtained using two different scintillation cameras and different lower threshold values for ROI determination

	u (cm^{-1})	
Lower threshold (%)	Camera 1	Camera 2
10	0.137	0.143
18	0.144	0.146

4.2 STUDIES IN NORMAL CONTROLS

(i) Correction for tissue attenuation using Lateral Image Method

Figure 4.2 illustrates typical solid retention histograms before and after correction of the data for tissue attenuation using the lateral image method. In the interval from 8 to 16 minutes there was a fall in count rate of 20% in the uncorrected data as food redistributed within the stomach (Fig 4.3). This fall was entirely attributable to the radionuclide moving away from the collimator surface while remaining within the stomach. In the following 16 minutes, as there was little redistribution of solid food, the count rate remained constant. The application of line correction factors to the data eliminated the apparent emptying of food from the stomach. The

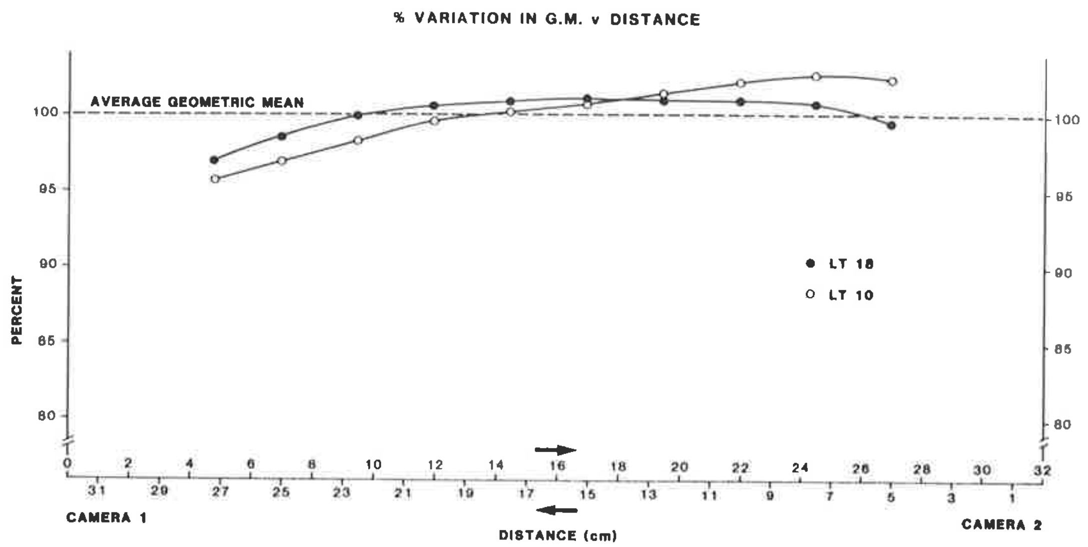


Figure 4.1

The relationship between the geometric mean value and the source position in water. The lower threshold used in region-of-interest determination was either 10% (LT10) or 18% (LT18). Data are expressed as a percentage of the average value.

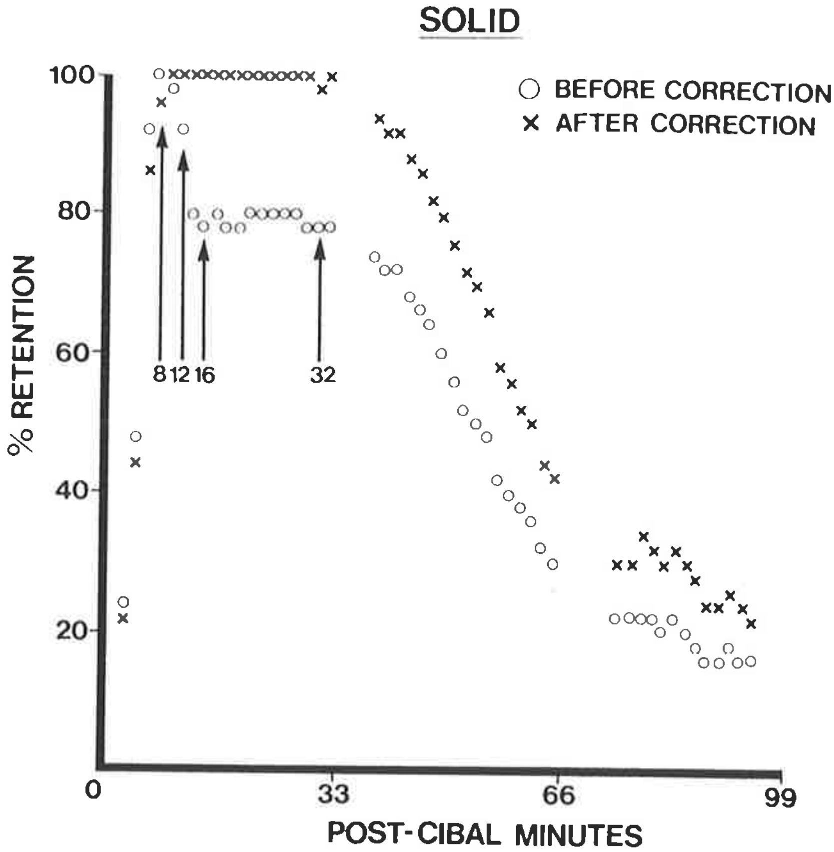


Figure 4.2

Gastric emptying of ^{99m}Tc-labelled liver before (o) and after (x) correction for tissue attenuation in control subject. Arrows indicate percentage remaining in stomach at 8, 12, 16 and 32 minutes. The scintiphotos for this subject are shown in Figure 4.3

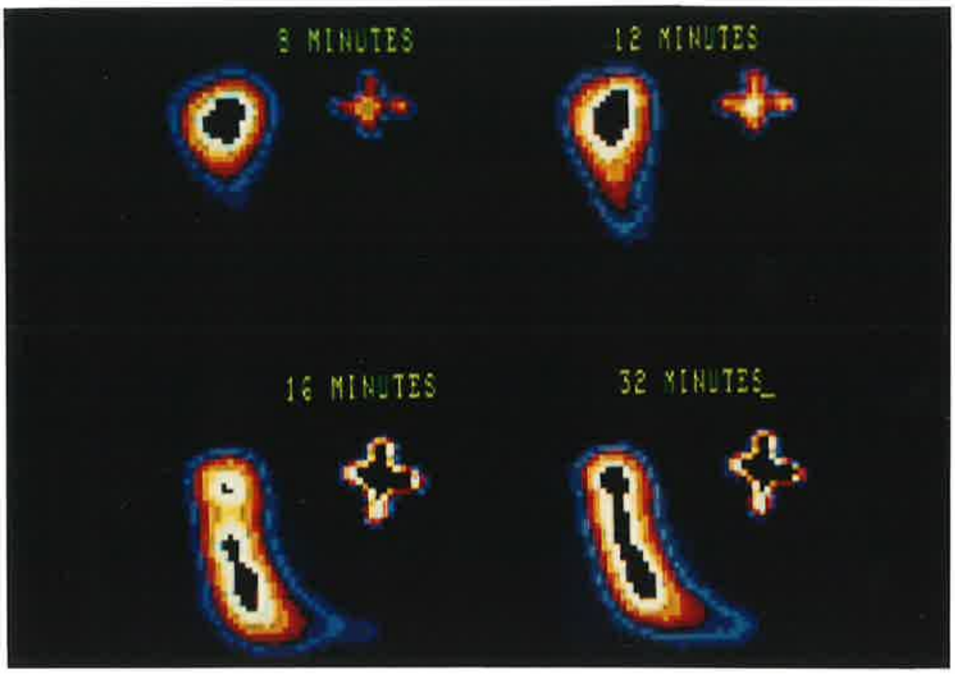


Figure 4.3

Scintiphotos showing the distribution of solid (^{99m}Tc-liver) in stomach of control subject at 8, 12, 16 and 32 minutes. Note: These are images of the stomach taken from the posterior projection.

resulting pattern showed a lag period before emptying (when food moved from the fundus to the antrum) followed by a linear emptying phase. In this study T_{50} changed from 49 minutes to 58 minutes (16%) as a result of correction.

Tissue attenuation effects in this subject were less marked for liquids, probably reflecting the higher energy of ^{113m}In (Fig 4.4). Correction altered the T_{50} from 19 minutes to 21 minutes (10%).

In the 24 normal controls from the reproducibility study, the mean percentage increase in T_{50} values, after correction for attenuation using the lateral image method, was 22% (range, 7-65) for solid and 17% (0-59) for liquid (Table 4.4).

Table 4.4

Effect of attenuation correction on solid and liquid T_{50}

$$\text{Difference} = \frac{\text{After correction-Before correction}}{\text{After correction}} \times 100\%$$

Solid (^{99m}Tc)	= 22 (7-65)
Liquid (^{113m}In)	= 17 (0-59)

mean value (range) of 24 control subjects

(ii) Lateral Image Method versus Geometric Mean Method

Figure 4.5a illustrates the four retention histograms for Subject A of the validation study. The count rate for the geometric mean curve remains relatively constant for the first 56 minutes (the visual lag period (VLP)), after which an approximate linear emptying phase was observed. During the first 56 minutes there was a fall in count rate of approximately 28% for the posterior detector, and an increase in count rate of approximately 36% for the anterior detector. This change in count rate is attributable entirely to large variations in attenuation, due to differences in the distance of the proximal and distal stomach from the detectors (Fig 4.5b). After correction for attenuation by the lateral image method, the posterior data closely approximated the geometric mean curve. The T_{50} value for the posterior corrected data was 103 minutes, only 1% different from the geometric mean value of 104 minutes.

Figure 4.6A shows the histograms for Subject E. In this subject, the posterior data were marginally improved after applying attenuation correction factors - there was still a significant error in the retention curve which was reflected in the parameters studied. For example, the T_{50} value varied from 83 minutes to 92 minutes after correction for attenuation-this was still 13% less than the geometric mean value of 106 minutes.

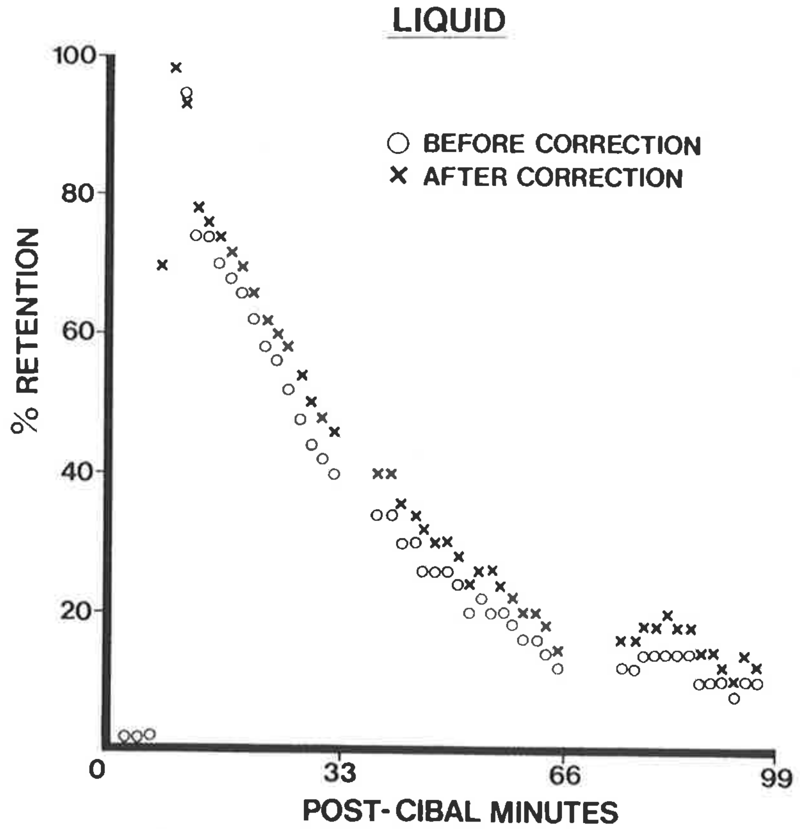
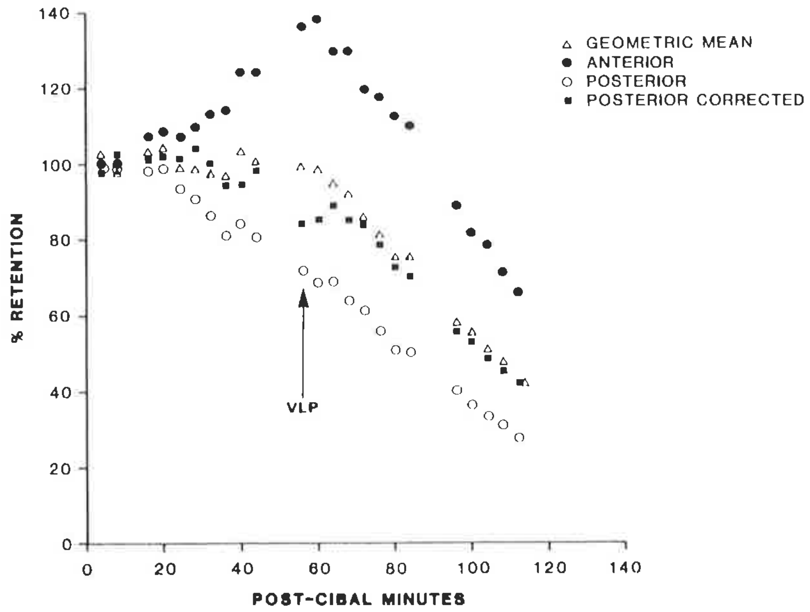


Figure 4.4

Gastric emptying of liquid (^{113m}In-DTPA) before (o) and after (x) correction for tissue attenuation in control subject.

(a)



(b)

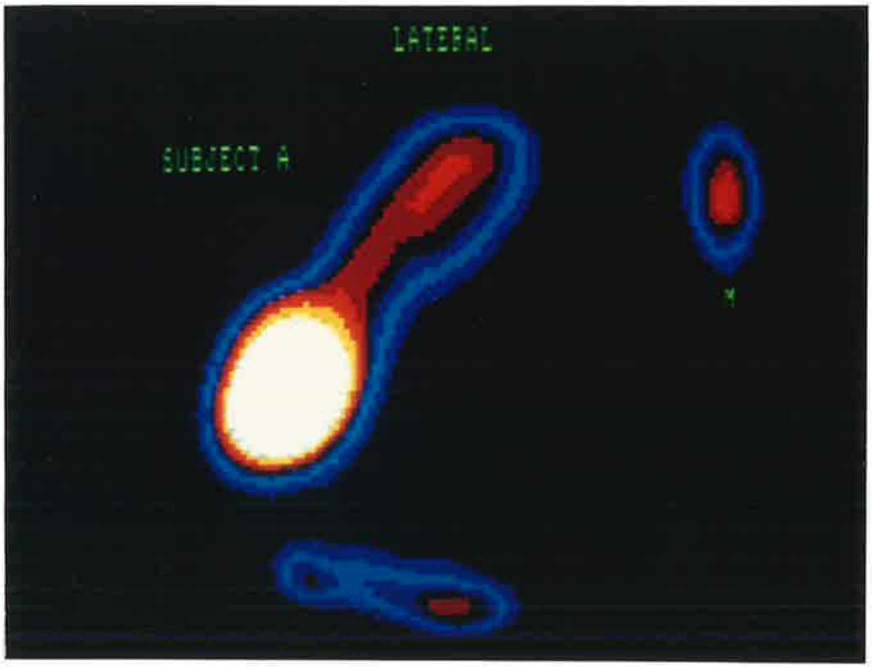
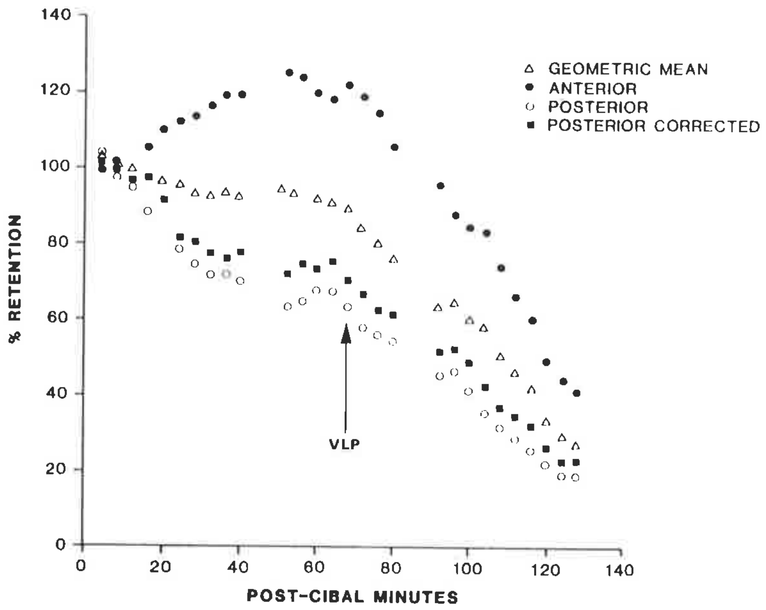


Figure 4.5 Data from Subject A.

(a) Histograms of retention against time for geometric mean, anterior detector, posterior detector and posterior data corrected for attenuation using the lateral image method. The visual lag period (VLP) is 56 minutes. The posterior data after correction for attenuation closely approximate the geometric mean data.

(b) Lateral image of the stomach with posteriorly located marker (M). There is a large difference in the distance (cm) of the proximal and distal stomach from the detector.

(a)



(b)

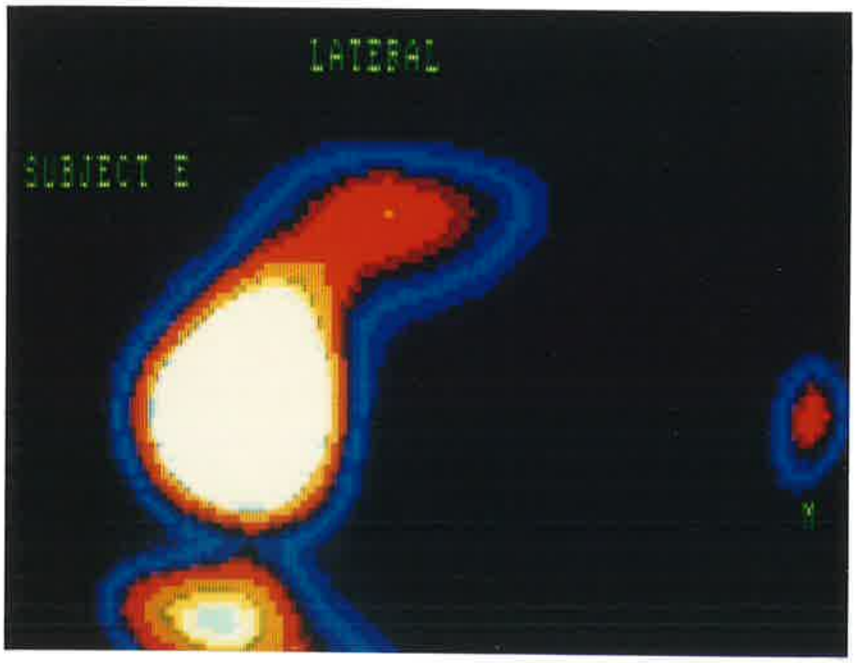


Figure 4.6 Data from Subject E.

(a) Histograms of retention against time for geometric mean, anterior detector, posterior detector and posterior data corrected for attenuation using the lateral image method. The visual lag period (VLP) is 69 minutes.

(b) Lateral image of the stomach with posteriorly located marker (M). The stomach shape results in movement of food perpendicular to the detector and attenuation correction is less affective.

The results for the five subjects studied are shown in Figure 4.7 and Table 4.5. If the geometric mean is used as the standard, the anterior detector alone overestimated the T_{50}, linear emptying rate and lag period values by 15, 13 and 48%, respectively, while the posterior detector alone underestimated these parameters by 15, 14 and 55%. The posterior corrected data underestimated the T_{50}, linear emptying rate and lag period by 2,5 and 4% respectively. The mean difference between the geometric mean method and the visual method in the estimation of lag period was 23%.

Table 4.5

Parameter values expressed as a percentage of the geometric mean value

	Method			
Parameter	Anterior	Posterior	Posterior corrected	Visual
T_{50}	115	85	98	-
	(105-118)	(78-96)	(87-107)	-
Linear emptying rate	113	86	95	-
	(95-131)	(70-99)	(80-109)	-
Lag period	148	45	96	123
	(118-181)	(18-82)	(51-148)	(98-174)

Mean value (range) of 5 control subjects

The lateral views for the five control subjects (Figs 4.5b, 4.6b, and 4.8) show considerable variation in stomach shape, with significant differences in the distance of the proximal and distal stomach from the posterior detector (difference mean: 5.7 cm, range: 3.9-7.4 cm).

(iii) Reproducibility

The reproducibility data for the parameters solid and liquid T_{50}, solid lag period, and solid linear emptying rate are illustrated in Figure 4.9. A wide variation between the subjects exists for these parameters. There was significant correlation between day 1 and day 2 ($p<0.01$) for the first three parameters ($r=0.82$, 0.76, 0.78, respectively). The correlation coefficient for the solid linear emptying rate was of borderline significance ($r=0.41$, $0.05<p<0.10$). The analysis of variance result is illustrated in Table 4.6.

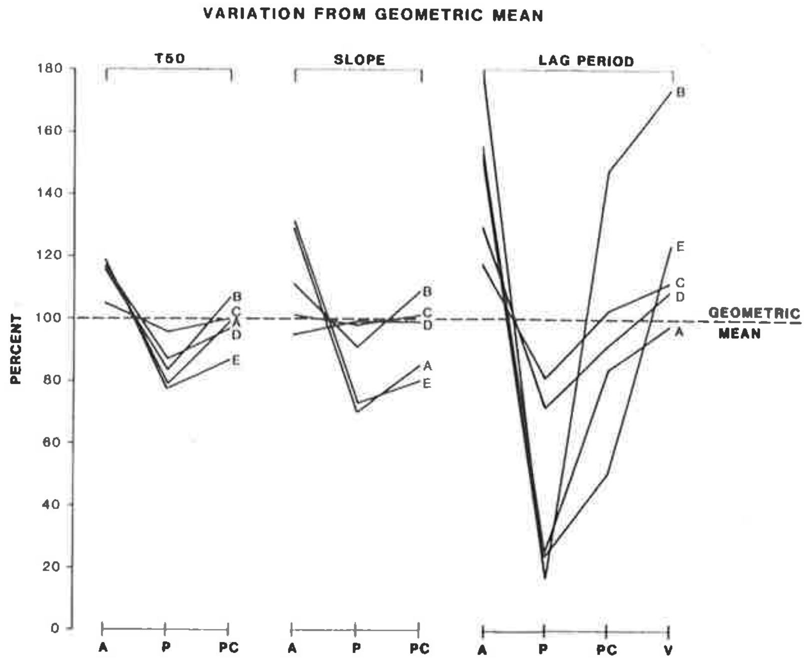


Figure 4.7

Values for the parameters T_{50}, slope (linear emptying rate) and lag period expressed as a percentage of the geometric mean value in the 5 subjects (A-E). These parameters were calculated from anterior (A), posterior (P) and posterior corrected (PC) data. The lag period was also determined from visual inspection of images (V).

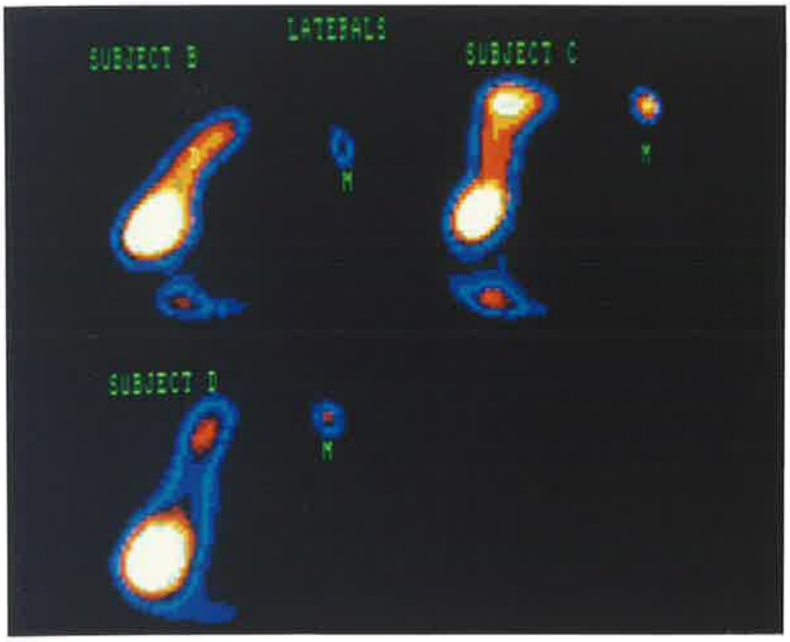


Figure 4.8

Lateral images of the stomach in Subjects B, C, and D. Considerable variation in stomach shape and in the distance of proximal and distal stomach from the posterior detector (M) is evident.

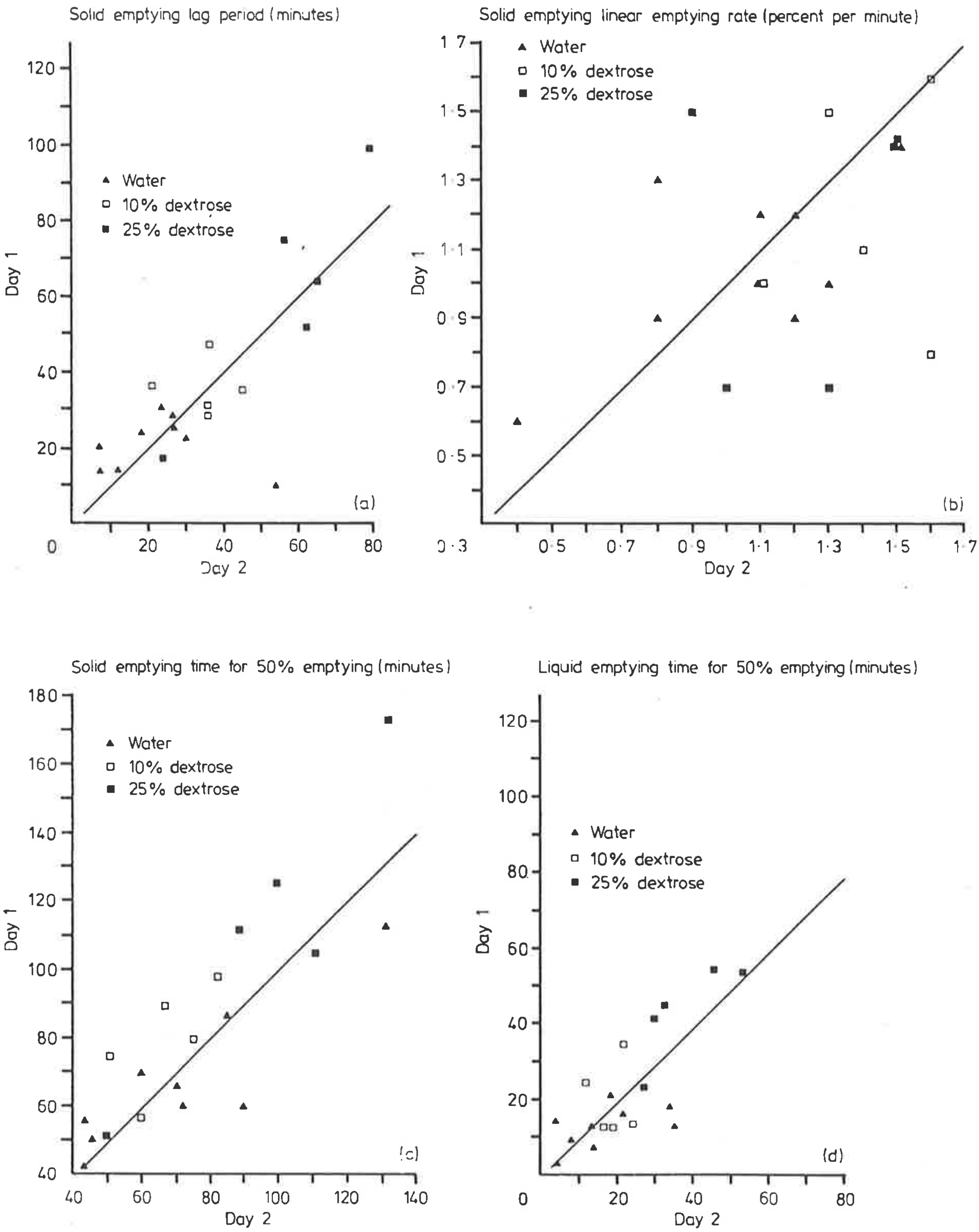


Figure 4.9 (a-d)

Reproducibility of gastric emptying in normal subjects. Data were obtained on two separate days and are plotted around line of identity (day 1 = day 2). The parameters illustrated are (a) solid lag period; (b) solid linear emptying rate; (c) solid T_{50}; (d) liquid T_{50}.

Table 4.6

Assessment of reproducibility using analysis of variance

		Effect	
	Day	Subject	Group
Solid lag period	ns	$p<0.05$	$p<0.01$
Solid T_{50}	ns	$p<0.01$	$p<0.01$
Solid linear emptying rate	ns	ns	ns
Liquid T_{50}	ns	$p<0.05$	$p<0.01$

ns = not significant ($p>0.05$)

The day-to-day variation (day effect) was not significant ($p>0.05$) for any of the four parameters: solid and liquid T_{50}, solid lag period, and solid linear emptying rate. The variation between subjects and between treatments (calories) was significant for all parameters ($p<0.05$) except the solid linear emptying rate, where the between subject variation was of only borderline significance ($0.05<p<0.10$). This variability of the data implies that paired studies in three individuals would be needed to detect a difference in gastric emptying time (solid T_{50}) of 30%, in five individuals for a difference of 20%, and in 19 individuals for a difference of 10% ($p=0.05$).

(iv) Assessment of the effects of alteration of the caloric content of the liquid component of a mixed solid/liquid meal

a. <u>Solid emptying</u>

In all subjects, solid emptied more slowly than liquid and was characterised by a lag period of variable duration, followed by linear emptying (Fig 4.10). The solid lag period was prolonged by the presence of both 10% and 25% dextrose in the liquid phase ($p<0.01$). The T_{50} value for solid was increased by 25% dextrose ($p<0.025$), but not by 10% dextrose. There was no difference between the three groups in the rate of linear emptying after the lag period (Table 4.6), and the delay of T_{50} with 25% dextrose reflected lengthening of the lag period.

b. <u>Liquid emptying</u>

The emptying of liquid was non-linear with a minimal observable lag period (Fig 4.10). Twenty five per cent dextrose delayed the T_{50} ($p<0.025$) while with 10% dextrose this parameter was not significantly altered (Table 4.7). The amount of liquid remaining at 10 minutes was increased by both 10% dextrose and 25% dextrose ($p<0.025$).

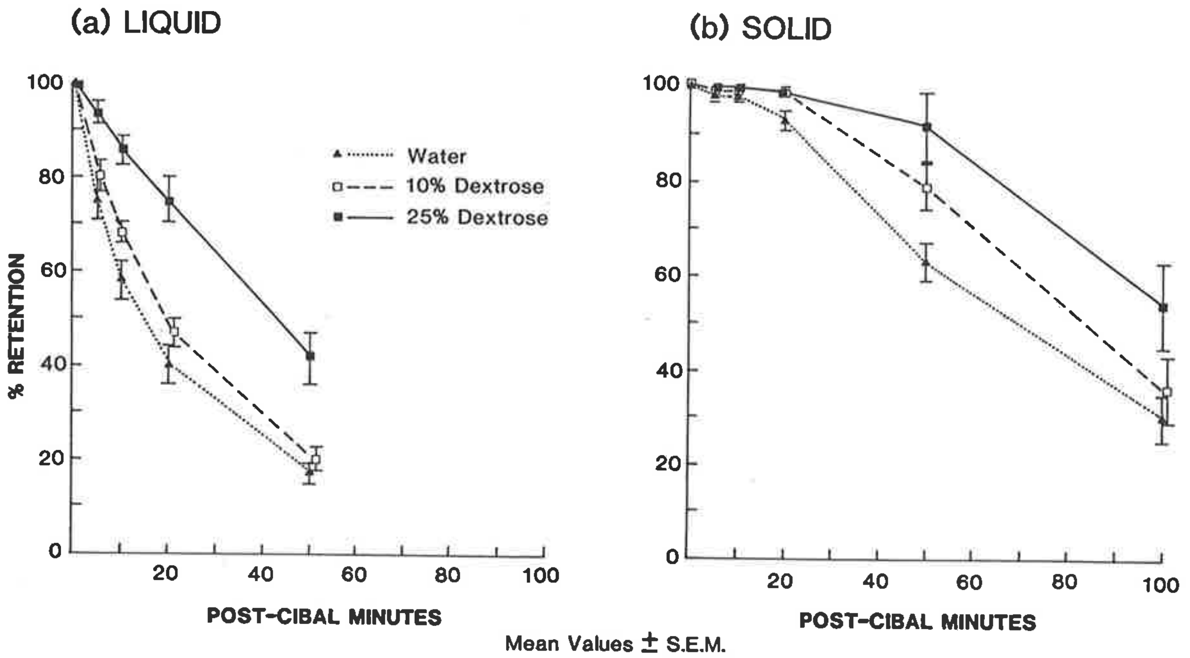


Figure 4.10

Effect of increasing liquid calorie content on (a) liquid and (b) solid emptying. Liquid meal was either water, 10% dextrose solution, or 25% dextrose solution.

Table 4.7

Effect of increasing the liquid calorie content on solid and liquid emptying

	Water	10% dextrose	25% dextrose
Number of subjects	11	7	6
Solid lag period (min)	21±2	37±6	60±9
Solid linear emptying rate (% min^{-1})	1.1±0.1	1.2±0.1	1.2±0.1
Solid T_{50} (min)	70±7	78±8	105±13
Liquid T_{50} (min)	15±2	20±2	46±7
Liquid retention at 10 min (%)	58±4	68±2	86±3

Data are mean values ± SEM

c. Relationship between solid and liquid emptying

There was a positive correlation between T_{50} for liquid and T_{50} for solid in all the groups ($r=0.65$). For the three groups the length of the solid lag period correlated directly with the liquid T_{50} ($r=0.75$, $p<0.001$).

d. Rate of delivery of calories to the duodenum

The total number of calories (solid and liquid) delivered to the duodenum at various time intervals in the first 50 minutes of the emptying study, are shown in Table 4.8. In both the solid and 10% dextrose group and the solid and 25% dextrose group, approximately 110 kcal (462 Kj) had left the stomach at 50 minutes. In the group of subjects who had received solid and water, the rate of delivery of calories was significantly slower (approximately 72 kcal (302 Kj) at 50 minutes).

Table 4.8

Effect of increasing the liquid calorie content on the rate of delivery of calories (solid and liquid) to the duodenum

Time after meal completion (min)	Total calories*(Kcal)# delivered		
	Water	10% dextrose	25% dextrose
5	1	16	10
10	2	23	22
20	16	36	40
50	72	111	109

* Mean values

1 Kcal = 4.2 Kj.

CHAPTER 5
DISCUSSION

5.1 Correction for errors in radionuclide gastric emptying studies

- (i) Compton scatter
- (ii) Radionuclide gamma-ray attenuation
- (iii) Subject movement

5.2 Reproducibility of radionuclide methods

5.3 Gastric emptying in normal subjects

- (i) Emptying patterns for a mixed solid and liquid meal
- (ii) The effect of calorie content of meal on gastric emptying

5.4 Summary of section II

5.1 CORRECTION FOR ERRORS IN RADIONUCLIDE GASTRIC EMPTYING STUDIES

(i) Compton scatter

The contribution of Compton scatter of the higher to the lower energy radionuclide in dual tracer studies, can be minimised by using relatively lower quantities of the high energy tracer (Christian et al, 1980). In many gastric emptying studies however, larger amounts of higher energy tracer are used to achieve good temporal resolution and correction factors must be applied. In phantom studies, Weiner and co-workers (1981) found that the percentage of downscatter from ^{113m}In into the ^{99m}Tc window, ranged from 39% (fixed region of interest) to 74% when downscatter was considered in the whole field of view. The latter figure is of interest only if the percentage remaining in the stomach is calculated as a fraction of the total abdominal activity. In the author's phantom studies using a fixed region-of-interest, downscatter values ranging from 21 to 75% were obtained, depending on the camera/collimator combination, the window width settings and the amount of scatter medium between source and detector.

The large difference in downscatter fraction between the Pho-Gamma 111 HP camera (21% at 6 cm) and the LFOV camera (55% at 5 cm) are probably due to different thicknesses in the sodium iodide crystal (HP = 0.5 inch, LFOV = 0.38 inch) and to different collimator construction. The thinner crystal detects the higher energy primary photons of ^{113m}In less efficiently than the thicker crystal, and the lower energy scatter photons about as efficiently, resulting in a higher downscatter fraction.

The downscatter fraction, if data is sampled from a single projection, is a function of the amount of tissue between the source and the detector (Table 4.1) - the scatter fraction is reasonably independent of depth for the geometric mean of anterior and posterior data (Hutton et al, 1987). Thus the use of a constant factor will result in some error in correction for data collected from a single projection. In the reproducibility study in normal subjects, rapid time sampling in the first 10 minutes (five second store every 10 seconds) enabled our correction to be tested invivo, and no significant change was observed in the solid count rate as the liquid (higher energy radionuclide) entered the stomach, confirming that adequate correction had been applied. As the majority of the liquid component of the meal emptied during the solid lag period, this correction is mainly of importance during this period.

Most investigators who perform dual isotope studies apply downscatter correction to the counts within the stomach region-of-interest (VanDeventer et al, 1983, Moore et al, 1984). In the author's studies, downscatter correction was applied to the images before the curves were produced. This method produces relatively scatter free images of the lower energy tracer (^{99m}Tc-solid), and permits a more accurate visual assessment of gastric emptying - this is essential for the visual determination of the pre-emptying period (lag period).

(ii) Radionuclide gamma-ray attenuation

a. Attenuation coefficient

The lateral image method for correction of tissue attenuation requires the use of the tissue attenuation coefficient for the radionuclide under study. Different values for this coefficient will be obtained depending on the methods used.

In the single camera experiment, a point source of ^{99m}Tc and the total field-of-view counts were used and a u value of 0.12 cm^{-1} was obtained.

The phantom study with two cameras used an "extended" source and a ROI based on a threshold method, and the calculated value of u ranged from 0.137 to 0.146, depending on the lower threshold and the camera used. Tothill and co-workers (1980) used an extended source and obtained a value of u = 0.12 cm^{-1} for ^{99m}Tc. Although it is not clear in the text, it appears that they used the counts in the total field of view. If this is correct, the lower value for u obtained by these authors is attributable to an increase in the proportion of scattered radiation accepted at depth. As a threshold method was used in the present invivo studies, the author considers the value of u = 0.14 cm^{-1} to be more appropriate.

The lateral image method of attenuation correction, together with the other methods currently used, assumes u to be constant within the patient. However, as the imaged area may contain significant amounts of air and bone, the potential limitations of this assumption must be recognised.

The difference in characteristics of the two collimators resulted in significantly more scatter being collected in Camera 1 at large depths (and therefore a lower value of u) than with Camera 2. These different values of u resulted in the geometric mean versus distance curve being non-symmetrical about the mid-point (Fig 4.1). This non-symmetry decreased as the lower threshold was raised from 10 to 18%. Nevertheless the variability of the geometric mean value (maximum variation from mean of -4.3%) was small. It indicated that the geometric mean method reliably corrected for changes in count rate due to depth, and could be used as the absolute standard for comparison with the lateral image method.

b. Errors due to attenuation

The need for attenuation correction in gastric emptying studies is a contentious point. Although some workers agree that attenuation effects can be considerable in some subjects (Tothill et al, 1978, 1980, Christian et al, 1980) others have stated that this effect is minimal (Harding et al, 1979, Meyer et al, 1983, VanDeventer et al, 1983, Rattner et al, 1981). The author's validation study using dual cameras indicates that large errors in the measurement of gastric emptying can occur if no correction is made. Using the geometric mean as the standard, the single anterior detector overestimated the T_{50} value by, on average, 15% (range 5-18%) while the posterior detector underestimated this parameter by 15% (range 4-22%).

The information obtained from the lateral projections, explains the reason for the significant error when using a single detector without correction. The variation in distance of the middle of the proximal and distal stomach from the posterior detector, for all five subjects of the validation study, was large (mean difference 5.7 cm), and in two subjects (A and B) differences greater than 7 cm were observed. These differences are significantly larger than those reported by other workers. Tothill and co-workers (1978, 1980) used a dual headed scanner to obtain the ratio of counts in the anterior detector to counts in the posterior detector (A:P ratio) for determination of the depth of the nuclide, and found that a mean forward movement for the solid phase of 1 cm was exceeded in three of the eight patients studied. It must be noted however, that the parameter they have measured is the mean depth of food in the stomach as a whole, and some food will have moved considerably more anteriorly than this mean value. Furthermore, the first scan was taken 10 minutes after food ingestion and some anterior movement of food would have already occurred. Meyer and co-workers (1983) used both the A:P ratio method and the peak-to-scatter ratio method (P:S) to detect posterior-anterior movement of the food. They detected 2-3 cm of anterior movement during the 3 hours of the test. Although these workers have measured a different parameter, their data does confirm that significant net anterior movement occurs in many studies. The use of a lateral image allows direct measurement rather than estimation of this movement.

Errors due to attenuation will be less when higher energy nuclides such as ^{113m}In are employed (Tothill et al, 1978, Table 4.4) and may be more marked with large meals (Christian et al, 1980, 1983, Rattner et al, 1981). However, as Tothill and co-workers (1980) and Meyer and co-workers (1983) each incorporated ^{99m}Tc in the solid phase marker, and used a meal size (185-455 g) similar to the one used in the present study, these factors are unlikely to account for the discrepancies in the amount of anterior movement measured.

The author has used posterior rather than anterior imaging, as this is a more comfortable position for the subject to adopt while eating, and if data are collected continuously for a prolonged period. With posterior detection, it is theoretically possible for attenuation due to the spine to produce additional errors and the distance of the stomach to the collimator is greater. However, as the errors obtained in the validation study with anterior or posterior detection alone were very similar (average error of 15% for the parameter T_{50}), these factors do not appear to have significantly influenced the results.

c. Common methods of attenuation correction

The most widely accepted method of correcting for depth attenuation has used the geometric mean of anterior and posterior data (Tothill et al, 1980, Christian et al, 1980, Jacobs et al, 1982). However, this method does have some limitations. As most nuclear medicine departments cannot afford to dedicate two camera/computer systems for 2-3 hours, the geometric mean method necessitates frequent repositioning of the subject, or camera, throughout the study.

This technique, however, does not lend itself to rapid data sampling, as frequent sequential anterior and posterior imaging is cumbersome and impractical. Important information may be lost or at best measured inaccurately. This includes determination of the value of "100% retention", analysis of distribution changes within the stomach (Sheiner et al, 1980, Jacobs et al, 1982, Urbain et al, 1989), estimation of the lag period (Siegel et al, 1988) and monitoring the rapid emptying rates that may occur in liquid emptying, particularly in patients after gastric surgery (Heading et al, 1976). An alternative method, which allows continuous monitoring, is to use a more expensive dual headed camera. However, upright imaging, which is more physiological than imaging in the supine position, may pose technical problems with some makes of this device.

Another technique for attenuation correction uses the peak to scatter ratio (P:S) (Meyer et al, 1983, VanDeventer et al, 1983). This method suffers from two sources of error when using ^{99m}Tc as the radionuclide (Meyer et al, 1983). Firstly, the gradient of the P:S ratio versus depth curve is minimal, particularly in the depth region typical for gastric emptying studies. This means that small shifts in the P:S ratio can result in large variations in the estimation of depth. Secondly, the P:S ratio is potentially influenced by scattered radiation from activity in the small bowel into the gastric ROI (Fahey et al, 1989). These two factors probably limit the use of the P:S ratio in the measurement of depth in gastric emptying studies using a low energy nuclide such as ^{99m}Tc.

Recently, Fahey and co-workers (1989) have advocated the use of the left anterior oblique projection (LAO) for the continuous acquisition of gastric emptying data. In a study which assessed solid emptying, the method compared favourably with the geometric mean method, due, the authors argue, to the fact that in the LAO projection "the activity within the stomach moves essentially parallel to the face of the Anger camera, thus minimising the variation of attenuation during the study". Although the results of this study look promising, a word of caution is warranted. There is considerable variation in stomach size and position within the abdominal cavity (personal observation in over 800 clinical gastric emptying studies), and the use of a single projection method, which does not assess the position of the stomach in relation to the detector, is open to serious error.

d. Lateral Image Method of attenuation correction

The lateral image method for attenuation correction enables continuous monitoring of gastric emptying using a single scintillation camera/computer system. This method does not exactly duplicate the results obtained using the geometric mean of opposing detectors, but a much closer estimate is achieved than would be obtained with the posterior data without correction (Figs 4.5,4.7). Table 4.5, which gives the mean values for the five subjects of the validation study, shows improvements for the parameter T_{50}, linear emptying rate and lag period of 13%, 9% and 51%, respectively.

The T_{50} parameter indicates that the correction was less effective (Figs 4.6,4.7) in one subject (E). This error can be attributed to the shape of the stomach in the lateral projection (Fig 4.6B). Initial movement of food in the proximal stomach was approximately perpendicular to the detector surface and appeared at the same level in the subject as seen from the posterior detector. Because of the direction of this movement, there was a decrease in count rate in the posterior corrected data of approximately 20% in the first 30 minutes before any food was seen to leave the stomach (VLP = 68 minutes). This error could be greatly reduced if changes in the count rate during the lag period are ignored. In this subject, if the count rate at 35 minutes is used as the "100% retention" value, a T_{50} value of 106 minutes is obtained, which is identical to that using the geometric mean. Consequently, in later studies (chapters 6, 7 and 8), the value of "100% retention" is taken as the total stomach count rate at the end of the pre-emptying (lag) period.

For the posterior corrected data, the lag period was determined both from curve analysis (LP) and also visually from the images (VLP). In three of the five subjects, both LP and VLP produced results similar to that of the geometric mean method (Fig 4.7). In patient E, the VLP approximated that of the geometric mean but the LP was much lower. The data for this subject, as discussed above, were not adequately corrected for attenuation using the lateral method and this probably accounts for the discrepancy. In Subject B, the VLP and the LP were similar but were larger than that obtained with the geometric mean method. The author has no explanation for this finding.

The validation study, in control subjects, indicates that attenuation correction is essential if an accurate measurement of gastric emptying is to be obtained with radionuclide methods. Despite some limitations, the lateral image method significantly reduces the errors due to attenuation in most subjects.

(iii) Subject movement

Little attention has been paid to errors due to patient movement during gastric emptying studies. In the present study, correction has been made for patient movement using a ^{99m}Tc marker attached to the subject's back. This method however, does not correct for movement of the stomach within the abdominal cavity. A description of a more detailed correction, which does allow for movement within the abdominal cavity is given in chapter 6.1(iii)b.

5.2 REPRODUCIBILITY OF RADIONUCLIDE METHODS

The reproducibility of radionuclide methods has been assessed by a number of previous workers (Chaudhuri 1974, Scarpello et al, 1976, Heading et al, 1976, Sheiner et al, 1980, Calderon et al, 1971, Brophy et al, 1986, Jonderko, 1990). Jonderko (1990) reported a nonsignificant between-day variation for solid gastric emptying in the short (1-3 days), and long (at least 3 months) term. Other workers (Scarpello et al, 1976, Brophy et al, 1986) have shown significant intra- and intersubject variability within normal subjects, and it is possible that the variability inherent in radionuclide gastric emptying tests may limit the technique in its ability to discriminate between normal and abnormal emptying (with only grossly delayed emptying results being outside the wide range seen in normals).

However, there are several reports of clear-cut differences in emptying between groups of subjects (Heading et al, 1976, Loo et al, 1984), or between treatments in the same group (Urbain et al, 1989), which indicate that the variability does not diminish the power of radionuclide techniques for the investigation of gastric emptying.

Reproducibility of the lateral image method was assessed by the author during physiological studies. Day-to-day variation in gastric emptying within individual subjects was not significant compared with the variation between subjects in each group and did not affect the sensitivity of the technique in its ability to discriminate between the three groups (saline, 10% dextrose and 25% dextrose) studied. Further to this point, statistical analysis indicated that only a small number of paired studies would be needed to detect a difference in gastric emptying time (solid T_{50}) between treatments - 3 paired studies for a difference of 30%, five for a difference of 20%, and 19 for a difference of 10% ($p=0.05$).

The reproducibility of radionuclide methods in patients with abnormal emptying (fast or slow) was not studied by the author.

5.3 GASTRIC EMPTYING IN NORMAL SUBJECTS

(i) Emptying patterns for a mixed solid and liquid meal

The emptying patterns for solid and liquid emptying are discussed in detail in chapter 8.1(iv), 8.3.

(ii) The effect of calorie content of meal on gastric emptying

The rate of gastric emptying for both solids and liquids is determined in part by the composition of the duodenal content. Previous investigators, using non-radionuclide meals, have shown that gastric emptying slows with increasing calorie content of a liquid meal, and that this delay is mediated by duodenal receptors (Hunt and Stubbs, 1975, Hunt el al, 1978, McHugh and Moran, 1979, Brener el al, 1983). In primates (McHugh and Moran, 1979) solutions of carbohydrate, protein and fat, slow gastric emptying in direct proportion to their calorie concentration in the range 0.2-1 kcal/ml (0.84-4.2 Kj/ml), so that the rate of delivery of energy to the duodenum is maintained at a constant level. Brener and co-workers (1983) found in humans that calories from a liquid glucose meal were delivered to the duodenum at a rate of approximately 2.1 kcal per minute. The slowing of gastric emptying may be mediated by the osmotic effects (Hunt and Stubbs, 1975, Hunt et al, 1978, McHugh and Moran, 1979), or alterations in calcium binding (Hunt and McHugh, 1982) produced in the duodenum by the digestion products of food. The way in which small intestine receptors produce a graded inhibition of gastric emptying is unclear. Lin and co-workers (1989) argue that the degree of gastric inhibition is related to the length of intestine exposed to nutrients. Increasing the nutrient load results in a longer length of bowel, and therefore more receptors, exposed to unabsorbed nutrients (due to saturation of mucosal absoptive mechanisms), and a slower rate of gastric emptying.

In the author's study, the progressive increase in calorie content of the liquid meal from 0 to 0.4 to 1 kcal/ml (0 to 1.7 to 4.2 Kj/ml) resulted in a delay in both liquid and solid emptying - the latter reflected a lengthening of the lag period, with no alteration in the rate of linear emptying.

The delay in liquid emptying with increasing calorie content of the liquid meal is consistent with an inhibitory effect mediated by duodenal receptors. As increasing the liquid calories also delayed the redistribution of solid food from fundus to antrum (without altering the rate of linear emptying), it is likely that the delay of both solid and liquid emptying reflected a reduction in fundal tone mediated by duodenal receptors (see also chapter 8.3). The direct relationship between the liquid T_{50} and the duration of the lag period supports this hypothesis.

In this study of a mixed solid and liquid meal, the rate of delivery of calories to the duodenum was approximately 2.2 kcal/minute (9.2 Kj/minute) in the two groups when liquid calories were given with the solid food. This result is similar to that previously obtained with liquid meals (Brener et al, 1983). In the group of patients who received water, calories entered the duodenum only after the solid lag period, partly accounting for the slower initial delivery of calories in this group.

The effect of increasing the calorie content of the liquid component of a mixed solid and liquid meal on intragastric distribution and gastric motility is discussed in detail in chapter 8.3.

5.4 SUMMARY OF SECTION II

In this section, a new radionuclide method, which enables simultaneous measurement of both solid and liquid gastric emptying, was described. The method, validated in human and phantom studies, uses factors derived from a lateral image of the stomach to correct for tissue attenuation. Data can be collected continuously with a single scintillation camera using this method - an essential requirement for detailed analysis of intragastric distribution (section III). The technique is reproducible and sensitive to physiogical changes, and should find a useful role in both the clinical and research setting.

SECTION III
PROXIMAL, DISTAL AND TOTAL STOMACH MEASUREMENT

CHAPTER 6 **METHODS**

CHAPTER 7 **RESULTS**

CHAPTER 8 **DISCUSSION**

CHAPTER 6
METHODS

6.1 **Proximal, distal and total stomach emptying of a solid meal in normal subjects**

- (i) **Subjects**
- (ii) **General methods**
- (iii) **Data analysis**

6.2 **The effect of intraduodenal lipid infusion on gastric motility and emptying of a solid meal**

- (i) **Subjects**
- (ii) **Performance of the test**
- (iii) **Data acquisition**
- (iv) **Data analysis**
- (v) **Statistical methods**

6.3 **The effect of liquid calories on gastric motility and emptying of a mixed solid and liquid meal**

- (i) **Subjects**
- (ii) **Performance of the test**
- (iii) **Data acquisition**
- (iv) **Data analysis**
- (v) **Statistical methods**

In the previous section, a new radionuclide method for the measurement of gastric emptying was described. This method has been further developed to enable assessment of proximal and distal stomach function. This section (chapters 6,7 and 8) describes the method and its use in two physiological experiments with combined manometry.

6.1 PROXIMAL, DISTAL AND TOTAL STOMACH EMPTYING OF A SOLID MEAL IN NORMAL SUBJECTS

(i) Subjects

Thirteen normal subjects (7 male, 6 female; median age 34 years (range 22-57); mean body weight 71 kg (range 47-89) participated in the study after informed consent had been obtained. All were non-smokers, on no medication and had no gastro-intestinal disease. The study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital.

(ii) General methods

Details of the solid and liquid meal, the radionuclide markers, the study protocol and the acquisition format were described previously (chapter 3.2(i)a-c). In this study only solid emptying was assessed.

(iii) Data analysis

The list data files were formatted into four or five 64x64 frame mode files (chapter 3.2(i)d). The data were reduced in frame rate (by adding frames together) to one frame per 1.7 minutes for the first 10 minutes - subsequently the rate was one frame per 5.1 minutes. The data collection periods (10 minutes for the first period, followed by 30 minute periods) were separated by short (3-5 minute) intervals.

a. Corrections

The data files (parts) that comprised the solid study were corrected for patient movement (by aligning the frames to the cross-shaped skin marker), radionuclide decay, Compton scatter and tissue attenuation using methods described in chapter 3.2(i)d. Correction for movement of the stomach within the abdominal cavity was also performed (see below - chapter 6.1(iii)b)

b. Regions-of-Interest (ROI) selection

Regions-of-interest (ROI) for the proximal, distal and total stomach were determined as follows. Initially, a composite image was used to define the total stomach ROI. This image included frames from the beginning of the study (when the majority of food was in the proximal stomach), as well as frames in which the distal stomach content was maximal. The individual frames were then inspected with reference to this fixed ROI, and any that were not exactly aligned (after the use of the previously described movement correction routine) were repositioned using an interactive computer program. A further composite image was then formed and a refined total stomach ROI drawn (Fig 6.1A). The proximal stomach region was defined as the "reservoir" area seen in all subjects for at least the first few post-cibal frames, and a proximal/distal stomach dividing line was drawn immediately below this region (Fig 6.1B). In most cases, this single set of ROI (proximal, distal and total stomach) was used for all parts of the study. If the total stomach ROI had to be modified in any of the parts to accommodate a change in shape of the stomach, the position of the dividing line was not altered.

c. Emptying curves

For each of the three ROI (proximal, distal and total stomach), activity-time curves, expressed as a percentage of the total meal versus time, were derived. The total stomach count rate at the end of the lag period (the frame preceding that in which activity appeared in the proximal small intestine) was used to determine the value for 100% retention. Total stomach values during the lag period greater than 100% (due to under-correction for attenuation, chapter 5.1 (ii)d) were set to 100%. The zero elements (from the non-acquisition periods) were replaced using linear interpolation and the activity-time curves were smoothed using 7 point polynomial smoothing. Time zero was considered the time of meal completion.

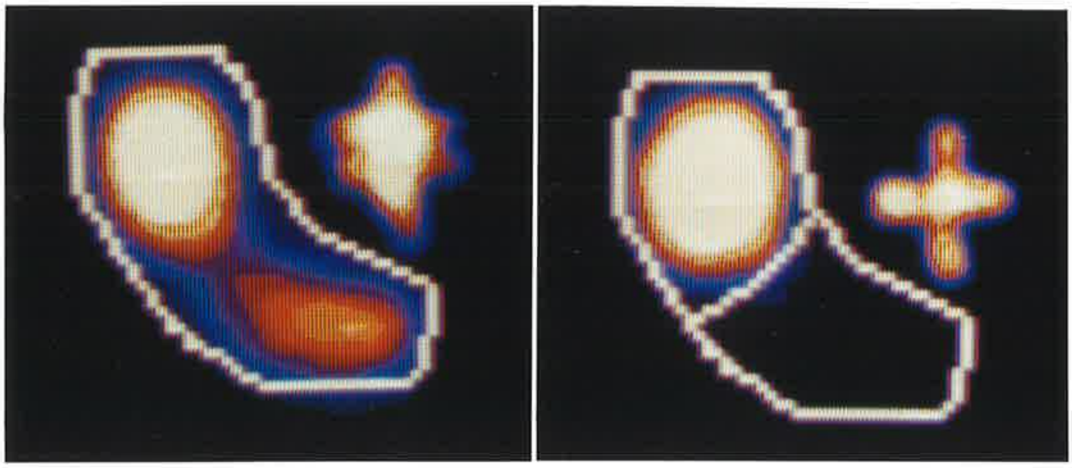
d. Emptying parameters

Various parameters were derived from these curves: for the ***total stomach***, these were - the lag period before food left the stomach (SLP), the average rate of linear emptying (expressed as %/minute), the time for 50% emptying (ST_{50}) and the percentage retention at 100 minutes after meal completion.

For the ***proximal stomach***, the parameters, time for 50% emptying (ST_{50}) and retention at 100 minutes were obtained.

The ***distal stomach*** parameters were, the maximum content (SMC) (%), a "filling time" parameter, time to 90% of SMC (ST_{90}) (the time to peak was not used as it is more readily influenced by statistical noise) and the parameter SLP-ST_{90}. The parameter SLP-ST_{90} was used as an indicator of distal stomach retention.

The distal stomach parameter SMC was also calculated before correction for tissue attenuation, and the difference (before and after correction) used as an indicator of the attenuation error as food redistributed within the stomach.



(a) (b)

Figure 6.1

a) The total stomach ROI drawn on a composite posterior image of the stomach. This image included frames from the beginning of the study as well as frames in which the distal stomach counts were maximal. A cross-shaped marker attached to the patient's back was used for image alignment.

(b) The line separating proximal and distal stomach regions is defined using the early "reservoir" area observed in the first few post-cibal frames.

e. Statistical analysis

Data were analysed using linear regression analysis.

6.2 THE EFFECT OF INTRADUODENAL LIPID INFUSION ON GASTRIC MOTILITY AND EMPTYING OF A SOLID MEAL

The study described in this and subsequent sections (7.2, 8.2) was a joint collaborative study with Dr. Richard Heddle who was responsible for the manometric analysis. A detailed description of the manometric assembly is given in Appendix II.

(i) Subjects

The studies were performed on 10 healthy asymptomatic volunteers, 6 male and 4 female, aged between 19 and 32 years. Written informed consent was obtained in each case and the study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital.

(ii) Performance of the test

After an overnight fast a manometric catheter assembly (see Appendix II) was introduced through an anaesthetized nostril. Recordings of pressure and two-point transmucosal potential difference (TMPD) indicated when the sleeve sensor was correctly positioned across the pylorus. The subject then sat with his back to a scintillation camera and normal saline was infused into the duodenum (via an infusion port in the catheter) at the rate of 1 ml/minute. After 15 minutes, each subject was given a standard solid test meal labelled with ^{99m}Tc (chapter 3.2(i)), which was consumed over 5 minutes and followed by 50 ml of unlabelled water. Gastric emptying of the solid meal and antral, pyloric and duodenal motility were then recorded simultaneously until the end of the study.

(iii) Data acquisition

a. Gastric Emptying

Data were acquired using a scintillation camera (Nuclear Chicago Pho-Gamma III HP) and computer system. Using Gamma-11 software, which enables simultaneous acquisition and analysis, the radionuclide images were examined on the "background" computer monitor as the study was acquired in "foreground". The amount of solid food emptied from the stomach was calculated immediately on completion of each image. When approximately 25% of the solid meal had emptied from the stomach, the intraduodenal infusion was switched from saline to an isotonic lipid emulsion, which was infused into the duodenum at 1 ml/minute (1.1 kcal/minute) for 45 minutes. At the conclusion of the lipid infusion, a normal saline infusion was recommenced and continued until the end of the study. The study was continued until either 80% of the solid meal had emptied from the stomach, or 45 minutes had elapsed since the cessation of the lipid infusion. Data were collected continuously apart from brief (3-5 minute) interruptions at 30 minute intervals to allow the subject to stand or sit away from the camera. The frame rate was one frame/minute for the first 30 minutes, followed by a frame rate of one frame/3 minutes till the completion of the study. At the end of data acquisition, 3.7 MBq of ^{99m}Tc-DTPA in 150 ml of water was given orally, and a one minute, left lateral image of the upper abdomen was taken.

b. Motility

The manometric catheter assembly monitored pyloric motility using a 5 cm long sleeve sensor - this also recorded, using sideholes at each end (antral and duodenal TMPD sideholes), both intraluminal pressure and TMPD. Motility was also recorded from 4 locations at 2 cm intervals orad of the sleeve (antral) and from 2 duodenal sideholes at 4 cm intervals from the aborad margin of the sleeve. The duodenal infusion port was located 10 cm distal to the sleeve sensor.

(iv) Data analysis

The study was divided into two 15 minute periods prior to lipid infusion, three 15 minute periods during lipid infusion and up to three 15 minute periods after lipid infusion. All times were referenced to the start of the lipid infusion, which was taken as 0 minutes.

a. Gastric Emptying

Data were corrected for patient movement, radionuclide decay and tissue attenuation (chapters 3.2(i)d, 6.1 (iii)b).

Regions-of-interest for the proximal, distal and total stomach were determined by a previously described method (chapter 6.1(iii)b).

The net fall in counts in each ROI, as a percentage of the total meal counts (counts in the total stomach ROI in the lag period), was determined for each 15 minute period. Falls in counts from the total gastric ROI were interpreted as reflecting the rate of gastric emptying.

b. Motility

All analyses were performed manually. Records were only analysed when the TMPD readings satisfied predetermined criteria for correct placement of the sleeve sensor across the pylorus (Houghton el al, 1988).

The number of pressure waves of amplitude ≥ 10 mm Hg recorded by each antral sidehole, the sleeve sensor straddling the pylorus and by each duodenal sidehole were counted and a mean rate/minute calculated for each 15 minute analysis period. Pressure waves recorded by the sleeve sensor were divided into isolated pyloric pressure waves (IPPWs) or non-localised pressure waves. IPPWs were defined as pressure waves that were recorded by the sleeve sensor, but were not associated with a pressure wave of any amplitude recorded in the antral or duodenal TMPD sideholes.

An antral motility index was derived for the 2 most distal antral sideholes by summing the wave amplitudes in each sidehole and expressing these as a score in mm Hg/minute.

(v) Statistical methods

Statistical inferences regarding changes with time in motility, and gastric emptying were made with the Friedman two-way analysis of variance by ranks. If this test was significant at the $p<0.05$ level, the Wilcoxon matched-pairs signed rank test was used to compare individual time periods.

6.3 THE EFFECT OF LIQUID CALORIES ON GASTRIC MOTILITY AND EMPTYING OF A MIXED SOLID AND LIQUID MEAL

The motility analysis for this study was performed by Drs. L. Houghton and N.W. Reid. The manometric assembly is described in detail in Appendix II.

(i) Subjects

The studies were performed on 15 healthy asymptomatic volunteers (13 male, 2 female) aged between 18 and 51 years. Written informed consent was obtained in each case and the study protocol was approved by the Research Review Committee of the Royal Adelaide Hospital.

(ii) Performance of the test

After the subjects had fasted for at least 14 hours, a manometric catheter assembly (see Appendix II) was introduced through an anaesthetized nostril. Recordings of pressure and two-point transmucosal potential difference indicated when the assembly was correctly positioned across the pylorus, and the subject then sat upright with his back against the detector of a scintillation camera. Fasting manometric recordings were obtained for 30 minutes, after which the subject ate the standard solid test meal (caloric value approximately 270 kcal, chapter 3.2(i)a) labelled with ^{99m}Tc. The meal was ingested within 5 minutes and was immediately followed by a 200 ml drink of either normal saline (8 subjects), or 25% dextrose in normal saline (7 subjects) (caloric value = 200 kcal, osmolality = 1775 mosmol/kg of H_2O) labelled with ^{113m}In-DTPA.

(iii) Data acquisition

a. Gastric Emptying

Data were acquired in 64x64 frame mode at a rate of one frame every 30 seconds for the first 30 minutes and then at a rate of one frame every 3 minutes for at least 2 hours until the end of the study. Data acquisition was interrupted briefly (3-5 minutes) at 30 minute intervals to allow the subject to stand or sit away from the camera. At the end of data acquisition, 3.7 MBq of ^{99m}Tc-DTPA in 150 ml of water was given orally, and a one minute, left lateral image of the upper abdomen was taken.

b. Motility

Intraluminal pressure (antral, pyloric and duodenal) and potential difference were recorded continuously using the manometric assembly (Appendix II).

(iv) Data analysis

a. Gastric Emptying

Data were corrected for subject movement, radionuclide decay, Compton scatter and gamma-ray attenuation (chapters 3.2(i)d, 6.1(iii)b).

Regions-of-interest for the proximal, distal and total stomach were defined using the early reservoir seen with the solid meal (chapter 6.1(iii)b). In the majority of studies of liquid emptying, the reservoir area was poorly defined. Consequently for each individual subject, the ROI used for the analysis of solid emptying were also used for the generation of liquid emptying curves.

For both solid and liquid emptying, proximal, distal and total stomach retention curves (expressed as a percentage of the total meal vs time) were obtained (chapter 6.1(iii)c). Time zero was defined as the time of meal completion. Various emptying parameters were derived from these curves.

Solid meal parameters: For the total stomach, these were the lag period (SLP), the amount of the meal remaining (retention) at 120 minutes after meal completion and the linear emptying rate.

For the proximal stomach, the parameter retention at 60 minutes was derived.

For the distal stomach, the maximum content expressed as a percentage of the total meal (SMC), and the time to reach 90% of SMC (ST_{90}) were calculated. The parameter SLP-ST_{90} was used as an index of the average retention time of solid food in the distal region.

Liquid meal parameters: For the total stomach, the lag period and the retention at 10 and 60 minutes were obtained.

For the proximal and distal stomach, the amount of the meal remaining at 10 and 30 minutes were measured, as well as the maximum distal stomach content (%).

b. Motility

In practice, only small sections of recording (range, 0%-30%; median, 2.6%) were excluded from analysis because the assembly was out of position.

The criteria used to analyze the manometric data have been described previously (Houghton et al, 1988). A coordinated pressure wave was defined as a single contraction, or cluster of two to eight contractions, occurring within 10 seconds in at least three separate but not necessarily adjacent channels, and separated by quiescence lasting at least 20 seconds. Propagation of a pressure wave in an aboral direction, was said to take place when the leading edge of the wave complex occurred > 1 second but < 5 seconds after a similar wave in the adjacent aboral recording site. Isolated pyloric pressure waves (IPPWs) were defined as pressure waves recorded by the sleeve sensor in the absence of pressure waves recorded by the adjacent antral and duodenal sideholes, within 10 seconds of the peak of the pyloric wave.

(v) Statistical methods

Data were evaluated using the Wilcoxon rank-sum test.

CHAPTER 7
RESULTS

7.1 Gastric emptying of a solid meal in normal subjects

- **(i) Emptying patterns for total, proximal and distal stomach**
- **(ii) Retrograde flow**
- **(iii) Proximal reservoir**
- **(iv) Contraction band**
- **(v) Movement errors**
- **(vi) Attenuation errors**
- **(vii) Emptying correlates**

7.2 The effect of intraduodenal lipid on gastric motility and emptying of a solid meal

- **(i) Gastric emptying**
- **(ii) Motility**

7.3 The effect of liquid calories on gastric motility and emptying of a mixed solid and liquid meal

- **(i) Gastric emptying**
- **(ii) Motility**

7.1 GASTRIC EMPTYING OF A SOLID MEAL IN NORMAL SUBJECTS

(i) Emptying patterns for total, proximal and distal stomach

Figure 7.1 illustrates the emptying curves for proximal, distal and total stomach in one subject. The total stomach curve demonstrates a lag period (SLP = 34 minutes) followed by an emptying phase. Emptying was seen to start slowly and then to approximate a linear emptying pattern. There was a gradual redistribution of food within the stomach (Fig 7.2(1-3)) and the distal stomach counts rose to a maximum value at 54 minutes and then fell without any appreciable plateau (Fig 7.1). The time at which the maximum distal stomach counts were obtained corresponded to the start of the linear emptying phase for the total stomach (Figs 7.1, 7.2(3)). Later in the study, the majority of the activity was observed in the distal stomach (Figs 7.1, 7.2(4)). In this subject, a region of diminished activity was seen at the level of the proximal/distal separation line during the emptying phase and persisted for at least 30 minutes. (Fig 7.2(3)).

Results for the 13 subjects are shown in Figure 7.3 and Tables 7.1 and 7.2. A considerable inter-individual variation in all parameters is apparent. Emptying of the solid meal from the total stomach showed two components - a lag period followed by an emptying phase which was approximately linear. In 2 subjects the linear emptying phase was followed by a plateau phase (where little food left the stomach) of greater than 15 minutes duration.

Table 7.1

Emptying parameters for proximal and total stomach

Parameter	Proximal	Total
Lag period (min) (SLP)	-	41 (21-57)
Linear emptying rate (% min^{-1})	-	0.82 (0.46-2.13)
Time for 50% emptying (min) (ST_{50})	48 (4-93)	97* (59-174)
Retention at 100 min (%)	14 (3-44)	48 (22-85)

median value (range) in 13 normal subjects

* in 3 subjects the ST_{50} value for total stomach was obtained from interpolation using the linear emptying slope

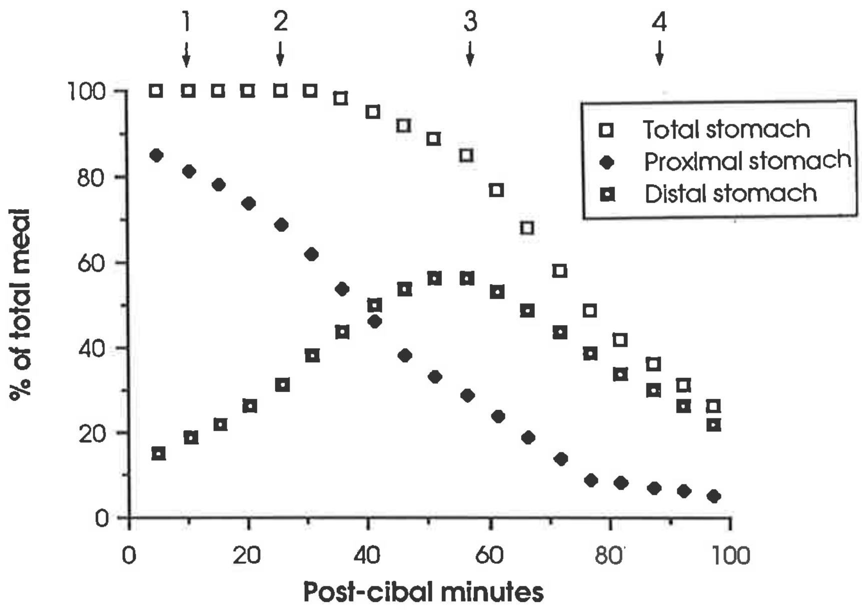


Figure 7.1

Composite total, proximal, and distal stomach emptying curves of the solid meal in subject A. The numbers refer to corresponding scintiphotos in Figure 7.2

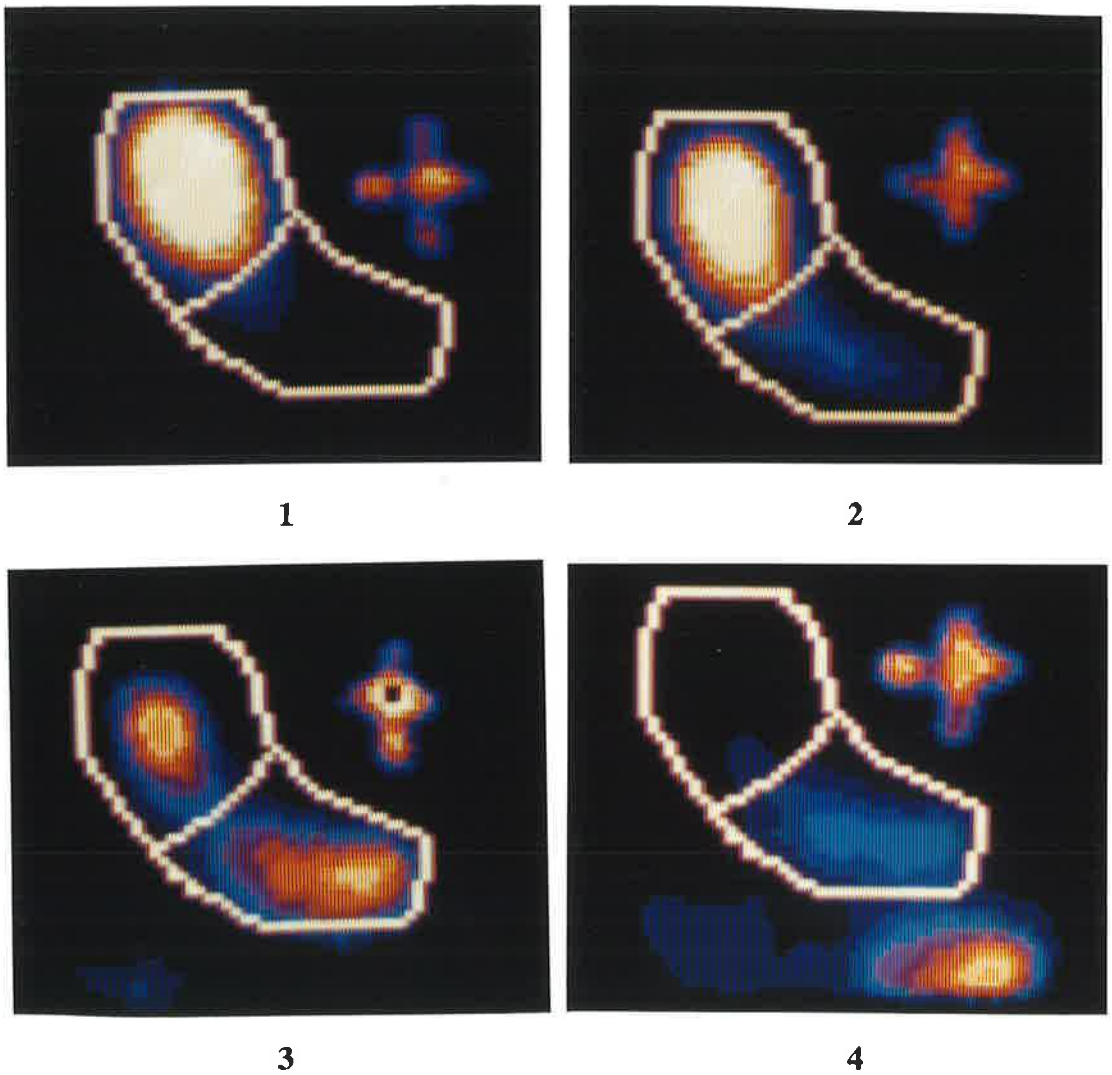


Figure 7.2

Scintiphotos showing the distribution of solid food in the stomach at (1) 10 minutes, (2) 25 minutes, (3) 56 minutes and (4) 87 minutes in subject A. The numbers refer to corresponding time points in Figure 7.1

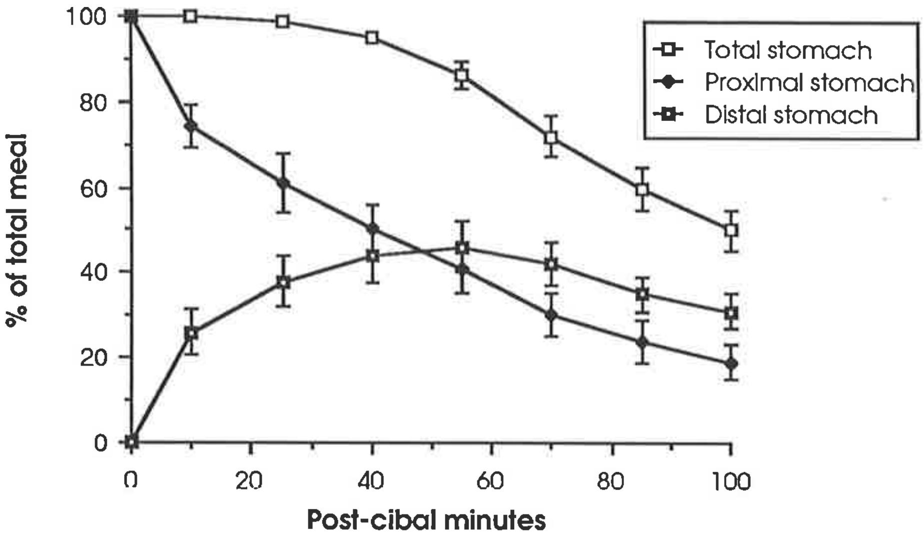


Figure 7.3

Composite total, proximal, and distal stomach emptying curves of the solid meal in 13 normal controls. Data are mean values ± S.E.M.

Table 7.2

Emptying parameters for distal stomach

Maximum content (%) (SMC)	35 (29 - 89)
Time to 90% of SMC (min) (ST_{90})	38 (11 - 73)
SLP-ST_{90} (min)	7 (-16 - 41)

median value (range) in 13 normal subjects

There was considerable variation both in the rate (as indicated by the parameter ST_{50}) and pattern of emptying from the proximal stomach. In 4 of the 13 subjects emptying was approximately linear for the majority of the emptying phase, while in a further 2 subjects emptying closely approximated a dual linear emptying pattern with a faster, followed by a slower phase. The pattern of emptying for the remaining 7 subjects was non linear.

There was also considerable variation in the distal stomach curves. In 10 of the 13 subjects the distal stomach counts rose progressively during the lag period and then diminished during the emptying phase (in 3 subjects, the distal counts did not fall significantly below the peak value (less than 90% of peak) by the end of the study, and in one of these the peak value may not have been obtained). In only 2 of the 10 subjects was a distinct plateau phase observed (Fig 7.4). In these subjects the distal stomach contents (SMC) remained above 90% of the peak value for 54 and 56 minutes, respectively. These 2 subjects also had the most rapid proximal stomach emptying (ST_{50} of 4 and 10 minutes), and the largest value of the distal stomach parameters SLP - ST_{90} (41 and 27 minutes) and SMC (86 and 89%).

Visual inspection of the images indicated that consumption of the liquid did not have any immediate effect on redistribution of the solid meal in any subject.

(ii) Retrograde flow

There was no evidence of retrograde movement of food from the distal to the proximal stomach in any of the subjects.

(iii) Proximal reservoir

A discrete proximal reservoir area (used to define proximal and distal stomach) was seen in 10 subjects while in the remaining 3 subjects, a reservoir was evident even though some food had left this proximal region.

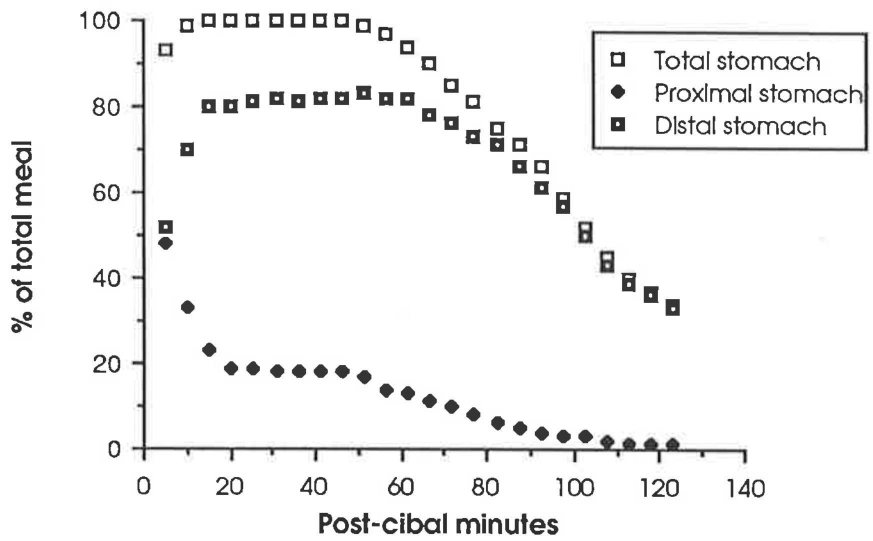


Figure 7.4

Composite total, proximal and distal stomach emptying curves of the solid meal in subject B. Rapid redistribution of food from the proximal to the distal stomach and a distal stomach plateau are evident,

(iv) Contraction band

In 7 of the 13 studies, a region of reduced activity between the proximal and distal regions ("contraction" band) was observed which persisted for at least 5 minutes. In 4 of these 7 subjects this region started high in the stomach and extended distally as food emptied from the stomach corpus, leaving 2 separate food-filled areas separated by a band which appeared devoid of solid food (Fig 7.5). In the remaining 3 subjects the band was seen only as a region of reduced activity (Fig 7.2(3)). In all cases the midpoint of this region closely approximated the line (obtained from the early reservoir area) used to define proximal and distal ROI (Figs 7.2(3), 7.5b).

(v) Movement errors

Figure 7.6 illustrates considerable misalignment of the image relative to the total stomach ROI in one subject, after correction for movement using the cross-shaped marker. This large degree of misalignment, caused by movement of the stomach within the subject, was observed in most of the subjects and necessitated further image alignment using an interactive computer program.

(vi) Attenuation errors

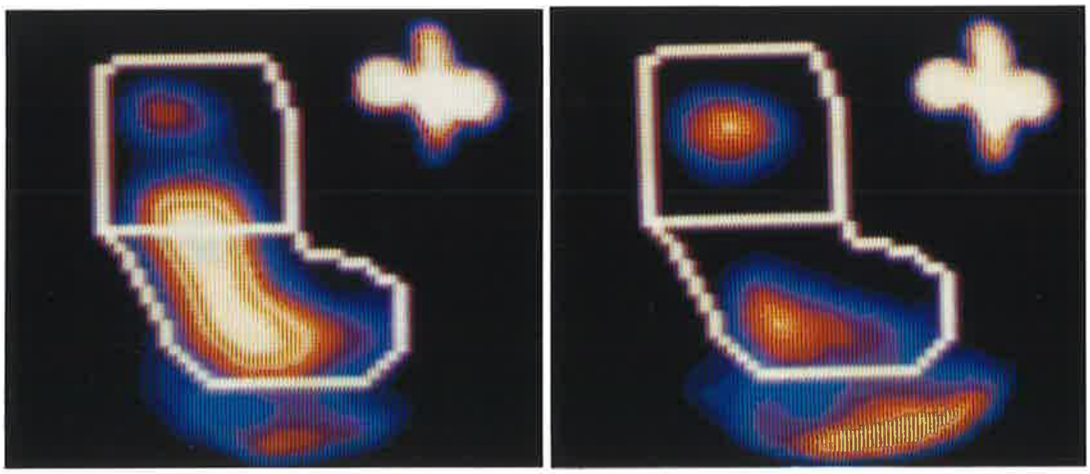
Errors due to tissue attenuation were also significant. In the 13 normal subjects the percentage increase in the distal stomach parameter SMC after correction for attenuation using the lateral image method was 33% (median, range 7-48%).

(vii) Emptying correlates

There was no significant correlation ($p > 0.05$) between the distal stomach parameter SMC ($r = 0.09$), or the proximal stomach parameter ST_{50} ($r = 0.36$) and the rate of emptying from the total stomach.

7.2 THE EFFECT OF INTRADUODENAL LIPID ON GASTRIC MOTILITY AND EMPTYING OF A SOLID MEAL

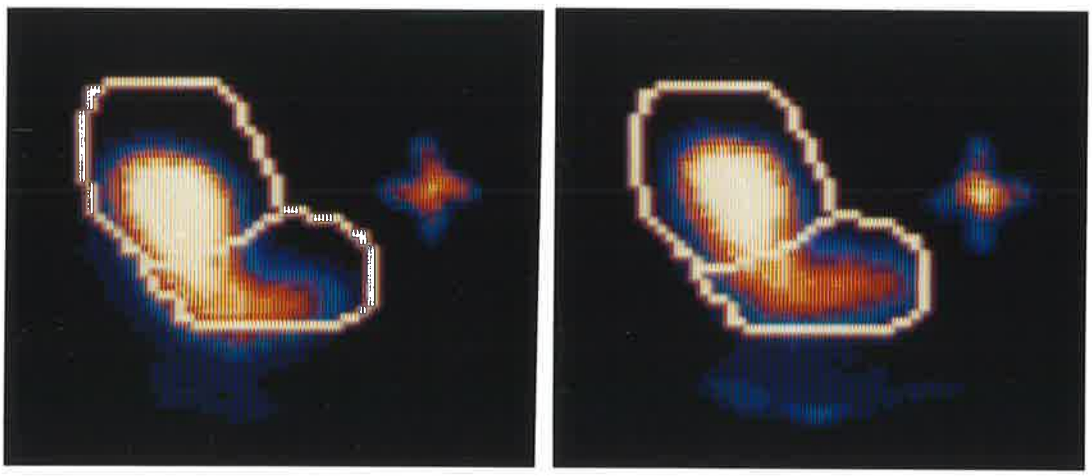
Simultaneous, technically satisfactory measurements of gastric emptying and motility were available for 76 of the 80 fifteen minute observation periods analysed. In only one subject were data missing from 2 periods rather than one.



(a) (b)

Figure 7.5

Scintiphotos showing a "contraction" band in one subject at (a) 50 minutes and (b) 100 minutes post-cibal. The band extended distally as food emptied from the stomach corpus.



(a) (b)

Figure 7.6

Two frames of a study corrected for subject movement using a cross-shaped marker. Movement of the stomach within the subject (a) necessitated further image alignment.

(i) Gastric emptying

a. Total stomach

Intraduodenal lipid had a significant ($p<0.01$) effect on the rate of emptying from the total stomach, with emptying having virtually ceased by the 30 to 45 minute period (Fig 7.7). The rate of gastric emptying increased again after cessation of the lipid infusion and was not significantly different from the pre-lipid period.

Individual subjects showed a variable latency between the onset of the lipid infusion and the slowing of gastric emptying. In 4 of 10 subjects, the rate of emptying during the 0 to 15 minute period was < 60% of the rate just before the start of the lipid infusion (Fig 7.8a); this slowing was delayed until the 15 to 30 or 30 to 45 minute periods in a further 5 subjects, whilst 1 subject showed no clear slowing of gastric emptying with the lipid infusion.

b. Proximal/distal stomach

The rate of emptying from the proximal stomach was reduced promptly and significantly by the lipid infusion ($p<0.05$), and increased again upon cessation of the lipid infusion ($p<0.05$) (Fig 7.7b). In 7 of the 10 subjects there was an increase in counts in the proximal stomach ROI during the 0 to 15 minute period. In each of these subjects there was a corresponding fall in counts in the distal stomach ROI, indicating retrograde flow from the distal to proximal stomach (Figs 7.7, 7.8). This retrograde movement of ingesta was also evident on the accompanying scintiphotos (Fig 7.9(3-4)). A similar increase in median counts in the proximal stomach ROI occurred during the 30 to 45 minute period (Fig 7.7).

(ii) Motility

a. Antral motility

The test meal consistently induced antral pressure waves with an underlying frequency of 3/minute . These antral pressure waves were markedly inhibited during the lipid infusion ($p<0.01$) (Fig 7.10), as was the motility index for the antral TMPD side hole ($p<0.01$).

A similar trend to suppression of antral motility was seen at the antral side hole 2 cm proximal, but did not reach statistical significance.

b. Pyloric motility

Lipid infusion was associated with a significant ($p<0.01$) increase in the number of isolated pyloric pressure waves (IPPWs) compared with the pre-lipid period. This stimulation appeared to carry over into the post-lipid periods (Fig 7.10).

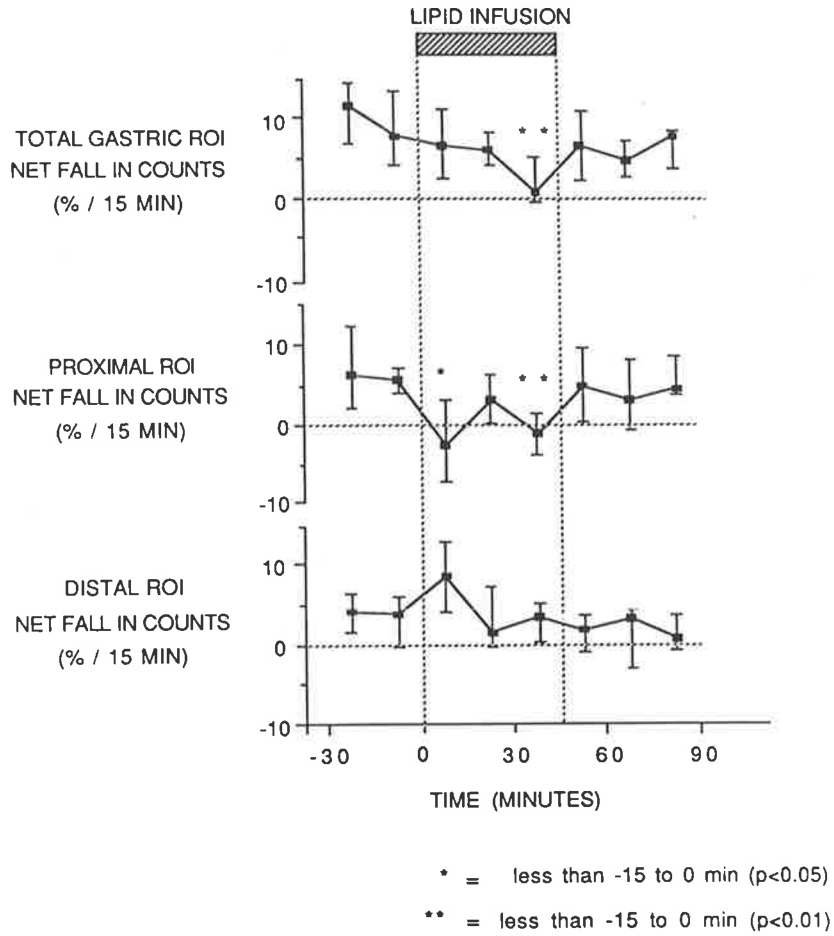


Figure 7.7

Percentage fall in counts/15 minute period for the total, proximal and distal gastric regions-of-interest. Data shown as median and interquartile range.

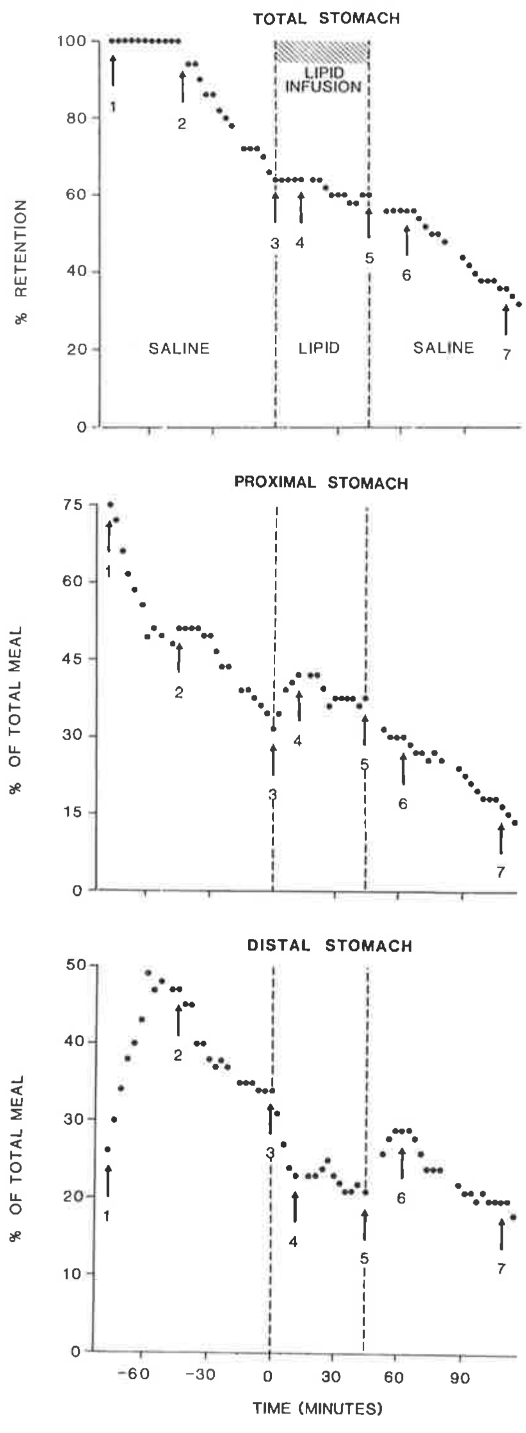
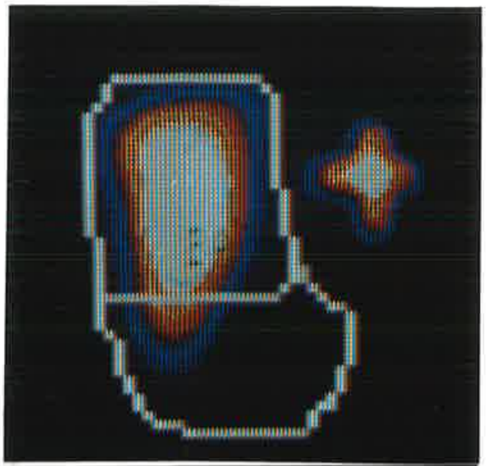


Figure 7.8

Total, proximal, and distal stomach emptying curves of the solid meal in a typical subject. During the lag period when no solid left the stomach, redistribution from the proximal to the distal stomach was seen. Relatively linear emptying from the stomach then occurred until the start of the lipid infusion, which slowed total gastric emptying. At this time there was an increase in the counts within the proximal region-of-interest, reflecting retrograde flow of ingesta from the distal to the proximal stomach. After the lipid infusion, redistribution from proximal to distal stomach recommenced, followed by a resumption of gastric emptying. The numbers refer to corresponding scintiphotos in Figure 7.9.

Figure 7.9

Scintiphotos taken (1) immediately after ingestion of the solid meal, (2) at the end of the lag period, (3) just prior to the lipid infusion, (4) after 12 minutes of lipid infusion, (5) at the end of the lipid infusion, (6) 17 minutes after the cessation of the lipid infusion and (7) near the end of the study. These scintiphotos confirm that the lipid infusion was associated with retropulsion of ingesta from the distal to proximal stomach. The numbers refer to corresponding time points in Figure 7.8



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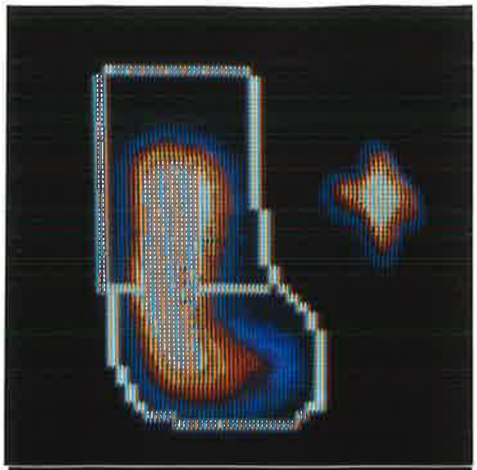

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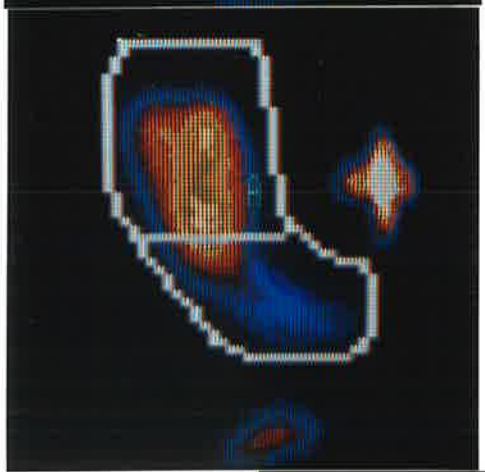

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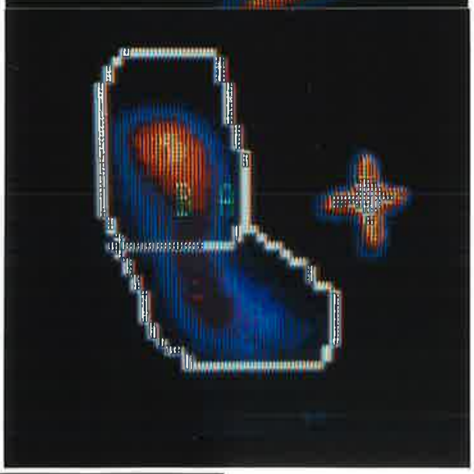

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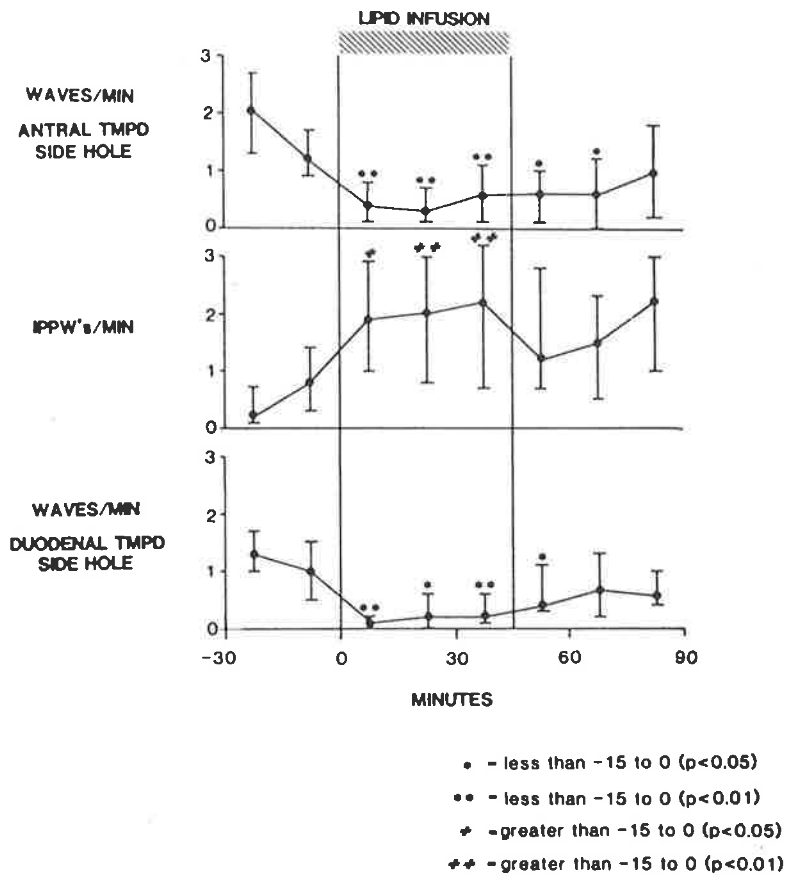


Figure 7.10

Effect of intraduodenal lipid infusion on the rate of isolated pyloric pressure waves (IPPWs) and pressure waves recorded from the antral and duodenal TMPD side holes. Data are shown as the median and interquartile range for each period.

c. Duodenal pressure waves

The number of pressure waves recorded by the duodenal TMPD sidehole during and immediately following the lipid infusion was significantly less than the rates before the lipid infusion (Fig 7.10). There was no statistically significant variation with time in the rate of duodenal pressure waves recorded by the side holes 4 and 8 cm distal to the sleeve sensor.

7.3 THE EFFECT OF LIQUID CALORIES ON GASTRIC MOTILITY AND EMPTYING OF A MIXED SOLID AND LIQUID MEAL

(i) Gastric emptying

Curves for proximal, distal and total stomach were obtained in 14 of the 15 subjects. In one subject (saline group) it was not possible to segment the stomach into proximal and distal subregions, because of a non typical profile (small, round stomach), and only total stomach data were included in the subsequent analysis.

a. Liquid emptying

Total stomach: After ingestion, liquid was rapidly dispersed through the whole stomach and there was a minimal lag period before stomach emptying commenced (Fig 7.11). The pattern of liquid emptying for saline was non-linear with a slope that decreased with time - dextrose emptied in an approximately linear fashion. For dextrose, the liquid lag period was longer, and there was greater retention of liquid at 10 minutes and 60 minutes (Figs 7.11, 7.12a, Table 7.3).

Proximal and distal stomach: The slower emptying of dextrose was associated with a significant increase in the amount of liquid in the distal stomach (Figs 7.11, 7.12c, Table 7.3) at 10 and 30 minutes ($p<0.01$) and in the maximum distal stomach content ($p<0.02$). In comparison there was no significant difference in the emptying rate of saline or dextrose from the proximal stomach (Table 7.3).

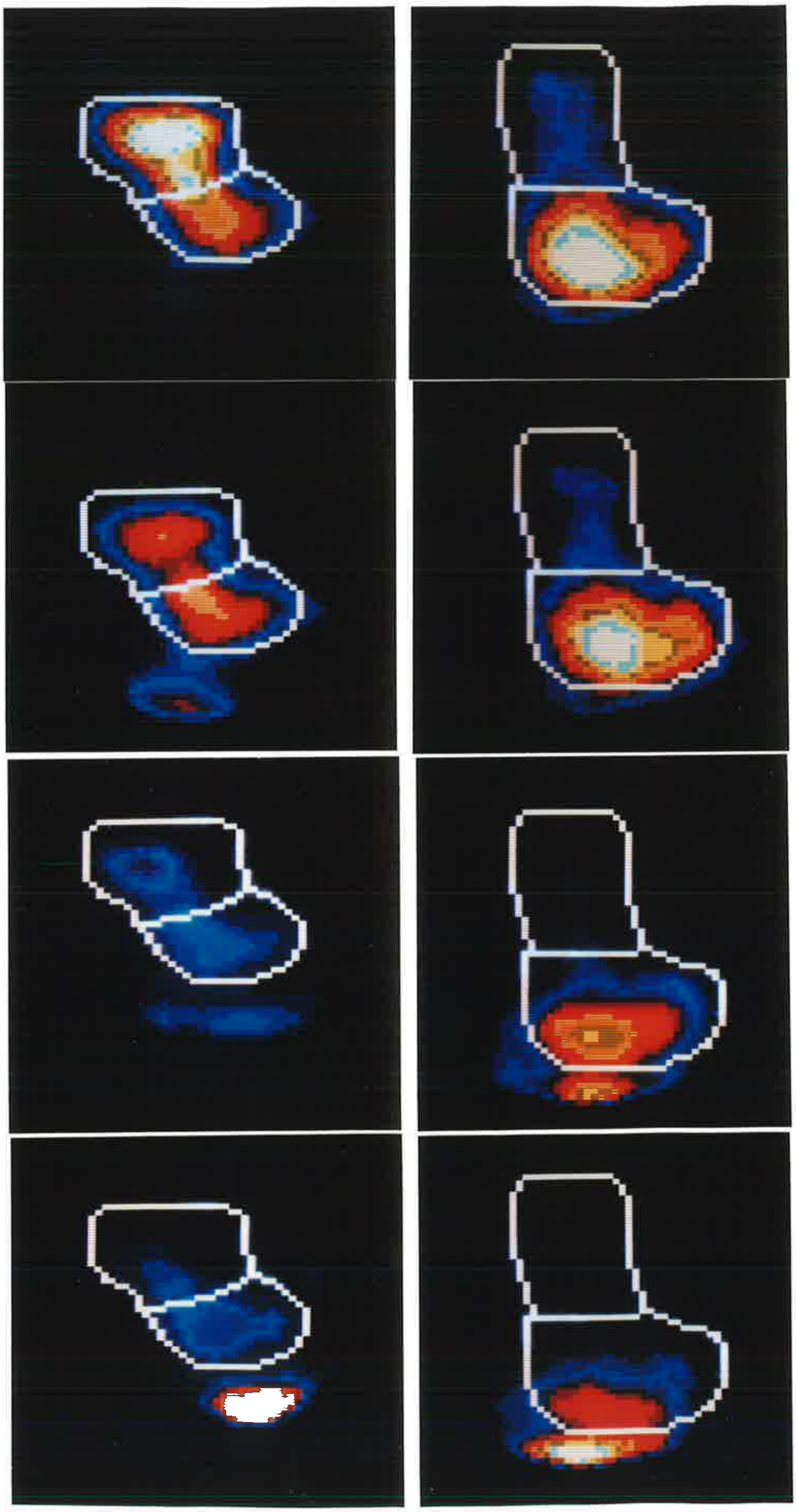
b. Solid emptying

Total stomach: Solid emptying from the total stomach was slower than liquid emptying and was characterised by an initial lag period, followed by an emptying phase which approximated to a linear pattern. Directly after ingestion, the solid component was observed to reside almost entirely in the proximal stomach ("reservoir") (Fig 7.13), after which there was a gradual redistribution of solid food from this reservoir area to the distal stomach (Figs 7.13, 7.14b-c). Incorporation of dextrose into the liquid phase of the meal delayed the whole stomach emptying of the solid component (Figs 7.13, 7.14a, Table 7.4). This delay was caused by a significant increase in the lag period ($p<0.02$) - there was no difference between the saline and dextrose meals in the linear rate of emptying of solids after the lag period.

Figure 7.11

Scintiphotos showing the distribution of the liquid component of a mixed solid/liquid meal (Left panel = saline, right panel = 25% dextrose) at 5, 10, 30 and 60 minutes.

SALINE | 25% DEXTROSE



5 minutes

10 minutes

30 minutes

60 minutes

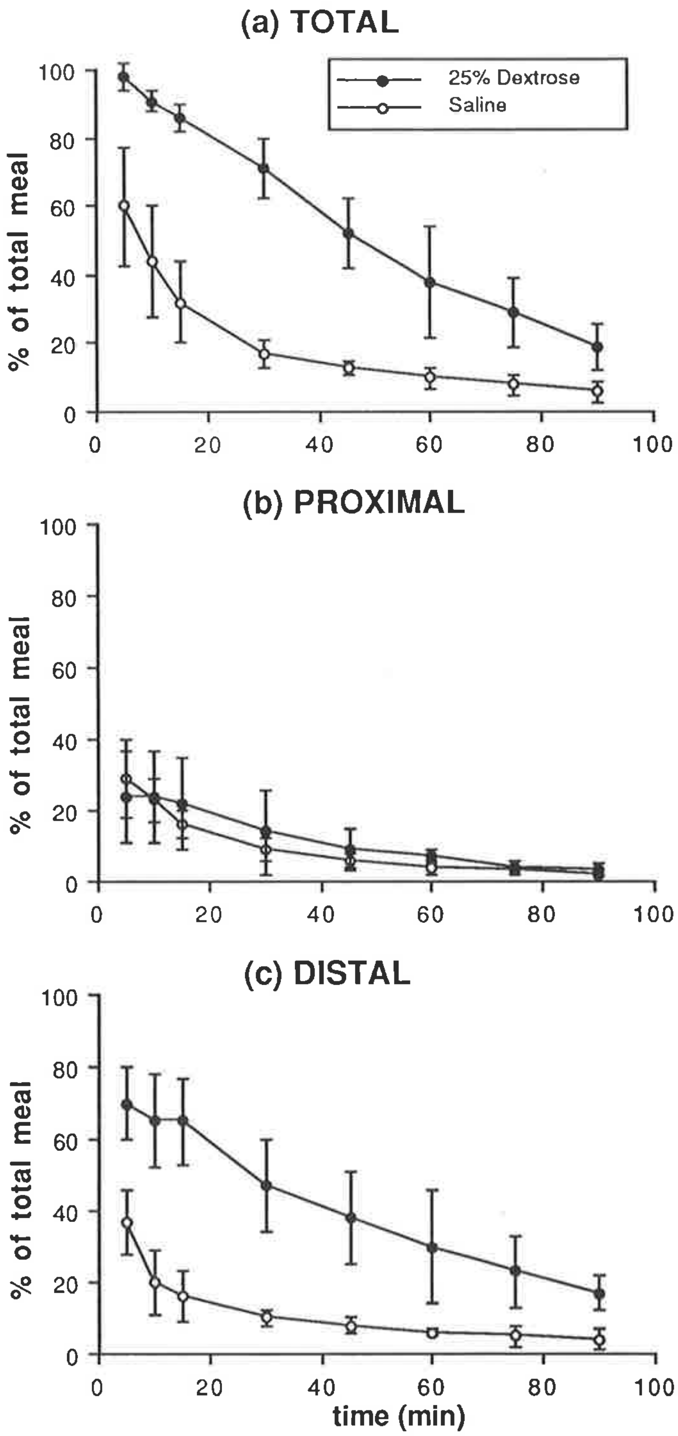


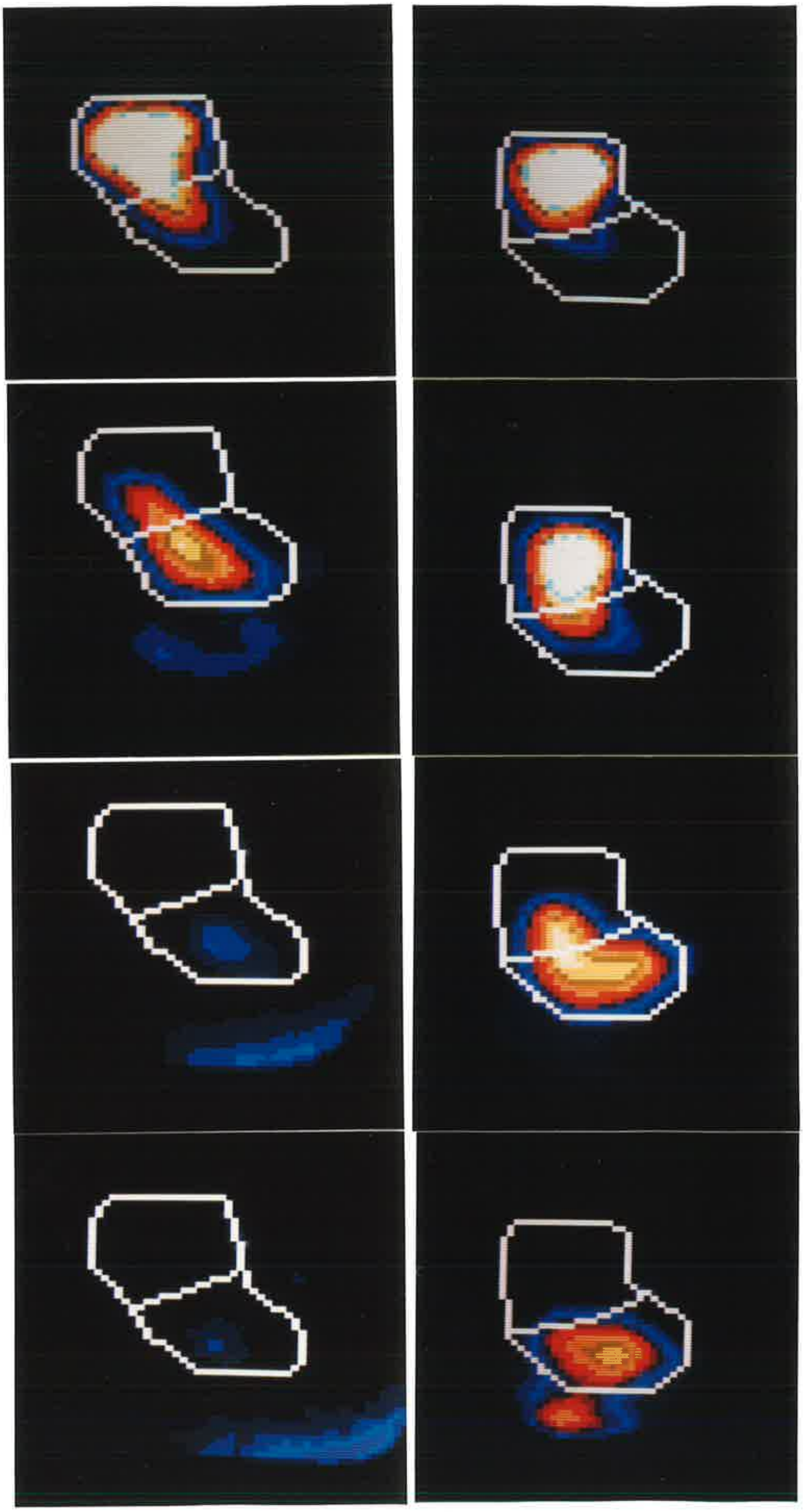
Figure 7.12

Composite total (a), proximal (b) and distal stomach (c) emptying curves of the liquid component of a mixed solid/liquid meal. The data are median values ± interquartile range.

Figure 7.13

Scintiphotos showing the distribution of the solid component of a mixed solid/liquid meal (left panel = saline, right panel = 25% dextrose) at 10, 60, 120, and 150 minutes.

SALINE | 25% DEXTROSE



10 minutes

60 minutes

120 minutes

150 minutes

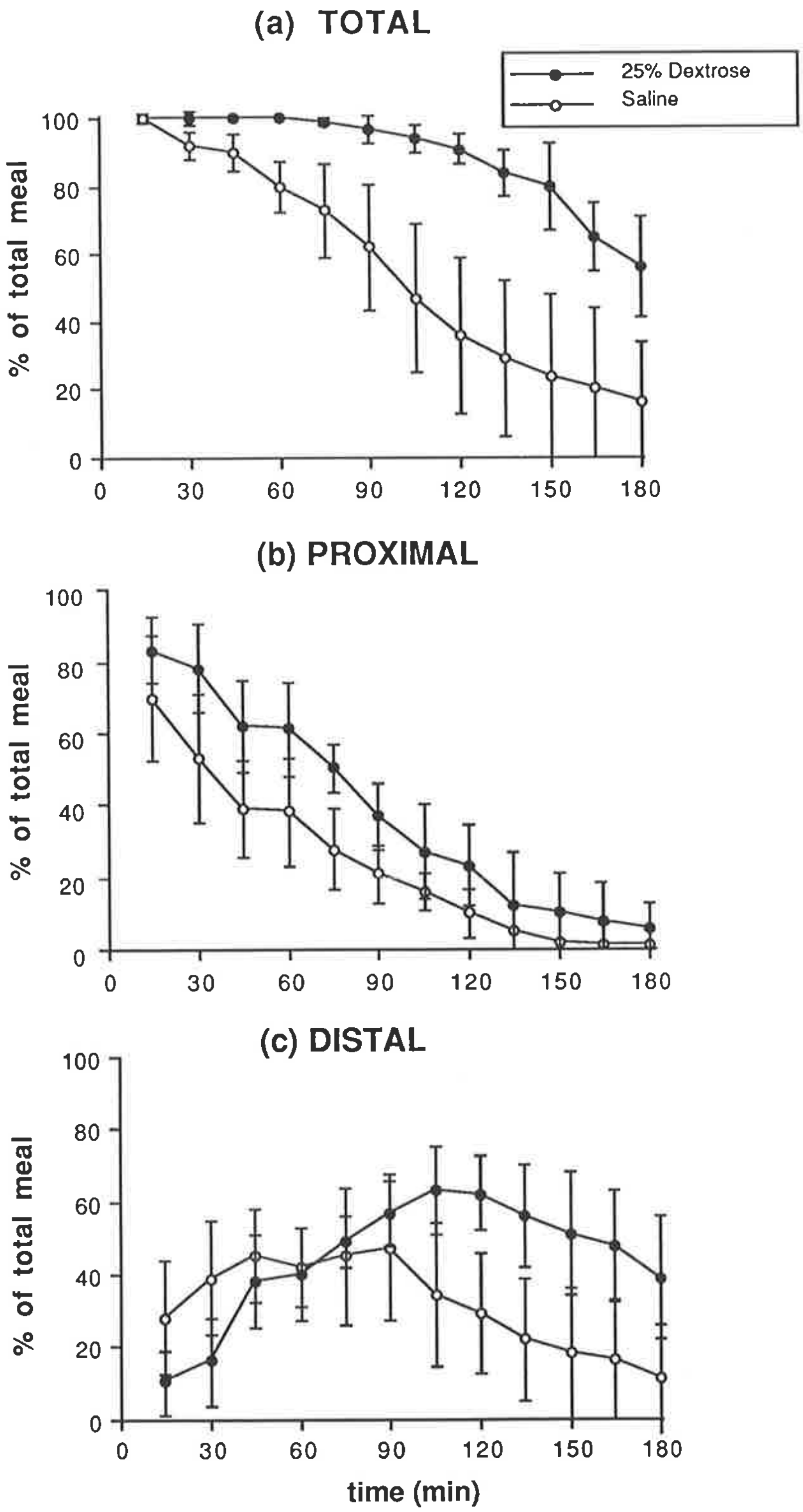


Figure 7.14

Composite total (a), proximal (b) and distal stomach (c) emptying curves of the solid component of a mixed solid/liquid meal. The data are median ± interquartile range.

Table 7.3

Effect of increasing the liquid calorie content of a mixed solid/liquid meal on liquid emptying

	Normal saline	25% dextrose
Total Stomach		
Lag period (min)	1 (0.5-3)	6 (3-7)**
Retention at 10 min (%)	44 (24-86)	91 (86-93)**
Retention at 60 min (%)	10 (4-16)	38 (16-59)**
Proximal Stomach		
Retention at 10 min (%)	23 (8-32)	24 (12-52)
Retention at 30 min (%)	9 (3-13)	14 (8-35)
Distal Stomach		
Retention at 10 min (%)	20 (13-63)	65 (40-81)**
Retention at 30 min (%)	10 (7-31)	47 (28-74)**
Maximum content (%)	41 (27-72)	72 (46-88)*

median (range)

* p <0.02 ** p <0.01

Table 7.4

Effect of increasing the liquid calorie content of a mixed solid/liquid meal on solid emptying

	Normal saline	25% Dextrose
Total stomach		
Lag period (min) (SLP)	37 (15-140)	95 (71-135)*
Retention at 120 min (%)	36 (3- 84)	91 (86-97)**
Linear emptying rate (% min^{-1})	0.68 (0.4-1.5)	0.57 (0.2-1.4)
Proximal stomach		
Retention at 60 min (%)	38 (16-54)	61 (40-92)*
Distal stomach		
Maximum content (%) (SMC)	65 (23-79)	69 (55-90)
Time to 90% of SMC (min) (ST_{90})	35 (20-76)	96 (91-124)**
SLP-ST_{90}	13 (-11-15)	0 (-20-13)

median (range)

* p< 0.02 ** p< 0.01

Proximal and distal stomach: The slower emptying of solids in the dextrose group could largely be explained by retention in the proximal stomach (Figs 7.13, 7.14b), this being greater at 60 minutes ($p<0.02$) (Table 7.4). Consequently it took longer to achieve 90% of maximal distal stomach content (SMC). Although SMC was greater in the dextrose group (Fig 7.14c) this difference was not statistically significant (Table 7.4). There was also no significant difference between the two groups in the parameter SLP-ST_{90}, which reflects residence in the distal stomach (Table 7.4).

(ii) Motility

Ingestion of the saline/burger mixed meal was associated with a nonsignificant increase in the rate of occurrence of coordinated pressure waves involving the antrum, but no change in IPPWs (Table 7.5). Coordinated events involving the antrum increased further with the onset of solid emptying, though not significantly, and were associated with an increase in IPPWs. In contrast, ingestion of the meal that contained dextrose was associated with a nonsignificant decrease in the rate of occurrence of coordinated pressure waves involving the antrum (Table 7.5) and a sharp increase in IPPWs. The rate of occurrence of IPPWs during the solid lag period of the dextrose/burger meal was greater than during the fasting period and during the solid lag period of the saline/burger mixed meal ($p<0.05$). As with the saline/burger meal, the onset of solid emptying was associated with an increase in coordinated pressure waves involving the antrum, but with a significant decline in the occurrence of IPPWs.

Table 7.5

Comparison of the rate of occurrence* of motor patterns during the fasting, solid lag and solid emptying periods after ingestion of either the liver burger/saline or liver burger/dextrose mixed meal

	Fasting	Solid lag	Solid emptying
Liver burger/saline meal			
Co-ordinated pressure waves (antrum)	0(0-60)	39(0-142)	58(24-147)
Isolated pyloric pressure waves (IPPWs)	0(0-44)	7(0-52)	22(10-64)[a]
Liver burger/dextrose meal			
Co-ordinated pressure waves (antrum)	27(0-67)	16(8-47)	58(30-144)[ab]
Isolated pyloric pressure waves(IPPWs)	0(0-14)	58(30-77)[a]	23(1-37)[ab]

* Number of pressure waves per hour
Data are median (range)
a: Significant difference from fasting ($p<0.05$)
b: Significant difference from solid lag period ($p<0.05$)

CHAPTER 8
DISCUSSION

8.1 Gastric emptying of a solid meal in normal subjects

- **(i) Errors in measurement**
- **(ii) Contraction band**
- **(iii) ROI selection**
- **(iv) Emptying patterns for proximal, distal and total stomach**

8.2 The effect of intraduodenal lipid on gastric motility and emptying of a solid meal

- **(i) Intragastric distribution and emptying**
- **(ii) Motility**

8.3 The effect of liquid calories on gastric motility and emptying of a mixed solid and liquid meal

- **(i) Solid/liquid discrimination**
- **(ii) Liquid emptying**
- **(iii) Solid emptying**

8.4 Summary of section III

8.1 GASTRIC EMPTYING OF A SOLID MEAL IN NORMAL SUBJECTS

(i) Errors in measurement

a. Movement Errors

Little attention has been paid to the errors caused by changes in the shape and position of the stomach during gastric emptying. This error can be considerable when fixed ROI are used in dynamic studies (Fig 7.6), but has either been ignored or, at best, a larger ROI drawn to accommodate movement (Glowniak and Wahl, 1985). The use of a large ROI to accommodate movement is unacceptable if regional analysis is to be performed. Analysis of intragastric distribution and emptying using functional images (Rudzki et al, 1986, Jonderko et al, 1987), also requires accurate correction for movement but in general this major source of error has been overlooked. Moore and co-workers (1981) used a marker attached to the patient's skin to correct for movement - this method however, does not account for stomach movement within the abdominal cavity. The technique described in this thesis corrects for both sources of movement. Subject movement is automatically corrected for, using a marker attached to the subject's back - further alignment of the images, required because of movement of the stomach within the subject, is performed using an interactive computer program which enables the images to be realigned to the gastric region-of-interest.

b. Attenuation Errors

The necessity for attenuation correction in radionuclide gastric emptying studies has been discussed previously (chapter 5.1(ii)b). In the present study, posterior imaging under-estimated the distal stomach parameter SMC by 33%, compared with the value obtained after correction using the lateral image method. From previously described experience chapter 5.1(ii)b), the author would predict that anterior imaging without attenuation correction would result in a comparable over-estimation of this parameter. The results of this experiment indicate that correction for tissue attenuation is essential, not only for the accurate measurement of total stomach emptying, but also for monitoring the changes in distribution of food within the stomach. The lateral image method of attenuation is preferable to the geometric mean method, when only one scintillation camera is used (and the subject is rotated in front of the scintillation camera at regular intervals (Christian et al, 1980)), as continuous data sampling is possible, enabling more detailed analysis of intragastric distribution and emptying.

(ii) Contraction band

The proximal and distal stomach have been considered as two distinct functional areas. The former comprises the anatomical fundus and part of the corpus, while the latter includes the remaining corpus and the antrum (Kelly, 1980). Although a number of workers have studied emptying from proximal and distal stomach using scintigraphic techniques (Barker et al, 1979, Sheiner et al, 1980, Moore et al, 1981, Jacobs et al, 1982, Lawaetz et al, 1982, Urbain et al, 1989), the methods used for defining these two areas have been poorly defined. Sheiner and co-workers (1980), who studied gastric emptying of a 250 g semisolid meal, used a narrow mid-gastric band of reduced radioactivity observed on the scintiphotos to define proximal and distal ROI, but did not comment on how frequently this band was observed. In a recent investigation with a 400 g egg meal, Urbain and co-workers (1989) observed a transverse band in all 5 subjects studied, near the upper 1/3 of the stomach and used this area to define proximal and distal stomach . Jonderko (1987) observed "an hour-glass like narrowing separating the two parts of the stomach" in only 14 of the 69 subjects studied with a solid meal (^{99m}Tc labelled egg). Moore and co-workers (1986) reported that the appearance of a transverse contraction band is dependent both on the size and nature of the meal used and on the orientation of imaging, being most easily demonstrated after large solid meals with images taken in the left anterior oblique projection. A contraction band was evident in all 10 subjects studied after "filling" meals (mean weight 1692 g) but only in 5 of the 8 subjects studied after a 300 g meal. The results of the present study, using a 250 g solid meal, in which a gastric contraction band was seen in 7 of the 13 subjects, are therefore consistent with this report.

What is responsible for this gastric transverse band, which was first observed in a human subject by William Beaumont (Beaumont, 1833)? This band was also observed in the excised canine stomach by Hofmeister and Schutz (1886), who called it the "sphincter antri pylorici" to denote its role in separating the pyloric antrum from the corpus, or stomach body. Stieve (1919), a German anatomist, noted a gastric transverse band at the level of the incisura angularis (a 'notch' impression on the lesser curvature in the distal stomach) in the autopsy specimens of 3 executed prisoners who had earlier eaten a large meal. This band, a thick circular contraction, was so strong that the finger could not be introduced into the antrum. Schindler (1936) frequently observed with the gastroscope, a prominent fold in the same region of the human stomach as that reported by Stieve. He and fellow gastroscopists called this fold the musculus sphincter antri.

Cannon (1898), in his X-ray studies of the cat stomach under normal conditions, did not see deep constrictions at the beginning of the pyloric antrum. He did however, induce a powerful contraction band after giving apomorphine, or mustard. He concluded that the transverse contraction band reported by earlier workers was probably the result of abnormal gastric stimulus. Beaumont (1833) admitted that the thermometer, introduced into the gastric fistula of his subject to study the motions of the stomach, was an irritant. Ewald (1891) argued that the contraction band observed by Hofmeister and Schutz (1886) may have been caused by abnormal stimulus due to anaemia. These arguments could be extended to the gastroscopic studies of Schindler (1936) and to the autopsy study of Stieve (1919).

However, the results of the present study and that of other workers using radionuclide methods (Sheiner et al, 1980, Moore et al, 1986, Urbain et al, 1989) suggest that the transverse band is a functional entity of the normalstomach. Moore and colleagues (1986) put forward a possible reason why the gastric transverse band has not been discussed in modern general or radiological texts. Conventional radiological investigations, used extensively to document anatomical features in man, fail to demonstrate the band, as barium contrast "meals are nonfilling, nonnutritive and liquid in consistency" (Moore et al, 1986).

Moore and colleagues (1986) have suggested, as had earlier workers, that this transverse band "appears to represent an anatomic separation between the gastric reservoir (fundus-body) and the antrum" - they state that it is possibly caused by contraction of a muscle bundle termed the lower segmental loop (Forssell, 1913), at the junction of the oblique and circular muscles of the stomach. In the present study, the contraction band started well above the mid-gastric region in 4 of the 7 subjects in whom a band was seen, and extended distally as food emptied from the stomach corpus (Fig 7.5). In only 1 of the 7 subjects was the band evident below the mid-gastric region, and it is perhaps more likely that the band resides in the corpus, possibly starting immediately below the fundus. This is consistent with the study of Urbain and colleagues (1989) who observed a transverse band near the upper 1/3 of the stomach. The anatomic basis for the band therefore, remains unclear.

The author agrees with Moore and co-workers (1986) that the band is not due to an isolated peristaltic contraction, as it was clearly visible in a number of 5 minute imaging periods. Peristaltic contractions occur at 3 cycles per minute - a rate too rapid to be detected by the method employed in the present study.

It is postulated that this band may play a major role in the redistribution and emptying of solid food from the stomach (chapter 8.3).

(iii) ROI selection

The method used in the present study to define the proximal and distal ROI, employed the early gastric "reservoir", which was consistently observed in the first few minutes after ingestion of the solid meal. Rapid data sampling (1 frame every 1-2 minutes) at the beginning of the study is required to ensure that this reservoir is demonstrated, as shown by 2 subjects in whom food moved very rapidly into the distal stomach. The position of the dividing line, obtained using the gastric reservoir, corresponded closely with the position of the gastric band seen in the 7 subjects, suggesting that the contraction band is responsible for the early gastric reservoir and is the same band reported by earlier workers using radionuclide methods.

As discussed in the previous section (chapter 8.1(ii)), the contraction band is not always seen, particularly when small meals are used. The use of the reservoir area, which is consistently seen immediately after ingestion of solid food, is therefore a more reliable method than using the contraction band in delineating proximal and distal stomach subregions.

(iv) Emptying patterns for proximal, distal and total stomach

a. Total stomach

The emptying of digestible solid food from the total stomach was biphasic with an initial lag period, followed by an emptying phase which closely approximated a linear pattern, at least for the majority of emptying. The existence of a lag period in gastric emptying of solid food has yet to gain full acceptance (see for example, Collins et al, 1986a). In this study a lag period in excess of 20 minutes (range 21-57 minutes) was demonstrated for each of the 13 control subjects. Accurate determination of this parameter was obtained by inspection of the individual images to determine the first appearance of food in the proximal small intestine. The importance of frequent data sampling in gastric emptying studies (1 frame every 3-6 minutes) for the accurate estimation of this parameter cannot be over-emphasised. The clinical importance of the lag period has been suggested by a number of workers (Sheiner et al, 1980, Camilleri et al, 1986). The lag period is dependent on intragastric redistribution (with food moving from proximal to distal stomach), antral motility (as antral contractions grind food particles to a size small enough to pass through the pylorus (Meyer et al , 1981)) and possibly the degree of mastication (Urbain et al, 1989). It has previously been suggested that antral motility is the most important factor in determining the duration of the lag period (Camilleri et al, 1986, Siegel et al, 1988, Urbain et al, 1989), but in only two of the 13 subjects did antral residence clearly contribute most to this period. In both of these subjects, although the proximal stomach emptied rapidly, the solid meal remained within the distal stomach for periods of 27 and 41 minutes (SLP - ST_{90}) before food left the stomach (Fig 7.4). For the remaining 11 subjects, redistribution was more gradual (Figs 7.1, 7.2) and indicated that redistribution is a major component of the lag period in the normal stomach.

b. Proximal and distal stomach

The emptying of solid food from the proximal and distal stomach regions did not conform to a single pattern. Although in 4 subjects the emptying from the proximal stomach was predominantly a single, linear component, most were multiphasic. There was also considerable variation in the rate of intragastric distribution between normal subjects which has not previously been reported. The distal stomach counts progressively increased as food moved out of the proximal stomach, peaked, and then diminished during the total stomach emptying phase (Figs 7.1, 7.3). Sheiner and co-workers (1980), using a 250g semisolid meal, observed an antral plateau and suggested that total stomach emptying was linear because of the ability of the antrum to maintain a constant volume. However, the results of the present study using the same meal size, in which distal stomach counts diminished during the linear emptying phase (Figs 7.1, 7.3), even in the 2 subjects in whom a distinct plateau was observed (Fig 7.4), indicated that constant antral volume is not required to maintain linear emptying. Further to this point, no significant correlation ($p > 0.05$) was found between the distal stomach parameter SMC and the rate of gastric emptying. It is possible however, that a critical volume, exceeded in all subjects, was a major factor. There was also no correlation ($p > 0.05$) between proximal stomach emptying (ST_{50}) and the rate of emptying from the total stomach.

8.2 THE EFFECT OF INTRADUODENAL LIPID ON GASTRIC MOTILITY AND EMPTYING OF A SOLID MEAL

The results of this study show that the retardation of gastric emptying of a solid meal induced by an infusion of lipid into the duodenum is associated with (1) redistribution of food from the distal to the proximal stomach, (2) consistent stimulation of isolated pyloric pressure waves (IPPWs), and (3) suppression of pressure waves in the antrum and in the duodenal cap. Although it has been proposed that the rate of solid gastric emptying is primarily determined by antral motility (Kelly, 1980, Camilleri et al, 1985), these observations raise the possibility that other motor phenomena may also be important. The results suggest a possible role for the proximal stomach, pylorus and proximal duodenum.

(i) Intragastric distribution and emptying

Infusion of lipid into the duodenum had a significant effect on the distribution of solid within the stomach. In 7 of the 10 subjects, there was an increase in counts in the proximal stomach ROI and a corresponding decrease in counts in the distal stomach ROI, during the first 15 minutes of lipid infusion (Fig 7.8). This change in count distribution was associated with an apparent increase in the area of the proximal stomach, along with a decrease in the area of the distal stomach (Fig 7.9). The fall in counts in the distal ROI reflected, not only retrograde flow, but also (in many of the subjects) continued emptying into the duodenum. Retrograde flow of gastric contents from distal to proximal stomach has also been observed in a recent study of Fone and co-workers (1990b). They reported that the delay in gastric emptying of a solid meal, in response to terminal ileal triglyceride infusion, was associated with retrograde movement of ingesta in 7 of 8 subjects studied.

What is responsible for retrograde flow in response to duodenal or terminal ileum lipid ? Although the present study was not able to assess proximal stomach motility, the data strongly suggest a role for the proximal stomach in regulating intragastric movement. Others (Azpiroz and Malagelada, 1985) have shown that fat within the small bowel causes relaxation of proximal gastric tone, but whether this would be sufficient to cause retropulsion of ingesta is uncertain. It seems likely that another mechanism, possibly an increase in antral tone, is also required to displace gastric contents back into the proximal stomach. The existence of antral tone could not be ascertained using the current manometric methods. However, the decrease in antral area, seen immediately after the commencement of lipid infusion, is suggestive of an increase in tone. Such an active force may also explain how ingesta continued to empty from the distal stomach into the duodenum in the face of marked suppression of antral pressure waves.

The nature of the feedback pathways mediating the response of retrograde flow and delayed emptying is unknown and has not been addressed in this study. The change in proximal and distal stomach emptying occurred promptly with the onset of lipid infusion, suggesting mediation via neural pathways. Total stomach emptying, however, showed a variable latency period in individuals and it is possible that hormonal pathways are also involved in the regulation process.

(ii) Motility

a. Pyloric

Tougas and co-workers (1987) have demonstrated, using simultaneous fluoroscopy and pyloric manometry, that the cessation of emptying of a barium suspension from the stomach induced by the intraduodenal infusion of a lipid emulsion, was associated with IPPWs. Also, retardation of solid and liquid gastric emptying in response to the ingestion of hypertonic dextrose is associated with a significant increase in IPPWs (chapters 7.3(ii), 8.3). In the present study, stimulation of IPPWs occurred within the first 15 minutes of the lipid infusion and persisted throughout the lipid infusion, whereas there was a variable latency prior to the onset of retardation of gastric emptying. This data suggests some role for the pylorus in the emptying of solids, although the lack of temporal association between stimulation of IPPWs and emptying in some of the subjects, indicates that other factors are involved in the regulation process.

b. Duodenal

Pressure waves recorded by the duodenal TMPD side hole showed marked suppression throughout the lipid infusion. This side hole was situated within the duodenal cap, and this finding is in accord with the suppression of contractions of the duodenal cap observed with fluoroscopy during the infusion of a lipid emulsion into the stomach (White et al, 1983, Tougas et al, 1987). There was no significant change in the rate of duodenal pressure waves recorded by the more distal side holes.

c. Gastroduodenal motor responses

The motility changes observed in this study, namely, stimulation of IPPWs and suppression of antral and duodenal motility, were also observed with terminal ileum fat infusion (Fone et al, 1990b). Furthermore, similar motor patterns have also been observed during retardation of gastric emptying due to ingestion of hypertonic dextrose (chapter 8.3) and also during stress (cold pain)

(Fone et al, 1990a). The close similarity in the motor responses to these different retardant stimuli (intraduodenal nutrients, ileal fat and stress) suggest that many of the feedback mechanisms act through a final common pathway (Fone et al, 1990b).

In conclusion, the findings of the present study suggest that changes in intragastric distribution of ingested solid, in pyloric motility and in proximal duodenal motility may act in concert with changes in antral motility to regulate the rate of solid gastric emptying. These observations support the multiple component model of gastric emptying (Meyer, 1987) and suggest that multiple mechanisms are involved in the close regulation of the gastric emptying of solids.

8.3 THE EFFECT OF LIQUID CALORIES ON GASTRIC MOTILITY AND EMPTYING OF A MIXED SOLID AND LIQUID MEAL

This study shows that the distribution of liquid in the human stomach differs markedly from solids when both are fed in a mixed solid/liquid meal. On ingestion, liquids rapidly dispersed throughout the stomach, with no evidence of preferential storage in the proximal stomach , whereas the solid component resided almost entirely in the proximal stomach reservoir and was then gradually redistributed to the distal stomach during the lag phase as the liquid emptied. The solid then emptied linearly from the stomach.

(i) Solid/liquid discrimination

Why do solids not redistribute in the same way as liquids? What is responsible for retention of solids in the fundus? The striking discrimination between the two phases strongly suggests the presence of a physical barrier that prevents the access of solids into a distal component, but allows passage of liquids. In a previously described study (chapters 7.1(ii), 8.1(ii)) the author observed a mid-gastric transverse band, and argued that it may play an important role in the redistribution and emptying of solid food from the stomach. It seems likely that a mid-gastric contraction band is responsible for the solid/liquid discrimination observed in the present study.

Further support for a role of the proximal stomach in the selective handling of food components is the study by Meyer and colleagues (1988), who showed that small plastic spheres (0.5-2.4 mm) emptied faster from the proximal stomach than 10 mm cubes of chicken liver. Hydrodynamic principles may apply in this discriminatory process, with small particles being carried down into the antrum by meal liquid and liquid secretions (Meyer, 1987).

The role of solid/liquid discrimination has usually been assigned to the distal stomach. In his studies using cats, Cannon (1898) observed that the pyloric "sphincter, separating the fluids from the solids, caused the solids to remain and undergo a tireless rubbing" before passing out of the stomach. This role for the distal stomach (pylorus and antrum) is not dissimilar to the role assigned to this region of the stomach by Kelly (1980). In his two component model, the antrum and pylorus act in a coordinated fashion to grind down solid particles to a size where they can exit with liquid. Supporting evidence for this model comes from studies in patients after surgery - for example, solid/liquid discrimination is markedly compromised after partial gastrectomy, with the rate of emptying of solids closer to that of liquids (Heading, 1980).

The hydrodynamic properties of the meal (particle size and density, and fluid viscosity) may also play an important role in solid/liquid discrimination in the distal stomach. Increasing the viscosity of the meal increased the rate of gastric emptying of 3.2 mm plastic spheres and increased the diameter of liver particles emptied (Meyer et al, 1986). Segregation of solids and liquids in the antrum by gravitational and contractile forces may lessen as the viscosity of the fluid increases (Meyer, 1987).

Thus, with the evidence to date, it appears that both the proximal and distal stomach have roles to play in the selective handling of solids and liquids in the stomach.

(ii) Liquid emptying

Tonal contractions of the proximal stomach are thought to be primarily responsible for controlling the emptying of liquids from the stomach (Kelly, 1980). The evidence for this point of view comes mainly from the results of surgical operations, particularly in the canine model. Surgical resection of the canine fundus (Wilbur et al, 1974), or vagal denervation of the proximal stomach (Wilbur and Kelly, 1973) have been shown to hasten liquid emptying, while distal antrectomy (Dozois et al, 1971) or vagal denervation of the distal stomach (Mroz and Kelly, 1977) had no effect on the rate of emptying of liquids.

In the present study, the incorporation of dextrose into the liquid phase of a mixed solid/liquid meal delays gastric emptying of that phase. Dextrose appeared to be retained largely in the distal stomach. These data do not altogether support the concept that the fundus is primarily responsible for controlling the rate of emptying of liquids but suggest instead a major role for the gastric antrum and/or pylorus. The manometric data suggests that suppression of antral activity and increased phasic pyloric activity could account for the pooling of dextrose in the antrum.

This data is consistent with the results of a number of recent experiments. Infusion of dextrose into the duodenum stimulates both tonic and phasic pyloric activity (Heddle et al, 1988c, Fone et al, 1989). Studies in animals (Prove and Ehrlein, 1982) and humans (Houghton et al, 1988) showed that liquids empty from the stomach in gushes, associated with coordinated contractions of the antrum, pylorus and duodenum.

(iii) Solid emptying

The distal stomach is thought to be primarily responsible for the emptying of solids (Kelly, 1980). Propulsive and retropulsive forces in the antrum, arising from coordinated activity in the terminal antrum and pylorus, grind solid particles to a size where they can exit from the stomach with fluids (Meyer et al, 1979,1981). In dogs, distal antrectomy has been shown to accelerate solid emptying (Dozois et al, 1971), while extrinsic denervation of the antrum reduces antral contractility and slows the emptying of plastic spheres (Mroz and Kelly, 1977).

The proximal stomach is thought to play a minor role in the emptying of solids. Proximal vagotomy in dogs (Wilbur and Kelly, 1973) and in humans (Sheiner et al, 1980) had minimal effect on the rate of solid emptying.

In the present study, the delay and pooling of dextrose in the antrum was associated with a corresponding delay in emptying of solids, due to a slower redistribution from proximal to distal stomach, with no significant increase in either the antral residence time, or the linear rate of emptying. This data supports the previously described finding (chapter 8.1(iv)), that redistribution is a major component of the lag period, and suggests that the gastric fundus has an important role to play in the emptying of solids. Although the proximal stomach may be seen as a passive reservoir, it is also likely that it acts to prime the antral pump, pressing solid material down into the antrum to be gradually disrupted by antral contractions until particles are small enough to pass through the pylorus. The interaction of dextrose with duodenal receptors may, like fat (chapter 8.2), relax the fundus tending to alter the balance of forces in favour of proximal stomach retention.

In conclusion, this study has shown that the proximal stomach may play a more important role in the emptying of solids, and the distal stomach a more important role in the emptying of liquids, than had previously been recognised.

8.4 SUMMARY OF SECTION III

In this section, intragastric distribution and emptying were assessed in normal subjects using a new method for defining proximal and distal stomach.

This technique has considerable potential as a non-invasive research tool, particularly when used in conjunction with other methods, such as manometry. With these combined studies, it is possible to provide a more detailed assessment of the complex integrated responses involved in the regulation of gastric emptying.

It is also envisaged that this method will have clinical application; in the diagnosis and characterization of disordered gastric emptying and in the assessment of the effects of various motility drugs.

APPENDIX I
RADIATION DOSIMETRY

The radiation dose to subjects from oral administration of radiolabelled solid and liquid meals is given below. The data is taken from ICRP Publication 53 (ICRP, 1988).

Activities used:

Solid meal 37-55 MBq of ^{99m}Tc labelled non-absorbable marker (invivo-labelled liver)

Liquid meal 18-28 MBq of ^{113m}In labelled non-absorbable marker (DTPA)

Model used:

The model used for the gastrointestinal tract is from ICRP Publication 30 (ICRP, 1979). The 4 compartments used in the model and the mean residence time (1.44 times the biological half-life) (Siegel et al, 1983) for each compartment is given below.

Organ	Mean Residence Time (hours)	
	Solid	Liquid
stomach	2.1	0.55
small intestine	4.0	4.0
upper large intestine	13.0	13.0
lower large intestine	24.0	24.0

Absorbed dose (mGy/MBq):

Organ	^{99m}Tc-solid	^{113m}In-liquid
stomach	6.1E-02	8.5E-02
small intestine	6.2E-02	1.4E-01
upper large intestine	1.1E-01	1.4E-01
lower large intestine	7.6E-02	3.8E-02
ovaries	2.3E-02	1.1E-02
testes	1.1E-03	4.8E-04
effective whole body dose equivalent (mSv/MBq)	2.4E-02	2.7E-02

Therefore total radiation burden = 0.89-1.32 mSv (^{99m}Tc-solid)

= 0.49-0.75 mSv (^{113m}In-liquid)

combined study = 1.38-2.07 mSv

Comment:

The radiation burden for the combined solid and liquid radionuclide study of 1.38-2.07 mSv compares favourably with radiological examinations of the gastrointestinal tract; for example, barium meal = 3.83 mSv, barium enema = 7.69 mSv (NRPB-R200, 1986), and is acceptable for sequential studies.

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APPENDIX II
MANOMETRIC METHODS

The manometric studies described in this thesis were performed by Drs. R. Heddle, N.W. Reid and L.A Houghton. The manometric assemblies used are outlined below.

a. Intralipid experiment (section 6.2)

The manometric assembly incorporated a 5 cm long sleeve sensor with a maximal external diameter of 6.2 mm, and sideholes at each end of the sleeve (antral and duodenal transmucosal potential difference (TMPD) sideholes) which recorded both intraluminal pressure and TMPD. There were 4 further antral sideholes at 2 cm intervals orad of the sleeve and 2 further duodenal sideholes at 4 cm intervals from the aborad margin of the sleeve. A duodenal infusion port was located 10 cm distal to the sleeve sensor.

b. Calorie experiment (section 6.3)

The eight-lumen manometric assembly incorporated a terminal mercury weight, three antral and four duodenal sideholes, and a 4.5 cm stiffened sleeve sensor (maximum diameter 6.5 mm) which was positioned across the pylorus.

In both experiments all side holes were perfused at 0.3 ml/min with a low-compliance pneumohydraulic pump. Pressures were recorded with pressure transducers interfaced to a 12 channel chart recorder (model 7D, Grass Inc., Quincy, Mass, USA). Transmucosal potential difference (TMPD) was measured via the saline columns which perfused the manometric sideholes at either end of the sleeve (Heddle et al 1988a, Houghton et al 1988). The gastric and duodenal TMPD values, measured by calomel half cells and a subcutaneous reference electrode (Heddle et al, 1988a, Houghton et al, 1988), were recorded at 2 minute intervals throughout the study.

APPENDIX III
PUBLISHED WORK BASED ON THE EXPERIMENTS DESCRIBED IN THIS THESIS

A. Papers published:

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

Collins PJ, Horowitz M, Shearman DJC, Chatterton BE. Correction for tissue attenuation in radionuclide gastric emptying studies : a comparison of a lateral image method and a geometric mean method. Br J Radiol 1984;57:689-95.

Collins PJ, Horowitz M, Chatterton BE. Proximal, distal and total stomach emptying of a digestible solid meal in normal subjects. Br J Radiol 1988;61:12-8.

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B. Papers submitted for publication

Collins PJ, Houghton LA, Read NW, Horowitz M, Chatterton BE, Heddle R, Dent J. The role of the proximal and distal stomach in the emptying of a mixed solid and liquid meal. Submitted to Gut. Accepted for publication 3/8/90

C. Published letters and abstracts

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