Fluid Movement and Motility of the Human Gastroduodenal Region

Observations with Real-Time Ultrasonic Imaging

Peter Mackenzie King

B.Sc., M.B.Ch.B., F.R.C.S.Ed.

Degree of Doctor of Medicine

University of Edinburgh

1987

"Too often - we can only see what we are looking for; absurd in the extreme...because one must observe whatever happens, even what one does not expect, especially what one does not expect."

(Richet, 1944)

Declaration

The work described in this thesis has been conducted with the assistance and advice of those acknowledged on pages iv and v.

I certify that this thesis has been composed by me alone.

Abstract

Real-time ultrasonic imaging, which is a safe non-invasive procedure, was applied to the study of the contractile activity of the gastric antrum, pylorus and proximal duodenum in man. The investigation demonstrated the feasibility of the technique, which was then used in normal subjects and in patients with upper gastro-intestinal disorders to explore the relationships between muscle contraction at the gastric outlet and the movements of intraluminal contents. The most novel observation was that gastric emptying of a liquid occurs as intermittent brief episodes through the pylorus which are substantially unrelated to the cyclical gastric peristaltic contractions.

In normal subjects changes in the composition of the test meal were observed to cause subtle alterations in the pattern of fluid movement without affecting gastroduodenal motility. In patients with reflux oesophagitis there was found to be a significant increase in the normal number of discrete episodes of gastroduodenal flow seen in each gastric cycle. In patients who had undergone either truncal vagotomy and pyloroplasty or highly selective vagotomy there was a significant increase in the number of discrete episodes of gastroduodenal flow observed in each gastric cycle compared to normal controls. In normal subjects proximal duodenal contractions occur on average after 60% of terminal antral and pyloric contractions, but, while highly selective vagotomy did not alter this percentage, the degree of antroduodenal co-ordination observed after truncal vagotomy and pyloroplasty was significantly less than in both the highly selective vagotomy and normal subjects.

The development of this non-invasive technique has enabled physiological observations to be made on the human gastroduodenal region which cannot presently be achieved by any other method.

Acknowlegments

The work which forms the basis for this thesis was carried out in a sabbatical year while I was a research fellow in the Department of Therapeutics and Clinical Pharmacology, Royal Infirmary, Edinburgh (RIE) in 1983 and was supported by Scottish Home and Health Department grant K/MRS/50/C423.

I acknowledge with gratitude the boundless advice and encouragement received from Dr. R C Heading who introduced me to the study of gastroduodenal pathophysiology.

The work documented in this thesis would not have been possible without the unstinting efforts of Mrs Anne Pryde. She gave me invaluable technical assistance and, in conjunction with myself, performed the analysis of the ultrasonic examinations recorded on videotape.

I am indebted to those of my colleagues - nurses, doctors and others - who kindly agreed to undergo the ultrasonic examinations and I also wish to thank those Surgeons and Physicians of the Royal Infirmary of Edinburgh who allowed me to study their patients.

All of the ultrasonic examinations were carried out by me, and I was responsible in the main part for the development of all aspects of the technique.

List of Abbreviations used in the text

´C	degrees centigrade
cm(s)	centimetre(s)
DC	proximal duodenal contraction
DTPA	diethylenetriamine penta-acetic acid
FF	gastroduodenal flow (emptying)
g(s)	gramme(s)
GOR	gastro-oesophageal reflux
HSV	highly selective vagotomy
In-113m	Indium-113m
Kg(s)	Kilogramme(s)
ml(s)	millilitre(s)
mm(s)	millimetre(s)
MBq	megabequerel (1 MBq = 1 milli-curie)
MHz	megahertz (1 hertz = 1 cycle per second)
mosm/l	milli-osmoles per litre
%	percent
p	probability
rpm	revolutions per minute
RF	duodenogastric flow (reflux)
RIE	Royal Infirmary, Edinburgh
sec(s)	second(s)
SD	standard deviation
Tc-99m	Technetium-99m
TAC	terminal antral contraction
TVP	truncal vagotomy and pyloroplasty

List of Contents

List of Contents continued

1.0.0 Introduction

For over a century investigators have devoted considerable effort in attempts to increase their understanding of gastric emptying. The many methods that they have used are not just a reflection of the progressive sophistication of the techniques available for such studies, but they also reflect the many difficulties that have been encountered during attempts to assess the complex physiological mechanisms involved.

Currently available methods for the study of gastric function do not provide detailed information about the movements of the intraluminal contents in relation to gastric contractile activity. Manometric methods permit observation of the timing and magnitude of intragastric pressure changes, and some simultaneous electrical recordings from the human stomach and duodenum have been obtained and, although both of these techniques provide information about muscle contraction, they do not identify the movement of intragastric contents. Simultaneous studies of antral contractions and gastric emptying in man have been undertaken using intubation methods, and also with scintigraphic procedures, but much of the current knowledge about the relationships between the flow of luminal contents and contractions of the human stomach, pylorus and duodenum has been obtained from radiological investigations using contrast media. There are, however, inherent problems with these techniques. Some may themselves either cause subtle alterations in the normal intragastric events or be unable to reflect them adequately. In addition, in humans, the use of many techniques is limited by considerations of comfort and safety for

the subject.

The widespread use of ultrasonic imaging as a diagnostic tool in the United Kingdom dates from 1975. The technique does not require the use of potentially hazardous ingested or injected contrast media to produce images of internal body organs; neither is it associated with the discomfort of intubation or other forms of instrumentation. Ultrasound, therefore, would seem an ideal method for prolonged study of the events at the gastric outlet.

In this thesis the current concepts on gastric emptying and the investigative techniques that have been used to develop those concepts are reviewed. There then follows a brief explanation of the principles of ultrasonic imaging and subsequently a detailed description of the methods by which the ultrasonic imaging technique was developed to allow simultaneous display of the stomach, pyloric canal and duodenum and subsequently to allow examination of the relationships between contraction of the stomach and duodenum and movements of luminal contents. The results of investigations using the ultrasonic technique in a variety of normal and pathological situations are also discussed.

2.0.0 Gastric Emptying - Current Concepts and Review of Investigative
       Techniques.

The composition of ingested material and the rate at which it enters
the stomach is, in the intact animal, regulated by behaviour
(Richter, 1942). In humans, behaviour patterns are largely modified
by easily identifiable and thus potentially understandable factors
such as social habit, hunger, and satiety (Wolf, 1981).   In
contrast, the subsequent fate of the gastric contents is less well
understood.   However, over the last 150 years extensive
investigations have been devoted to the manner in which the stomach
performs its function.

Although reports in the literature of gastric fistulas in human
subjects date back at least to 1564 (Cornax, 1564), William
Beaumont, who, in 1833, described his original and perceptive
observations on the stomach of Alexis St Martin (Beaumont, 1833)
made through a gastro-cutaneous fistula, is credited as the first
investigator into gastric pathophysiology. There have since then
been various reports of observations on human subjects with
accidentally or surgically created gastric fistulas (Carlson, 1912;
Gordon & Chernya, 1940; Wolf & Wolf, 1943; Reichsman et al, 1955).
However, the presence of a fistula is hardly physiological and
certainly of limited application in studies undertaken in normal
human subjects.

The information which has accrued about gastric function has been
gained through investigations running parallel in man and animal
subjects.

2.1.0 Current Concepts on Gastric Emptying

Ingested food is stored in the stomach where it is mixed with gastric secretions and transformed into chyme which is then delivered in a regulated manner to the digestive and absorptive processes of the small intestine. The transfer of gastric contents from the distal stomach to proximal duodenum occurs due to the creation of a transpyloric pressure gradient (Nelson & Kohatsu, 1971) by the interplay between the motor activity of the stomach and duodenum. This motor activity is modified by neural and hormonal mechanisms responding to the activity of receptors located in the stomach, duodenum and small bowel (Hunt, 1959).

2.1.1 Mechanisms responsible for gastric emptying

The functioning gastric unit can be considered to have four components: 1) the proximal stomach (fundus) which is thin walled and in which receptive relaxation (Cannon & Lieb, 1911) occurs to provide a capacious reservoir for ingested food; 2) the distal stomach (antrum) which has more muscular walls and is characterised by the occurrence of powerful regular contractions (Klein, 1926; Smith et al, 1957); 3) the pylorus which may have a sphincteric function to regulate gastric emptying (Fisher & Cohen, 1973) or may function as a one-way valve to prevent reflux (Anuras & Cooke, 1974; Stemper & Cooke, 1976), but its function is controversial; and 4) the proximal duodenum which contracts more in sequence with the terminal antrum than the rest of the duodenum (Weisbrodt et al, 1969) and in which are located many receptors thought to be important in the regulation of gastric emptying (Hunt & Knox, 1968).

Food on entering the stomach is accommodated in the proximal gastric fundus and body, the muscle of which relaxes to allow the reservoir to distend.   Although peristaltic contractions have not been demonstrated in the fundus, pressure studies (Lind et al, 1961; Aspiroz & Malagelada, 1985) have shown that regular slow contractions do occur which push the stored material towards the more distal antrum where powerful rythmic contractions mix and grind up the food before it passes through the pylorus into the duodenum (Carlson et al, 1966).   The process is, however, not as simple as it may at first seem. Normal meals are made up of many components, which may be either liquid or solid, and it has been shown that they are emptied from the stomach at different rates

(Chang et al, 1968; Meyer et al, 1976; Malagelada et al, 1979; Cortot et al, 1981).

Most studies investigating the mechanics of gastric emptying have utilised fluid meals because of the ease of control of the physiological stimuli (Sheiner, 1975). Interpretation of studies utilising solid or mixed solid-liquid meals is more difficult because there may be differences in the behaviour of the various solid components (Heading, 1982) owing to physical characteristics such as particle size and shape (Weiner et al, 1981), specific gravity and viscosity. However, the studies by Meyer and co-workers (Meyer et al, 1981) in humans using isotopically labelled chicken liver have shown that the chyme entering the proximal duodenum is a fine slurry containing particles less than 2mm in diameter and may be considered more liquid than solid. Thus, until there is a better standardisation and definition of a solid meal, interpretation of studies concerning the mechanisms resulting in gastric emptying using liquid meals, may in fact more accurately reflect the mechanisms involved in effecting discharge of gastric content to the duodenum.

Currently two theories are promoted concerning the mechanisms responsible for gastric emptying of liquids. The first suggests that gastric emptying is the result of the activity of a cyclical antral pump (Cooke, 1975; Davenport, 1977) which, as the antral wave moves distally to end in the terminal antral contraction, pushes the liquid gastric content through the pylorus until the flow is interrupted by pyloric closure. The rate of gastric emptying is thus thought to depend on the force and frequency of antral

contractions (Rock et al, 1981). Other investigators believe, however, that the distal stomach and pylorus play only a minor role in the gastric emptying of liquids (Crider & Earl Thomas, 1937; Dozois et al, 1971; Meyer, 1980), but are of greater importance in the emptying of solids. In the second theory it is suggested that the emptying of liquids from the stomach occurs as a steady flow caused by the pressure gradient across the gastroduodenal junction produced by the tonic contraction of the proximal stomach, interrupted only by pyloric closure (Jahnberg, 1977; Kelly, 1980). The observation that emptying of a liquid test meal occurs as an exponential or volume-dependent process is consistent with this theory.

The emptying of mixed solid-liquid meals is more complex. Shortly after ingestion of the meal there is a short period during which the emptying rate may either be faster or slower than the rate which subsequently becomes established (Wilbur & Kelly, 1973). This early period is termed the initial phase of gastric emptying. With mixed solid-liquid meals this initial period lasts around 10 minutes (Colmer et al, 1973), although with purely liquid meals it may be shorter. Thereafter most of the liquid component empties rapidly and exponentially, but there may be a lag phase before solid emptying occurs. The lag period before solids begin to empty reflects both the redistribution of food from fundus to antrum (Sheiner et al, 1980) and the time taken to reduce it into small particles, and is dependent on the nature of the solids ingested, gastric volume, fundal tone and antral contractile activity. Thereafter the emptying of solids occurs in a linear fashion thought to reflect the ability of the thick-walled antrum to maintain a

relatively constant volume (Sheiner et al, 1980).   The linear
emptying rate of solids is influenced by their physical
characteristics and reflects the efforts of the mixing and grinding
contractions of the antral mill (Carlson, 1977) which produce the
fine slurry that passes into the duodenum (Meyer et al, 1979).   The
mechanism by which the stomach retains ingested solids until they
are ground down to a relatively uniform size is poorly understood
(Earl Thomas, 1957; Malagelada, 1979).   It is, however, dependent
on the co-ordination of the contractile activity of the antrum,
pylorus and proximal duodenum.

2.1.2 Regulation of gastric emptying

The electrophysiology of the smooth muscle of the stomach, pylorus and proximal duodenum has been studied extensively in experimental animals using techniques, including destruction of nerves and tissues, and hormone infusions, not usually applicable to human studies. Nevertheless, because there seems to be little interspecies variation (Heading, 1980), the conclusions drawn from such studies are thought to reflect the situation in man.

Intrinsic regulation

The factors regulating gastric smooth muscle activity can be considered to operate at two levels. At the first level are intrinsic or local influences arising from the inherent electrical properties of smooth muscle. These result in the production of recordable electrical activity called the gastric slow wave (Kelly & Code, 1971; Duthie et al, 1971) (also known as the basic electrical rhythym, pacemaker potential or electrical control activity). Studies by Sarna and co-workers (1972) have shown that this electrical activity may be likened to an array of bidirectionally coupled relaxation oscillators in the stomach smooth muscle and, in a manner which resembles the pacemaker activity of the purkinje tissue of the heart, the dominant or most rapidly firing area determines the frequency of the slow waves. In man this dominant pacemaker is located on the greater curvature of the mid gastric body, and the electrical activity propagates rapidly around the stomach towards the lesser curvature and subsequently towards the pylorus distally. The smooth muscle of the fundus and

proximal gastric body does not generate or propagate slow wave activity (Kelly et al, 1969; Sarna et al, 1972). In man, gastric slow wave activity is omnipresent and in the normal stomach the dominant pacemaker fires off at regular 20-30 second intervals (Cooke, 1975). This frequency remains largely unaltered in various pathological conditions (Heading, 1980).

The gastric slow wave itself does not cause gastric muscle contraction, but is permissive in that the action potentials (also known as spike potential, fast activity or electrical response activity) occur only in association with the slow wave (Kelly, 1980). Thus the gastric slow wave activity regulates the frequency of occurence and direction of propagation of gastric smooth muscle contraction.

In man the gastric slow wave is conducted across the pylorus, and has been recorded in the duodenum for a variable distance distally (Duthie et al, 1971). Although the normal duodenal pacemaker fires off at around 12 times per minute, the contractile response of the proximal duodenum is modified by the gastric slow wave resulting in proximal duodenal contractions which occur more in relation to distal gastric contractions than those of the rest of the duodenum or small bowel. This co-ordination of the contractile activity of the gastroduodenal segment is thought to have important consequences on the movement of luminal contents across the pylorus.

Extrinsic Regulation

The coupling of the gastric slow wave and action potential to produce muscle contraction depends on the integrity of the local

nerve plexuses in the gastric wall which receive inputs from the sympathetic and parasympathetic systems (Martinson, 1965; Jansson, 1969). The influences of the autonomous nervous system via the coeliac and splanchnic plexi and the vagi (Mroz & Kelly, 1977), in association with the effects of hormones (Fisher et al, 1973; Dubois et al, 1978; Stadaas et al, 1978; Ouyang & Cohen, 1981), constitute what may be considered as the second level or extrinsic mechanism regulating motility. Through this extrinsic system are thought to be mediated the regulatory activities of the receptors in the stomach, duodenum and small bowel. These activities may additionally be modified by the central nervous system (Thomas & Baldwin, 1968; Thompson et al, 1982; Thompson et al, 1983).

Little precise knowledge is available about the pathways involved in the extrinsic regulatory mechanisms, particularily in humans. Identification of the neural pathways has been obtained from anatomical dissection and through observation of the effects of selective denervation in intact animals (Kelly & Code, 1969; Walker et al, 1974) and in man from studies in patients after surgery for peptic ulcer (Buckler, 1967). Stimulation of vagal motor fibres may either enhance or inhibit motility (Thomas & Baldwin, 1968), but the inhibitory effects are most pronounced in the proximal stomach. Relaxation of the fundus and proximal body to accommodate ingested food is triggered in part by the act of swallowing (receptive relaxation) (Cannon & Lieb, 1911) and in part by gastric distention (adaptive relaxation) (Jahnberg, 1977) and is mediated through the inhibitory motor neurons of the vagus acting to inhibit contractions, particularily of the oblique muscle layer (Christensen & Torres, 1975). This relaxation is known to be severely

compromised by vagotomy (Wilbur & Kelly, 1973). The sympathetic innervation has also both excitatory and inhibitory effects on gastric motility (Thomas & Baldwin, 1968), but these are less well understood.

The evidence for hormonal control stems from experiments with denervated transplanted target organs and with infusions of pure extracts of substances isolated from the gastro-intestinal tract. Hormones with gastro-intestinal effects include gastrin (Hunt & Ramsbottom, 1967; Cooke et al, 1972), cholecystokinin (Chey et al, 1970), secretin and related substances (Kwong et al, 1972), calcitonin (Cooke, 1975), prostaglandins (Cooke, 1975) and enterogastrone (Hunt & Knox, 1968). In pharmacological doses most of these hormones delay gastric emptying, but whether they have any physiological role is uncertain (Cooke, 1975).

Receptors

The emptying of a test meal from the human stomach is known to be influenced by the meals volume, pH, osmolality, fat content, calorific value and viscosity. The effects of these physical characteristics of ingested food are thought to be the result of their interaction with receptors postulated to be located mainly in the duodenum but also in the stomach and small intestine (Hunt & Spurrell, 1951). Although it is accepted that these receptors exert their regulatory effect on the mechanisms responsible for gastric emptying through the extrinsic system of nerves and hormones, the evidence for this is indirect and the pathways thought to be involved remain theoretical.

The presence of acids, hypertonic solutions, fats and aminoacids in the duodenum and small bowel has been shown to inhibit gastric motility in animals and some of their effects can be abolished by vagotomy (Thomas & Baldwin, 1968) or by ablation of the coeliac and superior mesenteric ganglia (Schapiro & Woodward, 1959). The effect of these factors on inhibition of motility is rapid (less than 1 minute) and this has led to the conclusion that a neural mechanism is involved (Cooke, 1974; Cooperman & Cook, 1976). This inhibitory mechanism is known as the enterogastric reflex (Cooke, 1975). However, in studies concerning neurohumoral mechanisms, ablation of the neural control may make the target organ less sensitive to hormones and so their involvement cannot be excluded (Cooke, 1975).

Volume

Paintal (1954) and then Iggo (1955) independently described mechano-receptors in gastric smooth muscle of sheep which respond to stretch or pressure and allow the fundus to relax and accommodate increased volume without increasing intragastric pressure or wall tension. This adaptive relaxation (Jahnberg, 1977) is distinct from the receptive relaxation (Cannon & Lieb, 1911) which occurs before food reaches the stomach, but both processes are mediated via the vagal non-cholinergic, non-adrenergic inhibitory neurons (Cooke, 1975) and both are affected by vagotomy (Wilbur & Kelly, 1973).

pH

Studies by Hunt and Knox (1962, 1969, 1972) and more recently by

Cooke (1974) have shown that acidification of the duodenum, particularily the first part, is a potent inhibitor of gastric emptying. It would appear that a feedback mechanism operates to allow a constant acid load to reach the duodenum (Cooke, 1975).

Osmolarity

The effect of osmolarity on gastric emptying has been recognised since the work of Carnot and Chassevant (1905). Subsequently Hunt (1960) demonstrated that hyper- or hypo-osmolar solutions of various solutes were emptied more slowly than the corresponding iso-osmolar ones. There are thought to be osmoreceptors distal to the pylorus responsible for this inhibition, and studies by Meerhoff and coworkers (1975) suggested that in humans they are situated in the duodenum. The inhibitory effect of amino-acids on gastric emptying also appears to be due largely to their osmolarity and not their molecular weight (Cooke & Moulang, 1972; Barker et al, 1978).

Fat content

The presence of fats (Hunt & Knox, 1968; Feldman et al, 1971) and particularily free fatty acids (Menguy, 1960) in the duodenum and small bowel is a potent inhibitor of gastric emptying. At present there is no firm evidence about the localisation of the receptors responding to fats or the mechanism by which they exert their effect, but earlier studies (Farrell & Ivy, 1926) using transplanted gastric pouches which suggested that the mechanism was in part mediated by hormones, coupled with the knowledge that partial abolition of the inhibitory effect occurs after vagotomy Thomas &

Baldwin, 1968), suggest that neurohumoral pathways are involved.

Calorific value

In man solutions of carbohydrate, protein and fat delay gastric emptying in direct proportion to their calorie concentration (energy density) (Hunt & Knox, 1968; Hunt & Stubbs, 1975). The effects are mediated by receptors in the duodenum and result in a constant rate of energy delivery to the duodenum (McHugh & Moran, 1979; Brener et al, 1983). Collins and his co-workers (1983) noted that increasing the liquid calorie intake delayed the redistribution of solid food from fundus to antrum, and suggested that the delay of both liquid and solid emptying that occurs might be due to a reduction in fundal tone.

Viscosity

Gastric emptying is known to be delayed by the addition of pectin (Hunt, 1954) or gel fibre (Holt et al, 1979) to test meals in humans, and Prove and Ehrlein (1982) have studied the effects of viscosity on gastroduodenal motility in dogs by using barium containing contrast media and have attempted to correlate the pattern of activity to gastric emptying. However, whether receptors exist that respond to the viscosity of a test meal remains unknown.

2.2.0   Review of Investigative Techniques

The techniques that have been developed over the last century and a half to evaluate gastric function are diverse.   For mainly technical reasons the methods for measurement of gastric emptying, i.e. the transfer of ingested material from stomach to duodenum, and those for the assessment of the gastroduodenal motor activity which is responsible for emptying, do not adequately reflect the two processes simultaneously (Heading, 1980).   This may be the prime reason why the complex relationships that exist between emptying and motility remain poorly understood.

2.2.1   Measurement of gastric emptying

The assessment of gastric emptying is quantitative (Cooperman &
Cook, 1976).   As the emptying of a test meal proceeds, the process
is reflected by a change in the volume and composition of the
gastric content or by its appearance in the duodenum.   The majority
of techniques for measuring gastric emptying involve quantifying
this material either directly or indirectly. Direct sampling may be
performed via intubation of the stomach or duodenum in both animal
and human subjects or via the creation of entero-cutaneous fistulae
in animals. Indirect methods employ radiographic procedures to
visualise barium containing contrast media and, more recently,
techniques employing radio-isotopes.

Intubation

The widespread use of techniques involving intubation to study
gastric emptying dates from 1844 when the invention of rubber
vulcanisation by Goodyear made possible the manufacture of flexible
tubes.   Von Leube (1883), who performed single aspirations of the
stomach contents seven hours following the ingestion of a beef
bouillon, potato purée and bread meal, is accredited as the first
investigator to carry out definitive studies of gastric emptying.
A few years later Marbaix (1898) used a similar method to
demonstrate that gastric distention stimulated gastric emptying.
Repeated regular sampling of gastric contents during the emptying of
a test meal was subsequently popularised by Rehfuss (1927) and
became known as the fractional test meal.   This technique, which
measures the total emptying time of a constituent of a meal and

provides only limited information about the pattern of its emptying (Sheiner, 1975), has, in addition, two inherent technical problems. Not only may aspiration of the remaining gastric contents be incomplete, but also no account is taken of the contribution of secreted gastric juice to the volume re-aspirated (Dubois, 1979). Nevertheless, a variation of this technique known as the saline load test (Goldstein & Boyle, 1965) was widely used until recently to provide a reasonably objective assessment in patients with gastric retention.

In an attempt to overcome the inherent problems of the fractional test meal, Hunt in the UK (Hunt & Spurrell, 1951) and de Salamanca in Spain (de Salamanca, 1956) developed the serial test meal. In this technique a liquid test meal containing a known concentration of a non-absorbable marker, such as phenol red, was instilled into the stomach and after a given interval the gastric contents were completely re-aspirated. Subsequent determination of both the marker and gastric acid concentrations in the aspirate allowed calculation of the fraction of the meal that had been emptied, independently of gastric secretion. By repeating the whole procedure on different days and by aspirating at different intervals, the emptying pattern of a meal could be determined. Using this technique Hunt has produced reliable and reproducible data on the effect of various components of ingested food, such as pH (Hunt & Knox, 1962), viscosity (Hunt, 1954), osmolality (Hunt, 1960) and fat content (Hunt & Knox, 1968), on the pattern of emptying of a liquid test meal. His many studies were carried out under research conditions with volunteer subjects. However, the need for repeated intubations on different days makes the serial test

meal inconvenient and time-consuming for both patients and clinicians (Rock et al, 1981) and the technique therefore did not gain wide clinical application.

To overcome the disadvantages of the serial test meal, George (1968) decribed the application of the dye dilution (Fick) principle to the determination of intragastric volume during the emptying of a single liquid test meal. This technique involves double sampling, that is aspirating small samples from the stomach just before and after the addition to the gastric content of a known amount of a non-absorbable marker at serial intervals. The gastric volume is determined by entering data into the Fick equation on known variables, which are the volume and concentration of aspirated samples and the amount of marker introduced into the stomach between samples. In the method originally described by George, the calculated intragastric volume represented both the remaining test meal and any added secretions (Dubois & Berman, 1974), but modifications were subsequently made to the technique to correct for gastric secretion (Hunt, 1974). The double sampling technique has been used in clinical practice and, although somewhat complex, it can provide reliable results. Its main disadvantage is that, because the dye dilution principle depends on homogenous distribution of the marker throughout the gastric contents, its use is limited to the study of liquid meals.

The most recent development of intubation techniques involves the placement of a tube through the pylorus into the duodenum to allow perfusion and aspiration from this site as well as from the stomach (Go et al, 1970; Fordtran & Walsh, 1973; Meeroff et al, 1973) and

since the early 1970s the use of this combined technique has become more widespread. Initially it was used to study only liquid emptying; but it has subsequently been used to study the emptying characteristics of solid meals as well, since observation showed that, during the emptying of solids, the chyme which ultimately enters the duodenum is liquid enough to be aspirated through a nasogastric tube (Malagelada, 1977). This technique has nevertheless certain disadvantages. Difficulty may be encountered during attempts to intubate the duodenum, and there is the possiblity that recovery of marker from the duodenum may be incomplete (Sheiner, 1975; Malagelada et al, 1976). There is, in addition, considerable debate about the effect that the physical presence of a transpyloric tube may have on the normal mechanisms operating in the gastroduodenal region (Fisher et al, 1982; Muller-Lissner et al, 1982 ;Read et al, 1983).

Enterocutaneous fistulae

The creation of gastric or duodenal fistulae to study gastric emptying is obviously confined to animal experiments. These techniques allow direct sampling and introduction of test solutions into the lumen of the gut via rubber cannulae (Thomas et al, 1934) placed between the gut wall and skin. Many researchers believe, however, that the use of fistulae is unphysiological (Sheiner, 1975) and that if used the normal mechanisms operating at the site of the fistula must be assumed to be affected. Thus in the interpretation of any results obtained by these techniques, the influence of these normal mechanisms must be excluded.

Radiological techniques

Routine clinical use of barium containing contrast media and X-rays to visualise internal body structures dates from the turn of the century (Cannon & Murphy, 1906). Barium meal studies are used to diagnose and evaluate many disorders of the stomach and duodenum and would appear to be well suited for studies of gastric function since the techniques are simple to perform, relatively well tolerated by patients and the apparatus is readily available (Cannon, 1911). Unfortunately the use of barium studies to assess gastric emptying has many disadvantages and, although the techniques have been used successfully to provide much information about gastroduodenal motility, they have largely been abandoned as a method for measuring gastric emptying characteristics (Cooperman & Cook, 1976; Dubois, 1979).

Liquid barium may irritate the gastric mucosa (Sun et al, 1959) and single contrast techniques obscure the gastric contents making interpretation of intraluminal movement difficult (Griffith et al, 1968). Attempts to overcome some of the problems include the use of enteric-coated barium granules (Horton et al, 1965) which are ingested along with solid meals, and the barium burger (Stordy et al, 1969). However the barium in these test meals may either precipitate out or be solubilised and empty with the liquid portion of the gastric contents, leaving the solid food behind. The main disadvantage of all radiological techniques is, however, that they cannot provide quantitative information about gastric emptying as it is proceeding (Kirsh, 1956; Sheiner, 1975) since it is impossible to estimate gastric volumes accurately from a two-dimensional

image. Thus only the time taken to empty all barium from the stomach can reliably be measured. In addition, despite advances in the development of image intensifiers, prolonged imaging using X-rays still carries the risk of exposing subjects to an unacceptable radiation hazard (Horowitz et al, 1982).

Techniques utilising radioisotopes

The use in man of radioisotopes, which produce externally detectable gamma ray emissions, to measure gastric emptying dates from 1966, when Chromium-51 was incorporated into a liquid test meal (Griffith et al, 1966) and a fixed scintillation counter used to measure the amount of radioactivity remaining in the stomach at sequential intervals as emptying proceded. Using radioisotopic techniques, the slope of the decline of the natural logarithm of the measured intragastric radioactivity represents the gastric fractional emptying rate (Dubois, 1979). This early technique gave inconsistent results because the probe was positioned blind over the area thought to be occupied by the stomach, and detection of radioactivity from a static single point was unable to reflect accurately the often uneven distribution of isotope throughout the stomach (Bromster et al, 1966).

The problem of the early scanning method was subsequently solved by the introduction of rectilinear scintiscanners (Goodall, 1966; Griffith et al, 1968) which produced an image of the area in which the isotope was distributed (i.e. the stomach) and allowed sequential quantitative meaurements of gastric radioactivity. The main disadvantage of scintiscanning is, however, that it can take

from 6 to 10 minutes to record a single observation and this may lead to inaccuracies in the estimation of the rate of emptying, particularily in subjects where gastric emptying is rapid (Sheiner, 1975). The development of the gamma camera linked to a computer has subsequently allowed the production of counts as frequently as every one minute (Harvey et al, 1970). In addition, the more recent introduction of dual window gamma cameras makes it possible to measure simultaneously the emptying of different components of a test meal which have been labelled with separate radioisotopes (Heading et al, 1976; Grimes & Goddard, 1977).

Radioisotopic techniques have several advantages over the previously mentioned methods of measuring gastric emptying. They do not require nasogastric or nasogastroduodenal intubation and this non-invasiveness makes them more readily acceptable to patients. The radioisotopes used in these studies include chromium (Griffith et al, 1966), cesium (Jones et al, 1970), iodine (Bromster et al, 1968), indium (Heading et al, 1971) and technetium (Calderon et al, 1971) and they are usually coupled to large molecules such as diethylenetriamine penta-acetic acid (DTPA) and not only are they minimally absorbed by the gut but also their adsorption to the mucosa is small (Malmud & Long, 1982). This results in subject radiation exposure which is typically less than during a barium enema examination (van Dam, 1971; Chaudhuri, 1974).

Radioisotopic techniques are, nevertheless, not without limitations. Their main disadvantage, which is common to all techniques using markers, is that what is actually being measured is the emptying rate of the marker. How accurately this reflects the emptying of

the labelled component of the meal is inversely proportional to the rate at which the marker dissociates from the food (Malagelada, 1979; Horowitz et al, 1982). The degree of binding between isotope and food depends on which isotope is used and the nature of the food to be labelled. Indium DTPA, which is widely used as an aqueous phase marker, is particularily adsorbed on to bread (Grimes & Goddard, 1977) and when water-soluble markers such as sodium chromate are used to label solid food they become partially distributed in the aqueous phase (Heading, 1982). The incorporation of radioisotopes intracellularily into chicken liver (Meyer et al, 1976) and bound to egg albumin (Kroop et al, 1979) has subsequently allowed firm labelling of some solid food. During the estimation of gastric emptying using these isotopic methods no account is taken of added gastric secretions, and so these do not reflect the actual volumes passing through the pylorus as emptying proceeds. Thus the results obtained by these techniques can be compared to those obtained by the serial test meal (Delin et al, 1978) or double sampling (George) methods (Dubois et al, 1976). It has, in addition, become recognised (Tothill et al, 1978) that considerable experimental variability can arise as a result of variations in the depth and distribution of radioactivity present in the stomach and also from variations in subject physique. The former problem can, however, be partially overcome by counting, with gamma cameras scanning from both the anterior and posterior aspects of the subject, either alternately (Christian et al, 1980) or simultaneously (Jacobs et al, 1982).

Other techniques

The plasma concentration of ingested substances depends on the extent of their absorption from the gut. Based on the knowledge that certain ingested solutes (e.g. paracetamol, glucose, alcohol) which are only slowly absorbed from the stomach are rapidly absorbed from the small intestine and that the plasma concentration of these substances is therefore directly related to the rate at which they empty from the stomach, it has been suggested that serial measurements of their plasma concentrations can be used as an index of gastric emptying (Heading et al, 1973). An interesting modification of this technique involves the use of a breathalyser to measure blood alcohol levels, thus avoiding the need for repeated venesection (Finch et al, 1974). These techniques are of limited clinical use, but they have been used in volunteers to compare the effects of different drugs (Nimmo et al, 1973; Nimmo et al, 1975; Thompson et al, 1982) and other substances (Holt et al, 1979) on gastric emptying.

2.2.2 Assessment of gastroduodenal motor activity

Gastroduodenal contractile activity has 3 measureable components. These are firstly, the force of the contractions, secondly, the height or amplitude of the contractile waves and thirdly, the timing and duration of their occurence. For technical and physiological reasons the techniques used to measure the force of contraction are different from those used to measure the amplitude. The force of contraction must be measured directly by invasive techniques employing pressure-sensitive devices introduced into the gut lumen or, in animals, implanted in the wall of the bowel. The amplitude of the contractions is assessed indirectly, however, by visualising the waves using barium containing contrast media coupled with fluoroscopic techniques, although isotopic techniques with the gamma camera have also been used recently (Jacobs et al, 1982). The timing and duration of contractions is measured by both the direct and indirect techniques, but information about this component can also be obtained from measurements of the electrical activity of the smooth muscle using suction or implanted electrodes.

Measurement of contractile force

Over the last century a number of different techniques have been developed to measure the force of gastroduodenal contractions. In humans, most of these techniques require intubation to allow measurement of the intraluminal pressure changes associated with the contractions, and the use of balloon manometers, open-tipped perfused catheter systems and miniaturised strain gauge transducers has been described.

Balloon manometers

The use of balloon manometers was first described in 1899 (Bayliss & Starling, 1899) when they were used to measure the force of intestinal contractions. A few years later the technique was used to measure gastric antral contractions (Cannon & Washburn, 1912. Carlson, 1912). The apparatus used to measure contractile force consists of a thin-walled balloon which may be filled with air, water or a fluid mixture containing radio-opaque contrast material to allow the position of the balloon to be visualised. The intraluminal pressure changes which impinge on the balloon are transmitted via a similarily filled tube to an external measuring device. The dimensions of the balloons used by different investigators vary. In general small balloons with volumes varying between 0.5mls (Carlson et al, 1966) and 25mls (Smith et al, 1957) have been used for assessment of the contractile activity of the pylorus and terminal antrum whereas larger balloons with a volume of 300mls to 1000mls (Stadaas & Aune, 1970; Jahnberg, 1977; Azpiroz & Malagelada, 1985 (ref 8)) have been used to assess fundal

contractility. In addition, techniques using a single balloon or multiple balloons spaced at intervals along a tube have both been described. The balloons are usually screened into position using fluoroscopy, although they have also been positioned under direct vision using endoscopy (Johnson et al, 1983). Pressure recordings have been made with the balloons positioned at various independent sites in the stomach and duodenum, and also using pull-through techniques which are thought to be particularily suitable for delineating zones of increased pressure (Andersson & Grossman, 1965) and which have been extensively used to assess pyloric function.

Although balloon manometer techniques have been used by many investigators over the years to assess gastroduodenal contractile activity, it has become clear that they have several disadvantages. As in all invasive techniques, considerations of subject comfort and safety limit the extent and duration of the investigations and, in common with other techniques involving intubation, the physical presence of the balloon and catheter may affect the gastroduodenal motility. There are, in addition, specific problems related to the balloon manometers themselves. Although small-volume balloon manometers measure intraluminal pressures accurately, they fail to detect contractions that do not impinge on, and thus do not deform, the balloon (Howarth et al, 1969). In contrast, large balloons, which on deformation do detect contractile activity do not produce an accurate record of intraluminal pressure, and they may also become impacted in the antrum or be forced into the duodenum (Smith & Code, 1958), thus influencing the motor activity of the gastroduodenal region.

Perfused catheter systems

Perfused open-tipped catheters have been used to measure intraluminal pressures since the 1960s and were developed as an attempt to overcome some of the disadvantages of balloon manometers. The pressure measuring device consists of single or multiple tubes with small side holes at their distal ends which may be passed nasogastrically or orogastrically and which are connected to pressure transducers at their proximal ends. The tubes are perfused with distilled water at a constant rate of 1 to 2mls. per minute and the intraluminal pressure changes are reflected by alterations in the constant perfusion pressure which are detected by the transducers. The outside diameter of the catheter assembly may vary from around 2mm (McShane et al, 1980) upto 6mm (Dooley et al, 1984) with multiple tubes with side holes spaced at intervals to record pressures from different sites.

Perfused catheter systems were originally used in research to assess the function of the sphincters at the anus (Harris et al, 1966) and the lower oesophagus (Pope, 1967), and have subsequently entered routine clinical use as method for the investigation of oesophageal motility disorders (McCallum, 1984) and at this site they have produced reliable and consistent results. This technique has also been used by many investigators to examine the motility patterns of the gastroduodenal region and, in particular, the action of the human pylorus. However at this site the technique has produced conflicting results. While several investigators (Fisher & Cohen, 1973; Valenzuela et al, 1976) have demonstrated that the pylorus functions as a physiological sphincter

responding to various stimuli, others (Kaye et al, 1976; White et al, 1981) using very similar perfused catheter techniques were unable to confirm these observations. In addition, McShane and co-workers (1980) have suggested that the zones of high pressure recorded in the former studies might have been related to muscle excitation and resistance to stretch induced by mechanical stimulation of the pylorus by the pressure-measuring device. More recently it has been shown in a combined radiological and manometric study (White et al, 1983) that perfused open-ended catheter systems fail to record contractions that do not occlude the distal side holes in the tubes and, although in the same study it was suggested that undetectable contractions would be unimportant, it would seem that these techniques have major limitations when used in attempts to assess the force of contractions in the gastroduodenal region.

Intraluminal strain-gauges

Miniature strain-gauge pressure transducers mounted on flexible tubes which could be used to measure intraluminal pressures were introduced in the early 1970s (Jacobs et al, 1972; Millar & Baker, 1973). Intraluminal strain-gauge transducers are said to have some advantages over conventional perfused catheter manometric techniques (Rees et al, 1978). Transducers have optimal compliance and operate independently of a perfusion system, which has the additional benefit of obviating the need for mathematical correction for the volume of perfused fluid should this technique be used in combination with gastric emptying studies. However the results produced by intraluminal strain-gauge transducers are otherwise similar to those obtained by perfused catheter systems, and the

technique also has the same limiting factors (Valori et al, 1986).

Extraluminal measurement of contractile force

Although the measurement of contractile force using implanted extraluminal devices is confined to animal studies these techniques deserve a brief mention, since the results obtained are thought to be applicable to the situation in man. Extraluminal techniques avoid possible obstruction of the normal flow of luminal contents and they do not cause mucosal irritation thus minimising the risk of initiating reflexes which might influence the normal physiological mechanisms (Weisbrodt et al, 1969).

Extraluminal force transducers were originally described in 1963 (Jacoby et al, 1963) and subsequently, in modified form, used for repeated monitoring of smooth muscle contractile activity (Anderson et al, 1968). The transducers are sutured to the serosa of the gut and, depending on their linear arrangement, can be used to measure the contractile activity in the circular (Weisbrodt et al, 1969) and/or longitudinal (Stemper & Cooke, 1975) muscle layers. The main disadvantage of these techniques lies with the fact that the strain-gauges cannot be recalibrated once implanted, and this prevents accurate determination of the relationship between the measured contractile force and luminal contractile activity (Gleysteen et al, 1979).

There is no accepted technique for measuring the force of intestinal contractions (Howarth et al, 1969). The rationale for performing measurements of contractile force has been based on the knowledge

that flow can occur only in the presence of a gradient in pressure between two intraluminal zones, and on the belief that intraluminal pressures are the direct result of contracile forces (Cannon, 1911). However, for the previously mentioned technical reasons, the relationships between the force of contractions and intraluminal pressures remains unclear (Weems, 1982). Furthermore, it has been shown in experiments in dogs that the larger the outside diameter of the sensing device, the greater the contractile pressures recorded (Brink et al, 1965). It has also been suggested that quantitative measurements of the force of contractions and, in particular, the arbitrary classification of antral contractions into types I and II (i.e. contractions which produce pressure deflections of either less or greater than 5cms. of water respectively) and type III (i.e. a rise in base-line pressure superimposed on either type I or II waves) (Code et al, 1952) may be of limited value (Kaye et al, 1976). Despite these criticisms, measurements of contractile force remain of value when they are used to assess relative changes in contractile activity in different physiological or pathological situations (Valenzuela et al, 1976).

Assessment of the amplitude of contractions

In man the size or amplitude of gastroduodenal contractions cannot be measured directly and has therefore been previously assessed indirectly by radiological techniques employing single or double contrast barium studies.

Around the turn of the century Cannon made his remarkable

observations on gastric contractile activity, initially in animals (Cannon, 1898) and subsequently in man, and described the passage of annular constrictions over the stomach towards the pylorus. The contractions, which varied in size, originated at different levels in the distal gastric body and occurred at a frequency of three per minute (Cannon, 1911). He popularised the concept that intraluminal flow was induced by relatively simple mechanical events which he termed peristalsis and rhythmic segmentation. These observations thereafter became the basis around which the majority of studies of gastroduodenal function were interpreted. Not until the development of the X-ray image intensifying tube in the 1950s made it possible to take dynamic pictures of the intragastric events without exposing the subject to excessive radiation, could Cannon's original observations be adequately re-assessed.

In humans cineradiology, in combination with intraluminal pressure measurements, has been used in attempts to determine the functional significance of the various waves recorded from the stomach and duodenum. Using balloon manometers to record pressures from the gastric antrum Smith and co-workers (1957) demonstrated that pressure waves designated either type I or II (page 32), depending on the pressure rise recorded, were associated with radiologically visible annular contractions which invariably progressed over the antrum towards the pylorus. Freidman and co-workers (1965), using perfused catheter techniques, attempted to determine the functional significance of monophasic waves recorded from the duodenum. They concluded that, although contractions might vary in amplitude and duration, they all serve either to mix or to propel the intraluminal contents.

As has already been stated (page 22), the duration of radiological studies is limited by the radiation dose to the subject. The results of the study by Smith and his co-workers (1957) contained only an average of three minutes of continious visualisation of the intragastric events in any one individual. The short duration of these observations must limit the interpretation of the relationships between gastric motility and intraluminal movement throughout the emptying of a test meal. In addition, it has become recognised that the normal gastroduodenal motility patterns may be altered not only by the irritative effects of liquid barium on the mucosa (Rock et al,1981), but also by the distention produced by gas used in double contrast studies (Dubois, 1979). Perhaps as a result of these limitations, the use of fluoroscopy in humans seems recently to have been confined to a means for screening the position of intraluminal pressure monitoring devices (Lederer et al, 1983; Stanghellini & Malagelada, 1983). In animals, however, where prolonged monitoring is possible, techniques using barium contrast media are still used to assess the relationships between contractile activity and gastric emptying (Prove & Ehrlein, 1982).

Scintigraphic techniques using radioisotopes, which are now widely used in gastric emptying studies, have been used recently in attempts to assess the associated contractile activity (Jacobs et al, 1982). In addition to measuring the gastric emptying characteristics of an isotopically-labelled test meal, the authors monitored the isotopic emissions from particular discrete points in the gastric antrum and found that these fluctuated in a sinusoidal manner with a frequency of 3 per minute. They concluded that the fluctuations were due to contractions passing over the antrum.

This technique would appear to represent a significant advance in the methods available for the simultaneous evaluation of gastric emptying and motility, but it does have certain limitations. Although non-invasive, the quantity of isotope used in the motility measurement was nearly 20 times greater than in a conventional emptying study (175MBq compared to 9MBq) and thus exposed the subjects to a significantly increased radiation dose. In addition, scintigraphic methods of assessing gastric emptying only reflect the net result of the mechanisms responsible, and cannot determine whether the associated contractile activity detected by this technique serves to mix and/or propel the intraluminal contents.

In animals the amplitude of gastroduodenal contractions can be measured directly by an inductograph (Louckes et al, 1960). This technique is based on the principle of inductive coupling between two electromagnetic coils which are positioned diametrically across the area to be studied. One coil is energised and the amplitude of the induced current in the other is inversely related to the distance between them. The coils can be stitched to the serosa of the gut and Louckes and his co-workers have extensively studied the motor activity of the pylorus and the gastric antrum.

Timing and duration of contractions

Information about the duration and the timing of occurence of the smooth muscle contractions in the stomach, pylorus or duodenum can be obtained from the techniques mentioned previously (pages 27

- 35) which have been used to measure the force of contractions or their amplitude. Information can also be obtained from measurements of the myo-electrical activity which is associated with the frequency of occurrence and direction of propagation of gastric smooth muscle contractions (Daniel & Chapman, 1963). Recordings have been made using either intraluminal or extra luminal electrodes.

The use of intraluminal electrodes, which are attached to the gastroduodenal mucosa by suction, was first described in dogs (Bortoff & Davis, 1968) and subsequently in man (Kwong et al, 1970). In humans they have been used to study the effects of vagotomy on gastric myo-electrical and motor activity (Stoddard et al, 1973; Stoddard et al, 1975). Extraluminal electrodes implanted under the serosa of the gut wall have been used for many years in animals (Richter, 1924; Daniel et al, 1959; Bass et al, 1961) and more recently in humans. Duthie and co-workers (1971) implanted electrodes in patients undergoing elective cholecystectomy and, in the post-operative period, monitored the electrical activity under resting conditions and also observed the effects of the ingestion of water, citrate and oleate. In another study electrodes were implanted at different sites in the stomach of patients undergoing various abdominal operations, and the pattern of propagation of the myo-electrical activity was monitored for the duration of the procedure (Hinder & Kelly, 1977).

The use of extraluminal implanted electrodes in humans studies is obviously limited. The intraluminal techniques, which are more readily applicable to normal research and clinical studies, are not

only limited by the drawbacks associated with all intubation techniques, but there are also problems specific to this technique when it is used to measure the timing and duration of contractions. Suction electrodes are best suited to measuring slow changes in membrane potential and, as a result, measurements of slow wave activity are more reliable than those of the action potentials which signify muscle contraction (Bortoff & Davis, 1968). The detection of slow wave activity does not necessarily mean smooth muscle contracion has occurred.

3.0.0 Real-time Ultrasonic Imaging

Ultrasonic imaging has been employed increasingly as a method for visualising internal body structures since the early 1970s. Initially widely used as a technique to allow the prenatal examination and diagnosis of fetal abnormalities 'in utero', it has subsequently become a routine diagnostic tool available in most X-ray departments. Ultrasonic imaging is non-invasive, and although, in experiments, ultrasound has been associated with adverse biological effects produced both by thermal damage to tissues and by cavitation (Liebskind et al, 1979; Stratmeyer, 1980), human diagnostic ultrasonic imaging is considered to be safe (Kinnear Wilson & Waterhouse, 1984; Cartwright et al, 1984).

3.1.0   Principles of Ultrasonic Imaging

The creation of an ultrasonic image is based on the fact that when a beam of very high frequency sound impulses (1.5 - 10MHz) is sent into a subject, the impulses are reflected back to a varying degree depending on the density of the medium through which they are passing (Donald et al, 1958). As in radar and sonar, the detection of the returning echoes can be used to generate information about the position and nature of the object being scanned. The production of the ultrasonic impulses and the detection of the returning echoes is accomplished by a transducer which utilises the piezo-electric effect to convert electrical energy into mechanical energy and vice-versa (Gordon, 1959). The transducer is connected to a signal amplifier and to an electronic device which analyses the electrical information from the returning echoes and displays it on an oscilliscope screen. Although the returning echoes can be displayed on the screen in a number of different ways, usually termed modes, the equipment used throughout this project utilises a display which is "brightness modulated" (B-mode) and produces what is termed a "B-Scan".   Each returning echo produces a single dot on the screen, the position of which reflects the distance between the transducer and the point of reflection, and the brightness of the dot depends on the density of the reflecting substance   (Kikuchi et al, 1957). Strong echoes appear white on the screen, whereas low-level echoes appear dark grey and those of intermediate strength lie at an appropriate point on a grey-scale range between white and black.

Ultrasonic scanning using a single static transducer produces a pencil thin image of the underlying area. Fluid-filled areas, such

as the lumen of the gall-bladder or distended urinary bladder, which do not reflect the ultrasound beam appear black, whereas organ boundaries, which are strongly echogenic, appear white. The parenchyma of tissues such as the liver or kidney appear on the screen as mid-grey. The information generated by a single static ultrasound transducer is, however, of limited value to most clinicians, since in order to obtain an image of the internal body structures, the operator must take a large number of scans at different positions and angles and simultaneously construct a mental picture of the underlying anatomy. A recognisable two-dimensional image, which can be considered to represent a "cross-section" through the structures under examination, is, however, more easily interpretable and can be obtained by a number of more sophisticated scanning techniques. Of these, rectilinear and sector scanning are the ones most often used to produce two-dimensional ultrasonic images in clinical practice. In the former technique, a number of transducers are mounted side by side and the multiple small parallel images are combined to produce one large scan (Somer, 1968; Bom et al, 1971). The multiple transducer assembly is somewhat bulky and has the disadvantages that it does not easily conform to the contours of the body surface and requires constant adjustments to be made to the configuration of the transducers as it is moved about (Bow et al, 1979). Sector scanners, which are smaller and thus more mobile, produce a two-dimensional image when a rotating transducer sweeps the ultrasound beam in an arc through the structures under examination (Donald et al, 1958). The transducer assembly used in this project, known as the probe, comprises four transducers mounted on a mechanically-rotated drum which is

seperated from the subject by a thin membrane (Bow et al, 1979). Rapid rotation of the transducers sweeps the ultrasonic beam through the tissues, and by firing the transducers at diferent times a 90 degree sector image is produced. The ultrasonic image is continuously updated at a speed which produces a dynamic picture of the motion of the internal body structures. This type of imaging is termed "real-time".

Although ultrasonic imaging, being non-invasive, would seem ideally suited for repeated or prolonged observation of internal structures (Holm & Mortensen, 1968), the technique has a number of limiting factors (McDicken, 1976) which are inherent in the technique, and are related to the fact that when ultrasound travels through tissues it becomes progressively attenuated by a number of phenomena, including reflection, scattering, refraction and absorption of the sound waves. Of these, reflection and absorption are the most significant.

Ultrasonic echoes are produced, as previously stated (page 39), by reflection of the sound waves from interfaces between tissues of differing densities. Although differences in the density of most tissue substances are not great, those of bone and particularily of air differ markedly from the others and very strong reflections occur at bone-soft tissue or air-soft tissue interfaces. Reflections from these substances are so great that they significantly attenuate the ultrasonic beam and thus, for all practical purposes, it can be considered impossible to visualise structures lying behind bone or to scan through air-filled bowel.

When an ultrasonic beam travels through tissues it becomes

progressively absorbed. As the distance (depth of penetration) from the outside of the tissues increases, the intensity and amplitude of the sound waves decrease exponentially. Absorption is also frequency-related and as the frequency of the sound waves increases (i.e. from 1 to 20MHz) the penetrating ability of the beam decreases because of greater absorption. This frequency-related penetrating ability is of great practical significance since the resolution of the ultrasonic image is also related to the frequency of the sound beam. However, in contrast to penetrating ability, as the frequency of the ultrasonic beam increases so does the resolution of the image.

When observations are being made on intra-abdominal structures, the clarity (or resolution) of the ultrasound image depends largely on the distance between the structures being examined and the scanning probe positioned on the anterior abdominal wall. This distance is related to the build of the subject and, as the distance increases, the resolution diminishes. However, as it is possible to alter the frequency and therefore the penetrating power of the ultrasound beam, this allows certain variations in body build to be compensated for. Probes of 3.5MHz (low frequency, medium resolution, deeper penetration) and 5MHz (high frequency, high resolution, low penetration) were available for use in this project.

3.2.0   Ultrasonic Imaging of the Gastro-intestinal Tract

The conventional techniques that have been used to assess gastric emptying and the related motor activity of the stomach and proximal duodenal have been reviewed in Section 2.2 (pages 16 - 37). Each of the techniques has its limitations and in particular, their use for repeated or prolonged observations on individual subjects may be associated with, at best, a certain amount of physical discomfort and, at worst, the risk of significant exposure to ionising radiation.   With the increasingly widespread availability of ultrasound scanning equipment, numerous investigators have described attempts to apply this non-invasive, non-radiological technique to the study of gastroduodenal function in man.

Visualisation of the stomach by ultrasonic imaging was initially used as a technique for the detection and examination of disease of the gastric walls (Lutz & Rettenmaier, 1973; Lutz & Petzoldt, 1976; Walls, 1976).   Adequate assessment of the stomach was, however, frequently found to be hampered by the presence of intragastric gas (Warren et al, 1978).   Filling of the stomach with liquid was advocated (Holm, 1971) in order to displace the intragastric gas and distend the gastric walls, thus producing an echo-free fluid-filled lumen.   This allowed the stomach wall to be more easily identified and provided a sonic window to deeper structures such as the tail of the pancreas (Holmes et al, 1973; Sample et al, 1975).

During the course of ultrasonic examinations of the fluid-filled stomach, contractions of the antral walls were often noted but, because the rapid emptying of the fluid from the stomach made the

technique somewhat transient and unreliable (Weighall et al, 1979), the subjects were often given an injection of hyoscine-N-butylbromide (Buscopan) or glucagon to inhibit gastric peristalsis and, by delaying gastric emptying, prolong gastric distention. Some investigators have used ultrasonic imaging specifically in attempts to assess gastric contractile activity.   Bateman and co-workers (Bateman et al, 1977) recorded gastric antral contraction rates using a B-scan plus time-motion (T-P mode) scan technique. However T-P mode does not produce an easily recognisable image of the area of the stomach under examination and thus provides only limited information about contractions.   Subsequently it was suggested (Holt et al, 1980) that simultaneous visualisation of the area under examination by real-time ultrasound would provide a dynamic image of the intragastric events and so might therefore permit an assessment of the spatial relationships between movement of the stomach walls and the luminal contents to be made.

Real-time ultrasonic imaging has been used in attempts to measure directly the rate of emptying of liquid (Bateman & Whittingham, 1982) and mixed solid-liquid test meals (Bolondi et al, 1985) from the human stomach.   In the former technique a real-time linear-array scanner consisting of 60 or more transducers was used to produce a series of parallel two-dimensional cross-sectional images of the liquid filled stomach.   From the multiple two-dimensional cross-sections a three-dimensional representation of the stomach was constructed and the intragastric volume calculated. After ingestion of a liquid test meal, its rate of emptying from the stomach could be calculated by repeating each multiple scan at regular intervals.   In this latter technique a high resolution

real-time scanner linked to a 3.5MHz linear array transducer was used to measure the changes in cross sectional area of the gastric antrum at 30 minute intervals after the ingestion of the solid-liquid test meal. Calculation of gastric emptying rates using ultrasound has recently been shown to correlate well with more conventional methods such as scintigraphy (Holt et al, 1986).

Following on from the initial study of Holt and co-workers (1980) Adam and co-workers (1982) reported the results of a small pilot study in which, using real-time imaging, they attempted to examine the relationship between gastric motility and the movement of echogenic particles of ground-up biscuit ingested along with a liquid test meal. They were successful in only a small number of the subjects examined, and they commented that simultaneous imaging of the distal stomach, pylorus and proximal duodenum was not only difficult but, perhaps because of anatomical variation, might be impossible in some normal subjects. Despite these difficulties they concluded that real-time ultrasonic imaging might have potential as a suitable technique for the investigation of gastroduodenal function in human volunteer subjects and patients, and might "help to resolve some of the important questions unanswered by previous methods used for the study of gastric motility and provide new information about the relationships between motor activity and movements of the luminal contents" (Adam et al, 1982). These comments provided the original stimulus for the present writer's attempts to develop the ultrasonic technique so that simultaneous visualisation of the stomach, pyloric canal and duodenum should be achieved reasonably consistently, and the relationships between contraction of the stomach and duodenum and

movements of luminal contents might be identified. This thesis documents these efforts and the subsequent application of the technique to the investigation of certain aspects of gastroduodenal function under differing normal and pathological conditions. The results of the investigations will be discussed in conjunction with the observations made by others using different techniques.

4.0.0   Subjects and Techniques

The work of Adam and co-workers (1982), referred to on page 45, had
suggested that real-time ultrasonic imaging might be suitable for
investigating gastrodudenal function. They had, however, encountered
some difficulties with the technique and had successfully observed
the internal events in only a small proportion of the subjects they
examined.   In this section is described the developement   and
subsequent refinement of the ultrasonic technique in an attempt to
make it both a reliable and reproducible method for simultaneous
visualisation of the motor activity of the distal stomach, pyloric
canal, proximal duodenum and the associated movements of the
contents of their lumena.

4.1.0   Subjects

The studies documented in this thesis were performed on volunteer subjects, the majority of whom were colleagues of the author who kindly gave up their free time to undergo the ultrasonic examinations, and on a number of patients with a variety of upper gastro-intestinal pathologies.

It was considered important that, during the development and subsequent application of the ultrasonic imaging technique to an area of investigation where its use was novel, the studies should initially be confined to normal subjects and in whom the method would be applied to the areas of physiological interest discussed in the previous section of this thesis concerning the current concepts of normal gastric emptying. The studies in normal subjects therefore constitute the bulk of the investigative work here recorded. Nevertheless, studies were also carried out on a number of volunteer patients with several different gastroduodenal pathologies *.

Detailed information about subjects participating in the investigations is presented in later sections of this thesis in conjunction with the details of the particular study in which they were involved.

* The author is most grateful to Mr IB Macleod, Mr D Lee and Dr RC Heading of the Royal Infirmary, Edinburgh for permission to examine their patients.

4.2.0   Real-time Ultrasonic Scanner

Throughout this work the ultrasonic images were obtained using the same scanner (Figure 1A, page 50), which was a commercially available B-mode sector scanning machine (GL Ultrasound Ltd) identical to those in use at the time as a routine diagnostic instrument in many X-ray departments in the United Kingdom.   The scanner consisted of a hand held-probe connected by a cable to a large, but relatively mobile, piece of electronic apparatus containing the controls for making fine adjustments not only to the nature of the ultrasonic beam generated by the transducers in the probe, but also to the characteristics of the image produced by the returning echoes.   The probes used produce ultrasonic waves of a single frequency only.   However, 2 separate probes, of 3.5MHz and 5.0MHz respectively, were available, and because they were quickly and easily detatched from the rest of the scanner, they could be interchanged as necessary in an attempt to compensate for any differences in body build encountered among the different subjects scanned.

The ultrasonic images were displayed on the small screen of the scanner (Figure 1B, page 51) on which were also shown details of the frequency of the probe in use (f), and the focus depth of the ultrasonic beam (d); moreover, information about each subject and/or test meal could be entered if required via the touch keyboard (k).   In addition there was a digital time and date display (t) which was updated every 5 seconds.   The small size of the screen on the scanner made viewing of the ultrasonic images difficult for anyone other than the operator sitting directly in

FIGURE 1A - Ultrasound Scanner (GL Ultrasound Ltd)
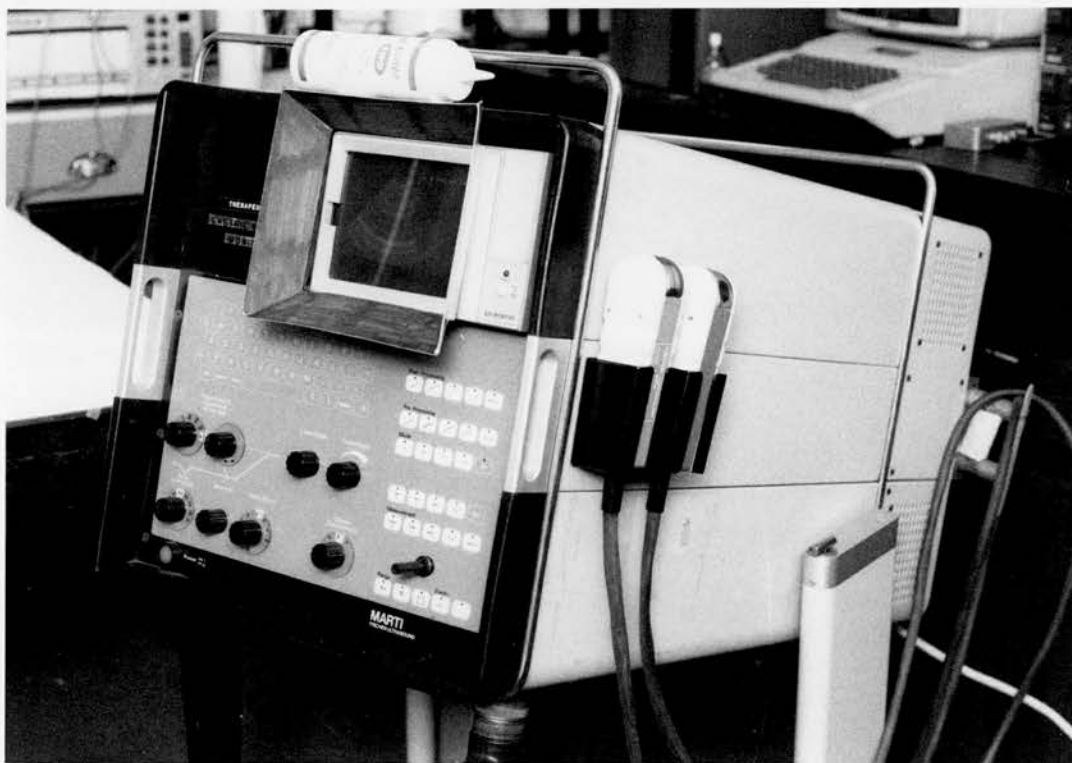
The rotating transducer real-time ultrasonic scanner utilises either
a 5MHz or a 3.5MHz probe.   The scanner is, despite its bulk,
relatively portable.   The interchangeable handheld probes can be
seen stored in the brackets on the side panel of the scanner.

FIGURE 1B - Close up of the front panel of the ultrasound scanner to
show the screen detail

The small screen at the top right-hand corner of the front panel of
the scanner displays the ultrasonic images. There are also details
about the frequency of the probe in use (f), its depth of focus (d)
and the digital time and date display (t) is updated every 5
seconds. Information about each subject or test meal can be entered
via the touch keyboard (k) on the lower half of the panel.

front of the controls, and so the picture was also displayed on a larger remote video monitor. Not only did this arrangement enable a greater number of observers to view the intra-abdominal events, but it also allowed the subject being scanned to see what was going on. The images were simultaneously stored on videotape by using a standard VHS recorder, so that they could be subsequently reviewed and analysed.

4.3.0   Scanning Technique

The initial objectives in the development of the ultrasonic imaging
technique were rapid and reliable identification of the stomach and
duodenum of the subjects examined and the subsequent maintainence of
the images during the period of each study.

The image produced by the sector scanner can be considered
two-dimensional and represents a cross-section through the
underlying structures which is parallel to the direction of rotation
of the transducers in the probe.   In order to obtain simultaneous
visualisation of a number of intra-abdominal structures, it must
therefore be possible to orientate the probe so that the imaging
plane transects them all.

Variations in subject anatomy may sometimes make it difficult to
determine the precise location and orientation of the more mobile
intra-abdominal organs such as the fundus and proximal antrum of the
stomach.   However, the retroperitoneal structures are relatively
fixed in position, and their relationships to other structures can
be used as a reference to facilitate orientation of the ultrasonic
image.   In most subjects the 1st part of the human duodenum and
pylorus lie retro-peritonealy (Oliva et al, 1981), and in any
individual the pylorus is said to lie deep to the midpoint of a
transverse plane (Figure 2, page 54) situated half-way between the
xiphisternum and the umbilicus (transpyloric plane).   Consequently
the examination of any subject was begunenced by positioning the
ultrasonic probe at this point and scanning transversely.
Thereafter small adjustments were made to the orientation of the
probe to bring the stomach and/or duodenum into view.

FIGURE 2 - Line drawing of transpyloric plane

ULTRASONIC IMAGING OF ANTRUM, PYLORUS AND DUODENUM.
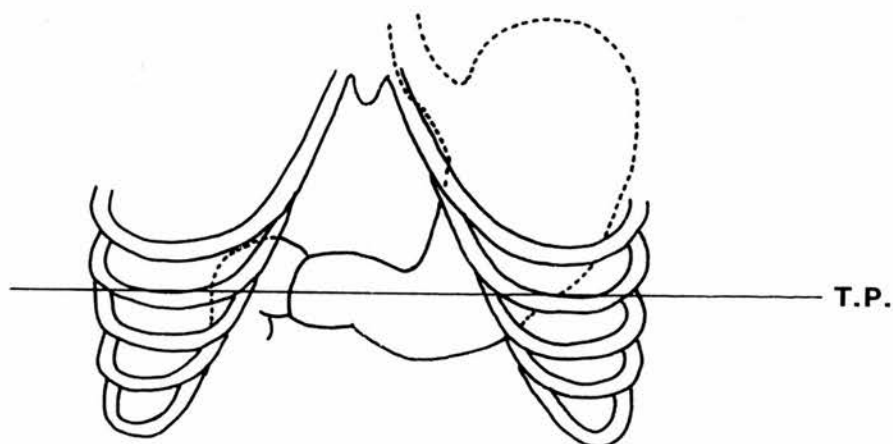
T.P. - TRANSPYLORIC PLANE
ULTRASOUND PROBE POSITIONED TO
OBTAIN A TRANSVERSE SECTION

Ultrasonic examinations are begun by positioning the handheld probe on the anterior abdominal wall of the subject at the midpoint of the transpyloric plane. The pylorus lies deep to this point. Adjustments are then made to the orientation of the probe to allow visualisation of the gastroduodenal region.

FIGURE 3 - Ultrasonic image of the gastroduodenal region before ingestion of liquid
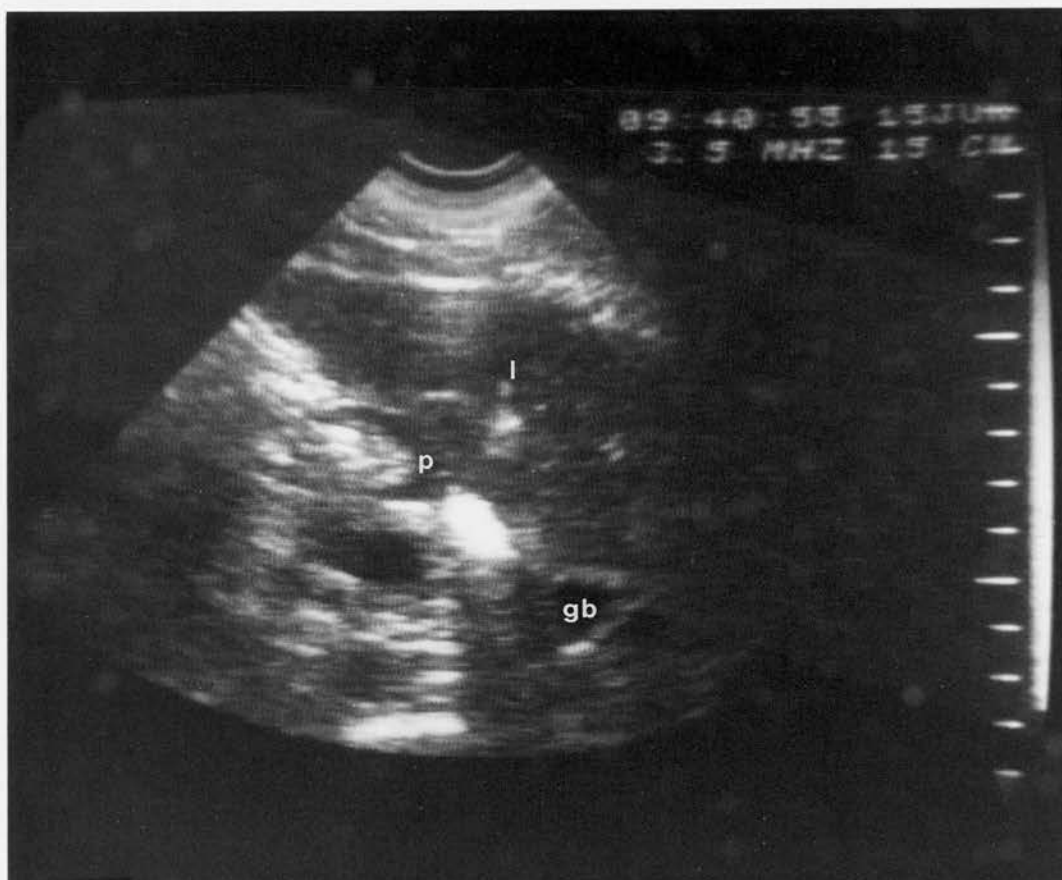
Transverse B-scan, using a 3.5MHz probe, of the upper abdomen at the level of the transpyloric plane. The anterior abdominal wall is at the top of the image. The pylorus (p) can be seen as an olive shaped area just to the left of centre of the image, lying below the liver (l). The sonolucent area of the gallbladder (gb) is situated to the right of centre towards the bottom of the image.

The scans were performed after an overnight fast, and in fasted subjects the proximal antrum and fundus of the stomach are not readily identifiable, but the pylorus is often visualised as an olive-shaped area which has an anechoic periphery caused by the muscle in the wall of the stomach, and an echogenic centre created by gastric mucosa, mucus, and the difference in acoustic impedance between the gastric wall and lumen (Fakhry & Berk, 1981), lying anterior to the aorta, inferior vena cava and lumbar spine (Figure 3, page 55). The easily recognisable sonolucent area of the gall-bladder, which often lies close to the duodenum, also provides a useful landmark. Respiratory and other movements by the patient rendered it neccessary for the orientation of the probe on the anterior abdominal wall to be maintained by hand so that minor adjustments could be continuously made to compensate for these movements.

The ultrasonic scans were always performed with the subject seated upright (Figure 4, page 57). In this position any intragastric gas, which if present in the area under examination would scatter and attenuate the ultrasonic beam, collects high in the fundus well away from the distal stomach (Warren et al, 1978). In addition, in the upright position overlying gas containing bowel such as the transverse colon tends to hang down below the level of the pylorus. Posture, however, is said to have little effect on gastric emptying of nutrient liquids in normal individuals (Hunt et al, 1965; Burn-Murdoch et al, 1980; Muller-Lissner et al, 1983); the subsequent comparisons which will be made between the results of the studies using this technique and those of the many other investigators who have performed their studies on gastroduodenal

57

FIGURE 4 - Subject being scanned in seated position

Ultrasonic scanning of the upper abdomen is performed with the subject seated upright. Any intragastic gas, which tends to reflect and scatter the ultrasonic beam and distort the image, collects in the gastric fundus well away from the areas under observation.

function in recumbent subjects should therefore not be unreasonable.

During the initial stages of each ultrasound examination, that is before the ingestion of any test meals, an effort was made to optimise the clarity of the ultrasonic image. In practical terms, the image clarity was found to depend on the build of the subject and, although the ability to interchange the 3.5 and 5.0 MHz probes allowed most normal variations in body build to be coped with, in obese individuals satisfactory visualisation of the internal anatomy could not be achieved. The unsuccessful attempts to scan a number of overweight individuals are documented in Section 6 (page 170).

4.4.0   Test Meals

The emptying pattern of any test meal from the normal human stomach depends largely on the physical characteristics of the meal.   These characteristics have been discussed previously (pages 12-15) and in summary are volume, pH, osmolality, fat content, calorific value, viscosity and whether its components are liquid or solid.   Under ordinary circumstances meals consist of a mixture of solids and liquids, but the presence of undigested solid material in the lumen of the stomach causes excessive scattering and reflection of the ultrasonic beam and so distorts the image that visualisation of the intraluminal events is impossible.   It is for this reason that the observations with real-time ultrasonic imaging have at present been confined to liquid meals.   As scientific advances are made in the field of ultrasonics it may become possible to use this non-invasive technique to monitor intragastric events in the presence of more solid test meals.

Experiences from early attempts to apply the ultrasonic imaging technique to the study of events at the gastric outlet suggested that   certain   of   the   test   meal   characteristics should be standardised throughout a series of investigations.   This was neccessary not only to permit the effect of alterations in single test meal characteristics to be assessed, but also to facilitate visualisation of the distal stomach, pylorus and proximal duodenum.

An ingested volume of 500mls was found by several investigators who previously examined the stomach with ultrasonic imaging (Warren et al, 1978; Weighall et al, 1979) to   induce moderate gastric distention   and   the   anechoic   fluid   filled   lumen   rendered

visualisation of the walls of the gastric antrum, pylorus and proximal duodenum much easier.   Subsequently test meals of this volume were also used in studies where ultrasonic imaging was specifically applied to the investigation of gastric function (Bateman et al, 1977; Holt et al, 1980; Bateman & Whittingham, 1982).   Ingestion of a volume of 500mls is known to interupt the interdigestive cycle of fasting individuals (Rees et al, 1979) and results in a pattern of gastroduodenal motor activity which resembles that of the post-prandial period.   It was therefore assumed that, after ingestion of the 500ml test meal used throughout this study, each subject would enter a comparable phase of gastric motor activity.   In addition, although gastric emptying times vary according to the nature of the test meal, under normal circumstances a 500ml volume of liquid might be expected to have emptied from the human stomach within 30 minutes (Meeroff et al, 1975). Consequently the events occurring at the gastroduodenal junction of the subjects in this study were visualised using the imaging technique and simultaneously recorded for up to 30 minutes following the ingestion of a test meal.

The test meals were warmed to a temperature of 37´C, which was considered necessary because variations in the temperature of ingested material may influence its rate of emptying from the stomach.   In addition, lower temperatures are associated with inhibition of gastric contractions (Bateman et al, 1977).   It was therefore felt that if the test meals used in this study were all at 37´C then temperature-induced variations in gastric emptying and gastroduodenal motility between different subjects would be eliminated.

Other physical characteristics of each test meal were varied according to the criteria of the particular study in which the effect of their variation was being assessed. Throughout each study the composition of a particular test meal ingested on seperate occasions by each subject remained constant. This was feasible because the test meals were prepared using a "recipe" of measured constituents shortly before the subject was due to undergo the ultrasound examination. The details of the "recipe" for the different test meals are documented in later sections of this thesis in relation to the relevant study.

After preparation of each test meal the pH was measured by a Radiometer GK 2321C combined glass pH electrode (Radiometer, Copenhagen), and the osmolality was assessed by measurement of the freezing point depression of a small sample of the liquid. The osmolality measurements were carried out with a Digimatic Osmometer (Advanced Instruments Inc, Massachusetts) by the technical staff of the Medical Renal Unit of the Royal Infirmary, Edinburgh.

The subjects ingested the 500ml test meals over one to two minutes, and during this time the passage of the liquid into the stomach was monitored. The actual ingestion of the test meal was accomplished by the subject drinking it through a straw, which reduces the amount of air swallowed while drinking and helps to minimise the artefacts produced by air bubbles in the liquid (Crade et al, 1978). Subsequently, when the observations were reviewed and then analysed, the time at which ingestion of the test meal was completed was deemed time zero (the actual start of the observations). Calculation of the interval between time zero and

the start of the subsection of the observations in which the relationships between the gastroduodenal contractions and intraluminal fluid movements were analysed in detail was necessary to ensure that the results from each subject came from a comparable portion of the postprandial period.

4.5.0   Liquid Phase Sonic Marker

The fluid-filled lumen of the stomach appears as a black sonolucent area when examined using ultrasound (Figure 5, page 64). Although this echo-free area enhances visualisation of the gastric walls, the lack of echoes makes it impossible to determine whether there is any movement of the intraluminal fluid. It was therefore considered necessary to incorporate in the test meal a particle of a suitable size which, when suspended in the luminal contents, would be detectable by the ultrasound technique. It was felt that the visible movement of the particles would then reflect the movement of the liquid.

Any particles which might prove to be satisfactory liquid phase sonic marker would have to fulfil a number of criteria. The particles would have to be large enough to render them sufficiently echogenic to be visible ultrasonically, but not so large that their behaviour would represent that of intraluminal solids rather than liquids; and since the emptying characteristics of solids less than 2mm in diameter have been shown to be indistinguishable from liquids (Meyer et al, 1981), a particle size of up to 2mm would be permissible. In order to maintain the individual particle size once ingested along with a test meal, they should neither be susceptible to breakdown by the digestive processes they exhibit any tendency to aggregate into larger clumps. Ingestion of the particles should not expose the subject to any risk and, in addition, their composition should not influence the physical characteristics of the test meal (e.g. negligible calorific value). Finally the particles should remain in suspension in the

FIGURE 5 - Ultrasonic image of the fluid filled stomach after ingestion of a test meal without echogenic particles

Transverse B-scan using a 5MHz probe. The gastric antrum (a) is distended with fluid and appears as a dark sonolucent area to the left in the image. The gallbladder (gb) is clearly visible below the liver (l).

intraluminal liquid so that their movements do indeed reflect the movements of the fluid in which they are suspended.

In their attempts to produce echogenic particles, Adam and co-workers (1982) asked their subjects to chew and then swallow pieces of a small plain biscuit along with 500-1000mls of fluid. It was therefore felt that a re-assessment of their method, in the context of the criteria discussed above, would be an appropriate first step in the development of a suitable liquid-phase sonic marker.

Three individual subjects were studied on twelve separate occasions in attempts to visualise intragastric fluid movement using pieces of biscuit as a sonic marker. Each subject drank a 500ml test meal composed of water at 37´C, to which had been added diluting orange to taste, and simultaneously chewed up half a rich tea biscuit into fine pieces which were washed down with the liquid. The intragastric events were monitored using the 5.0MHz probe and recorded on the videotape.

On reviewing the observations a number of problems became apparent, most of which were related to particle size. The chewing of the biscuit to break it up into smaller particles was in itself subject to a certain degree of individual variability. Furthermore, during normal mastication the tongue tends to compress food in the mouth into a bolus which is then swallowed (Ganong, 1979). The effect of these factors could be seen in the video recordings where the biscuit appeared in the lumen of the stomach as echogenic particles in sizes varying from minuscule up to over 1cm (Figure 6, page 66). In addition, only a few minutes after ingestion of the test meal the

FIGURE 6 - Ultrasonic image of the gastric antrum after ingestion of a test meal containing biscuit particles.
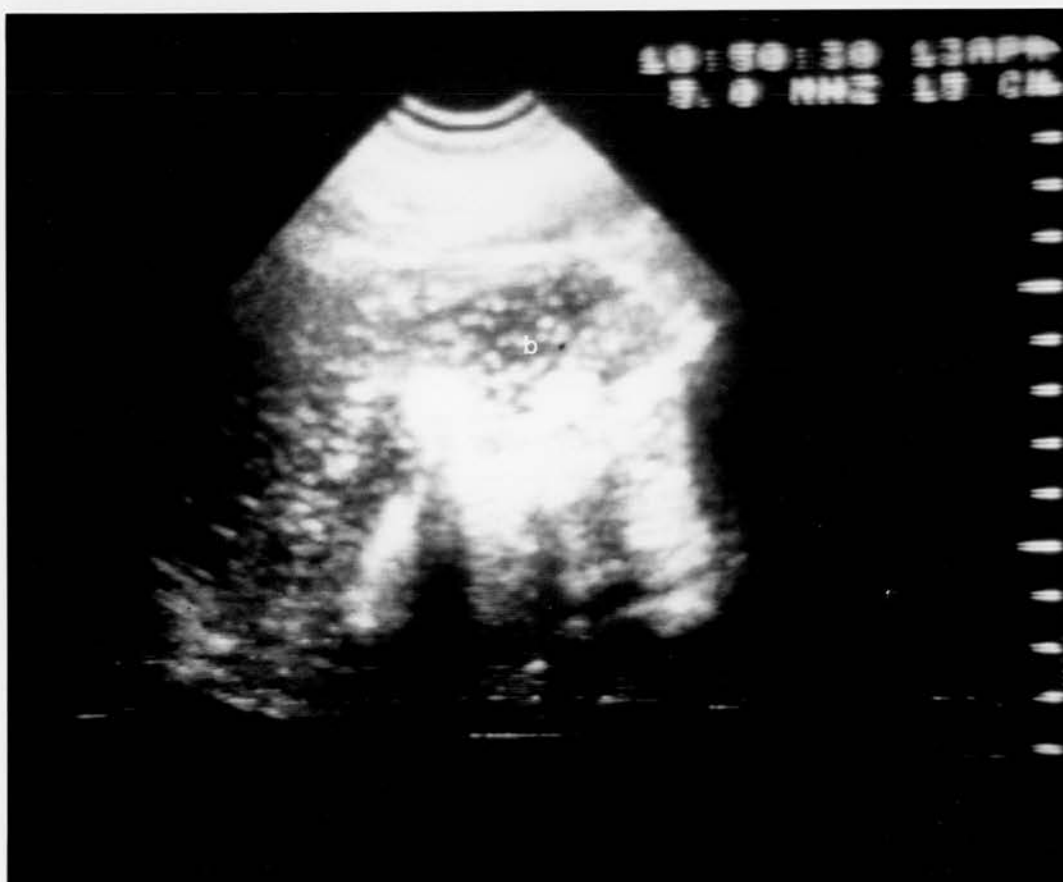
Transverse B-scan using a 5MHz probe. The gastric antrum is distended with fluid containing echogenic particles (b) of varying sizes.

FIGURE 7 - Ultrasonic image of the gastric antrum later in the recording with a test meal containing biscuit particles

Transverse B-scan using a 5MHz probe. The larger particles of biscuit (b) are beginning to settle out towards the posterior wall of the antrum.

concentration of particles in the liquid-filled lumen could be seen to be diminishing, presumably because of a combination of particles emptying into the duodenum, and in particular, settling out of the larger particles. The particles which had settled out could be seen as a bright echogenic rim to the luminal aspect of the inferior gastric walls (Figure 7, page 67). This diminution of particle density made subsequent visualisation of the movements of the residual intraluminal fluid impossible. On another occasion, in an attempt to resolve the problems concerning the size of the particles, the biscuit was first lightly ground into small crumbs and added to the test meal before it was ingested. This resulted in a fairly homogeneous biscuit soup, but unfortunately the fine particles could not be visualised in the gastric lumen. Ultimately it was concluded that particles of biscuit were unsuitable as a liquid-phase sonic marker.

Methylcellulose in aqueous suspension has been reported to be a satisfactory liquid with which to distend the stomach and thus provide a transonic window through which the retro-peritoneal structures may be visualised using ultrasound (Warren et al, 1978). During their observations when using methylcellulose, the authors commented that the liquid contained inert, viscid mucilages, stable in both acid and alkaline solutions and which were sonically visible in the gastric lumen. In view of these findings it was decided that an attempt should be made to manufacture echogenic mucilages according to the method described by them.

The methylcellulose was prepared by firstly moistening the dry powder with distilled water heated to around 95°C and then when the

powder was fully hydrated, it was quickly cooled with cold water which was added to produce a 1% concentration. This produced a rather viscous cloudy suspension containing mucilages of many sizes. Next the solution was strained though a gauze to remove the larger of the mucilages. "In vitro" ultrasonic scanning of the resultant suspension, when freshly prepared, did reveal the presence of echogenic particles. However, because the preparation time for the methylcellulose suspension was around 60 minutes, it was felt that, in order to save time when performing studies on volunteers who would usually arrive for study first thing each morning after fasting overnight, a large stock volume of the liquid should be prepared to allow 500ml aliquots to be used in each test meal. Strangely, after the freshly-prepared liquid had been left to stand for a few hours the suspension cleared and when scanned the mucilages were no longer detectable. In view of the unstable nature of the methylcellulose mucilages, and also because it was in fact felt that the viscous suspension was somewhat unphysiological, "in vivo" scanning of an ingested test meal of the liquid was not performed.

The major problem that dogged the early stages of the development of a liquid-phase sonic marker was simply the difficulty in finding a suitable substance, preferably one already in a particulate form which measured around 1-2mm in diameter and which remained unaltered in the liquid test meal. In one attempt to produce echogenic particles, activated charcoal powder was added to 500mls of water. This resulted in a fine suspension of black particles, but when the test meal was ingested these particles could not be detected in the gastric lumen by the ultrasound scanner.

Another series of attempts to manufacture echogenic particles involved the use of gelatine and subsequently agar. Both of these substances can be mixed with water which has been heated to just below its boiling point, and solidifies when the solution cools. While the solution was still liquid it was possible to pour it into a very shallow trough so that when it solidified the result was a thin layer of jelly 1-2mm thick. A circular punch with an internal diameter of 2mm was then used to cut small pellets from the layer. "In vitro" the jelly pellets exhibited no tendency to clump and remained relatively well suspended in the test meal.

In a preliminary study which was undertaken to see if the small pellets of jelly were in fact visible ultrasonically in the stomach when ingested, commercial dessert jelly (gelatine) was cut into 0.5cm cubes and swallowed along with a 500ml test meal. The cubes proved to be easily detectable in the gastric lumen (Figure 8, page 71), but it was noted that from 10 to 15 minutes after their ingestion the cubes had become smaller. It appeared that the gelatine cubes were either simply dissolving in the liquid filled stomach or were being digested by the gastric juices.

Using agar instead of gelatine to produce the small pellets resulted in echogenic particles which were stable when ingested. Figure 9 (page 72) illustrates the ultrasonic appearance of the agar particles in the gastric lumen. The agar pellets seemed to have great potential as a satisfactory liquid phase sonic marker, but they were nevertheless associated with a number of drawbacks. Around 500 pellets were required in each test meal to produce a sufficient density of particles in the gastric lumen to allow the

FIGURE 8 - Ultrasonic image of the gastric antrum after ingestion of a test meal containing cubes of jelly
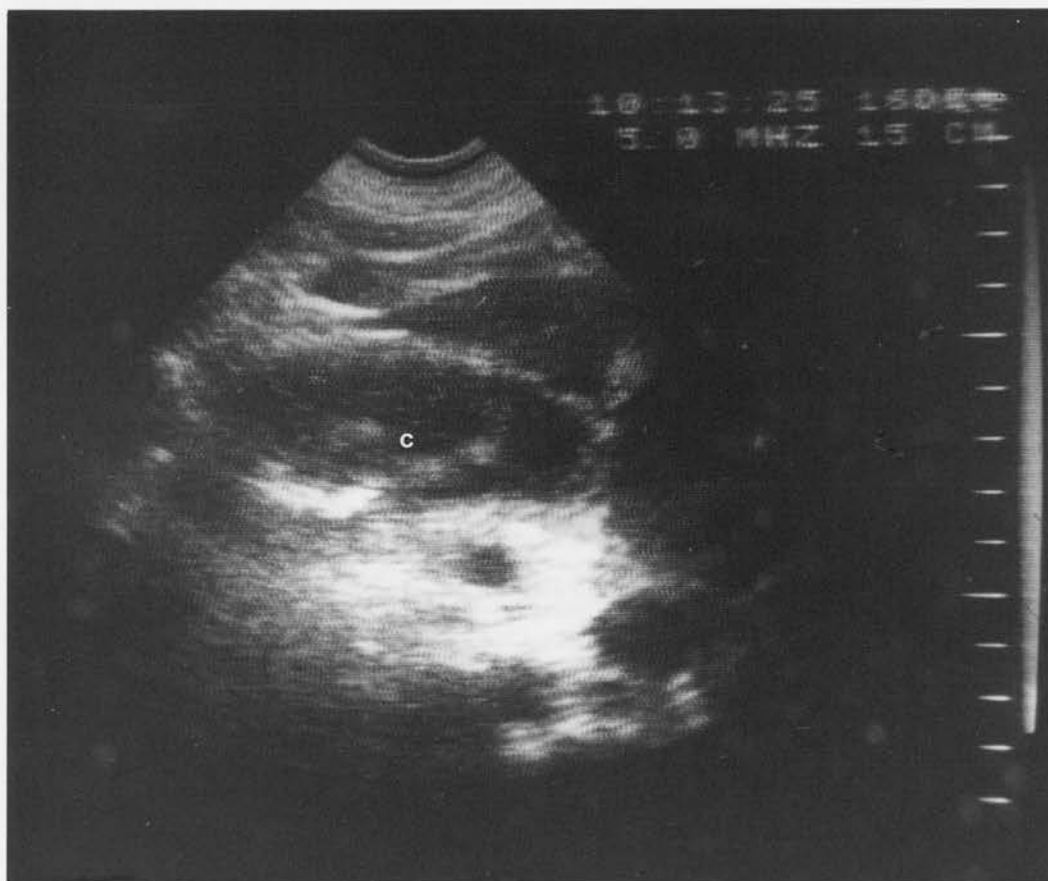
Transverse B-scan using a 5MHz probe. The cubes of jelly are visible as large echogenic particles (c) suspended in the contents of the distended antrum.

FIGURE 9 - Ultrasonic image of the gastric antrum after ingestion of a test meal containing agar particles
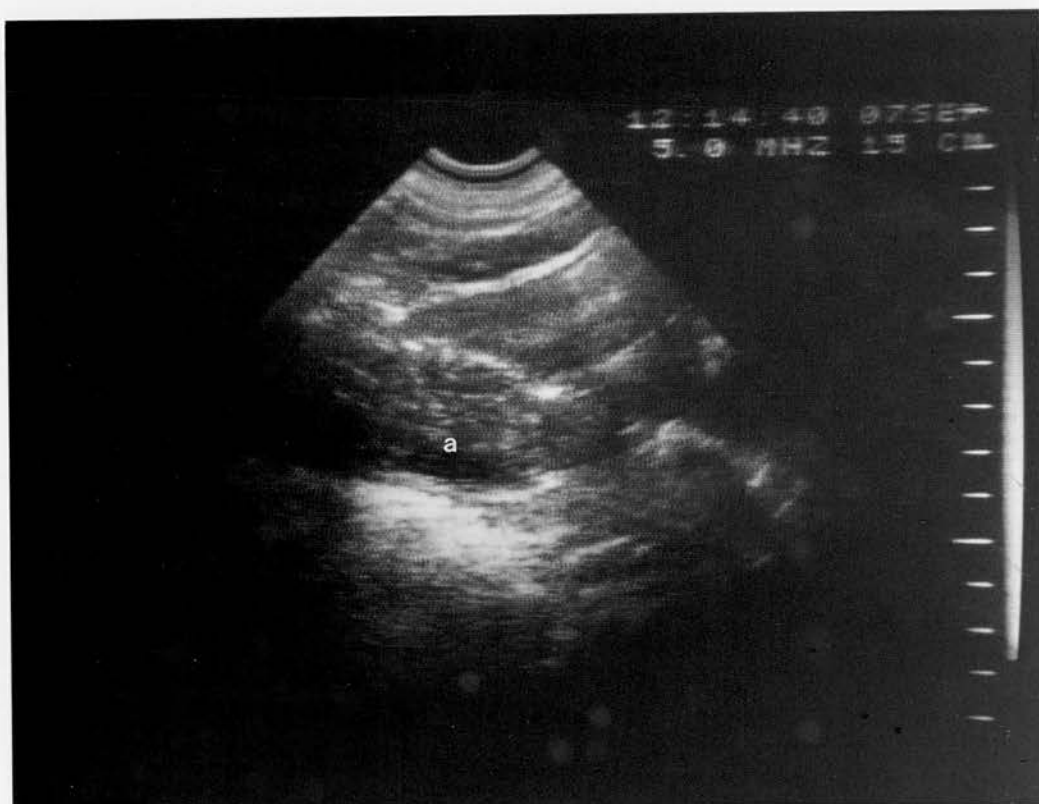
Transverse B-scan using a 5MHz probe. The gastric antrum is distended and contains a large number of uniformly sized echogenic agar particles (a).

recognition of fluid movement and, because of the limited equipment available, each one had to be individually cut from the thin agar sheet. The use of this single technique to manufacture a sufficient quantity of particles for the test meals was thus felt to be impractical. In an effort to speed up the manufacture of the agar pellets, a multiple punch capable of cutting several scores of pellets simultaneously was designed. The construction of this device was to be carried out by a firm of precision engineers, but since there would be some delay before the device would be available, it was decided to abandon the use of the agar particles temporarily and continue the search for another suitable liquid-phase sonic marker.

Natural bran flakes, which are actually the outer layers (husks) of wheat grain removed during the milling process, are readily available from health food shops and are inexpensive. These bran flakes vary in size from powder to around 0.5cm and it was thought that the smaller flakes might make satisfactory echogenic particles.

By a process of alternatively sieving the flakes through wire mesh of two different sizes, discarding the material less than 1mm, chopping up that greater than 2mm in a blender and then repeating the whole process, it was possible to manufacture a large quantity of uniformly sized small bran particles. Multiple random sampling of the particles once they had been immersed in the test meals showed the majority to have a wet particle size of 1.5mm. "In vitro" exposure of the bran to gastric juice showed it to be indigestible, and the particles themselves exhibited no tendency to aggregate into larger clumps. The particles did tend after a while

FIGURE 10 - Test meal containing bran particles before ingestion

All test meals contain 0.5g of fine bran particles which, when suspended in the gastric contents, produce recognisable ultrasonic echoes. The movements of these particles reflects that of the test meal in which they are suspended.

to settle out of suspension, but it was hoped that once ingested they would remain suspended in the liquid phase long enough to reflect its movement for the duration of each study. Subsequently, by a process of trial and error, it was discovered that if 0.5g of the chopped and sieved bran particles were added to each 500ml test meal (Figure 10, page 74) this resulted in a sufficient density of echogenic particles suspended in the stomach to allow the detection of intraluminal fluid movement.

A number of normal subjects, all of whom had ingested a 500ml test meal containing the bran particles, were scanned using the ultrasonic technique. In each one, echogenic particles were visualised moving in the lumen of the stomach, pylorus and proximal duodenum. As a result of these preliminary observations it was felt that the bran particles could fulfil the majority of the criteria required for a suitable-liquid phase sonic marker. However, in order to confirm that the movement of the bran particles did in fact reflect that of the liquid, it was decided to compare the gastric emptying characteristics of the bran and the liquid. If the bran and liquid emptied from the stomach at the same rate, then it would be reasonable to assume that movement of the bran particles reflected movement of the intraluminal fluid in which they were suspended.

The gastric emptying measurements were carried out using scintigraphic techniques similar to those discussed in Section 2.2.1 (pages 22-24). Advice on the design of the isotopic emptying studies was given by by Dr P Tothill of the Department of Medical Physics, Royal Infirmary, Edinburgh, in whose department the studies

were also performed. In total, seven normal volunteers underwent the gastric emptying tests. These seven were also examined by the ultrasonic technique on separate occasions, and the results of these observations are documented in later sections of this thesis along with those of the other subjects who ingested the same test meals.

The radionuclides utilised were Indium-113m to label the bran particles, and Technetium-99m as the liquid-phase marker. The methodology of the labelling techniques and the gastric emptying studies are described in more detail in Appendix 7.1.0 (pages 183-187). The results of the studies are, however, discussed below. Each subject, who was standing, consumed a labelled 500ml liquid test meal containing 0.5g of labelled bran particles. Then, using a dual isotope gamma camera, the abdomen of each subject was scinti-scanned at regular intervals during the following 60 minutes. The amount of each isotope remaining in the stomach after successive intervals was measured and from these results the emptying characteristics of the Indium-113m and Technetium-99m could be calculated.

The intragastric activities of each isotope expressed as a percentage of the original activity against time are shown in Tables 1A and 1B (page 77). The results from individual subjects with the same isotope were combined, and a mean and standard deviation calculated for each successive scinti-scan. The results were statistically analysed using Students t test and have been plotted for comparison in Figure 11 (page 78). During the first 10 to 20 minutes after ingestion of the test meal there was no significant

Table 1A - Percentage of Indium-113m activity remaining in the stomach during the emptying of a test meal

	>------Time post ingestion (minutes)------<					
Subjects	10	20	30	40	50	60
1	73.5	72.5	77.5	75	68	66
2	53	54	48	49	68	66
3	69	68	78	76	73	75
4	73	72	77	88	81.5	79
5	53	54	49	49	68	66
6	80	86.5	87.5	89	89	65.5
7	81.5	87.5	94	84	67.5	53.5
Mean	69	71	73	73	74	67
SD	11.7	13.6	17.9	17.2	8.5	8.1

Table 1B - Percentage of Technetium-99m activity remaining in the stomach during the emptying of a test meal

	>------Time post ingestion (minutes)------<					
Subjects	10	20	30	40	50	60
1	65	66	55	47.5	43.5	36
2	78	62	45	34	27	25.5
3	60	50	42	34	26	24.5
4	78.5	72	58	39	29	23.5
5	53	30	17.5	12	9.5	6.0
6	70	55	42.5	32	22	14
7	53	34.5	21.5	11.5	8.5	6.0
Mean	65	53	40	30	24	19
SD	10.7	15.8	15.5	13.5	12.1	11.1

FIGURE 11 - Percentage activity of Indium-113m and Technetium-99m activity remaining in the stomach during the emptying of a liquid test meal
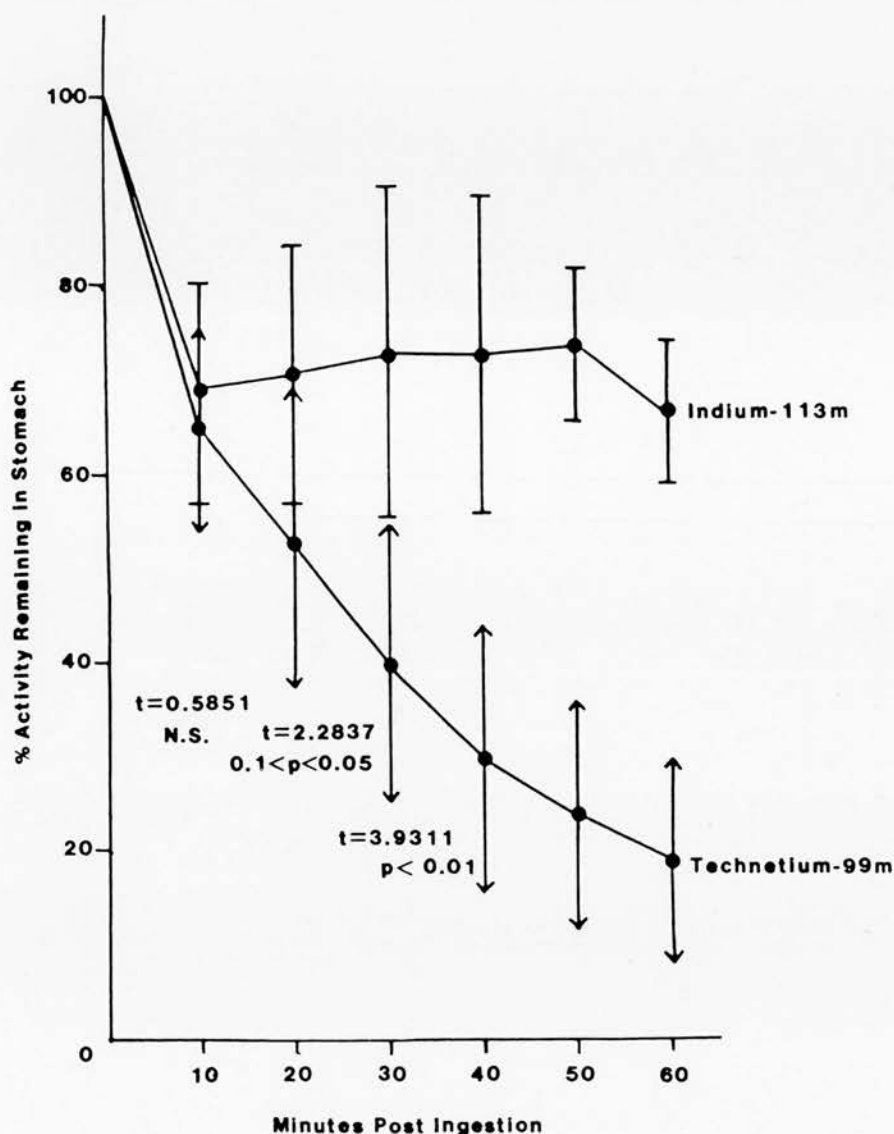
Indium-113m is used to label the bran particles and Technetium-99m for the liquid. The mean values of the percentage activity of each isotope are plotted at 10 minute intervals. During the early period (upto 10 mins) of emptying there is no significant difference between the emptying of the 2 isotopes but after 20 minutes the difference becomes progressively greater.

difference between the emptying of the Indium-113m and Technetium-99m. Thereafter, however, their emptying characteristics were significantly different. This difference can be seen to be due to the persistantly high percentage of the Indium-113m activity remaining in the stomach. This was presumed to be due to Indium-113m labelled bran particles settling out of the liquid and being left behind in the stomach as the liquid emptied.

It was ultimately concluded that, in the circumstances, the bran particles were the most satisfactory liquid-phase sonic marker available, and the observations obtained with the ultrasonic imaging technique documented in the later sections of this thesis were all made using the bran particles. However, in view of the results from the gastric-emptying studies, it was felt that any attempts at detailed analysis of the observations made with the bran particles as a liquid phase sonic marker should be confined to a section of the intra-abdominal events occuring as soon as possible after the ingestion of the test meal.

4.6.0 Analysis of the Ultrasonic Observations

The ultrasonic imaging technique was used, as previously mentioned (page 45), to allow simultaneous visualisation of the motor activity of the distal stomach, pyloric canal and proximal duodenum and also the associated movements of the intraluminal contents. To do this, the video recordings of the ultrasonic observations made following the ingestion of any test meal were reviewed to identify those periods when a clear image of the above structures was maintained without interruption and was coupled with a sufficient density of bran particles suspended in the luminal contents to identify movement accross the pylorus. Figure 12 (page 81) is taken from such a period of recording. In the context of the studies documented later, where the primary objective was the investigation of transpyloric flow, the view was taken that even momentary loss of the plane of imaging through the pyloric channel was not permissible, and so the sections of the recordings that were considered suitable for detailed analysis were often of short duration. It was, however, arbitrarily decided that a section to be analysed should last at least 2 minutes.

Identification of the sections of the recordings suitable for analysis was usually more rapidly accomplished by viewing a fast replay of the observations, since the resultant time-scale compression markedly enhanced the appreciation of movement. The selected sections were, however, then analysed at normal speed.

The interpretation of visual observations made using any imaging technique on the intra-abdominal events occurring after ingestion of a test meal is very subjective and must therefore be associated

FIGURE 12 - Ultrasonic image of the gastroduodenal region illustrating the criteria for analysis
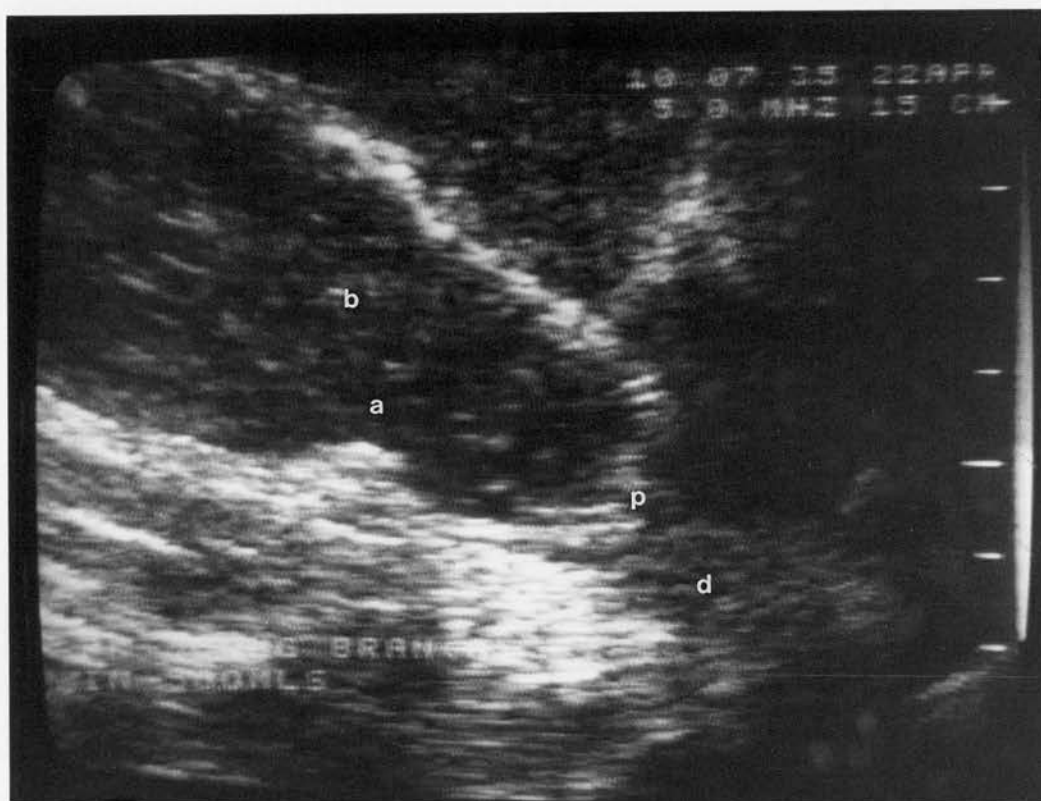
Transverse B-scan using a 5MHz probe. The recorded image is considered suitable for analysis when the gastric antrum (a), pylorus (p) and first part of the duodenum (bulb) (d) are visualised simultaneously, in conjunction with a sufficient concentration of echogenic bran particles (b) suspended in the luminal contents to allow the detection of transpyloric movement.

with a degree of observer variability. For these reasons it was decided at an early stage in the ultrasonic studies that certain easily recognisable intra-abdominal events should be specifically looked for, and that the timing and duration of their occurence in relation to each other should be measured.

Much of the controversy surrounding the theories concerning the mechanisms responsible for gastric emptying is related to the role of the contractile activity of the gastroduodenal segment. This contractile activity has 3 measurable components and, as previously discussed (page 26), these are the force of contraction, their amplitude and the timing of their occurence. With ultrasonic imaging it might be possible to measure both the amplitude and the timing of contractions. However, the amplitude of antral contractions is known to change as they migrate distally, and also because their shape depends largely on the plane of imaging when they are visualised two-dimensionally. It was therefore decided to limit the observations on contractile activity to the timing and duration of occurence of terminal antral contractions (TACs). The contraction of the terminal antrum is the final event in the migration of the antral contractile wave as it travels distally along the gastric walls. For the purposes of this study, the terminal antral contractions were timed from the point where contraction of the opposing walls obliterated the lumen, until they subsequently relaxed and the lumen once more became patent. It was decided to record the timing and duration of contractions of the proximal duodenum (DCs) in a similar fashion.

The detailed observations on intraluminal fluid movement were

confined to the pyloric channel. It was realised that particle movement in and out of the imaging plane might lead to a false impression of movement, particularly in the relatively voluminous gastric antrum and duodenal bulb. However, because the pyloric channel is comparitively narrow and transpyloric fluid movement tends to be linear in a gastroduodenal direction (also designated as forward flow) (FF) or a duodenogastric direction (also designated as retrograde flow) (RF), it was felt that by maintaining the imaging plane through this region any observed particle movement would be a true representation of the events. Therefore the timing and duration of episodes of particle movement across the pylorus and the direction of that movement were noted.

In an effort to minimise errors due to observer variability the section of the recorded observations undergoing detailed analysis was reviewed on several occasions, so that each event (i.e. TAC, DC, FF, RF) was studied by two independent observers on at least on six occasions.

The transfer of the timing and duration of the intra-abdominal events visualised on the ultrasound screen on to "hard copy" was accomplished by using a simple push button event marking system and a continuous 4-channel chart recorder (Figure 13, page 84). One observer, who held a seperate push-button in each hand, watched the video recording for the occurence of terminal antral and proximal duodenal contractions and pressed the appropriate button whenever these events occured. The other observer also held two push-buttons and used them to denote the occurence and direction of particle movement through the pylorus. After the third review of each

FIGURE 13 - Analysis of the ultrasound recordings using the push-button event marking system

Analysis of the ultrasound recordings in performed by 2 independant observers who use a push-button event marking system to transfer the observed events (ie Terminal Antral and Proximal Duodenal Contractions and Gastroduodenal and Duodenogastric Particle Movement across the pylorus) onto a 4-channel chart recorder.

FIGURE 14 - Analysed chart record
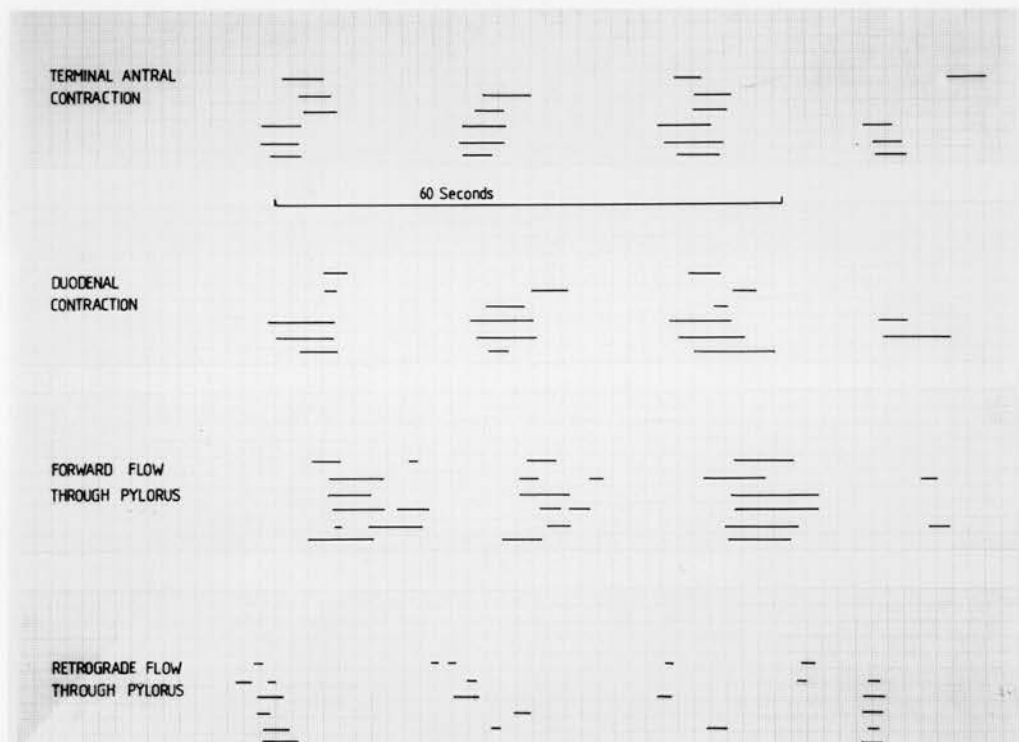
Four channel chart recording of repeated analysis of the timed
events from a single subject. Individual observations, represented
by a single line, on each event are subsequently compared and
averaged to provide a ´best estimate´ of the timing and duration of
terminal antral and proximal duodenal contractions and particle
movement through the pylorus.

section undergoing analysis, the observers swapped over.

An example of repeated analysis of a section from a video record with the event marking system is illustrated in Figure 14 (page 85). An event was judged to have occured if two or more closely grouped observations by seperate observers were marked on the chart paper but, in order to provide a "best estimate" of the timing and duration of each event judged to have occured, an average was made of the individual observations on that event.

Some observer variation can be seen in Figure 14, particularly in regard to duodenogastric flow (RF). An indication of this variation can be seen from the number of individual observations on the chart which cannot be included in any group of observations. Detailed information concerning the degree of observer variability associated with this method of analysing the ultrasonic recordings is documented later in Section 5.1.2 (page 102) as part of the results of a study performed in a group of normal subjects who ingested a single test meal.

Figures 15-18 (pages 87-90), which are taken from a section of the same video recording from one subject, illustrate the result of the analysis of the ultrasound observations and the subsequent transfer of the timing and duration of the events on to a completed chart plot. An ultrasound scan is shown in the top half of each figure, and below, plotted on a time-scale calibrated in seconds, are the timing and duration of the terminal antral (TAC) and proximal duodenal (DC) contractions and episodes of gastroduodenal (FF) and duodenogastric (RF) flow through the pylorus. Three consecutive gastric cycles have been plotted, with the ultrasound pictures

FIGURE 15 - Ultrasonic image of the gastroduodenal region: events are in mid-cycle

T.A.C.
D.C.
F.F.
R.F.
secs.
0   30   60
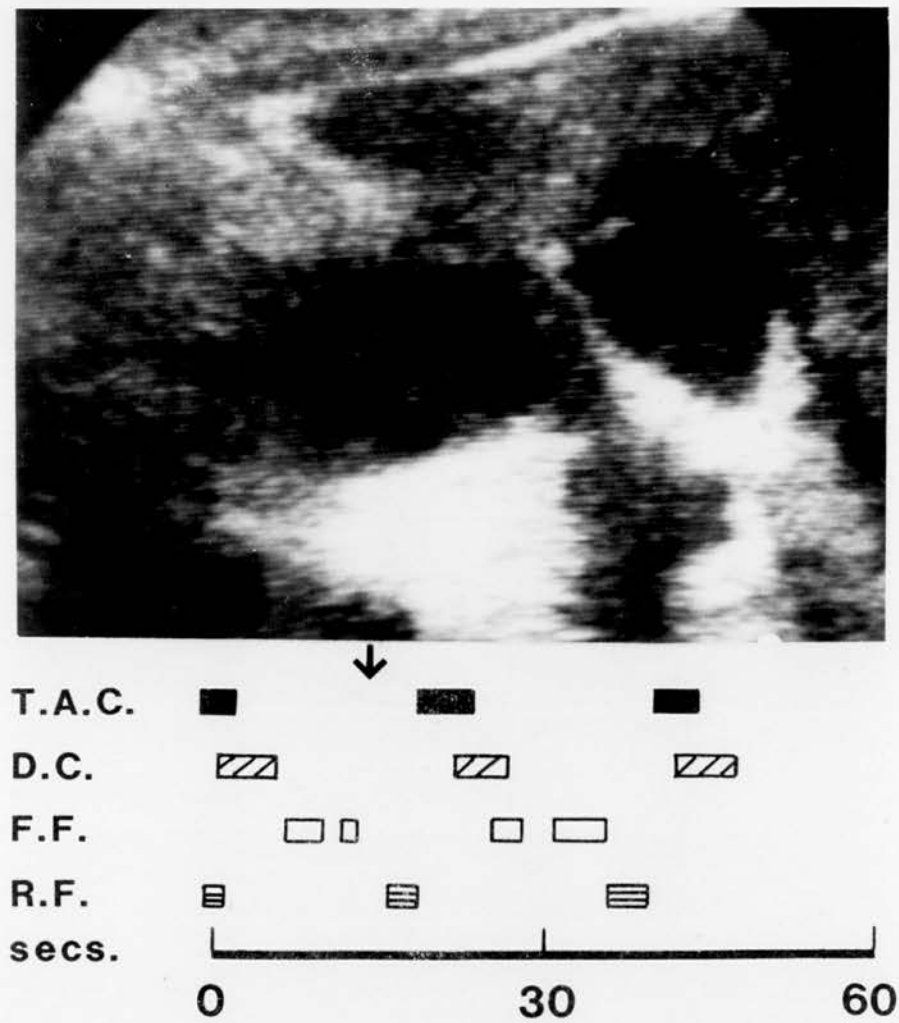
Figures 15-18 are a consecutive series of images from a single analysed section of an ultrasound recording and illustrate the transfer of the timing and duration of the observed intra-abdominal events onto a chart plot illustrated in the lower half of each figure. The black arrow at the top of each chart plot indicates the point in the recording when the picture was taken.
TAC - Terminal antral contraction; DC - Proximal duodenal contraction; FF - Gastroduodenal movement; RF - Duodenogastric movement.

In figure 15 the events are in mid-cycle.

FIGURE 16 - Ultrasonic image of the gastroduodenal region: distal migration of antral contraction
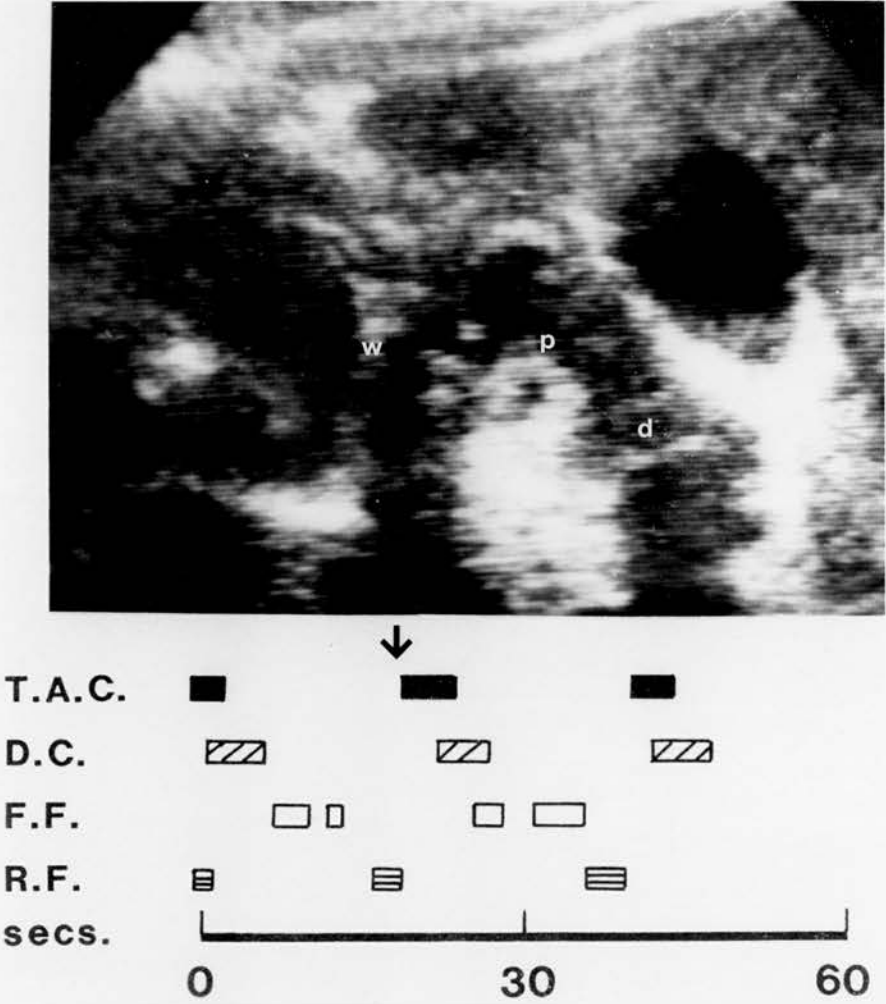
Five seconds later in the recording, an antral wave (w) is migrating distally and is about to end in a terminal antral contraction. The pylorus (p) and proximal duodenum (d) are still patent.

FIGURE 17 - Ultrasonic image of the gastroduodenal region: terminal antral and pyloric contraction
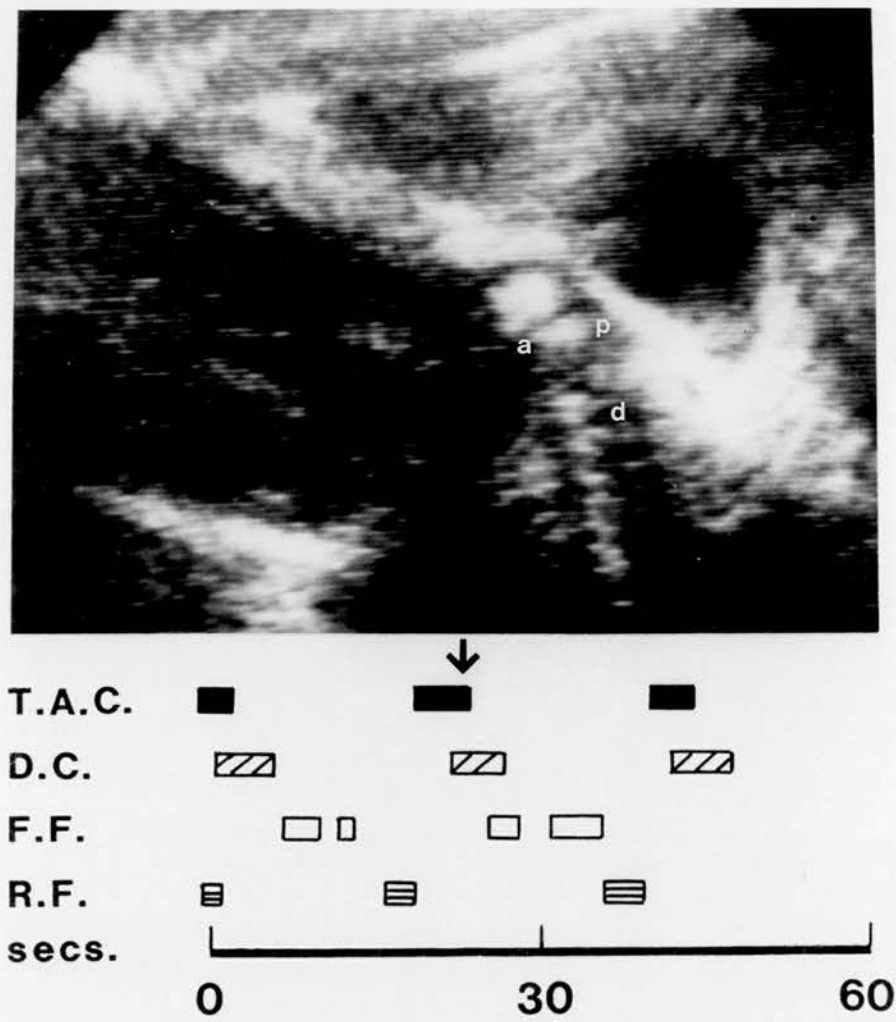
After a further 5 seconds the terminal antrum (a) and proximal duodenum (d) have contracted and the pylorus (p) is closed.

FIGURE 18 - Ultrasonic image of the gastroduodenal region: relaxation has occurred and the lumena are widely patent
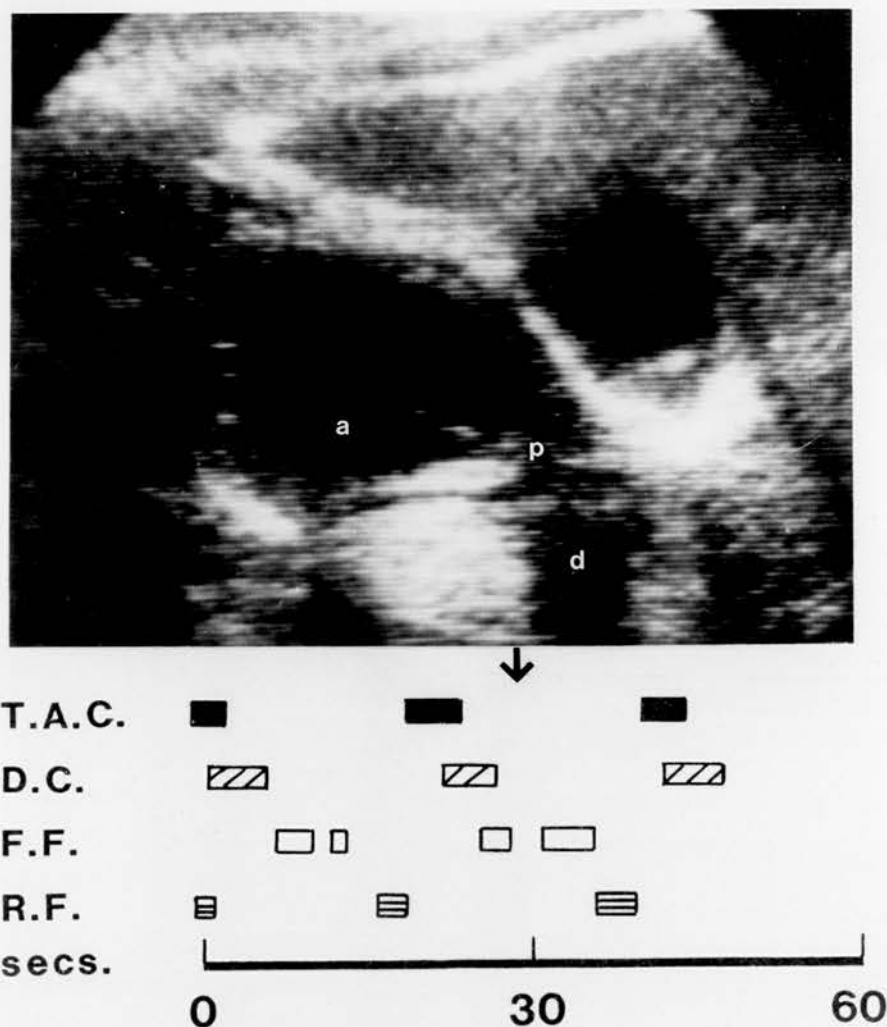
Ten seconds after the events in Figure 17, the terminal antrum (a), pylorus (p) and proximal duodenum (d) have relaxed, and the picture shows their lumena to be widely patent.

91

corresponding to the events of the middle cycle. The black arrow at the top of the plot shows the time in the cycle at which the picture was taken. In Figure 15 the events are in mid-cycle. There is no antral wave visible in the distal stomach (letter (a) on figure) and the pyloric (p) and proximal duodenal (d) lumena are widely patent. Ten seconds later (Figure 16), an antral wave (w) has migrated distally and is just about to end in the terminal antral contraction. The pylorus (p) and proximal duodenum (d) are still wide open. Although not apparent from these still pictures, the accompanying plot shows that a short episode of duodenogastric (RF) flow through the pylorus occured as this antral wave approached the pylorus. A further five seconds later (Figure 17), the terminal antral contraction (a), pyloric closure (p) and proximal duodenal (d) contraction have occurred and the ultrasound scan shows their lumena to be obliterated. In the final figure of this series (Figure 18), the terminal antrum (a), pylorus (p) and proximal duodenum (d) have relaxed and their lumena are once again widely patent. Just after this, a short episode of gastroduodenal flow (FF) can be seen to have occurred. The cycle of events was then repeated.

Each time a subject was scanned by the ultrasonic technique and satisfactory visualisation of the events at the gastroduodenal junction was achieved, a similar chart plot was constructed from the analysed section of the video recording. The chart plots not only allowed calculation of the temporal relationships between the contractile activity of the terminal antrum and proximal duodenum and transpyloric fluid movement in individual studies, but also the comparison of results from several studies.

4.7.0 Statistical Tests

The result of the section of each ultrasonic recording which was analysed was the chart plot showing the pattern of the observed events. From this the total number of times each event (ie TAC, DC, FF, RF) occurred and the duration of each occurrence could be calculated. For each of the four events a mean value for their duration was then calculated. In addition, the interval between the mid-points of successive terminal antral contractions (TAC) was deemed the gastric cycle time and a mean cycle interval (time) was calculated for each subject.

Statistical comparisons between paired data were made using the Student's t test, but, in addition, analysis of variance was employed when multiple groups of results were being compared. Throughout this thesis differences were considered not significant if $p > 0.05$ (one tail). Most of the numerical analysis was carried out on an Apple II computor using programmes specially written to process the data obtained from the chart plots.

5.0.0 <u>Results Section</u>

5.1.0 <u>Normal Subjects with a Single Test Meal</u>

During the early attempts to use the ultrasonic imaging technique to examine the relationships between gastro-duodenal contractile activity and intraluminal fluid movement, scans were performed in a relatively large number of different individuals who all ingested an identical test meal. Satisfactory visualisation of the intra-abdominal events was not obtained in all of the subjects examined in this study, but as the author became more experienced with the technique the success rate in subsequent scans improved.

The method of analysing the sections from the satisfactory ultrasonic recordings using the event marking system was examined in detail in this study, and an indication of the degree of observer variability is documented as validation of the method.

5.1.1 Subjects and test meal

Scans were performed on 17 normal volunteers and details of their age, sex and weight are shown in Table 2 (page 95) along with an indication of those in whom the intra-abdominal events were successfully visualised and subsequently analysed. Nine of the volunteers were male and eight female, all within an age range of 21-62yrs; the males were significantly heavier than the females (t=4.6; p<0.001), but no-one of either sex could have been described as obese.

The test meal used in this study consisted of 400mls of water flavoured with 100mls of diluting orange (Kia-Ora) warmed to 37´C to which was added the 0.5g of bran particles. The pH of the test

95

Table 2 - Age, sex, and weight of 17 subjects

No.	Subject	Age	Sex	Weight(kg)	Recording Analysed*
1	PK	29	Male	70	Yes
2	JD	30	Male	70	Yes
3	AP	31	Female	60	No
4	GS	26	Male	76.5	Yes
5	IG	32	Male	73	No
6	JB	32	Female	62.7	No
7	EW	27	Female	56	Yes
8	JK	32	Female	60.25	No
9	JL	62	Male	60	Yes
10	LS	21	Female	60.5	No
11	IA	36	Male	64.5	Yes
12	JLs	26	Female	50.5	No
13	BG	25	Female	57	Yes
14	DE	23	Male	64	Yes
15	AB	23	Male	80	Yes
16	MD	23	Female	54.5	No
17	AK	32	Male	69.5	Yes

*Criteria denoting suitability for analysis: 1) clear image of the distal antrum, pyloric channel and duodenal bulb; 2) sufficient density of the bran particles to allow the detection of fluid movement; 3) maintenance of the image for a minimum of 2 minutes.

meal was 2.8 and its osmolality was 285mosm/l (iso-osmolar).   Each
subject ingested the test meal and was then scanned by the 5.0mHz
probe.   The resultant video recordings were then reviewed and the
satisfactory sections selected for analysis.

5.1.2 Results

In 10 of the 17 subjects recordings were obtained in which a clear
image of the distal antrum, pylorus and proximal duodenum combined
with a sufficient density of bran particles in the lumena was
maintained without interuption for a minimum of 2 minutes and up to
a maximum of 4 minutes.   On some occasions it would have been
possible to continue the analysis for up to 10 minutes but in the
context of this study a 4 minute limit seemed sufficient.   Three of
the 10 subjects had satisfactory recordings carried out on 2
separate occasions and another subject had 3 separate recordings
with sections suitable for analysis.   These 15 analysed sections of
ultrasonic observations formed the basis for this study.

A suitable section for analysis was not obtained from 7 of the 17
subjects (see Section 6, page 170).   However the general pattern of
intraluminal fluid movement and terminal antral and proximal
duodenal motor activity, when visualised, was similar to that from
the 15 satisfactory recordings.

The 15 sets of analysed sections of observations lasted a total of
53.5 minutes and contained 116 complete peristaltic cycles: the
number of events observed and their mean duration are shown in Table
3 (page 97).   The mean gastric peristaltic cycle time observed in
each subject is shown in column 4 of table 3 and the range is from

Table 3 - Number and mean duration of events

Direction of fluid movement across the pylorus

Sub-ject	Observ-ation (no)	Cycles (no)	Mean cycle time * (sec)	±SD	DCS§ (no)	DC/TAC ratio£	Gastroduodenal flow >-------------<				Duodenogastric flow >-------------<			
							Epi-sodes (no)	Cycles @ episodes (no)	Mean duration (sec)	±SD	Epi-sodes (no)	Cycles @ episodes (no)	Mean duration (sec)	±SD
1	1	4	29.6	0.6	5	1.0	5	4	5.4	2.9	4	4	3.8	0.9
	2	9	29.4	4.1	10	1.0	11	9	5.6	1.7	9	8	9.6	3.3
2	3	8	26.8	3.7	9	1.0	8	7	2.9	1.1	14	7	2.0	0.6
	4	9	24.0	2.9	9	0.9	13	8	2.7	1.6	10	8	1.8	0.6
	5	6	24.4	6.5	7	1.0	11	6	3.7	1.1	8	4	1.9	0.6
3	6	6	24.5	5.1	7	1.0	9	6	5.2	2.4	5	5	1.8	0.7
	7	7	22.8	0.7	7	0.87	9	6	2.4	1.4	8	5	1.6	0.7
4	8	8	24.6	3.5	8	0.89	9	7	2.8	0.9	8	7	2.3	1.0
	9	9	25.2	3.2	7	0.78	13	7	2.8	1.3	7	6	1.8	0.7
5	10	9	23.2	2.0	7	0.7	13	8	2.9	1.1	8	4	1.5	0.5
6	11	9	18.9	2.8	8	0.8	15	8	2.3	1.2	12	8	2.0	0.8
7	12	12	18.7	1.7	9	0.69	3	3	2.0	0.6	8	8	1.8	0.5
8	13	6	21.3	3.3	4	0.57	4	4	2.5	0.6	5	5	1.6	0.8
9	14	6	19.5	3.7	6	0.86	6	4	2.8	1.9	8	5	1.7	0.5
10	15	8	24.9	3.8	8	0.89	9	7	3.7	1.7	8	7	2.3	1.1

* Cycle time measured from midpoint of each terminal antral contraction (TAC). § Contraction of first part of duodenum. £ Number of duodenal contractions occurring after contractions of the terminal antrum expressed as a ratio.

Table 4 - Comparison of mean gastric cycle times in the subjects studied on more than one occasion

Subject*	Observ- ation£	Mean cycle time	t	p
1	1	29.6	0.115	0.1<p<0.5
	2	29.4		
2	3	26.8	1.72	0.1<p<0.2
	4	24.0		
2	4	24.0	0.16	0.1<p<0.9
	5	24.4		
3	6	24.5	0.87	0.4<p<0.5
	7	22.8		
4	8	24.6	0.37	0.7<p<0.8
	9	25.2		

* Subjects 1-4 (Table 3) had observations carried out on a number of separate occasions. £ The observations are numbered consecutively as in Table 2 and have been compared in pairs using Student's t Test.

18.7 to 29.4 seconds. Statistical analysis of the cycle times from each of the 15 sections showed a significant difference in the mean cycle times between sets of data when compared with the intervals within each set (F=7.38: p<0.01). The standard deviation between the mean cycle times of the 15 sets of observations was considerably greater than within each indivual set (9.25 compared with 3.41). More interestingly, however, there was no significant difference in cycle times between the sets of data from the individuals who had been satisfactorily recorded and analysed on different occasions (Table 4, page 98). Each subject, using this particular test meal, would appear to have cycle times which remain relatively constant but may differ from the next individual.
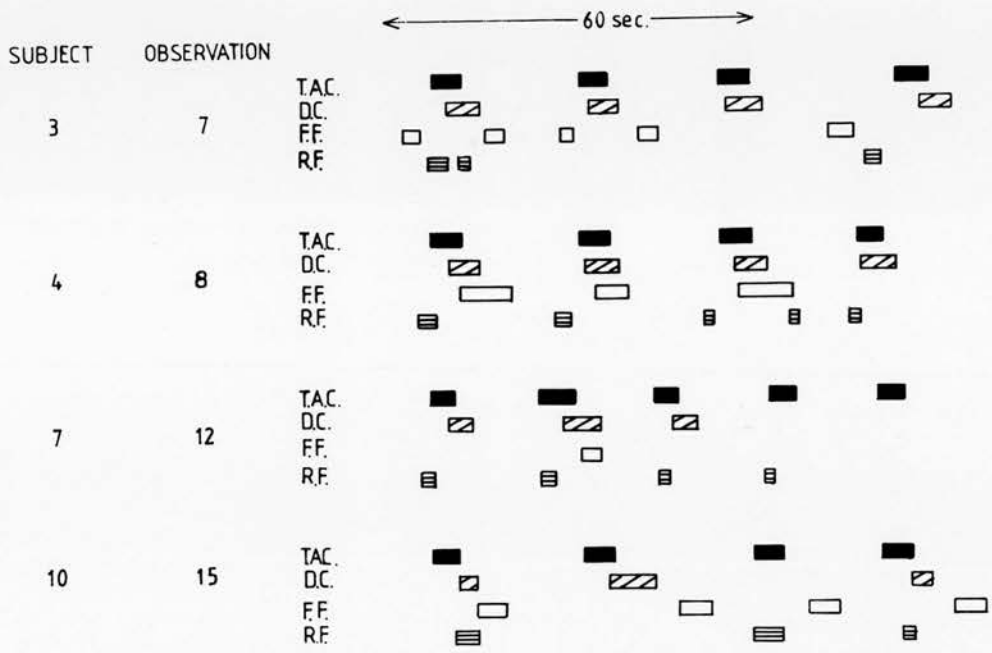
The duration of the terminal antral contraction was about 4 seconds (Mean 3.93 seconds, SD ± 0.8) with little individual variation. Pyloric closure invariably occurred as the gastric peristaltic wave reached the pylorus at the midpoint of the terminal antral contraction. Contractions of the first part of the duodenum were associated with 86% of the terminal antral contractions. Ninety-two per cent of these duodenal contractions occurred immediately after the terminal antral contraction, 5.5% simultaneously and only 2.5% (3) were ectopic. There was some variation in the duration of the contraction of the first part of the duodenum which lasted about 5 seconds (Mean 4.93 seconds, SD ± 1.75).

Transpyloric fluid movement, as reflected by the movement of the bran particles, occurred as brief episodes during the time when the pylorus was open. Gastroduodenal flow was seen to occur in 81% of the 116 complete cycles, and lasted about 2-4 seconds (overall mean

3.0 seconds, SD ± 1.2). Seventy-five per cent of these episodes occurred after relaxation of the terminal antrum, pylorus and duodenum, with the remaining 25% occurring just before the terminal antral contraction. Duodenogastric flow, in episodes lasting up to about 5 seconds (overall mean 2.5 seconds, SD ± 2), occurred in 78% of observed gastric cycles. Sixty-one per cent of these episodes occurred just before the terminal antral contraction with 39% following it. Although the impression given by a large number of observations is that many of the episodes of duodenogastric flow occurred just after a distinct episode of gastroduodenal flow, there was no consistent or measurable pattern between or within individuals.

In Figure 19 (page 101) the pattern of the timing and duration of the intra-abdominal events from part of the analysed section of 4 separate subjects has been plotted and illustrates the general pattern seen in all 15 recordings. The mean cycle times for subjects 3, 4 and 10 are all similar, but that of subject 7 is somewhat shorter. Duodenal contractions can be seen to occur just after the midpoint of the majority of terminal antral contractions. Episodes of gastroduodenal flow occur mainly as the terminal antrum and proximal duodenum relax, although in subject 3 two episodes occur just before the start of the terminal antral contraction. Only one episode of gastroduodenal flow was observed in this sequence of cycles from subject 7 despite an opening and closing pylorus and steadily advancing antral contractions. Although the duration of gastroduodenal flow in subject 3 is shorter than subject 4, it could be seen from the video recording that the rate of

101

FIGURE 19 - Combined chart plots from four subjects

The pattern of the timing and duration of terminal antral
contractions (TAC), proximal duodenal contractions (DC), and
episodes of gastroduodenal flow (FF) and duodenogastric flow (RF)
through the pylorus from 4 separate subjects are plotted to
illustrate the events and to allow comparisons to be made.

particle movement in the former was considerably greater than the latter. Duodenogastric flow can be seen to have occurred in most cycles.

It is clear that the direction of particles movement and its duration do not refect the flow rate through the pylorus, and thus the volume of fluid passing through the pylorus cannot be inferred from the duration of the period of flow. However, an impression could be gained from the number of particles which were seen to pass through the pylorus and the rate at which they moved. There appeared to be much variation in the rate of both gastroduodenal and duodenogastric movement of particles.

The detailed results of the use of the event marking system to construct a chart plot of the timing and duration of the intra-abdominal events are shown in Table 5 (page 103). As previously stated in Section 4.6 (page 83), each analysed section of the ultrasound recordings was reviewed a total of 6 times during which the two independent observers marked on the chart when the events occurred. An actual event was judged to have occurred if two or more closely grouped marks by different observers appeared on the chart. Any marks that did not represent an event were judged unused and considered to result from observer variability.

The observer variability for each of the 4 events (i.e. TAC, DC, FF, RF) was calculated by dividing the unused marks by the total number of marks on the chart plots from the 15 analysed sections. The observer variability was greatest in relation to the episodes of duodenogastric flow (23%), but the overall variability of the technique was considered acceptable at 15%.

Table 5 - Observer variability in the event marking system

Sub-ject	Obser-vation	>---TAC----<		>----DC----<		>----FF----<		>----RF----<	
		Unused	Total	Unused	Total	Unused	Total	Unused	Total
1	1	1	24	1	20	4	24	9	28
	2	18	79	4	65	23	101	20	96
2	3	6	48	1	43	15	50	12	78
	4	2	55	1	48	4	59	9	49
	5	0	40	1	38	13	70	11	42
3	6	5	39	5	41	13	52	33	49
	7	1	41	0	30	11	58	5	33
4	8	4	58	4	38	12	59	13	61
	9	0	52	0	30	4	54	8	33
5	10	0	49	0	30	7	61	14	39
6	11	1	59	6	43	11	76	12	72
7	12	2	49	8	41	5	12	6	34
8	13	1	21	0	10	8	18	8	20
9	14	9	57	16	48	3	46	4	58
10	15	2	39	2	23	7	39	5	29
		7.3% TAC		8.9% DC		17.9% FF		23.4% RF	

Overall Observer Variability = 14.9%

Observer variability was assessed as the percentage of individual marks on the chart plot constructed for each event (ie TAC, DC, FF and RF) which were considered to lie outside the groups of marks representing events that were judged to have occurred.

5.1.3 Discussion

The most unexpected observation made in this first study using the ultrasonic technique was the timing of occurrence and the episodic pattern of the movement of gastric luminal contents through the pylorus. The findings indicate that emptying of liquids from the stomach occurred in discrete episodes of 2-5 seconds only, and that the majority of these occurred as the terminal antrum, pylorus and proximal duodenum relax at the end/start of each gastric peristaltic cycle. The brief episodes of gastroduodenal flow often terminated abruptly, and sometimes were immediately followed by a period of duodenogastric flow. This pattern appears to be in conflict with the traditional view that gastric emptying of liquids occurs either as gushes in response to the pumping action of the antral peristaltic contractions (Cooke, 1975; Davenport, 1977; Jacobs et al, 1982; Brener et al, 1983), or as a steady flow induced by a pressure gradient maintained and regulated by the tone of the proximal stomach (Strunz & Grossman, 1978; Rees et al, 1979; Malagelada, 1979; Kelly, 1980) and interrupted only by the intermittent closure of the pylorus (Kelly, 1980). Clearly the intermittent pattern of transpyloric flow observed in this study can bear no direct relationship to a steadily advancing antral peristaltic contraction, nor can it be attributed to constant intragastric pressure.

Because fluid movement can only occur as a response to a pressure gradient across the pylorus (Rock et al, 1981; Weems, 1982), it would seem that rapid fluctuations in this pressure gradient must occur. Whether there are rapid changes in the contractile tone of

the proximal stomach, or rapid fluctuations in intraduodenal pressure remains to be determined. These findings, however, clearly invite further consideration of the concept that the discharge of fluid from the stomach is regulated as much by a process of duodenal receiving as by gastric emptying.

In 78% of all gastric cycles, episodes of duodenogastric (retrograde) flow through the pylorus were observed. Sixty-one per cent of these occurred while the antral contraction was approaching the pylorus and still remained non-occlusive, but then these episodes ended abruptly as the pyloric channel was obliterated by the terminal antral contraction. The remaining 39% occurred after relaxation of the terminal antrum and pylorus when their lumena were once again patent. Most episodes of duodenogastric flow though the pylorus were not associated with demonstrable contraction of the proximal (i.e. first part) duodenum, and the impression given by the video image was that duodenal contents from the second part passed through the relaxed first part of the duodenum and pylorus into the stomach. Occasional contractions of the second part of the duodenum were observed to occur in mid-cycle when the pylorus was still patent, and these were associated with retrograde flow into the stomach. None of the observed episodes of duodenogastric flow, however, was associated with recognisable true retroperistaltic waves originating in the second part of the duodenum, which have been described in humans in the presence of peptic ulceration (Johnson, 1979). In addition, on several occasions when the second part of the duodenum was well visualised, contractions of this part were seen to occur when the pylorus was closed and retrograde flow into the stomach did not then occur. While these findings are

consistent with other evidence which suggests that duodenogastric reflux occurs in healthy individuals (Keane et al, 1981; Sonnenberg et al, 1982; Thompson, 1982; Muller-Lissner et al, 1983), it should be noted that many of the observed episodes of duodenogastric flow followed immediately after an episode of flow from the stomach to the duodenum.   It is therefore possible that the refluxed fluid had not become mixed with intraduodenal bile or pancreatic secretions and thus it did not necessarily represent duodenogastric reflux in the usual sense of the term, which implies that duodenal fluid containing bile has entered the stomach.   Nevertheless, these observations have clearly demonstrated that a period of duodenogastric (retrograde) flow at the pylorus occurs during most gastric peristaltic cycles in normal man.

Mean gastric peristaltic cycle times ranged in this study from 18.8 to 29.6 seconds, and were entirely consistent with the reported frequency of gastric slow wave activity at 2.1 to 3.7 cycles per minute (Davenport, 1977).   In addition, the consistently similar mean cycle times of subjects in this study confirms the statement that the cycle times of individuals remain consistent to within 10% (Davenport, 1977).

Ninety-seven per cent of observed contractions of the proximal duodenum (1st part) occurred immediately after or simultaneously with the terminal antral contraction. Although the frequency of the duodenal pacemaker is around 11 cycles per minute, it is recognised that the motility of the 1st part differs from the rest of the duodenum (Freidman et al, 1965) and that the terminal antrum, pylorus and proximal duodenum function as the gastroduodenal unit

(White et al, 1983). Migration of the antral slow wave activity across the pylorus is thought to modify the response of the muscle of the proximal duodenum to the firing of the duodenal pacemaker (Bortoff & Davis, 1968) and produces a progressive wave of contraction in the gastric antrum, pylorus and proximal duodenum.

The single test meal used in this study was iso-osmolar with a pH of 2.8 and a volume of 500mls. Thus, although it was not possible to be certain about any influence the physical characteristics of the test meal might have on gastroduodenal motor activity and emptying, this study established a definable base for future comparisons.

5.1.4 Summary

Events at the gastroduodenal junction were successfully visualised in 10 out of 17 normal subjects who each ingested a test meal of dilute orange juice containing bran particles as a sonic marker. A total of 116 complete gastric cycles were observed and, in 86% of these, associated proximal duodenal contractions were seen. Transpyloric fluid movement, as reflected by the movement of the bran particles, occurred as brief episodes during the time the pylorus was open. Gastroduodenal flow, in episodes lasting 2-4 seconds, was seen to occur in 81% of the 116 complete cycles, and 75% of these episodes occurred just after the relaxation of the terminal antrum, pylorus and proximal duodenum. The remainder occurred shortly before the terminal antral contraction. Duodenogastric flow, in episodes of up to 5 seconds, occurred in 78% of observed cycles, with the majority occurring immediately before contraction of the terminal antrum.

These findings indicate that transpyloric fluid movement occurs in brief episodes lasting a few seconds only, and that duodenogastric (retrograde) flow across the pylorus occurs in normal individuals.

5.2.0   <u>Antroduodenal Motor Co-ordination in Normal Subjects</u>

The pattern of contractile events at the human gastroduodenal junction remains controversial. The many different techniques that have been used to study this region have been discussed in Section 2.2.2 (pages 26-37) and are, to an extent, a reflection of the difficulties that have been encountered during attempts to establish the pattern. In particular, there is some dispute about whether the human pylorus has an ability to contract independently of the terminal antrum and proximal duodenum (Atkinson et al, 1957; Edwards, 1961; Kaye et al, 1976; McShane et al, 1980; White et al, 1981).

In this study the contractions of the terminal antrum, pylorus and proximal duodenum have been specifically examined in a number of normal subjects, in an attempt to identify the pattern.

5.2.1   Subjects and test meal

Studies were carried out on 22 normal subjects of whom 10 were male and 12 female, ranging in age from 21 to 62 years.   The test meal was composed of 400mls of water to which was added 100mls of diluting orange (Kia-Ora).   It was warmed to 37´C and had a pH of 2.8 and an osmolarity of 285mosm/l.

After ingestion of the test meal, the contractile events at the gastroduodenal region were observed using the ultrasonic scanning technique. The video recording was later independently reviewed by two observers who noted the timing and duration of terminal antral contractions (TAC), pyloric closure (PC) and proximal duodenal

contractions (DC) during a section of the events where a period of motor activity could be continiously visualised. The terminal antral contractions (contractions of the immediate prepyloric area) and proximal duodenal contractions were both timed using the event marking system from the point where the opposing walls of the respective part began to occlude the lumen until they subsequently relaxed and the lumen became patent again. Pyloric closure, which occurred at the midpoint of the duration of contractions of the terminal antrum, is encompassed in the measurements of the timing and duration of the terminal antral contractions.

5.2.2 Results

Ten of the 22 subjects had recordings performed on 2 separate occasions, and 32 sets of observations therefore form the basis for this study. The sections selected for analysis began on average 5.7 ± 3.9 minutes (Mean ± SD) after ingestion of the test meal and each lasted about 4 minutes. In total, 110 minutes of observations were analysed and these contained 259 cyclic periods of motor activity.

In Figure 20 (page 111) part of the analysed sequence of motor activity from 5 seperate subjects is plotted on a time base calibrated in seconds, and illustrates the general pattern of events seen in all 32 recordings.

FIGURE 20 - Pattern of contractile events from five subjects
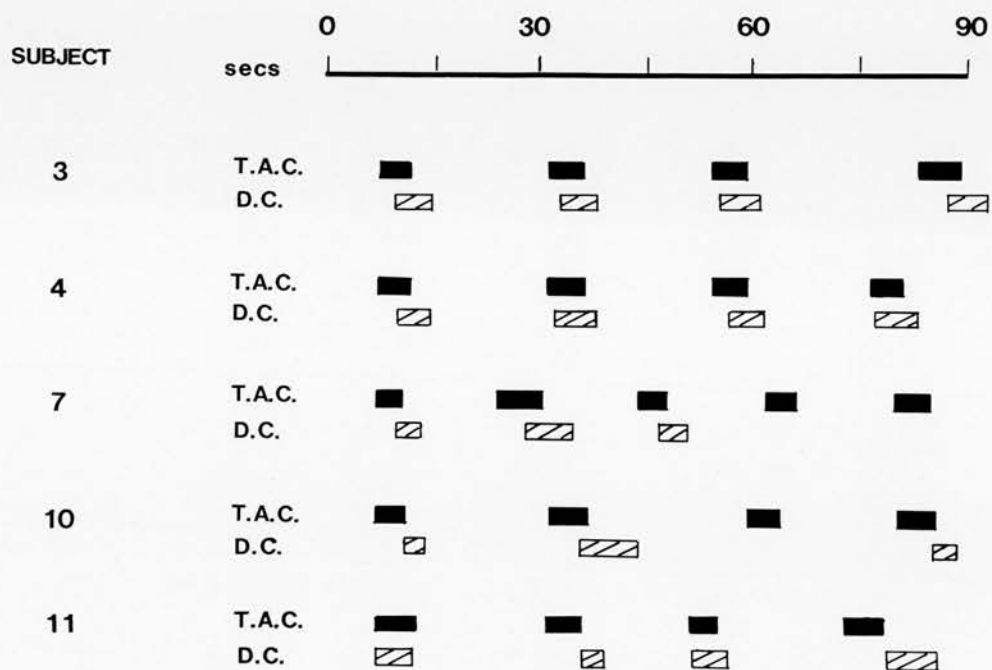
The pattern of contractile events from 5 separate subjects are plotted for comparison. Terminal antral contractions (TAC) occur around every 20 seconds. Contractions of the proximal duodenum (DC), when they occur, can be seen to do so in sequence with those of the terminal antrum.

Table 6 - Number and mean duration (secs) of events in 22 subjects

Sub-ject	Obser-vation	No of cycles	Mean cycle time ± SD		Mean duration TAC ± SD		DC/TAC ratio	Mean interval PC to start of DC ± SD		Mean duration DC ± SD	
1	1	9	24.0	2.9	3.9	0.6	0.9	+0.7	1.2	5.5	2.3
	2	10	22.2	2.2	3.8	0.6	0.8	−0.5	1.2	4.7	1.8
2	3	8	24.9	3.8	4.9	1.9	0.89	+1.0	2.2	3.5	1.7
	4	8	21.2	5.7	3.4	0.6	0.56	+0.3	1.3	4.3	0.9
3	5	6	27.6	2.6	3.8	0.9	0.29	+3.3	0.3	3.9	1.4
4	6	9	29.4	4.1	3.8	0.7	0.9	+5.4	3.5	8.9	3.1
	7	4	29.6	0.6	3.2	0.6	1.0	+2.2	2.9	8.4	4.2
5	8	11	18.9	2.5	3.6	0.4	0.67	+0.6	0.6	3.4	1.1
6	9	11	20.1	1.9	3.0	0.6	0.58	+1.9	1.9	4.0	1.3
	10	8	24.4	2.2	3.6	0.5	0.67	+3.1	2.1	2.9	0.8
7	11	8	18.8	1.1	2.4	0.4	0.33	+0.8	0.8	3.4	2.0
	12	7	21.5	5.7	4.0	1.8	0.75	−0.6	3.2	3.6	1.2
8	13	10	22.1	3.2	4.8	1.1	0.73	+0.8	1.2	6.9	4.9
	14	10	20.2	0.9	3.3	0.9	0.55	−2.2	2.1	8.2	7.7
9	15	6	18.1	2.8	2.4	0.7	0.14	−1.1	−	4.2	−
	16	8	19.4	1.9	3.7	0.4	0.78	+1.7	2.6	5.3	1.3
10	17	6	25.7	4.2	3.5	0.8	0.29	0.0	−	5.5	2.8
11	18	4	20.4	1.9	3.8	1.2	0.8	−0.3	2.0	4.5	1.5
12	19	9	25.2	3.2	4.1	1.2	0.7	+0.6	1.4	4.6	1.3
	20	8	24.6	3.5	4.5	0.8	0.89	+0.2	1.1	4.7	1.2
13	21	8	18.1	1.8	3.8	1.1	0.56	−1.9	2.5	6.4	3.7
14	22	7	21.5	2.9	2.7	0.5	0.75	−0.2	1.0	4.0	1.1
15	23	12	18.7	1.7	4.3	0.7	0.69	+1.5	0.9	3.7	0.8
	24	10	21.9	3.0	3.4	0.7	0.7	−0.5	2.4	4.6	2.4
16	25	12	17.9	1.8	3.1	0.3	0.6	+1.1	3.5	4.1	1.4
17	26	10	20.0	2.9	3.5	1.2	0.3	+4.2	1.9	1.9	0.6
18	27	8	20.0	1.9	3.4	0.5	0.56	+1.8	0.9	2.7	1.1
19	28	6	24.5	5.2	2.7	0.4	1.0	+1.0	1.4	4.3	1.8
	29	7	22.8	0.7	4.5	0.9	0.87	−0.6	0.6	5.9	1.5
20	30	6	21.3	3.3	3.6	1.1	0.6	+0.6	1.0	3.5	1.3
21	31	7	23.3	1.1	3.4	0.8	0.62	−1.1	1.6	5.8	1.6
22	32	6	19.4	3.7	2.6	0.3	0.9	+0.1	0.6	3.1	0.9

DC/TAC ratio - number of DCs divided by the number of TACs in an analysed section.

PC - Pyloric Closure.

Terminal antral contractions occurred in 98% of the cyclical periods of motor activity, and the duration of the interval between the midpoints of successive TAC´s was deemed the gastroduodenal cycle time. Individual mean cycle times ranged from 17.9 to 29.6 seconds (frequency 2.0 - 3.3 cycles per minute) (Table 6, page 112). The duration of the TAC was found to be relatively constant among individuals at around 4 seconds (mean 3.6 ± 0.6 seconds) and pyloric closure was seen to occur at the midpoint of these contractions. The pylorus then opened as the terminal antrum relaxed and remained patent until the arrival of the next TAC. Sixty-seven per cent of TACs were associated with contraction of the proximal duodenum (duodenal bulb). Their temporal relationships to the point of pyloric closure were then calculated. Ninety-four per cent of all DCc occurred about 1 second (range 1 second before to 2 seconds after) pyloric closure. Only 6% of DC´s were ectopic, in that they occurred outwith this time range and were apparently uncoordinated with the terminal antral contraction. Proximal duodenal contractions lasted about 5 seconds (mean 4.7 seconds $\pm$ 1.7 seconds) and were significantly longer in duration than terminal antral contractions (t=3.5; p<0.0025).

5.2.3 Discussion

The pattern of gastric motor activity seen after ingestion of a liquid test meal may depend not only on what phase of the interdigestive cycle the subject was in at the time of meal ingestion (Rees et al, 1978; Rees et al, 1979 (ref 251)), but also the nature of the meal itself (Cooke, 1975; Rees et al, 1979 (ref 250)). However, the motor response to the 500ml test meal used in

this study was similar in each set of observations and, as it seems unlikely that the subjects were all in the same stage of interdigestive motor activity when the meal was ingested, this demonstrates that the interdigestive cycle had been interupted and that the observations made in this study relate to the "fed" (post-prandial) pattern of motor activity.

Contractions of a viscus vary both in amplitude and strength (Smith & Code, 1958; Freidman et al, 1965). The ultrasonic observations can reflect the amplitude and frequeny of contractions, but not their force. Although it might have been possible to differentiate antral contractions according to their amplitude, this was not done (see Section 4.6, page 82) and what was recorded was the occurrence of the terminal antral contractions as these mark the most distal point of migration for antral waves of varying amplitudes. Similarily, only the timing of pyloric closure and proximal duodenal contractions were recorded.

Contractions of the gastric antrum progress distally towards the pylorus and are under the control of a pacemaker potential (gastric slow wave) which is omnipresent, occurring as a regular rhythm with a reported frequency of around 2 to 3.5 cycles per minute (Duthie et al, 1971; Davenport, 1977). Although contractions may sometimes appear non-rhythmic, they are separated by intervals which are related to this frequency and this is the maximum rate they can attain. In any observed period of antroduodenal motor activity, the percentage of antral contractions (percentage activity) recorded is reported to vary from 0% to 100% of the possible maximum (Stoddard et al, 1973; Davenport, 1977; Rees et al, 1978). In the present

study, terminal antral contractions were observed to occur almost continuously with a mean frequency which ranged from 2.0 to 3.3 cycles per minute. Although the percentage activity of the distal antrum may be influenced by the test meal (Weisbrodt et al, 1969), the finding of 98% activity in this study may simply reflect the sensitivity of the method.

Pyloric closure was observed to occur with each terminal antral contraction and was not seen at any other time. The pylorus opened as the terminal antrum relaxed, and remained open until the next TAC reached it. Furthermore, during the 2% of the observed periods of cyclical motor activity where the terminal antral contractions did not occur, the pyloric channel remained widely patent. These observations are in keeping with other evidence suggesting that the human pylorus is patent for most of the gastric cycle (Gibb, 1942; Atkinson et al, 1957; Kaye et al, 1976; McShane et al, 1980; White et al, 1981), closing only when the terminal antral contraction reaches it. 'In vivo' studies in animals using various non-physiological stimuli (Lerman et al, 1981) have suggested the innervation of the pylorus may differ from that of the terminal antrum and proximal duodenum, and 'in vitro' studies have shown that the circular muscle of the pylorus may also react differently to chemical and hormonal stimuli (Fisher & Cohen, 1973). These differing responses of the pylorus to various stimuli may be associated with a capacity for independent function in the animals studied. However, there are known to be interspecies differences (Weisbrodt et al, 1969) and the results of this study with the ultrasonic technique provide no evidence of independant pyloric function in the postprandial situation in humans.

The contractile activity of the proximal duodenum is thought to be more closely related to that of the gastric antrum and pylorus than to its more distal parts (Weisbrodt et al, 1969; Lederer et al, 1983). Although the frequency of the duodenal pacemaker is around 11 cycles per minute, the gastric slow wave migrates across the pylorus, where it can be recorded a variable distance along the duodenal bulb, and may modify the response of the proximal duodenal muscle to the firing of the duodenal pacemaker (Duthie et al, 1971). In animal studies, the activity of the duodenal cap is usually less than that that of the terminal antrum and pylorus regardless of the meal ingested (Weisbrodt et al, 1969) and in the present study the percentage of TACs that were followed by contraction of the proximal duodenum varied from 14% to 100%. However, 94% of the proximal duodenal contractions that did occur did so about 1 second after pyloric closure, indicating that these contractions are more closely co-ordinated with those of the antrum and pylorus than with the more distal duodenum.

This study has been carried out with a single test meal and it therefore remains possible that different patterns of gastroduodenal motility may occur with other meals. However, in the 259 periods of cyclical motor activity observed in the 22 normal human subjects of this study, independant pyloric closure did not occur once.

5.2.4 Summary

The temporal relationships among contractions of the terminal antrum, pylorus and proximal duodenum were studied in 22 normal subjects who had ingested a single liquid test meal. A total of 259

cyclical periods of motor activity were observed. Individual mean gastroduodenal cycle times ranged from 17.9 to 29.6 seconds (2.0 - 3.3 cycles/min). Terminal antral contractions (TACs) were observed in 98% of cycles, and pyloric closure invariably occurred at the midpoint of these contractions. The pylorus then opened as the terminal antrum relaxed and remained open until the next TAC. Only 67% of TAC's were associated with contractions of the proximal duodenum (DC), but 94% of the DC's occurred about 1 second (range 1 second before to 2 seconds after) after pyloric closure. Only 6% of DCs were ectopic, in that their occurrence was apparently not co-ordinated with the TAC's.

These observations demonstrate that the human terminal antrum, pylorus and proximal duodenum usually contract in a sequential co-ordinated manner, presumably under the control of the gastric slow wave. Independent pyloric contraction did not occur under these physiological conditions.

5.3.0 Normal Subjects with 4 Different Test Meals

This study records the effects of varying the nature of the liquid test meal on the contractile pattern and flow at the gastric outlet. These observations were performed in a group of normal subjects in whom visualisation of the intra-abdominal events could be consistantly achieved with the ultrasonic technique.

5.3.1 Subjects and test meals

Scans were carried out in a group of 10 normal subjects in which the sexes were evenly distributed and the average age was 28 years. Each subject ingested 1 of 4 different test meals on each of 4 seperate occasions, and the subsequent events at the gastric outlet during the emptying of the meals was monitored using the ultrasonic technique.

The 4 test meals each had a volume of 500mls, were all iso-osmolar (285mOsm/l) and warmed to 37´C. They were prepared as follows:

1) Low pH - 100mls of diluting orange (Kia-Ora) added to 400mls of water; pH 2.8

2) Neutral pH - 66.6mls of diluting orange in 433.4mls of water plus 2.5g of sodium bicarbonate; pH 7.0

3) Protein - 2 protein extract cubes (Oxo), weighing 11.5g each, dissolved in 500mls of water plus 0.8g of sodium bicarbonate; pH 7.0

4) Glucose - 25g glucose in 500mls; pH 7.0

Each meal also contained 0.5g of the bran particles as the sonic marker.

5.3.2   Results

Each of the subjects was studied with the 4 test meals.   The
analysed sections were all taken from a similar time in the
immediate postprandial period (mean 4.5 minutes, SD $\pm$ 1.5 minutes)
from the start of ingestion of the test meal and each lasted
between 2.5 and 5 minutes.   In total, between between 76 and 95
gastric cycles in about 35 minutes of observation time were analysed
with each test meal (Table 7, page 120).

Individual mean cycle times for the 4 test meals are shown in Table
8 (page 120).   There was no significant individual variation in the
mean cycle times for the different meals, and the overall means for
the 10 observations with each meal were almost identical (F = 0.4;
NS).

The proportion of terminal antral contractions that were associated
with a contraction of the proximal duodenum varied considerably
between individuals (Table 9, page 121). However, in each of the 4
groups approximately 60% of terminal antral contractions were
associated with a contraction of the proximal duodenum, and there
was no significant difference between the test meals (F = 0.5; NS).

The temporal relationship of contractions of the proximal duodenum
to terminal antral contractions did not vary significantly with the
4 meals studied.   Seventy-two per cent of DCs occurred while the
terminal antrum was contracted, 22% occurred about 3 seconds
(mean 3.1 seconds, SD $\pm$ 0.7 seconds, F = 1.56; NS) after the
midpoint of the TAC when it had begun to relax and the lumen of

Table 7 - Number of complete gastric cycles observed, and related observation time for each of the four test meals

Meal	Number of cycles	Total observation time (minutes)
Low pH	76	34.5
Neutral pH	89	36.0
Protein	85	35.0
Glucose	95	38.0

Table 8 - Mean gastric cycle times (seconds) and mean cycle frequency in four test meals

Sub-ject	Low pH		Neutral pH		Protein		Glucose	
1	24.0	2.9	22.3	2.9	19.6	3.7	22.1	1.7
2	24.9	3.8	26.6	2.3	23.2	2.8	24.5	3.1
3	29.6	0.6	22.5	2.7	19.4	2.2	23.8	6.0
4	18.9	2.5	18.8	2.3	17.6	2.3	18.7	1.9
5	24.4	2.2	17.5	2.0	19.2	1.4	19.9	1.7
6	18.8	1.1	20.2	4.1	20.1	2.6	15.9	3.3
7	20.3	0.9	21.5	2.6	23.2	1.4	20.2	4.8
8	19.4	1.9	20.3	2.4	19.7	1.8	27.4	3.5
9	21.4	4.2	21.9	1.8	23.1	3.0	19.9	2.5
10	20.4	1.9	20.7	2.2	23.6	4.9	20.6	4.1

(Column header: Mean cycle times $\pm$ SD, Test meal)

Frequency range*	2.0 - 3.2	2.3 - 3.4	2.5 - 3.4	2.2 - 3.8

* cycles per minute

Table 9 - Percentage of terminal antral contractions associated with proximal duodenal contractions

% of TACs associated with DCs

Sub-ject	Low pH	Neutral pH	Protein	Glucose
1	90	64	30	67
2	90	57	90	70
3	100	38	40	70
4	67	69	50	90
5	67	60	67	58
6	33	36	38	64
7	55	70	90	50
8	78	56	92	14
9	22	50	30	33
10	80	92	50	67

Table 10 - Mean duration (seconds) of terminal antral (TAC) and proximal duodenal (DC) contractions

Meal	Mean TAC	± SD	Mean DC	± SD
Low pH	3.7	0.7	5.0	2.0
Neutral pH	3.0	0.4	3.8	0.7
Protein	3.0	0.2	3.0	0.6
Glucose	2.8	0.3	3.6	1.0

both it and the pylorus were once again patent. The remaining 6% occurred at other times in the cycle and seemed uncoordinated with contractions of the terminal antrum. The mean duration of contractions of the terminal antrum and proximal duodenum are shown in Table 10 (page 121). The duration of DCs was always longer than that of the corresponding TAC.

As in the earlier studies, movement of fluid through the pylorus occurred in intermittent brief episodes. Episodes of gastroduodenal flow were observed in over 90% of the cycles with all test meals (Table 11, page 123). There were slightly fewer cycles with episodes of gastroduodenal flow when the subjects ingested the low pH meal but this did not reach statistical significance (F= 1.6; NS). With all 4 meals the duration of these intermittent episodes of forward flow was around 2 to 3 seconds, although the duration of the episodes occurring with the acid and neutral pH meals was longer than with the protein and glucose meals (p<0.05) (Table 11, page 123).

The number of discrete episodes of gastroduodenal flow that were observed in any cycle varied from 0 to 4. The mean number of episodes of gastroduodenal flow per cycle with the 4 test meals varied from 1.6 to 2.2, and there was significant variation among the meals (F= 3.34; p<0.05) (Table 11, page 123). Further analysis revealed that the mean number of episodes of gastroduodenal with the acid and neutral pH meals did not differ significantly (t= 0.6; NS) and neither did the number of episodes per cycle with the protein and glucose meals (t= 0.5; NS). However, the number of episodes per cycle seen with both the former meals was fewer than that of both

Table 11 - Pattern of episodes of gastroduodenal flow

Meal	% Cycles with episodes	Mean duration	± SD	Mean no /cycle	± SD	% after TAC
Low pH	92	3.1	1.0	1.6	0.5	70
Neutral pH	96	2.8	0.7	1.7	0.3	66
Protein	97	2.4	0.3	2.0	0.5	74
Glucose	99	2.3	0.4	2.2	0.7	61

Table 12 - Mean interval (seconds) between start of episodes of gastroduodenal flow and midpoint of terminal antral contraction (TAC)

Meal	Episodes before TAC	± SD	Episodes after TAC	± SD
Low pH	5.8	2.4	5.3	1.3
Neutral pH	7.0	1.9	4.9	0.8
Protein	6.3	2.1	5.6	0.8
Glucose	6.4	0.9	6.4	1.7
Mean	6.3	1.8	5.5	1.2

the latter (p<0.05).

These discrete episodes of gastroduodenal flow occurred at different times during the gastric cycle and by comparing their timing to that of the terminal antral contraction it was possible to gain some indication of the pattern (Table 12, page 123). The majority of the episodes of gastroduodenal flow (68%) occurred about 5 seconds (mean 5.5 ± 1.2, F= 2.5; NS) after the midpoint of the terminal antral contraction, i.e. when the gastric outlet relaxes at the end/start of each gastric cycle. The remainder occurred about 6 seconds (mean 6.3 ± 1.8, F= 0.88; NS) before the midpoint of the TAC as the antral wave moves distally towards the pylorus. However, when pairs of meals were compared, the proportion of episodes of gastroduodenal flow occurring after the TAC with the glucose meal (61%) was significantly fewer than with either the low pH of protein meals (70%; p<0.05 and 74%; p<0.01 respectively) (Table 11, page 123).

Duodenogastric movement of fluid through the pylorus occurred less frequently than gastroduodenal movement, and was observed in 56% of gastric cycles. Table 13 (page 125) illustrates the pattern of occurrence of these episodes. There were no significant differences among the 4 meals in any of the characteristics studied. The mean duration of episodes of duodenogastric flow was around 2 seconds and, on average, less than 1 episode was seen per cycle. In contrast to gastroduodenal flow, the majority (59%) of these episodes occurred about 5 seconds (mean 5.5 ± 2.4, F= 0.1; NS) before the terminal antral contraction. The remainder occurred about 6 seconds (mean 5.8 ± 2.8, F= 0.6; NS) after the midpoint of the terminal

Table 13 - Pattern of episodes of duodenogastric flow

Meal	% Cycles with episodes	Mean duration	± SD	Mean no /cycle	± SD	% before TAC
Low pH	64	1.9	0.8	0.8	0.3	60
Neutral pH	54	2.2	0.5	0.7	0.4	66
Protein	57	2.2	0.6	0.7	0.3	56
Glucose	50	2.1	0.5	0.6	0.3	53

Table 14 - Comparison between the duration of pyloric patency and transpyloric fluid movement expressed as a percentage of the cycle duration*.

Meal	Pyloric patency		Gastro-duodenal flow		Duodeno-gastric flow	
	Max %	Min %	Max %	Min %	Max %	Min %
Low pH	83.3	68.4	47.0	8.6	15.7	2.2
Neutral pH	85.7	74.7	37.4	12.4	11.3	2.4
Protein	85.7	73.5	34.5	14.6	13.8	2.8
Glucose	86.4	75.9	43.0	11.7	12.4	2.1

* The durations of pyloric patency, gastroduodenal and duodenogastric flow were calculated from the complete sections analysed in each of the 10 subjects.

antral contraction.

5.3.3 Discussion

Ingestion of the 4 liquid test meals used in this study resulted in regular sequential contractions of the gastric antrum and proximal duodenum with a frequency of 2 to 3 cycles per minute. The terminal antral contractions were non-occlusive (i.e. the opposing gastric walls did not meet) until they reached the terminal antrum where the "systolic" terminal antral contraction obliterated the lumen of the distal 2 - 3cms of the stomach including the pyloric channel. Contractions of the proximal duodenum, which were occlusive, usually occurred while the pyloric channel was occluded, resulting in the gastroduodenal segment contracting in a sequential manner. Subsequent relaxation also occurred in this sequence. The amplitude of the antral contractions and their temporal relationship to both pyloric closure and proximal duodenal contraction appeared similar with each of the test meals. The percentage of terminal antral contractions that were followed by contractions of the proximal duodenum varied considerably among different individuals and there was no discernable pattern of individual change after ingestion of each of the 4 test meals. This individual variation is consistent with the findings of the preceding study (page 112, Table 6; page 116, lines 12-13), although overall, there was no significant alteration in the pattern of gastroduodenal contractions among each of the test meal groups.

As initially observed in the previous study with a single test meal, transpyloric fluid movement occurs as a number of intermittent

brief episodes in each gastric cycle, and this was confirmed in this study with 4 different test meals.

The majority of the episodes of gastroduodenal flow occurred just after relaxation of the terminal antrum, pylorus and proximal duodenum. If the antral wave were pumping fluid through the pylorus, gastroduodenal flow might be expected to occur most frequently in the later part of the cycle. Moreover, duodenogastric movement of fluid was seen to occur on many occasions as the antral wave approached the pylorus and indeed, the movement of the liquid gastric contents was usually unaffected by the steadily advancing antral contractions. These observations agree with those which suggest that the antral peristalsis plays no more than a minor role in effecting the emptying of liquids from the stomach (Crider & Earl Thomas, 1937; Dozios et al, 1971; Kelly, 1980; Meyer, 1980).

In any subject the pyloric channel was patent for about 70% of each gastric cycle, yet transpyloric fluid movement occurred for only 30% of the duration of each cycle (Table 14. page 125). For gastroduodenal fluid movement to occur throughout the whole time the pylorus is open, there would require to be a sustained pressure gradient from stomach to duodenum. Any pressure gradient acting across the pylorus depends on the relative intraluminal pressures in the stomach and duodenum. Several authors have carried out pressure/volume studies which demonstrate that the tone of the fundus of the stomach is the major factor contributing to intragastric pressure (Stadaas & Aune, 1970; Strunz & Grossman, 1978; Kelly, 1980), but less information is available on the regulation of intraluminal pressure in the duodenum. The

observations from this study with ultrasonic imaging suggest that rapid fluctuations must occur in the gastroduodenal pressure gradient, but whether these are due to changes in intragastric pressure, intraduodenal pressure or both cannot be deduced from these observations.

The small but significant changes in the pattern of transpyloric flow which were observed with the different test meals used in this study are probably mediated through the effect of the test meal on the receptors located mainly in the duodenum (discussed previously on page 12) and which participate in the regulation of gastric emptying. Whether these receptors act locally to alter the duodenal resistance to flow, or by some reflex pathway modify the tone of the proximal stomach remains unknown.

This study has demonstrated that in normal human subjects, given 4 different liquid test meals, the basic pattern of gastroduodenal contractile activity is unaltered. Transpyloric fluid movement occurs in intermittent brief episodes lasting a few seconds only with gastroduodenal flow (gastric emptying) occurring principally just after the sequential relaxation of the terminal antrum, pylorus and proximal duodenum at the end/begining of each gastric peristaltic cycle. This basic pattern of flow is subtly altered by the nature of the test meal, and these alterations may represent the operation of mechanisms regulating gastric emptying activated by duodenal receptors responding to physical or chemical properties of the meal.

5.3.4 Summary

The effect of 4 different liquid test meals on gastroduodenal motor activity and related transpyloric fluid movement was studied in 10 normal subjects.

The mean interval between antral contractions (TACs) and the frequency of occurrence of related contractions of the proximal duodenum were similar in all 4 meals (F = 0.3: for both). Gastroduodenal flow though the pylorus was observed in 95% of cycles and occurred as up to 4 episodes per cycle, each lasting 2 to 3 seconds. The duration of these episodes with the pH 2.8 and pH 7.0 meals was longer than with the protein and glucose meals (p<0.05). There were, however, fewer episodes of forward flow in each cycle with the pH 2.8 and pH 7.0 meals than with the other 2 meals (p<0.05). The majority of episodes of gastroduodenal flow (68%) occurred after relaxation of the TAC. Duodenogastric flow was observed in 56% of cycles and occurred, on average, as less than 1 episode lasting about 2 seconds each cycle. The pattern of duodenogastric flow was similar in all meals and the majority of these episodes (59%) occurred shortly before the terminal antral contraction.

Changes in the nature of the test meal appear to cause subtle alterations in the basic pattern of transpyloric fluid movement, presumably reflecting the influence of the test meal on control mechanisms governing gastric emptying.

5.4.0 Normal Subjects with 5% and 10% Glucose Meals

In this study the patterns of antroduodenal contractile activity and transpyloric fluid movement were examined during the emptying of 2 test meals which varied in osmolarity and calorific value.

5.4.1 Subjects and test meals

Studies were carried out on a group of 10 healthy subjects. The sexes were equally distributed and the average age was 29.8 years (range 22 to 36 years). The subjects in this group were·different from those in the previous study with 4 different test meals, and the results have therefore been examined separately in this section.

The 2 test meals each had a volume of 500mls and were warmed to 37´C. They were prepared as follows:

1) 5% Glucose - 25g glucose in 500mls; pH 7.0, 285mOsm/l

2) 10% Glucose - 50g glucose in 500mls; pH 7.0, 485mOsm/l

Each meal also contained 0.5g of the bran particles as the sonic marker.

Subjects ingested each test meal after an overnight fast and the subsequent events occuring at the gastroduodenal junction during their emptying were monitored using the ultrasonic technique and simultaneously recorded on to video tape.

Table 15 - Total number of complete gastric cycles observed and related total observation time for the 5% and 10% Glucose meals

Meal	Number of cycles	Total observation time (minutes)
5% Glucose	98	38.0
10% Glucose	97	37.0

5.4.2 Results

A separate section of the recorded events from each subject was analysed for the 2 test meals. Each analysed section began at a similar point in the postprandial period after ingestion of the test meal (5% Glucose: 1.8 + 2.3 minutes, 10% Glucose: 0.8 + 1.1 minutes; t= 1.09, NS) and lasted around 3.5 minutes (range 3 - 4 minutes). Nearly 100 complete gastroduodenal cycles were observed in a total of around 37 minutes of observations in each group (Table 15, page 131).

Individual mean antroduodenal cycle times are shown in Table 16 (page 133).   The overall mean cycle times for the 2 groups were similar at around 22 seconds, and the range of cycle frequencies were identical.   Pyloric closure invariably occured with each terminal antral contraction, but the percentage of terminal antral contractions that were associated with contractions of the first part of the duodenum varied from 0 to 100% (Table 17, page 133). There was, however, no significant difference in the degree of antroduodenal co-ordination between the 2 groups (t= 2.23; NS).

Transpyloric fluid movement occurred as a number of discrete episodes of both gastroduodenal and duodenogastric flow, and was reflected by the intermittent to and fro movement of bran particles across the open pylorus.

Table 18 (page 134) shows the pattern of gastroduodenal episodes. Gastroduodenal flow was observed in over 90% of the cycles from the analysed sections with both the 5% and 10% glucose meals.   The pattern of these episodes was similar in each group with on average

133

Table 16 - Mean antroduodenal cycle times (seconds) and mean cycle
frequency in the 5% and 10% Glucose meals

	Mean cycle times ± SD	
Sub-	>--------Test meal---------<	
ject	5% Glucose	10% Glucose
1	22.1 1.7	23.7 2.6
2	24.5 3.1	25.2 3.9
3	23.8 6.0	27.2 5.5
4	23.2 2.6	22.2 2.3
5	19.9 1.7	23.3 4.0
6	15.9 3.3	21.9 0.7
7	20.2 4.8	15.8 3.1
8	27.4 3.5	21.8 4.3
9	21.5 5.1	18.9 6.2
10	20.6 4.1	22.9 4.8
Overall Mean	21.9 3.1	22.3 3.2
Frequency range*	2.2 - 3.8	2.2 - 3.8

* cycles per minute

Table 17 - Percentage of terminal antral contractions (TACs)
associated with proximal duodenal contractions (DCs)

	% of TACs associated with DCs	
Sub-	>-------Test meal-------<	
ject	5% Glucose	10% Glucose
1	67	25
2	70	0
3	70	22
4	80	82
5	58	38
6	64	100
7	50	0
8	14	30
9	62	8
10	67	55

Table 18 - Pattern of episodes of gastroduodenal flow

Meal	% Cycles with episodes	Mean duration	± SD	Mean no /cycle	± SD	% after TAC
5% Glucose	97	2.2	0.5	2.3	0.7	55
10% Glucose	91	2.0	0.4	2.4	1.0	56

Table 19 - Pattern of episodes of duodenogastric flow

Meal	% Cycles with episodes	Mean duration	± SD	Mean no /cycle	± SD	% before TAC
5% Glucose	55	2.1	0.5	0.7	0.2	52
10% Glucose	44	2.0	0.5	0.7	0.7	56

around 2.5 discrete episodes each lasting about 2 seconds in each cycle.

The pattern of the episodes of duodenogastric flow (reflux) are shown in Table 19. These episodes were observed much less frequently than those episodes where the flow was in a gastroduodenal direction and occured in only around 50% of the cycles from the analysed sections. On average less than one episode of duodenogastric flow lasting around 2 seconds was seen in each antroduodenal cycle with both test meals.

5.4.3 Discussion

The classic studies by Hunt and his co-workers demonstrated that the calorie efflux from the stomach is regulated by a negative feedback mechanism operating through duodenal receptors (Elias et al, 1968; Hunt & Knox, 1968; Barker et al, 1974). This feedback loop acts in some as yet unknown manner to maintain a constant calorie delivery to the absorptive process of the small intestine (Hunt, 1956; Hunt, 1961; Barker et al, 1978). This regulation is reflected in the emptying characteristics of liquid nutrient meals which empty in a linear fashion independent of ingested volume (Hunt & Stubbs, 1975; Brener et al, 1983). The emptying of non-nutrient meals, in contrast, is exponential and the rate is influenced by the ingested volume (Marbaix, 1898; McHugh & Moran, 1979; Brener et al, 1983). The emptying curves of similar volumes (150mls) of nutrient and non-nutrient liquid test meals are illustrated in Figure 22 (page 136) which has been adapted from the data of Brener and co-workers (1979).

FIGURE 21 - Gastric emptying of 400ml test meals of N/Saline (290 mosmol/l), 5% Glucose (290 mosmol/l) and 12.5% Glucose (690 mosmol/l)*
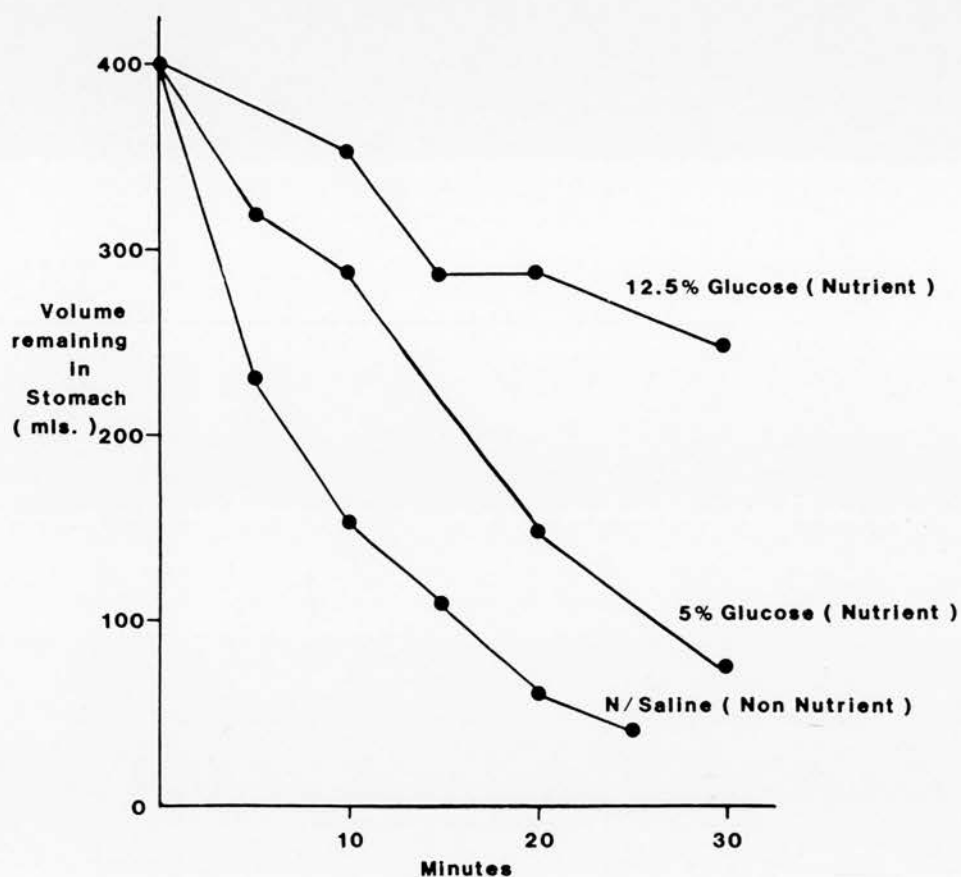
Gastric emptying was assessed using serial test meal method.

The non-nutrient N/Saline can be seen to have emptied rapidly and exponentially, while the emptying of the nutrient meals (5% & 12.5% Glucose) have emptied more slowly in a linear fashion.

* Data adapted from Brener et al, 1983

Several studies have shown that a solution of 10% glucose empties from the stomach at a detectably slower rate than 5% glucose (Barker et al, 1974; Meeroff et al, 1975). It would therefore seem not unreasonable to suppose that the 5% and 10% glucose meals used in this study would also empty at differing rates and that this might be reflected by differences in their patterns of transpyloric fluid movement. The patterns of transpyloric fluid movement observed in this study were in fact similar with both test meals and thus these observations appear to conflict with the findings of the other studies mentioned above. More recent studies, however, have suggested that in the fasted subject, when the stomach and duodenum are relatively empty, ingested nutrient meals initially empty under "open loop" conditions, passing a volume of fluid into the duodenum as an unregulated gush (McHugh et al, 1975). This initially rapid efflux of gastric contents continues until the nutrient content, acting via the duodenal receptors, activates the feedback mechanisms and the subsequent emptying of the meals proceeds under "closed loop" conditions (McHugh & Moran, 1979; Seigel et al, 1982; Brener et al, 1983). This initial uncontrolled phase of the emptying of nutrient meals may last up to 20 minutes (McHugh & Moran, 1979). The ultrasonic observations were all made well within this early phase and the similar pattern of fluid movements seen with the 5% and 10% meals may reflect the emptying of test meals of identical volumes under "open loop" conditions before the effects of their differing nutrient and osmotic properties on duodenal receptors become apparent.

The results in this section using 5% and 10% glucose meals are compatible with those obtained in the study with 4 test meals

documented in Section 5.3 (pages 118-129). The small, but significant, differences in the patterns of transpyloric fluid movement that were seen in the 4 meal study occured between the non-nutrient (low and neutral ph) test meals and the nutrient (glucose and protein) test meals. Presumably the emptying of the nutrient meals was begining to be influenced by the control mechanisms mediated through the duodenal receptors which regulate the calorie efflux from the stomach, but which do not affect the emptying of non-nutrient meals.

The effect of calorie content and osmolarity on duodenogastric reflux has not previously been examined. In this study reflux was observed in over 50% of the analysed gastroduodenal cycles and, although there was no difference in the pattern between the groups, the findings do once more demonstrate that some reflux is a normal phenomenon in normal subjects.

The pattern of antroduodenal motor activity was not affected by the changes in calorie content and osmolarity of the test meal used in this study. There is now, as discussed previously (pages 7, 104 & 127) much evidence to suggest that antroduodenal motility may have little role to play in the regulation of liquids from the stomach, and the findings of this study also seem consistent with this concept. In contrast to this, however, White and co-workers (1983), who recently compared the effects of physiological saline, 10% Intralipid and 10% Dextrose on gastroduodenal motility in 10 normal subjects, found that, although 10% dextrose abolished fasting motor activity in 50% of their subjects, in 6 of the 10, frequent rythmic contractions of the pylorus appeared from 5 to 24 minutes

after the infusion of the test meal. These authors concluded that changes they observed in gastroduodenal motility, and in particular the pyloric motility indices, were consistent with a role for the antroduodenal region in the control of liquid emptying from the stomach.

5.4.4 Summary

The effect of 5% and 10% glucose on the patterns of transpyloric fluid movement and antroduodenal motility was examined in 10 normal subjects.

Overall mean antroduodenal cycle times were similar with each test meal (5% 21.9 + 3.1 seconds; 10% 22.3 + 3.2 seconds) and there was no alteration in antroduodenal co-ordination. Gastroduodenal fluid movement occurred, on average, around 2 episodes per cycle (5% 2.3; 10% 2.4) each lasting about 2 seconds (5% 2.2; 10% 2.0), and these episodes were seen in over 90% of cycles in both groups. Duodenogastric flow, however, was seen in only around 50% of cycles and occurred, on average, less than 1 episode per cycle lasting around 2 seconds.

The similar pattern of transpyloric fluid movement seen during the early emptying of these 2 different liquid meals presumably reflects the emptying of identical volumes under "open loop" conditions, before the effects of their nutrient and osmotic properties on duodenal receptors activates mechanisms regulating their emptying.

5.5.0   Patients with Gastro-oesophageal Reflux and Healthy Controls

Gastric emptying is known to be altered in patients with gastro-oesophageal reflux (GOR) (Little et al, 1980; McCallum et al, 1981; McCallum et al, 1982) and, in addition, there have been studies suggesting that duodenogastric reflux might be important in the pathogenesis of reflux oesophagitis (Gillison et al, 1972; Kaye & Showalter, 1972; Stol et al, 1974). In view of these findings, it seemed that a study of the pattern of fluid movement across the pylorus and associated gastroduodenal motility in a group of patients with GOR might be a worthwhile undertaking, particularily if compared to that from a group of normal controls.

5.5.1   Subjects and test meal

Studies were performed on 10 patients with proven gastro-oesophageal reflux and 10 normal subjects as controls. The patients were initially contacted by letter and all gave their informed consent to the ultrasonic examination. All 10 patients had previously been shown to have abnormal reflux into the lower oesophagus by 24hr pH probe monitoring (DeMeester et al, 1980) and all were still symptomatic at the time of the ultrasonic examination.

Each of the 2 groups of subjects, who were studied after an overnight fast, ingested a 500ml liquid test meal composed of 433.4mls of water at 37´C to which was added 66.6mls of diluting orange and 2.5g of sodium bicarbonate to bring the pH of the meal up to neutral (pH 7.0). The test meal was isotonic and contained 0.5g of the bran particles. The events at the gastric outlet were

then monitored using the ultrasonic technique.

5.5.2   Results

The sections of the ultrasonic recordings selected for analysis from the subjects in the 2 groups were all taken from comparable times in the immediate postprandial period.   The analysed sections in the control group began on average 5.1 + 2.7 minutes after ingestion of the test meal, while those in the GOR group began on average after 4.2 + 3.8   minutes (t= 0.62; NS).   In all, around 90 cyclical periods of gastroduodenal motor activity were observed in each group (Control 91, GOR 94).

The pattern of gastroduodenal motor activity observed in each group was similar. Table 20 (page 142) shows the mean gastric cycle times and the ratio of related contractions of the proximal duodenum to terminal antral contractions of each subject in the 2 groups.   The overall mean gastric cycle time in the control group was 21.3 + 2.4 seconds and was almost identical to that of the GOR group, which was 21.3 + 2.5 (t= 0.03; NS).   The overall mean ratio of contractions of the proximal duodenum to those of the terminal antrum were also similar (Control 0.60 + 0.16, GOR 0.66 + 0.23: t= 1.12; NS).

Transpyloric fluid movement occurred in both groups as intermittent brief episodes when the pylorus was patent. The timing of occurrence and the duration of the individual episodes was obtained from the chart plots of the 10 subjects in each group.

The pattern of episodes of gastroduodenal flow is summarised in Table 21 (page 143), which shows the mean values from each group.

Table 20 - Mean gastric cycle times (seconds) and ratio of proximal duodenal to terminal antral contractions

Sub-ject	Control			GOR		
	Mean cycle time	± SD	DC/TAC ratio*	Mean cycle time	± SD	DC/TAC ratio*
1	22.3	2.9	0.64	23.5		0.82
2	26.6	2.3	0.57	19.8	3.9	0.67
3	22.5	2.7	0.38	21.0	1.1	1.0
4	18.8	2.3	0.69	24.3	2.8	0.56
5	17.5	2.0	0.6	21.3	4.2	0.83
6	20.2	4.1	0.36	25.6	1.7	0.78
7	21.5	2.6	0.7	18.0	1.4	0.17
8	20.3	2.4	0.56	20.3	3.8	0.67
9	21.9	1.8	0.5	20.1	2.3	0.5
10	20.7	2.2	0.92	18.7	4.3	0.58

* Ratio of contractions of the proximal duodenum to those of the terminal antrum

Table 21 - Pattern of episodes of gastroduodenal flow

Sub-ject	% Cycles with episodes	Mean dur-ation*	± SD	Mean no. /cycle	± SD	% after TAC
Control	96	2.8	0.7	1.7	0.4	66
GOR	100	2.3	0.4	2.7	0.3	62

(* - seconds)

Table 22 - Pattern of episodes of duodenogastric flow

Sub-ject	% Cycles with episodes	Mean dur-ation*	± SD	Mean no. /cycle	± SD	% before TAC
Control	54	2.1	0.5	0.7	0.4	66
GOR	63	2.1	0.5	0.8	0.3	63

(* - seconds)

Gastroduodenal flow was observed in 96% of cycles in the controls, and in all cycles in the GOR group. Significantly more episodes of gastroduodenal flow occurred in each cycle in the GOR group than in controls (t= 6.4; p<0.001). However, the mean duration of these episodes in both groups was no different and was around 2.5 seconds (t= 2.1; NS). Over 60% of episodes of gastroduodenal fluid movement occurred within 5 seconds (Controls 4.9 seconds, SD + 1.1 seconds; GOR 5.3 seconds, SD + 1.3 seconds) after relaxation of the pylorus and terminal antrum.

The pattern of duodenogastric flow (reflux) is shown in Table 22 (page 143) The episodes were observed in many cycles in both the control and GOR groups, but there was no difference in their mean duration (t= 0.5; NS) or the mean number of episodes per cycle (t= 0.2; NS). The majority of these episodes of duodenogastric flow (Control 66%, GOR 63%) occurred within 5 seconds (Controls 5.5 seconds, SD + 2.5 seconds; GOR 4.6 seconds, SD 1.6 seconds) before the terminal antral contraction.

5.5.3 Discussion

Numerous studies have been performed on all aspects of the emptying and reflux of material out of and in to the stomach, but only a relative few have specifically examined these phenomena in patients with oesophagitis secondary to gastro-oesophageal reflux (GOR).

Those investigators who have examined gastric emptying in patients with GOR have usually found it emptying to be delayed. Little and co-workers (1980) measured the emptying of a solid test meal labelled with Technetium-99m sulphur colloid added to oatmeal from

the stomach using sequential gamma camera measurements, and found delayed emptying in patients with oesophagitis compared to normal subjects. McCallum and co-workers (1982), who used a mixed solid and liquid test meal with Technetium-99m sulphur colloid labelled chicken liver as a solid phase marker and Indium-111m-DTPA to label the liquid component, found solid emptying to be delayed in 57% of their GOR patients. However, the rate of liquid emptying in these patients was similar to normal controls. Csendes and Henriquez (1978), using the double sampling technique with gastric intubation, also found the emptying of a liquid test meal to be similar in GOR patients and controls. In patients with GOR who have delayed gastric emptying, the gastric prokinetic agent metoclopramide has been shown to enhance gastric emptying (Fink et al, 1983).

The cause of the delay in gastric emptying found in GOR is unclear (Burns, 1984), but it has been suggested that it might be secondary to a vagal paresis caused by the involvement of the vagus nerve fibres which are in direct contact with the oesophageal smooth muscle in a panmural extension of the oesophagitis (Little et al, 1980). More recently, it has been suggested that vagal impairment may be common in patients with GOR (Ogilvie et al, 1985). However, in that study the vagal impairment was found not just to be confined to the gastrointestinal tract, and the authors felt it was therefore unlikely to be simply a consequence of GOR and might in fact be important in its pathogenesis.

In this study using real-time ultrasonic imaging to examine the moment to moment characteristics of transpyloric fluid movement during the early stages of the emptying of a liquid test meal in

patients with GOR, a significant difference has been found in the pattern of this fluid movement when compared to normal subjects. Although these observations do not directly reflect the volume of flow through the pylorus or the rate of gastric emptying, because fluid movement (flow) only can occur in the presence of a pressure gradient between the lumen of the stomach and that of the duodenum, the results suggest that in patients with GOR this pressure gradient acts in a gastroduodenal direction more often than in controls. The magnitude and direction of the pressure gradient across the pylorus depends on the relative intraluminal pressures in the stomach and proximal duodenum (Strunz & Grossman, 1978; Rock et al, 1981; Weems, 1981). Although in this study these pressures were not measured, it is perhaps reasonable to infer that in the GOR patients the intragastric pressure was higher more often than in controls.

The tone of the fundus of the stomach is considered to be of prime importance in the emptying of liquids (Kelly, 1980) and this fundal tone is influenced by the vagus nerve (Jahnberg, 1977). Interruption of the inhibitory impulses from the vagus causes impairment of the ability of the fundus to relax and accomodate the volume of a test meal, and this effect is manifest as an increased rate of liquid emptying from the stomach of vagotomised subjects compared to normal controls (Aune, 1969; Koster & Madsen, 1970; Stadaas, 1974). Thus if, as has previously been suggested, the vagal fibres to the fundus are compromised by the inflammatory process in oesophagitis, then the significant increase in the number of gastroduodenal episodes of flow per gastroduodenal cycle seen in GOR subjects in this study might be a reflection of increased gastric emptying of the liquid test meal.

It is extremely difficult to measure duodenogastric reflux accurately (Keighley et al, 1975). The role of duodenogastric reflux in the pathogenesis of reflux oesophagitis in subjects with an intact stomach is unclear.   Under experimental conditions, bile and pancreatic juice are injurious to the oesophageal mucosa (Helsingen, 1960; Moffat & Berkas, 1965), and in patients who have undergone gastric surgery bile can undoubtably be a cause of oesophagitis (Windsor, 1967).

Several investigators who have studied duodenogastric reflux of bile in patients with symptomatic oesophagitis   found it to be significantly greater in these patients than in controls (Gillison et al, 1969; Stol et al, 1974).   In these studies duodenal or gastric intubation was utilised to permit the direct detection of refluxed material. In contrast, Little and co-workers (1984), who used an intragastric pH probe to monitor their patients for 24 hours, found a decreased frequency of alkaline duodenogastric reflux episodes.   However, Matikainen and co-workers (1981), who used non-invasive chole-scintigraphy to detect duodenogastric reflux, found the incidence of reflux in controls and patients with GOR to be similar.   A possible basis for these apparently conflicting results may lie with the suggestion that intubation itself may influence the results (Tolin et al, 1979; Muller-Lissner et al, 1982), and that reflux of duodenal contents and reflux of bile do not necessarily parallel each other (Muller-Lissner & Fraass, 1985).

In this study, by using real-time ultrasound which is non-invasive, duodenogastric movement of fluid across the pylorus was seen to occur in many gastroduodenal cycles and the pattern of the episodes

was similar in the control and GOR groups.

What has become clear about duodenogastric reflux is that it is a normal occurence in healthy subjects (Muller-Lissner et al, 1983). Thus the presence of bile in the stomach in itself cannot, as was previously widely believed (Rokkjaer, 1980), be considered pathological, but rather that the demonstration of abnormal reflux will depend on the use of techniques which will allow it to be quantified (Heading, 1983). The present ultrasonic technique does not allow the volume of flow across the pylorus to be measured, and therefore, although this study has shown that duodenogastric reflux does occur in GOR as well as confirming its occurence in normal subjects, it has shed no additional light on the role of duodenogastric reflux in gastro-oesophageal reflux.

The pattern of contractions of the terminal antrum and proximal duodenum observed during the emptying of the test meal used in this study was similar in the GOR and control groups. These results conflict with those of Behar and Ramsby (1978) who used a perfused catheter system to measure antroduodenal contractility during the emptying of a semi-solid meal, and found a decreased number of antral contractions in patients with GOR compared to normal controls. However, antral contractile activity probably plays little part during the emptying of liquid test meals from the stomach (Dozios et al, 1971; Kelly, 1980: Meyer, 1980), and it must therefore remain possible that the difference between the nature of the test meal employed in this study and that of Behar and Ramsby is responsible for these conflicting results.

5.5.4 Summary

The pattern of transpyloric fluid movement and associated antroduodenal motility in the first few minutes after ingestion of fluid has been compared in patients with proven gastro-oesophageal reflux (GOR) and healthy controls.

A similar number of cyclical periods of antroduodenal motor activity (GOR 94 and Control 91) were observed in each group. Mean antral cycle times and the frequency of occurrence of related proximal duodenal contractions were also similar. Transpyloric fluid movement occurred as a number of discrete episodes in each cycle. Gastroduodenal flow was more frequent in the GOR group (mean 2.7 + 0.4 episodes per cycle) than in controls (mean 1.7 + 0.3) (t= 6.4; p<0.001). The mean duration of these episodes in both groups was similar at around 2.5 seconds. Duodenogastric flow (reflux) was observed in many cycles (GOR 63%; Controls 54%), but there was no difference in the mean number of episodes per cycle (GOR 0.79; Control 0.74) or their mean duration (2 seconds for both).

Transpyloric fluid flow only occurs when a pressure gradient is created across the open pylorus. These observations indicate that in GOR the gastroduodenal pressure gradient is positive more frequently than in normal controls. The pattern of gastroduodenal liquid flow but not duodenogastric reflux differs in GOR patients and controls.

5.6.0 <u>Patients after Truncal Vagotomy and Pyloroplasty or Highly Selective Vagotomy</u>

In the United Kingdom at present the two most commonly performed operations for chronic duodenal ulceration are truncal vagotomy and pyloroplasty (TVP) and highly selective vagotomy (HSV).

Dragstedt originally introduced the concept of vagal denervation of the parietal cell mass of the stomach to abolish the extrinsic stimulus to gastric acid secretion in 1943 (Dragstedt & Owens, 1943). At that time he performed truncal vagotomy to denervate the stomach totally, but a significant number of his patients were troubled by post-operative gastric retention (Dragstedt et al, 1947). This gastric retention was thought to occur because total gastric vagotomy resulted in paralysis of the peristaltic contractions responsible for gastric emptying (Oberhelm & Dragstedt, 1955). Dragstedt advised that truncal vagotomy should be accompanied by a gastric drainage procedure (Dragstedt & Camp, 1948). Truncal vagotomy and pyloroplasty has been shown over the years to be associated with a recurrent ulceration rate of around 8% and and an incidence of side-effects (i.e. diarrhoea and dumping) of 12% (Stoddard et al, 1978).

In 1957 Griffiths and Harkins suggested that gastric stasis could be avoided after vagotomy if the nerves to the antrum were preserved. Highly selective vagotomy was subsequently introduced in 1970 (Johnston & Wilkinson, 1970) as an operation to denervate only the parietal cell mass. Its main advantage over TVP was said to be the very low (1-2%) incidence of side-effects (Humprey et al, 1972; Makey et al, 1979). This was thought to be the result of

normal or near normal gastric emptying regulated by the antroduodenal region with its vagal innervation intact (Amdrup & Jensen, 1970). HSV initially seemed to have ulcer re-occurence rates comparable with TVP (Humphrey & Wilkinson, 1972); however several recent long-term reviews have suggested that reoccurence may occur in 20% or more of patients (Koffman et al, 1983; Hoffman et al, 1984). Many now feel that the advantages of HSV are outweighed by the high incidence of recurrent ulceration.

Since the introduction of TVP and, to a slightly lesser extent, HSV, continuing research has shed additional light on the effect of these procedures on the mechanisms responible for gastric emptying and its regulation. Much of the work, especially that concerning motility, has, however, been carried out in animal studies using invasive techniques (Griffith & Harkins, 1957; Amdrup & Griffith, 1969; Wilbur & Kelly, 1973; Sarna & Daniel, 1975; Mroz & Kelly, 1977). In human subjects the results are conflicting (Sheiner et al, 1980), and one reason for this is said to lie in the methods available for assessing gastric motility. It was therefore decided to use the non-invasive ultrasonic technique in human subjects to examine the effect of these two procedures on the contractile activity of the distal stomach and proximal duodenum and the pattern of the associated intraluminal fluid movement.

5.6.1 Subjects and test meal

Studies were performed on 3 groups of 10 subjects (Table 23, page 153). The subjects who had undergone either TVP or HSV were on average 10 months post-op. All seemed to have had a good result

from their surgery, and could therefore be classified according to the modified Visick grading of symptoms as grade I or II (Goligher et al, 1968). None of the subjects in the control group had had previous gastro-intestinal symptoms.

After fasting overnight each subject ingested a 500ml test meal containing 0.5g of bran particles. The test meal had a pH of 7.0 and was isotonic. It was prepared by adding 66.6mls of diluting orange and 2.5g of sodium bicarbonate to 433.4 mls of water at 37´C. During the emptying of the test meal the intra-abdominal events were monitored using the ultrasonic technique.

5.6.2 Results

The video recording from each subject was reviewed and a section selected for detailed analysis. The sections from each of the 3 groups were all taken from comparable times in the postprandial period (Table 24, page 153). This was around 4 minutes after each subject had drunk the test meal. A total of between 33 and 35 minutes of observations was analysed for each group.

Regular antral contractions were observed in all of the analysed sections from the 3 groups. The percentage motor activity ranged from 55% to 100%, and there was no significant difference between the groups. The mean percentage motor activity for TVP was 88% $\pm$ 17%, for HSV was 92% $\pm$ 12% and for controls 97% $\pm$ 19%.

The mean gastroduodenal cycle times, measured as the interval between successive antral contractions, are shown in Table 25 (page 154). The mean cycle times in each group were similar at

Table 23 - Subject details

Group	No. of Subjects	Mean Interval Post-Op (mths)	Visick Grade I	II
TVP	10	10.7 (7-13)	7	3
HSV	10	10.1 (6-17)	5	5
Control	10	-	-	-

Table 24 - Details of analysed observations

Group	Time after ingestion to start of analysis*	Total duration of analysis*
TVP	3.5 ± 3.4	33
HSV	3.9 ± 3.5	37
Control	5.1 ± 2.7	36
	F=0.73 N.S.	

* - Minutes

Table 25 - Mean gastroduodenal cycle interval and percentage of terminal antral contractions (TACs) associated with proximal duodenal contractions (DCs)

Group	Mean cycle time (secs)	% of TACs with DCs
TVP	19.9 ± 2.3	34%
HSV	21.0 ± 1.7	60%
Control	21.2 ± 2.4	59%
	F=1.05 N.S.	F=3.1 p<0.05

approximately 20 seconds. In each of the 3 groups antral contractions began in the proximal antrum and then progressed distally. However, in the TVP subjects they subsequently faded out just before the gastroduodenal junction and, unlike in the HSV and control subjects, there was no actual terminal antral occlusion or pyloric closure. It could be seen from the video tapes that the normal structure of the gastroduodenal junction had been disrupted in the TVP subjects (Figure 22, page 157) to the extent that the pyloric narrowing seen in both the normal controls and in the HSV subjects was absent.

The percentage of terminal antral contractions (TACs) that were associated with contractions of the proximal duodenum (DCs) are also shown in Table 25 (page 154). In both the HSV and control subjects around 60% of TACs were associated with DCs. However, in the TVP subjects this percentage was only 34% and this was significantly less (p<0.05) than in the two other groups.

Emptying in all 3 groups of subjects occurred, not as a steady flow, but as intermittent brief episodes of stop-start movement across the gastroduodenal junction. Fluid was seen to move mainly from stomach to duodenum, but there were also numerous occasions when it moved in a retrograde or duodenogastric direction.

Table 26 (page 156) shows the pattern of gastroduodenal flow. Fluid was seen to move from the stomach into the duodenum in nearly all the cycles from the analysed sections. In the TVP and HSV groups there were on average 2.5 discrete episodes of gastroduodenal flow per cycle. This was significantly more than in the control group. These episodes lasted on average about 2.5 seconds and were of

Table 26 - Pattern of episodes of gastroduodenal flow

	TVP	HSV	Control	
% of cycles with flow	99%	97%	96%	N.S.
Mean no. of episodes/cycle	2.6	2.4	1.7	p<0.05
Mean duration of episodes (secs)	2.5	2.5	2.8	N.S.
% episodes after TAC	60%	63%	64%	N.S.

Table 27 - Pattern of episodes of duodenogastric flow

	TVP	HSV	Control	
% of cycles with flow	52%	62%	54%	N.S.
Mean no. of episodes/cycle	0.6	0.8	0.7	N.S.
Mean duration of episodes (secs)	2.0	2.0	2.1	N.S.
% episodes before TAC	48%	66%	63%	N.S.

FIGURE 22 - Ultrasonic scan of the gastroduodenal region in a subject after truncal vagotomy and pyloroplasty

Transverse B-scan using a 3.5MHz probe. The gastric antrum (a), pyloric channel (p) and duodenal bulb (d) are distended with fluid. Their normal contours have been altered by the pyloroplasty. In particular, the pyloric channel (p) is wider than in normal subjects, mainly due to distortion of its anterior wall (w).

similar duration in each group.   In   each of the 3 groups the majority of episodes of gastroduodenal flow occured a few seconds after the antroduodenal region had relaxed at the end/start of each antroduodenal cycle.

Table 27 (page 156) shows the pattern of duodenogastric reflux. This occurs much less frequently than gastroduodenal flow, but nevertheless episodes of reflux were observed in over half of all antroduodenal cycles. On average fewer than 1 episode occured per cycle and lasted around 2 seconds. In the HSV and control subjects the majority of these episodes of reflux occured just before the terminal antral contraction. However, in the TVP group, where there was no pyloro-antral contraction, the episodes seemed more evenly distributed through out each cycle.

5.6.3 Discussion

There is   evidence that many of the changes in gastric myo-electrical activity, contractility and emptying seen after TVP and HSV are transient, and that the patterns return towards normal during the months following surgery (Cowley et al, 1972; Howlett et al, 1976; Guerts et al, 1977). Furthermore, in order to obtain a true reflection of the effect of TVP and HSV on gastric function, it has been suggested that studies should be postponed until at least 3 months have elapsed since surgery (Cobb et al, 1971). In this study each patient was at least 6 months post-op.

In man there have been very few studies of the effect of TVP or HSV on gastroduodenal myo-electrical and contractile activity. Hinder & Kelly (1977) studied gastric slow wave activity pre-operatively and

in the immediate post-operative period in 11 patients undergoing HSV, and found that it was largely unaltered. Stoddard and co-workers (1973) who studied 21 patients undergoing either truncal, selective or highly selective vagotomy, also found that when the patients were re-examined 5 days post-op, the frequency of slow waves was unaltered. They also monitored antral contractions with open-tipped catheters and pressure transducers and found that, although all types of vagotomy resulted in a decrease in mean percentage motor activity, the reduction was particularily marked after truncal vagotomy.

The frequency of antral contractions is related to that of the gastric slow wave, and the maximum contraction frequency equals the slow wave frequency. A mean percentage contractile activity of 100% implies that an antral contraction occurs with every slow wave. In the present study the mean percentage contractile activity in patients after both TVP (88%) and HSV (92%) was lower than in controls (97%), but the difference did not reach statistical significance. The overall mean percentage activity of 90% observed in vagotomised patients in this study is considerably higher than the 4.8% to 8.4% seen by Stoddard and co-workers (1973). This discrepancy may be related to the fact that their study was carried out in fasting subjects, whereas the present observations were made in the immediate postprandial period. It may, however, also be related to the differing sensitivities of the methods used. The present observations do, however, confirm the observation mentioned above, made by Hinder & Kelly (1977) and Stoddard and co-workers, that the frequency of antral contractions and, by implication, the gastric slow wave frequency remain normal

after truncal and parietal cell vagotomy.

The ultrasonic images revealed that, after TVP, obliterative terminal antral and pyloric contractions do not occur. This phenomenon has been previously observed in dogs (Kelly & Kennedy, 1975) and is thought to be the result of the pyloroplasty.

In Section 5.2.2 (page 113) the results showed that in normal subjects the antroduodenal region usually contracts in the co-ordinated sequence terminal antral contraction, pyloric closure and then proximal duodenal contraction. However, proximal duodenal contractions do not always occur after every terminal antral and pyloric contraction, and in normal subjects only do so about 60% of the time. In this study, the frequency of proximal duodenal contractions in the TVP subjects was significantly less than in both HSV and control subjects suggesting a significant difference in the co-ordination of pyloro-antral and proximal duodenal contractions after TVP compared with HSV and control subjects in whom the antroduodenal region is structurally intact. Uncoordination of antral and proximal duodenal contractions has also been observed in animals after different types of pyloroplasty (Ludwick et al, 1969; Ormsbee & Bass, 1976; Reiser & Holle, 1982). It is possible, therefore, that it is the pyloroplasty, rather than the vagotomy, which has the most deleterious effect on the integrity and motor function of the antroduodenal region.

In contrast to myo-electrical and contractile activity, the effect of TVP and HSV on gastric emptying of liquids has been extensively studied in man. The emptying of liquids is mainly related to gastric fundal tone. Vagal denervation of the fundus

impairs its ability to relax and accomodate ingested food (Olbe & Jackson, 1963; Weisbrodt et al, 1969; Stadaas & Aune, 1970), and after both TVP and HSV emptying begins sooner and is more rapid than normal (Moberg et al, 1972; Donovan et al, 1974; MacGregor et al, 1977; Gulsrud et al, 1980). These alterations in the normal patterns of liquid emptying are illustrated in Figure 23 (page 162), which has been constructed with data adapted from Clarke & Alexander-Williams (1973) who monitored the emptying of a 750ml test meal of 10% Glucose in patients after TVP and HSV. The finding in this study that significantly more episodes of gastroduodenal flow occur per cycle after TVP and HSV presumably reflects the proximal gastric denervation. Although it has been shown that there is a small tendency for the effects of vagal denervation on fundal adaptive relaxation to improve with time, in man they persist for at least a year (Stadaas, 1980).

The effect of pyloroplasty on gastric emptying is unclear (Muller-Lissner et al, 1982). In some studies, pyloroplasty resulted in a decrease in gastric emptying (Buckler, 1967; Ludwick et al, 1969), but acceleration of emptying has also been reported (Ormsbee & Bass, 1976). In this study the presence of a pyloroplasty, in conjunction with vagal denervation of the gastric fundus, seems to have little additional influence on the early emptying of liquids.

Whereas fundal tone is thought to be the main influence on liquid emptying, the antroduodenal region is thought to be of paramount importance in the regulation solid emptying (Wilbur & Kelly, 1973). Figure 24 (page 163) has been prepared from data adapted from the

FIGURE 23 - Gastric emptying of 750mls of 10% glucose in patients after truncal vagotomy and pyloroplasty (TVP) and highly selective vagotomy (HSV) and in controls *
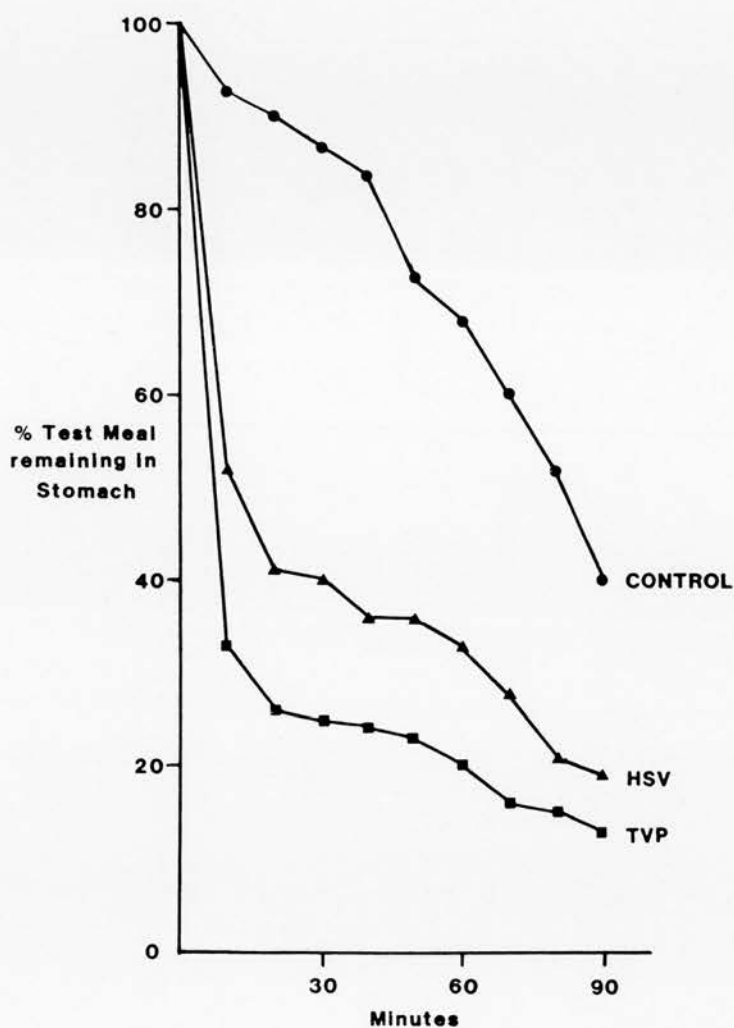
The emptying studies were performed using double sampling dye dilution technique.

The emptying of the test meal is more rapid after TVP & HSV than in controls.

* Data adapted from Clarke & Alexander-Williams, 1973

FIGURE 24 - Gastric emptying of a solids meal in patients after truncal vagotomy and pyloroplasty (TVP), highly selective vagotomy (HSV) and normal controls *
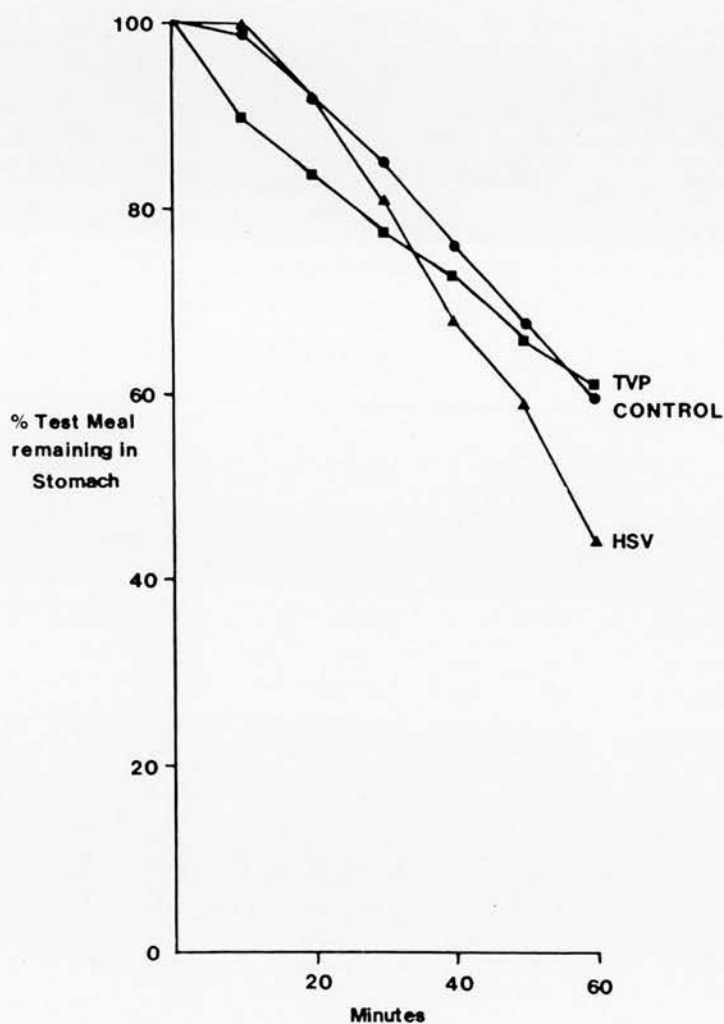
Emptying studies were performed using a solid meal labelled with technetium-99m macroaggregates of ferrous hydroxide and gastric isotopic activity assessed by gamma camera.

Rapid early emptying is seen after TVP, whereas after HSV early emptying is similar to controls.

* Data adapted from Sheiner et al, 1980

results of Sheiner and co-workers (1980) and illustrates the effects of TVP and HSV on the emptying of an isotopically-labelled solid meal measured by a gamma camera. When vagotomy has been performed, pyloroplasty results in precipitous early emptying of solids (Colmer et al, 1973; Wilkinson & Johnston, 1973). In a number of patients this is thought to lead to dumping and diarrhoea. However, after HSV, early gastric emptying is similar to normal controls (Brandsborg et al, 1977; Horton et al, 1982). The reduced incidence of dumping and diarrhoea seen after HSV compared with TVP is probably the result of a physically-intact antroduodenal region, rather than because it has an intact vagal innervation.

Although it is now recognised that some duodenogastric reflux occurs in healthy subjects (Keane et al, 1981; Sonnenberg et al, 1982; Muller-Lissner et al, 1983; Brough et al, 1984), there is still debate about the effect of peptic ulcer surgery on this phenomenon and the clinical significance of the reflux. A number of recent studies have reported an increase in duodenogastric reflux following procedures which include removal, disruption or bypass of the pylorus (Lawson, 1976; Hoare et al, 1977; Mackenzie et al, 1977; Dewar et al, 1982), and, while most would agree that HSV results in a comparative reduction in duodenogastric reflux, others have found duodenogastric reflux to be unchanged (Wormsley, 1972) or reduced after TVP (Kilby, 1970). In addition, as discussed in Section 5.5.3 (page 148), it is not clear when duodenogastric reflux becomes pathological. In dogs it has been shown that duodenogastric reflux produces a gastric hypersecretory state associated with antral gland hyperplasia (Thomas, 1982). However, both of these changes were prevented by truncal vagotomy, and the author concluded that even if

duodenogastric reflux is increased after pyloroplasty, then the accompanying vagotomy may have a protective effect. Furthermore, in asymptomatic subjects, although HSV results in less duodenogastric reflux, it does not result in a significant improvement in antritis compared with TVP (Dewar et al, 1983). On the other hand, symptomatic patients after TVP, with bile vomiting and endoscopically proven gastritis, do show a significant increase in the amount of reflux when compared to aymptomatic controls or asymptomatic patients after HSV (Brough et al, 1984).

In the present study, in asymptomatic patients after TVP or HSV during the emptying of a liquid test meal, episodes of duodenogastric reflux not only occurred when the antroduodenal region was disrupted by pyloroplasty, but also after HSV. There was no difference, however, in the pattern of reflux between patients after either operation and controls. In addition the results once again confirm the finding of other studies that some reflux seems to be a normal phenomenon in healthy subjects.

5.6.4 Summary

The pattern of contractions and fluid movement at the gastroduodenal junction has been examined in patients after truncal vagotomy and pyloroplasty (TVP) or highly selective vagotomy (HSV), and in healthy controls.

Antral cycle times were similar in each group. Significantly fewer proximal duodenal contractions were seen to follow terminal antral contractions after TVP (34%) than HSV (60%) or controls (59%) ($p < 0.05$). Fluid movement occured as intermittent brief episodes

during each cycle. Significantly more episodes of gastroduodenal flow were seen per cycle after TVP (2.6) and HSV (2.4) than in controls (1.7) (p<0.05). The duration of episodes was similar at 2.5 seconds. Duodenogastric flow (reflux) occured in around 50% of cycles and with a similar pattern in each group.

The pattern of antral contractions remains normal after TVP and HSV; TVP, however, does result in significant antroduodenal motor uncoordination. The significant increase in episodes of gastroduodenal flow after TVP and HSV presumably reflects proximal gastric vagal denervation.

6.0.0 <u>General Discussion</u>

The investigations using the real-time ultrasonic imaging technique have been documented in detail in Section 5 (pages 93-166), where the findings were discussed in conjunction with the work of other investigators who studied similar aspects of gastroduodenal function but with different techniques. Over the years, as technology has advanced, these techniques have become progressively more sophisticated. Gastric emptying and duodenogastric reflux, which were once assessed by using intra-gastric or intra-duodenal tubes and relatively simple aspiration methods, are nowadays assessed using radio-isotopes. These isotopes, for example of Indium, Technetium and Chromium, are incorporated into various components of both liquid and solid test meals, and their intraluminal activity is measured using by complex gamma cameras linked to on-line computers. Gastroduodenal motility was, until recently, assessed using seperate techniques such as balloon manometry, perfused catheter systems and intra- and extra-luminal strain gauges. Despite these technological advances, it is precisely because the two groups of investigative techniques have evolved separately that there has been continued uncertainty about the relationships between intraluminal fluid movement and contractile activity. Studies have, of course, been made with various combinations of the two groups of techniques in attempts to evaluate the relationships between intraluminal movement and motility, but only recently has it become possible to assess these two aspects of gastroduodenal function using a single technique.

Adam and co-workers, as mentioned on page 45, originally stated in

1982 that ultrasonic imaging might have potential as a suitable technique for simultaneous study of gastric motility and the movement of the luminal contents, and in the same year Jacobs and co-workers described their studies (see page 34) using radio-isotopes and a gamma camera. The results of this latter investigation were limited to an appraisal of the net effects of motility on emptying, but, because the former study suggested that ultrasonic imaging might provide additional information, there seemed sufficient justification to undertake the work documented in this thesis.

In general, the ultrasonic technique proved to be a reliable and reproducible method for studying the relationships between contractions of the walls of the antroduodenal region and movements of the luminal contents. Studies with the ultrasonic technique were carried out in a variety of physiological and pathological situations, and the results obtained (Section 5, pages 93-166) were consistent with those of others. Although the ultrasonic technique was associated with a number of advantages when compared to other investigative techniques, it became clear during the investigations that it also had limitations and several disadvantages.

The main advantage of ultrasonic imaging is undoubtably its non-invasive nature and at the present time it is the least invasive technique available for assessing gastroduodenal function. Not only does it not expose the subject undergoing examination to the potentially harmful effects of ionising radiation, but the actual method of scanning proved entirely acceptable to all those who

underwent the examination. No subject complained of any disagreeable sensation, and indeed those patients examined were delighted to learn that no "tubes or needles" were involved.

The ultrasound scanner used throughout the investigations was identical to several already in use in the X-ray department of the local hospital (RIE) and it seems likely that similar observations could be made wherever there is access to real-time scanning equipment. However, successful visualisation of the internal structures does require that their ultrasonic image be maintained constantly for several consecutive minutes. This strict requirement for a continous, uninterrupted image of the gastroduodenal region was the main criterion that had to be fulfilled before any of the ultrasonic recordings was considered acceptable for detailed analysis. In common with most investigative techniques, obtaining and subsequently maintaining the ultrasonic image largely depends on the operator, and satisfactory observations will undoubtably be achieved more often by someone who is not only familiar with the technique, but also performs repeated examinations on a regular basis.

The main limitations of the technique are related to the physical properties of the ultrasound beam. Ultrasound is strongly reflected by dense materials, and for all practical purposes such materials can be considered impenetrable. Solid meals were not studied, since it was found that the presence of large chunks of food in the gastric contents caused excessive scattering of the ultrasound beam and distortion of the image. In addition, structures lying behind the rib cage can be difficult to visualise.

Thus, when attempts are being made to visualise the gastric fundus, the beam must be angled upwards from the epigastrium to pass under the costal margin. This often makes visualisation of the entire stomach difficult (Mascatello et al, 1977), and in some cases it may be impossible (Kremer & Grobner, 1981).

As was discussed in Section 3.1.0 (page 40), the ultrasonic image can be considered a two-dimensional cross-section through the tissues under examination, and for adjacent structures to be visible simultaneously they must lie in the same plane. In addition, the clarity of the image is inversely related to the distance between the probe and the structures under examination. This distance is largely related to the depth of subcutaneous fat. In the majority of subjects examined it was possible to visualise the terminal antrum of the stomach, pylorus and proximal duodenum, but there were two groups of subjects where this proved impossible. Surprisingly, one of the groups was almost entirely composed of thin young women in whom the pyloric channel appeared to lie very near the anterior abdominal wall, pushed out of the plane of the gastric antrum and proximal duodenum by a prominent vertebral column. The other group contained individuals who could have been described as overweight at the time they underwent the ultrasonic examination.

A number of subjects who had previously undergone cholecystectomy were examined by the ultrasonic technique. There is evidence to suggest that cholecystectomy may influence duodenogastric reflux (Warshaw, 1979; Mackie et al, 1982; Brough et al, 1984) and it seemed worthwhile to attempt to scan a group of these patients to see whether any differences in the normal pattern of reflux could be

detected. Unfortunately all 5 subjects examined fell into the overweight group mentioned above and this study had to be abandoned.

Although it seems likely that marked variations in the relative positions of internal organs will continue to make their simultaneous visualisation by real-time ultrasound impossible, the increasing sophistication of instruments that will undoubtably become available may improve the resolution and thus the clarity of the image that can be obtained. The presence of excessive subcutaneous fat may then prove less of a limitation.

The two-dimensional nature of the ultrasonic image does impose a further limitation on the technique, and this concerns the observation of intraluminal fluid movement as reflected by the movement of the echogenic particles. Movement of the bran particles in to or out of the imaging plane may give rise to false indications of movement which may be related either to particle movement occuring in a large three-dimensional structure, such as the terminal antrum, or to movement of the imaging plane in relation to the particles. It was, however, because of this potential problem that, during the investigations documented in this thesis, the observations on fluid movement were confined to the pyloric channel. Although swirling type motions of the bran particles were observed, particularily in the duodenum, it was felt that flow through the relatively narrow pylorus would be linear in a gastroduodenal or duodenogastric direction only. The observed transpyloric movements of the echogenic particles might therefore reasonably be assumed to reflect intraluminal events accurately at that point.

The main disadvantages of the ultrasonic technique are related to

the way in which the observations recorded on the video tape were subsequently analysed and converted into numerical data to permit statistical comparisons to be made between sets of data. This proved to be a particularily time-consuming task and, although attempts were made to develop a more satisfactory method of analysis throughout the course of the investigations, no better method could be found. The problem arose because subjective visual information from one source (i.e. ultrasound images) needed to be translated into objective numerical data. There was no electrical or mechanical device available to do this task automatically, and so it was performed by two human observers who independantly watched repeated replays of the ultrasound recordings, and noted when specific intra-abdominal events occured. These events had to be easily identifiable by both observers, and the points at which timing began and ended needed to be well defined. Four specific events were quantified: these were firstly, contractions of the terminal antrum of the stomach; secondly, contractions of the first part (bulb) of the duodenum; thirdly, episodes of particle movement in a gastroduodenal direction; and fourthly, episodes of particle movement in a duodenogastric direction. Considering all the factors that are thought to be associated with gastric emptying and its regulation, numerical analysis of only four events does appear somewhat restricted. It was, however, precisely because of the inherent limitations of the ultrasonic imaging technique that detailed analysis was confined to these four events. Nevertheless, by examining the results of the analysis in the context of the findings of other investigators, the inferences gained from the observations could be related to various aspects of gastroduodenal

function.

Despite its time consuming nature, the method of analysis did prove to be reliable and reproducible. The overall observer variability was around 15%. The observations on motility were, in general, less prone to observer-related variations in interpretation than those on particle movement. Variability was calculated at around 8% for the former and 20% for the latter. The increase in observer variablity seen with the observations on particle movement was thought probably to be related to the wide range of velocities of this movement which were observed. Flow, as reflected by movement of the particles, ranged from an almost imperceptible drift to rapid jets through the lumen of the pylorus. Because all perceived movement was to be noted by each observer, it seemed likely that discrepancies would more often arise during the analysis of the timing and duration of the episodes of transpyloric fluid movement.

In the course of the investigations, a total of 220 individual examinations were carried out using the ultrasonic imaging technique. The majority of these (77%) were in normal volunteer subjects in whom the effect of varying certain characteristics of the test meal (composition, pH, calorific value and osmolarity) was examined. It had been intended to make some observations on the kinetic effects of pharmacological agents such as pentagastrin and metoclopramide, but, after also undertaking studies on patients with a variety of upper gastro-intestinal pathologies, it became clear that adequate definition of physiological behaviour was essential first. In addition, the Medical Physics department of the Royal Infirmary of Edinburgh has recently developed a means of reliably

identifying the position of instruments such as biopsy needles introduced into tissues during ultrasound scanning. It may prove possible, using a modification of this technique, to localise the side holes of a perfused intraluminal pressure catheter, and so correlate the observations that might be made during simultaneous manometric and ultrasonic studies of gastroduodenal motility. Such studies of gastroduodenal function are, of course, just some of the aspects which remain potential topics for examination with the ultrasonic imaging technique.

As previously stated (page 4), the stomach functions as a reservoir for ingested food which it transforms into chyme and then delivers in a controlled manner to the rest of the gut. Current research suggests that the various aspects of this function can be apportioned to separate but inter-related parts of the stomach. The proximal stomach (fundus) is regarded as the actual reservoir, whereas the distal stomach serves to grind and mix the gastric contents and then propel them through the pylorus. The contractile activity of these two regions are quite distinct. Although peristaltic type contractions have not been observed in the fundus, pressure studies in man (Lind et al, 1961; Azpiroz & Malagelada, 1985) have detected the occurrence of regular slow tonic contractions lasting around 20 seconds with a maximal frequency of around 1 contraction per minute. This is in contrast to the contractile activity of the distal stomach, where it has long been recognised that visible contractions of varying amplitude occur with a maximal frequency of 3 per minute (Cannon, 1911). However, to deduce that the differing roles of the proximal and distal stomach are the direct result of their contractile activity is somewhat of

an over simplification.

The movement of intraluminal liquid across the pylorus both in a gastroduodenal (gastric emptying) and in a duodenogastric (reflux) direction is thought to due to the presence of a gastroduodenal pressure gradient (Nelson & Kohatsu, 1971), and changes in the pattern of flow across the pylorus are assumed to reflect alterations in the pressure gradient. This pressure gradient is thought to be regulated by the contractile activity of the stomach and duodenum, although the exact relationships remain unknown.

Much of the current knowledge concerning the relationship between gastroduodenal motility and transpyloric flow originates from radiological studies using barium containing contrast media (Smith et al, 1957; Freidman et al, 1965; Prove & Ehrlein, 1982). However, interpretation of the direction of movement of an uninterrupted column of barium which extends from the antrum to the duodenal bulb may be impossible (Smith et al, 1957; Griffith et al, 1968; Fisher et al, 1982). Simultaneous studies of intraluminal flow and contractility have also been undertaken in man using intubation (Kaye et al, 1976; Rees et al, 1979 (ref 251)). The manometric methods of assessing contractility used in these studies have been discussed previously (pages 27-32). Doubt has been cast on the ability of perfused catheter systems to record the occurrence of contractions that do not occlude the side-holes of the catheter (Christensen, 1981; White et al, 1983; Mearin et al, 1986) and, in addition, it has been suggested that the physical presence of a intraluminal device may influence not only the pattern of contractions (McShane et al, 1980; Valori et al, 1986) but also

intraluminal fluid movement (Tolin et al, 1979; Muller-Lissner et al, 1982). As a result of these difficulties, there is still considerable uncertainty about the relationships between muscle contractions and intraluminal pressure changes.

The studies with the ultrasonic technique were an attempt to examine the characteristics of fluid movement across the pylorus and its relationship to gastroduodenal motility by using a non-invasive method with a temporal resolution greater than presently available manometric techniques, and without the problems of contrast studies. The observations were made in subjects who had ingested a 500ml liquid test meal and thus relate to the postprandial period where the "fed" pattern of contractile activity is distinctly different from the "fasting" pattern descibed by others as the interdigestive motor activity (Cooke, 1975; Rees et al, 1979 (ref 250)).

In all the ultrasonic studies carried out in normal subjects, the most consistent finding was the episodic nature of fluid movement across the pylorus as reflected by movements of the small echogenic bran particles. These intermittent episodes were of short duration, lasting a few seconds only, and occurred a variable number of times during each gastric cycle. On average 2 episodes of gastroduodenal flow each lasting 2 to 3 seconds, were observed in most gastric cycles. In contrast, duodenogastric flow, which was observed much less frequently, occurred on average just less than once per gastric cycle, in episodes lasting around 2 seconds. A further most interesting observation was the relationship of the episodes of transpyloric movement to the contractions of the terminal antrum and

proximal duodenum. Gastroduodenal flow was observed mainly to occur after the terminal antral contraction as the gastroduodenal region relaxed and its lumen regained patency. In constrast, episodes of duodenogastric flow occurred mainly in the short interval just before the terminal antral contraction. However, although the pylorus was patent for about 70% of the duration of any gastric cycle, and despite the presence of steadily-advancing antral contractions, no flow in either direction was observed during approximately half of this time.

These findings have previously been discussed in relation to the current theories concerning the mechanisms responsible for the emptying of liquids from the stomach (pages 104 and 127), but it is worth summarising the major points and reconsidering their interpretation.

Figure 25 (page 179), which is based on a similar figure by Carlson (1977), illustrates diagramatically the basic pattern of the timing and duration of contractions of the terminal antrum, pylorus and proximal duodenum and also that of the episodes of transpyloric fluid movement.

Contractions of the gastric antrum progress distally towards the pylorus every 20 - 30 seconds in man, ending in contraction of the immediate prepyloric region (terminal antral contraction, TAC). The pylorus contracts synchronously with the second half of the terminal antral contraction. Contractions of the proximal duodenum begin while the pylorus is closed, but do not usually end until the pylorus and terminal antrum have begun to relax and their lumena are already patent. These observations made in normal man with the

ultrasonic technique are, as discussed previously (pages 114-116), in complete agreement with established views on the pattern of gastroduodenal contractile activity.

The pattern of transpyloric fluid movement is depicted by the arrows in Figure 25 (page 179). The traditional views on gastric emptying of liquids, of which there are two, suggest that emptying occurs either as gushes in response to the pumping action of antral peristalsis (open arrows) (Cooke, 1975; Jacobs et al, 1982; Brener et al, 1983) or as a steady flow (not shown in Figure 25) in response to the tonic contraction of the proximal stomach (Strunz & Grossman, 1978; Rees et al, 1979 (ref 250); Malagelada, 1979; Kelly 1980), interrupted only by pyloric closure. Clearly, the pattern of flow observed by the ultrasonic technique (black arrows) cannot be directly attributable to a steadily advancing antral contraction, nor to the tonic contraction of the proximal stomach. These brief fluctuations in transpyloric flow must reflect alterations in the intraluminal pressures in the stomach and/or duodenum. If, as these observations suggest, the contractile activity of the proximal and distal stomach are not solely responsible for the flow patterns, then perhaps it may be that fluctuations in the intraluminal pressure in the distal duodenum, where the frequency of contractions is known to be much greater than 2 - 3 per minute, play a role. The concept that the duodenum, where many of the receptors known to influence gastric emptying are situated, is responsible for the fine regulation of transpyloric fluid movement would seem an attractive one and worthy of further consideration.

The conclusions drawn from the present observations must, of course,

FIGURE 25 - Patterns of antroduodenal contractile activity and transpyloric fluid movement *
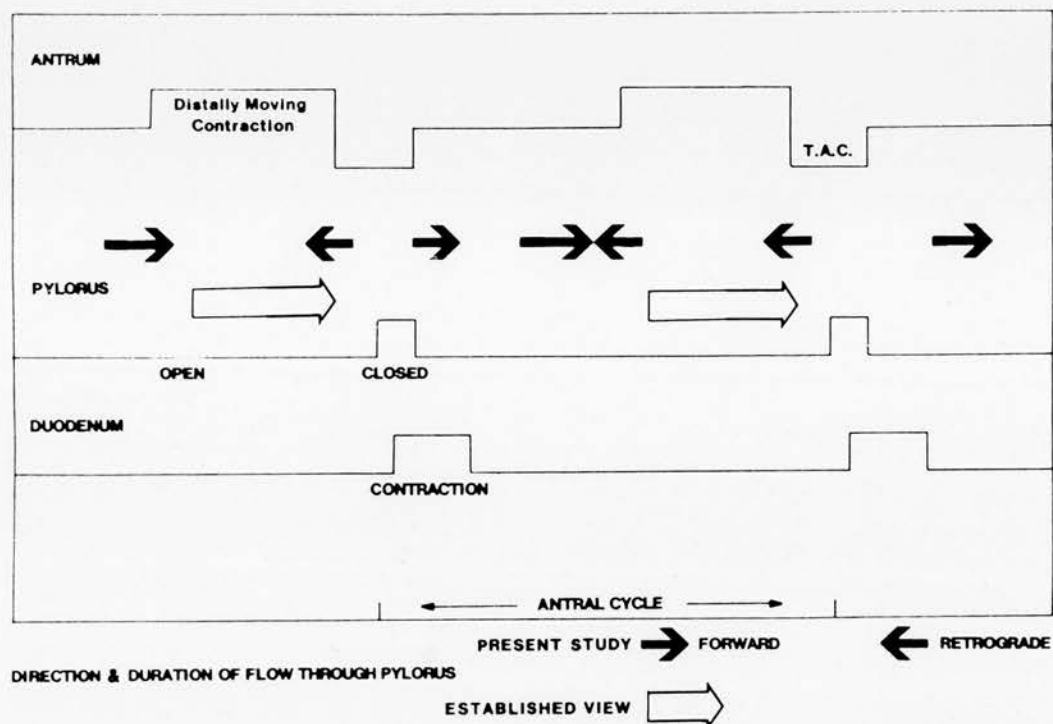
The relative timing and duration of contractions of the terminal antrum (TAC), pylorus and proximal duodenum are depicted by the raised or lowered segments of each of the 3 lines respectively. The associated patterns of transpyloric fluid movement are illustrated by the arrows. The black arrows depict the findings of the present study, while the open arrows represent one of the traditional views.

* Based on a similar figure by Carlson (1977).

be tempered by the realisation that the findings relate to the behaviour of intragastric liquids, and, moreover, that they do not encompass the full range of physical characteristic of normal ingested foodstuffs. In particular, neither the behaviour of liquids of varying viscosity nor lipid-containing test meals have as yet been examined with the ultrasonic technique. It therefore remains possible that differing patterns of antroduodenal motility and transpyloric fluid movement may occur in other situations.

There is, nowadays, increasing awareness that the symptoms and signs of many upper gastro-intestinal disorders are related to disturbances in gastric emptying and the mechanisms responsible for its regulation. Over the years the numerous investigations that have been carried out in both man and animals have resulted in considerable progress in the understanding of gastroduodenal function. Nevertheless, there is still dispute about many aspects of normal function, several of which have been discussed and a number examined by the ultrasonic technique. Until these points are clarified, attempts to assess the clinical significance of investigations in patients may be hampered. Thus there is ample justification for further research into normal as well as abnormal gastroduodenal function.

In summary, this thesis documents the refinement and application of real-time ultrasonic imaging as a non-invasive technique to allow observation of events at the gastric outlet in humans. The ultrasonic technique enables physiological observations to be made which cannot presently be achieved by any other method. It has produced some novel findings, particularily concerning the timing of

fluid movement across the pylorus in relation to the peristaltic contraction. I believe, therefore, that the technique merits continued development to enhance and apply its now-established place as a method for the investigation of gastric emptying and the mechanisms responsible for its regulation in man.

7.0.0 <u>Appendices</u>

7.1.0 Isotopic Emptying Studies

The use of test meals labelled with radionuclides in conjunction with upper abdominal scintigraphy as a means of measuring gastric emptying has been discussed in Section 2.2.1 (pages 22-24). Sagar and co-workers (1983) described the use of the isotopic marker Technetium-99M labelled commercial All-Bran(R) which, when ingested as part of a normal meal, could be used to measure gastric emptying. The technique of labelling of the natural bran particles used as the sonic marker in the liquid test meals of the present study was based on modifications of their methods.

The aim of the isotopic studies was to determine whether the emptying of the echogenic bran particles mirrored that of the liquid in which they were suspended during the period the ultrasonic observations were being performed. After discussion with Dr P Tothill of the Department of Medical Physics, Royal Infirmary, Edinburgh, it was decided to use Indium-113m (In-113m) to label the bran particles and Technetium-99m (Tc-99m) to label the liquid.

7.1.1 Preparation of In-113M bran

A volume of In-113m generator eluate (Hydrochloric acid) containing 10-20MBq was added to 0.5g of the bran particles and made up to 10mls with sterile water. The mixture was thoroughly mixed for 30 minutes and centrifuged at 4000rpm for 5 minutes. The supernatant was removed and then a fresh 10mls of sterile water was added to wash the bran. The mixture was recentrifuged as before, and the supernatant removed. The washing with fresh sterile water and centrifugation was repeated until the In-113m activity of the

Table A.1 - Comparison of isotopic activity of labelled bran particles and supernatant after repeated washes.

Wash	Bran activity +	Supernatant activity *
1	100	12.5
2	95	2.8
3	89	1.3
4	87	0.9
5	82	0.8
6	82	0.7
7	79	0.55

+ Bran activity (expressed as a percentage of the In-113m activity after the 1st wash) falls due to a combination of radionuclide decay and leaching of the In-113m from the bran

* Supernatant activity is expressed as a percentage of the corresponding bran activity

Table A.2 - In-113m activity in the liquid phase

Time after addition of In-113m Bran*	>---- Activity in liquid-phase£ ----<	
	Orange juice	OJ + Gastric Juice
0	0	0
14	6.6	7.9
24	8.3	10.5
34	8.4	11.1
44	10.0	12.2
54	10.9	13.4
64	11.3	12.9

* Minutes

£ The activity of the In-113m in the liquid-phase is expressed as a percentage of the corresponding activity bound to the bran.

supernatant was less than one per cent of the bran activity. The preparation of the labelled bran was a comprimise between keeping the time involved short to minimise the effects of radionuclide decay, while effectively removing unbound isotope from the supernatant. Table A.1 (page 184) compares the isotopic activity of the bran particles and the supernatant after successive washings at 5 minute intervals. Four washes were considered sufficient.

7.1.2 Preparation of Tc-99m liquid

The labelling of the liquid phase of the test meal was accomplished by adding 10-15 MBq of Tc-99m-DTPA to 500mls of dilute orange juice (100mls of Kia-Ora and 400mls of tap water) at 37˙C.

7.1.3 Stability of the labels

The ability of the In-113m to remain bound to the bran, and that of the Tc-99m to remain in the liquid phase, were examined under conditions simulating a test meal.

Table A.2 (page 185) shows the percentage of the total In-113m activity found in the liquid-phase at intervals over 60 minutes after the addition of labelled bran to 500mls of unlabelled orange juice. In the third column of Table A.2, the labelled bran was added to a mixture of 400mls of orange juice and 100mls of gastric juice aspirated from a patient undergoing gastric acid studies. This was an "in vitro" attempt to simulate the conditions in the stomach after ingestion of the test meal. The activity of the liquid was measured by sampling 10ml aliquots at intervals, then by measuring the activity of the samples and correcting for decay of

the label, the total activity could be calculated. Although around 12% of the In-113m initially bound to the bran eventually leached off into the liquid phase in both test meals, the stablity of the bran labelling was considered acceptable.

The stability of the Tc-99m-DTPA liquid marker was assessed by adding 0.5g of unlabelled bran to 500mls of labelled orange juice and measuring the Tc-99m activity bound to the bran after 30 minutes. When corrected for decay, it was found that only 4.2% of the total activity had become bound to the bran.

7.1.4 Emptying studies

The isotopic emptying studies were performed using a dual headed rectilinear scanner (J & P) linked to a computer. The intragastric activity of each isotope was measured at intervals and expressed as a percentage of the first measurement made immediately after ingestion of the test meal. The results of the investigation are described in section 4.5.0 (pages 75-79).

7.2.0 <u>List of Figures</u>

7.3.0 <u>List of Tables</u>

7.4.0 Presentations

Some of the results documented in this thesis have been presented to the meetings listed below.

Fluid oscillations across the human pylorus. King, PM, Adam, RC, Pryde, A, McDicken, WN and Heading, RC. Presented to Scottish Society for Experimental Medicine, Edinburgh, Nov. 1983. Abstract: Scot Med J 29: 44, 1984.

Dynamic relationships of events at the human gastroduodenal junction. Non-invasive observations with real-time ultrasound. King, PM, Adam, RC, Pryde, A, McDicken, WN and Heading, RC. Presented to Surgical Research Society, London, Jan. 1984. Abstract: Br J Surg 71: 378, 1984.

Human transpyloric fluid movement and related gastroduodenal motor activity. The effects of 4 different test meals. King, PM, Pryde, A and Heading, RC. Presented to 2nd European Symposium on Gastro-intestinal Motility, Oxford, Sept. 1984.

The co-ordinated motor activity of the human terminal antrum, pylorus and proximal duodenum. King, PM, Pryde, A and Heading, RC. Presented to 8th World Congress of the C.I.C.D., Amsterdam, Sept. 1984. Abstract: Dig Surg 1: 69, 1984.

Antroduodenal motility and fluid movement post-vagotomy. King, PM. Presented to Annual Surgical Meeting, Department of Clinical Surgery, University of Edinburgh, Feb. 1986.

Transpyloric fluid movement and associated antroduodenal motility in patients with gastro-oesophageal reflux and controls. King, PM, Pryde, A and Heading, RC. Presented to 3rd European Symposium on Gastrointestinal Motility, Brussels, Belgium, Jun. 1986.

Effects of truncal vagotomy and pyloroplasty and highly selective vagotomy on antroduodenal motility and transpyloric fluid movement. King, PM, Pryde, A and Heading, RC. Presented to British Society of Gastroenterology, Cardiff, England, Sept. 1986. Abstract: Gut 27: 1256, 1986

7.5.0 <u>PUBLICATIONS</u>

The aspects of this thesis which have already been published are listed below.

Relationships of human antroduodenal motility and transpyloric fluid movement: non-invasive observations with real-time ultrasound. King, PM, Adam, RC, Pryde, A, McDicken, WN and Heading, RC. Gut 25: 1384-1391, 1984.

The co-ordinated motor activity of the human gastroduodenal region. King, PM, Heading, RC and Pryde, A. Dig Dis Sci 30: 219-224, 1985.

Transpyloric fluid movement and antroduodenal motility in patients with gastro-oesophageal reflux. King, PM, Pryde, A and Heading, RC. Gut: In Press.

(Published Abstracts are listed with the associated presentation on the previous page)

8.0.0 Bibliography

(1)   Adam RD, Heading RC, Anderson T, McDicken WN: Application of
        real-time ultrasonic imaging to the study of gastric motility: in
        Motility of the digestive tract: Ed Wienbeck M: Raven Press, New
        York, 1982

(2)   Amdrup E, Griffith CA: Selective vagotomy of the parietal cell
        mass. Part I: with preservation of the innervated antrum and
        pylorus: Am J Surg 170: 207-214, 1969

(3)   Amdrup E, Jensen H-E: Selective vagotomy of the parietal cell
        mass preserving innervation of the undrained antrum:
        Gastroenterol 59: 522-527, 1970

(4)   Anderson JJ, Bolt RJ, Ullman BM, Bass P: Differential response
        to various stimulants in the body and antrum of the canine
        stomach: Amer J Dig Dis 13: 147-156, 1968

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

(6)   Anuras S, Cooke AR: An inhibitory mechanism at the gastroduodenal
        junction: J Clin Invest 54: 529-535, 1974

(7)   Atkinson M, Edwards DAW, Honour AJ, Rowlands EN: Comparison of
        cardiac and pyloric sphincters: Lancet 2: 918-922, 1957

(8)   Azpiroz F, Malagelada JR: Physiological variations in canine
        gastric tone measured by an electronic barostat: Am J Physiol
        248: G229-G237, 1985

(9)   Azpiroz F, Malagelada JR: Tonic activity of the human stomach
        during fasting: Quantification by an electronic barostat:
        Gastroenterol 88: 1312, 1985

(10)   Aune S: Intragastric pressure after vagotomy in man: Scand J
        Gastroent 4: 447-452, 1969

(11)   Barker GR, Cochrane GMcL, Corbett GA, Hunt JN, Roberts SK:
        Actions of glucose and potassium chloride on osmoreceptors
        slowing gastric emptying: J Physiol 237: 183-186, 1974

(12)   Barker GR, Cochrane GMcL, Corbett GA, Dufton JF, Hunt JN, Roberts
        SK: Glucose, Glycine and diglycine test meals as stimuli to
        duodenal osmoreceptors slowing gastric emptying: J Physiol 283:
        341-346, 1978

(13)   Bass P, Code CF, Lambert EH: Electrical activity of
        gastroduodenal junction: Am J Physiol 201: 587-592, 1961

(14)   Bateman DN, Leeman S, Metreweli C, Willson K: A non-invasive
        technique for gastric motility measurement: Br J Radiol 50:
        526-527, 1977

(15)   Bateman DN, Whittingham TA: Measurement of gastric emptying by real-time ultrasound: Gut 23: 524-527, 1982

(16)   Bayliss WM, Starling FH: The movements and innervation of the small intestine: J Physiol 24: 99-143, 1899

(17)   Beaumont W: Experiments and observations on the gastric juice and the physiology of digestion: Plattsburgh, N.Y.F.P. Allen, 1833

(18)   Behar J, Ramsby G: Gastric emptying and antral motility in reflux esophagitis: effect of oral metoclopramide: Gastroenterol 74: 253-256, 1978

(19)   Bolondi L, Bortolotti M, Santi V, Calletti T, Gaiani S, Labo G: Measurement of gastric emptying time by real-time ultrasonography: Gastroent 89: 752-759, 1985

(20)   Bom N, Lancee CT, Honkoop J, Hugenholtz PG: Ultrasonic viewer for cross-sectional analysis of moving cardiac structures: Biomed Eng 6: 500-508, 1971

(21)   Bortoff A, Davis RS: Myogenic transmission of antral slow waves across the gastroduodenal junction in situ: Am J Physiol 215: 889-897, 1968

(22)   Bow CR, McDicken WN, Anderson T, Scorgie RE, Muir AL: A rotating transducer real-time scanner for ultrasonic examination of the heart and abdomen: Br J Radiol 52: 29-33, 1979

(23)   Brandsborg O, Brandsborg M, Lovgreen NA, Mikkelsen K, Moller B, Rokkjaer M, Amdrup E: Influence of parietal cell vagotomy and selective gastric vagotomy on gastric emptying rate and serum gastric concentration: Gastroenterol 72: 212-214, 1977

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

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

(26)   Bromster D, Carlberger G, Lundh G: Measurement of gastric emptying-rate: Lancet 2: 224-225, 1966

(27)   Bromster D, Carlberger G, Lundh G: Measurement of gastric emptying rate using I-131-HSA (A methodological study in man): Scand J Gastroent 3: 641-653, 1968

(28)   Brough WA, Taylor TV, Torrance HB: The surgical factors influencing duodenogastric reflux: Br J Surg 71: 770-773, 1984

(29)   Buckler KG: Effects of gastric surgery upon gastric emptying in cases of peptic ulceration: Gut 8: 137-147, 1967

(30)   Burn-Murdoch R, Fisher MA, Hunt JN: Does lying on the right side increase the rate of gastric emptying: J Physiol 302: 395-398, 1980

(31)   Burns TW: Motor disorders of the esophagus: diagnosis and treatment: S Med J 77: 956-961, 1984

(32)   Calderon M, Sonnemaker RE, Hersh T, Burdine JA: Tc-99m human albumin microspheres (HAM) for measuring the rate of gastric emptying: Radiol 101: 371-374, 1971

(33)   Cannon WB: The movements of the stomach studied by means of the roentgen rays: Am J Physiol 1: 359-382, 1898

(34)   Cannon WB: The mechanical factors of digestion: Ed. Green. Longmans, New York: 136-163, 1911

(35)   Cannon WB, Lieb CW: The receptive relaxation of the stomach: Am J Physiol 29: 267-273, 1911

(36)   Cannon WB, Murphy FT: The movements of the stomach and intestines in some surgical conditions: Ann Surg 43: 512-536, 1906

(37)   Cannon WB, Washburn AL: An explanation of hunger: Am J Physiol 29: 441-445, 1912

(38)   Capper WM, Airth GR, Kilby JO: A test for pyloric regurgitation: Lancet 2: 621-623, 1966

(39)   Carlson AJ: Contributions to the physiology of the stomach: Articles 1-23: Am J Physiol 31: 151, 1912

(40)   Carlson HC: In Physiology of the digestive tract: Ed. Davenport HW, Year Book Med Publ Inc, 1977

(41)   Carlson HC, Code CF, Nelson RA: Motor activity of the canine gastroduodenal junction: a cineradiographic, pressure and electric study. Am J Dig Dis 11: 155-172, 1966

(42)   Carnot P, Chassevant A: (a) Modifications subies dan l'estomac et le duodenum par les solutions salines suivant leur concentration moleculaire. Le reflex regulateur du sphincter pylorique: Compt Rend Soc Biol 58: 173-176, 1905

(43)   Cartwright RA, McKinney PA, Hopton PA, Birch JM, Hartley AL, Mann JR, Waterhouse JAH, Johnston HE, Draper GJ, Stiller C: Ultrasound examinations in pregnancy and childhood cancer: Lancet ii: 999-1000, 1984

(44)   Chang CA, McKenna BD, Beck JT: Gastric emptying rate of the water and fat phases of a mixed test meal in man: Gut 9: 420-424, 1968

(45)   Chaudhuri TK: Radioisotope tracer techniques-a more accurate method of quantitating gastric emptying: J Nucl Med 15: 197-198, 1974

(46)   Chey WY, Hitanant S, Hendricks J et al: Effect of secretin and cholecystokinin on gastric emptying and gastric secretion in man: Gastroenterol 58: 820-827, 1970

(47)   Christensen J: Motility of the colon: In: Johnson LR, ed. Physiology of the gastrointestinal tract. New York: Raven, 445-471, 1981

(48)   Christensen J, Torres EI: Three layers of the opossum stomach: responses to nerve stimulation: Gastroenterol 69: 641-648, 1975

(49)   Christian PE, Moore JG, Sorensen JA, Coleman RE, Welch DM: Effects of meal size and correction technique on gastric emptying time: studies with two tracers and opposed detectors: J Nucl Med 21: 883-885, 1980

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

(51)   Cobb JS, Bank S, Marks IN, Louw JH: Gastric emptying after vagotomy and pyloroplasty: relation to some postoperative sequelae: Dig Dis 16: 207-215, 1971

(52)   Code CF, Hightower NC, Morlock CG: Motility of the alimentary canal in man: Am J Med 13: 328-351, 1952

(53)   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 24: 1117-1125, 1983

(54)   Colmer MR, Owen GM, Sheilds R: Pattern of gastric emptying after vagotomy and pyloroplasty: Br Med J ii: 448-450, 1973

(55)   Cooke AR: Duodenal acidification: Role of the first part of the duodenum in gastric emptying and secretion in dogs: Gastroenterol 67: 85-92, 1974

(56)   Cooke AR: Control of gastric emptying and motility: Gastroenterol 68, 804-816, 1975

(57)   Cooke AR, Chvasta TE, Weisbrodt NW: Effect of pentagastrin on emptying and electrical and motor activity of the dog stomach: Am J Physiol 223: 934-938, 1972

(58)   Cooke AR, Moulang J: Control of gastric emptying by amino acids: Gastroenterol 62: 528-532, 1972

(59)   Cooperman AM, Cook SA: Gastric emptying - Physiology and measurements: Surg Clin N Am 56: 1277-1287, 1976

(60)   Cornax M: Medical consultations apud aegnoteos secundum artem et experientiam salubriter instituendae enchiridion, Bale: 1564 (Cited by CG Cumston) Med J Rec 124: 229, 1926

(61)   Cortot A, Phillips SF, Malagelada JR: Gastric emptying of lipids
         after ingestion of a solid-liquid meal in humans: Gastroenterol
         80: 922-927, 1981

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

(63)   Crade M, Taylor KJW, Rosenfield AT: Water distention of the gut
         in the evaluation of the pancreas by ultrasound. Am J Roentgenol
         131: 348, 1978

(64)   Crider JO, Earl Thomas J: A study of gastric emptying with the
         pylorus open: Am J Dig Dis 4: 295-300, 1937

(65)   Csendes A, Henriquez A: Gastric emptying in patients with reflux
         esophagitis or benign strictures of the esophagus secondary to
         reflux compared to controls: Scand J Gastroent 13: 205-207, 1978

(66)   Daniel EE, Carlow DR, Wachter BT, Sutherland WH, Bogoch A:
         Electrical activity of the small intestine: Gastroenterol 37:
         268-281, 1959

(67)   Daniel   EE,   Chapman KM: Electrical   activity   of   the
         gastrointestinal tract as an indication of mechanical activity:
         Am J Dig Dis 8: 54-102, 1963

(68)   Davenport HW: Physiology of the digestive tract. 4th ed. Year
         Book Medical Publishers Inc: Chicago, 1977: 41-57

(69)   Delin NA, Axelsson B, Johansson C, Poppen B: Comparison of gamma
         camera and withdrawl methods for the measurement of gastric
         emptying: Scand J Gastroenterol 13: 867-872, 1978

(70)   DeMeester TR, Wang CI, Wernby JA, Pellegrini CA, Little AG,
         Klementschitsch P, Bermudez G, Johnson LF, Skinner DB:
         Techniques, indications and clinical use of 24 hour esophageal pH
         monitoring: J Thor Cardiovasc Surg 79: 656-670, 1980

(71)   de Salamanca FE, Tamarit Torres J: Estudios de fisiologia
         gastrica: Consejo   Superior   de Investigationes Cientificas,
         Instituto de Medicina Experimental, Madrid, 1956

(72)   Dewar P, King R, Johnston D: Bile acid and lysolecithin
         concentrations in the stomach in patients with duodenal ulcer
         before   operation   and after treatment by highly selective
         vagotomy, partial gastrectomy, or truncal vagotomy and drainage:
         Gut 23: 569-577, 1982

(73)   Dewar EP, Dixon MF, Johnston D: Bile reflux and degree of
         gastritis after highly selective vagotomy, truncal vagotomy, and
         partial gastrectomy for duodenal ulcer: World J Surg 7: 743-750,
         1983

(74)   Donald I, MacVicar J, Brown TG: Investigation of abdominal masses
         by pulsed ultrasound: Lancet i: 1188-1195, 1958

(75)   Donovan IA, Gunn IF, Brown A, Alexander-Williams J, Clarke RJ: A comparison of gastric emptying before and after vagotomy with antrectomy and vagotomy with pyloroplasty: Surg 76: 729-732, 1974

(76)   Dooley CP, Reznick JB, Valenzuela JE: Variations in gastric and duodenal motility during gastric emptying of liquid meals in humans: Gastroenterol 87: 1114-1119, 1984

(77)   Dozois RR, Kelly KA, Code CF: Effect of distal antrectomy on gastric emptying of liquids and solids: Gastroenterol 61: 675-681, 1971

(78)   Dragstedt LR, Camp EH: Follow-up of gastric vagotomy alone in the treatment of peptic ulcer: Gastroenterol 11: 460-465, 1948

(79)   Dragstedt LR, Owens FM: Supra-diaphragmatic section of the vagus nerves in the treatment of duodenal ulcer: Proc Soc Exp Biol Med 53: 152-154, 1943

(80)   Dragstedt LR, Harper PV, Tovee EB, Woodward ER: Section of the vagus nerves to the stomach in the treatment of peptic ulcer: complications and end results after four years: Ann Surg 126: 687-699, 1947

(81)   Dubois A: Pathophysiology of gastric emptying: methods of measurement and clinical significance: J Clin Gastroenterol 1: 259-266, 1979

(82)   Dubois A, Berman M: Gastric emptying and secretion. Kinetic analysis and physiological model. In Proceedings of the IVth International Symposium on Gastrointestinal Motility. Mitchell Press. Vancouver, Canada: 523-536, 1974

(83)   Dubois A, Van Eerdwegh P, Line B, Gardner JD: A new method for simultaneous determination of gastric emptying and secretion: In Proceedings of the Vth International Symposium on gastrointestinal Motility. Typoff-Press, Herentals. Belgium, 244-247, 1976

(84)   Dubois A, Nompleggi D, Myers L, Castell DO: H2 receptor stimulation increases gastric emptying: Gastroenterol 74: 1028, 1978 (Abstr)

(85)   Duthie HL, Kwong NK, Brown BH, Whittaker GE: Pacesetter potential of the human gastroduodenal junction: Gut 12: 250-256, 1971

(86)   Earl Thomas J: Mechanics and regulation of gastric emptying: Physiol Rev 37: 453-474, 1957

(87)   Edwards DAW: Physiological concepts of the pylorus: Proc R Soc Med 54: 930-933, 1961

(88)   Elias E, Gibson GJ, Greenwood LF, Hunt JN, Tripp JH: The slowing of gastric emptying by monosaccharides and disaccharides in test meals: J Physiol 194: 317-326, 1968

(89)   Fakhry JR, Berk RN: The "Target" Pattern: Characteristic sonographic feature of stomach and bowel abnormalities: AJR 137: 969-972, 1981

(90)   Farrell JI, Ivy AC: Studies on the motility of the transplanted gastric pouch: Am J Physiol 76: 227-228, 1926

(91)   Feldman M, Shapiro BJ, Berkowitz D: Comparison of effects of medium chain and long chain triglycerides on the role of gastric emptying (Abstr): Gastroenterol 60: 774, 1971

(92)   Finch JE, Kendall MJ, Mitchard M: An assessment of gastric emptying by breathalyser: Br J clin Pharmac 1: 233-236, 1974

(93)   Fink SM, Lange RC, McCallum RW: Effect of metoclopramide on normal and delayed gastric emptying in gastroesophageal patients: Dig Dis Sci 28: 1057-1061, 1983

(94)   Fisher R, Cohen S: Physiological characteristics of the human pyloric sphincter: Gastroenterol 64: 67-75, 1973

(95)   Fisher RS, Lipschutz W, Cohen S: The hormonal regulation of pyloric sphincter function: J Clin Invest 52: 1289-1296, 1973

(96)   Fisher RS, Malmud LS, Bandini P, Rock E: Gastric emptying of a physiologic mixed solid-liquid meal: Clin Nucl Med 7: 215-222, 1982

(97)   Fordtran JS, Walsh JH: Gastric acid secretion rate and buffer content of the stomach after eating: results in normal subjects and in patients with duodenal ulcer: J clin Invest 52: 645-657, 1973

(98)   Freidman G, Wolf BS, Waye JD, Janowitz HD: Correlation of cineradiographic and intraluminal pressure changes in the human duodenum: an analysis of the functional significance of monophasic waves: Gastroenterol 49: 37-49, 1965

(99)   Ganong, WF: Review of Medical Physiology: 9th Ed: Lange Medical Publications, California, 1979: 371-395

(100) George JD: New clinical method for measuring the rate of gastric emptying: the double sampling test method: Gut 9: 237-242, 1968

(101) Gibb WT: A theory concerning the manner in which the stomach empties itself: An Intern Med 16: 94-103, 1942

(102) Gillison EW, Capper WM, Airth GR, Gibson MJ, Bradford I: Hiatus hernia and heartburn: Gut 10: 609-613, 1969

(103) Gillison EW, de Castro VAM, Nyhus LM, Kusakari K, Bombeck CT:
       The significance of bile in reflux esophagitis: Surg Gynec Obstet
       134: 419-424, 1972

(104) Gleysteen JJ, Gohlke EG: The antrum can control gastric emptying
       of liquid meals: J Surg Res 26: 381-391, 1979

(105) Go VLW, Hoffman AF, Summerskill WHJ: Simultaneous measurements of
       total pancreatic, biliary, and gastric outputs in man using a
       perfusion technique: Gastroenterol 58: 321-328, 1970

(106) Goldstein H, Boyle JD: The saline load test: a bedside evauation
       of gastric retention: Gastroenterol 49: 375-380, 1965

(107) Goligher JC, Pulvertaft CN, de Dombal FT, Conyers JH, Duthie HL,
       Feather DB, Latchmore AJC, Harrop-Shoesmith J, Smiddy F,
       Willson-Pepper J: Five- to eight-year results of Leeds/York
       controlled trial of elective surgery for duodenal ulcer: Br Med J
       2: 781-787, 1968

(108) Goodall: The effect of vagotomy and a drainage procedure on the
       rate of gastric emptying (Abstr): Br J Surg 53: 995, 1966

(109) Gordon D: Echo-encephalography: ultrasonic rays in diagnostic
       radiology: Br Med J i: 1500-1504, 1959

(110) Gordon OL, Chernya YM: Physiology of the gastric secretion in
       man; studies on patients with gastric fistula and artificial
       esophagus: Klin Med (No 12) 18: 63-71, 1940

(111) Griffith CA, Harkins HN: Partial gastric vagotomy - an
       experimental study: Gastroenterol 32: 96-102, 1957

(112) Griffith GH, Owen GM, Kirkman S, Shields R: Measurement of rate
       of gastric emptying using chromium-51: Lancet 1: 1244-1245, 1966

(113) Griffith GH, Owen GM, Campbell H, Shields R: Gastric emptying in
       health and in gastroduodenal disease: Gastroenterol 54: 1-7, 1968

(114) Grimes DS, Goddard J: Gastric emptying of wholemeal and white
       bread: Gut 18: 725-729, 1977

(115) Guerts WJC, Winckers EKA, Wittebol P: The effects of highly
       selective vagotomy on secretion and emptying of the stomach: Surg
       Gynaecol Obstet 145: 826-836, 1977

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

(117) Harris LD, Winas CS, Pope CE: Determination of yield pressures; a
       method for measuring anal sphincter competence: Gastroenterol 50:
       754-760, 1966

(118)   Harvey RF, Mackie DB, Brown NJG, Keeling DH, Davies WT: Measurement of gastric emptying time with a gamma camera: Lancet 1: 16-18, 1970

(119)   Heading RC: Gastric motility: Front Gastrointest Res 6: 35-56, 1980

(120)   Heading RC: Gastric emptying: a clinical perceptive: Clin Sci 63: 231-235, 1982

(121)   Heading RC: Duodenogastric reflux: Gut 24: 507-509, 1983

(122)   Heading RC, Tothill P, Laidlaw AJ, Shearman DJC: An evaluation of indium-131 DTPA chelate in the measurement of gastric emptying by scintiscanning: Gut 12: 611- 615, 1971

(123)   Heading RC, Nimmo J, Prescott LF, Tothill P: The dependance of paracetamol absorption on the rate of gastric emptying: Br J Pharmacol 47: 415-421, 1973

(124)   Heading RC, Tothill P, McLoughlin GP, Shearman DJC: Gastric emptying rate measurement in man: a double isotope scanning technique for simulataneous study of liquid and solid components of a meal: Gastroenterol 71: 45-50, 1976

(125)   Helsingen N: Oesophagitis following total gastrectomy in rats: Acta Chir Scand 119: 230-245, 1960

(126)   Hinder RA, Kelly KA: Human gastric pacesetter potential: Am J Surg 133: 29-33, 1977

(127)   Hoare AM, Jones EL, Alexander-Williams J, Hawkins CF: Symptomatic significance of gastric mucosal changes after surgery for peptic ulcer: Gut 18: 295-300, 1977

(128)   Hoffman J, Jensen H-E, Schulze S, Poulsen PE, Christiansen J: Prospective controlled vagotomy trial for duodenal ulcer: results after five years: Br J Surg 71: 582-585, 1984

(129)   Holm HH: Ultrasonic scanning in the diagnosis of space- occupying lesions of the upper abdomen: Br J Radiol 44: 24, 1971

(130)   Holm HH, Mortensen T: Ultrasonic scanning in diagnosis of abdominal disease: Acta Chir Scand 134: 333-341, 1968

(131)   Holmes JH, Findley L, Frank B: Diagnosis of pancreatic pathology using ultrasound: Trans Am Clin Climatol Assoc 85: 224, 1973

(132)   Holt S, Heading RC, Carter DC, Prescott LF, Tothill P: Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol: Lancet 1: 636-639, 1979

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

(134) Holt S, Cervantes J, Wilkinson AA, Wallace JHK: Measurement of gastric emptying rate in humans by real-time ultrasound: Gastroenterol 90: 918-923, 1986

(135) Horowitz M, Cook DJ, Collins PJ, Harding PE, Shearman DJC: The application of techniques using radionuclides to the study of gastric emptying: Surg Gynecol Obst 155: 737-744, 1982

(136) Horton JW, McClelland RN, Weger RV: Effect of parietal cell vagotomy on gastric emptying in duodenal ulcer disease: Am J Surg 143: 86-89, 1982

(137) Horton RE, Ross FGM, Darling GH: Determination of the emptying-time of the stomach by the use of enteric coated barium granules: Br Med J i: 1537-1539, 1965

(138) Howarth FH, Cockel R, Roper BW, Hawkins CF: The effect of metoclopramide upon gastric motility and its value in barium progress meals: Clin Radiol 20: 294-300, 1969

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

(140) Humphrey CS, Wilkinson AR: The value of preserving the pylorus in the surgery of duodenal ulcer: Br J Surg 59: 779-783, 1972

(141) Humphrey CS, Johnston D, Walker BE, Pulvertaft CN, Goligher JC: Incidence of dumping after truncal and selective vagotomy with pyloroplasty and highly selective vagotomy without drainage proceedure: Br Med J 3: 785-790, 1972

(142) Hunt JN: The viscosity of a test-meal: its influence on gastric secretion and emptying: Lancet 1: 17-18, 1954

(143) Hunt JN: Some properties of an alimentary osmoreceptor mechanism: J Physiol (Lond) 132: 267-288, 1956

(144) Hunt JN: Gastric emptying and secretion in man: Physiol Rev 39: 491-553, 1959

(145) Hunt JN: The site of receptors slowing gastric emptying in response to starch in test meals: J Physiol (Lond) 154: 270-276, 1960

(146) Hunt JN: The osmotic control of gastric emptying: Gastroenterol 41: 49-51, 1961

(147) Hunt JN: A modification to the method of George for studying gastric emptying: Gut 15: 812-813, 1974

(148) Hunt JN, Knox MT: The regulation of gastric emptying of meals containing citric acid and salts of citric acid: J Physiol (Lond) 163: 34-45, 1962

(149) Hunt JN, Knox MT, Oginski A: The effect of gravity on gastric emptying with various test meals: J Physiol 178: 92-97, 1965

(150) Hunt JN, Knox MT: Regulation of gastric emptying: In Handbook of Physiology, vol 4, Alimentary Canal, ed Code: 1917-1935, Am Physiol Soc, Washington DC, 1968

(151) Hunt JN, Knox MT: A relation between the chain length of fatty acids and the slowing of gastric emptying: J Physiol (Lond) 194: 327-336, 1968

(152) Hunt JN, Knox MT: The slowing of gastric emptying by nine acids: J Physiol (Lond) 201: 161-179, 1969

(153) Hunt JN, Knox MT: The slowing of gastric emptying by four strong acids and three weak acids: J Physiol (Lond) 222: 187-208, 1972

(154) Hunt JN, Ramsbottom N: Effect of gastrin II on gastric emptying and secretion during a test meal: Br Med J 4: 386-387, 1967

(155) Hunt JN, Spurrell WR: The pattern of emptying of the human stomach: J Physiol (Lond) 113: 157-168, 1951

(156) Hunt JN, Stubbs DF: The volume and energy content of meals as determinants of gastric emptying: J Physiol (Lond) 245: 209-225, 1975

(157) Iggo A: Tension receptors in stomach and urinary bladder: J Physiol 128: 593-607, 1955

(158) Jacobs F, Akkermans LMA, Yoe OH, Hoekstra A, Wittebol P: A radioisotope method to quantify the function of fundus, antrum, and their contractile activity in gastric emptying of a semi-solid and solid meal: In Motility of the Digestive Tract: Ed Weinbeck, M: Raven Press, 1982

(159) Jacobs R, Killam H, Barefood C et al: Human application of a catheter with tip-mounted pressure and flow transducers: Rev Surg 29: 149-152, 1972

(160) Jacoby HI, Bass P, Bennet DR: In vivo extraluminal contractile force transducers for gastrointestinal muscle: J Appl Physiol 18: 658-665, 1963

(161) Jahnberg T: Gastric adaptive relaxation: Scand J Gastroent 9: suppl 46: 1-32, 1977

(162) Jansson G: Extrinsic nervous control of gastric motility: an experimental study in the cat: Acta Physiol Scand 326: suppl, 1-42, 1969

(163) Jansson G, Martinson J: Some quantitative consideration of vagally induced relaxation of the gastric smooth muscle in the cat: Acta Physiol Scand 63: 351-357, 1965

(164) Johnson AG: Peptic ulcer and the pylorus: Lancet 1: 710-712, 1979

(165)   Johnson AG, Eyre-Brook IA, Linhardt GE, Smallwood RH: Does the human pylorus close in response to an isolated duodenal cap contraction? Studies with a new technique: In Gastrointestinal Motility: 252-254. Ed Labo & Bortolotti, publ Cortina International, 1983

(166)   Johnston D, Wilkinson AR: Highly selective vagotomy without a drainage procedure in the treatment of duodenal ulcer: Br J Surg 57: 289-296, 1970

(167)   Jones T, Clark JC, Kocak N, Cox AG, Glass HI: Measurement of gastric emptying using the scintillation camera and Cs-129: Br J Radiol 43: 537-541, 1970

(168)   Kaye MD, Showalter P: Pyloric incompetence in reflux esophagitis: Clin Res 20: 733, 1972

(169)   Kaye MD, Mehta SJ, Showalter JP: Manometric studies of the human pylorus: Gastroenterol 70: 477-480, 1976

(170)   Keane FB, Dimagno EP, Malegalada JR: Duodenogastric reflux in humans: its relationship to fasting antroduodenal motility and gastric, pancreatic, and biliary secretion: Gastroenterol 81: 726-731, 1981

(171)   Keighley MRB, Asquith P, Edwards JAC, Alexander-Williams J: The importance of an innervated and intact antrum and pylorus in preventing postoperative duodenogastric reflux and gastritis: Br J Surg 62: 845-849, 1975

(172)   Kelly KA: Gastric emptying of liquids and solids: roles of proximal and distal stomach: Am J Physiol 239: G71-G76, 1980

(173)   Kelly KA, Code CF: Effect of transthoracic vagotomy on canine gastric electrical activity: Gastroenterol 57: 51-58, 1969

(174)   Kelly KA, Code CF: Canine gastric pacemaker: Am J Physiol 220: 112-117, 1971

(175)   Kelly KA, Code CF, Elveback LR: Patterns of canine gastric electrical activity: Am J Physiol 217: 461-470, 1969

(176)   Kelly M, Kennedy T: Motility changes in the antrum after proximal gastric vagotomy: Br J Surg 62: 215-220, 1975

(177)   Kikuchi Y, Tanaka K, Wagai T, Uchida R: Early cancer diagnosis though ultrasonics: J Acc Soc Am 29: 824-833, 1957

(178)   Kilby JO: Duodenogastric reflux and pyloric surgery: Gastroenterol 58: 593-595, 1970

(179)   Kinnear Wilson LM, Waterhouse JAH: Obstetric ultrasound and childhood malignancies: Lancet ii: 997-999, 1984

(180)   Kirsh TE: Motility of the small intestine in nonflocculating
        medium: A review of 1973 roentgen examinations: Gastroenterol 31:
        251-258, 1956

(181)   Klein E: Gastric motility. I. The origin and character of gastric
        peristalsis: Arch. Surg (Chic) 12: 571-582, 1926

(182)   Koffman CG, Hay DJ, Ganguli PC, Elder JB, Gillespie IE, Mantoudis
        SM, Tweedle DEF, Schofield PF, Palmer M: A prospective randomised
        trial of vagotomy in chronic duodenal ulceration: 4 year
        follow-up: Br J Surg 70: 342-345, 1983

(183)   Koster N, Madsen P: The intragastric pressure before and
        immediately after truncal vagotomy: Scand J Gastroent 5: 381-383,
        1970

(184)   Kremer H, Grobner W: Sonography of polypoid gastric lesions by
        the fluid-filled stomach method: J Clin Ultrasound 9: 51-54, 1981

(185)   Kroop HS, Long WB, Alavi A, Hansell JR: Effect of water and fat
        on gastric emptying of solid meals: Gastroenterol 77: 997-1000,
        1979

(186)   Kwong NK, Brown BH, Whittaker GE, Duthie, HL: Electrical
        activity of the gastric antrum in man: Br J Surg 57: 913-916,
        1970

(187)   Kwong NK, Brown BH, Whittaker GE, Duthie HL: Effect of gastrin I,
        secretin, and cholecystokinin-pancreozimin on the electrical
        activity, motor activity, and acid output of the stomach in man:
        Scand J Gastroent 7: 161-170, 1972

(188)   Lawson HH: The role of the pyloric antrum and Hofmeister valve in
        the development of the chronic gastric mucosal reaction: Br J
        Surg 63: 592-595, 1976

(189)   Lederer PC, Lauterbach H, Schmitt W, Domschke W, Lux G:
        Coordination of gastric and duodenal interdigestive motility and
        the effect of metoclopramide: Gastrointestinal Motility, Ed Labo
        & Bortolotti. Cortina International, 1983

(190)   Lerman SH, Mason GR, Bathon EM, Ormsbee HS: Pyloric motor
        response to sympathetic nerve stimulation in dogs: Surg 89:
        460-465, 1981

(191)   Liebeskind D, Bases R, Elequin F, Neubort S, Leifer R, Goldberg
        EE, Koenigsberg M: Diagnostic Ultrasound: Effects on the DNA and
        growth patterns of animal cells: Radiology 131: 177-184, 1979

(192)   Lind JF, Duthie HL, Schlegel JF, Code CF: Motility of the gastric
        fundus: Am J Physiol 201: 197-202, 1961

(193)   Little AG, DeMeester TR, Kirchner PT, O´Sullivan GC, Skinner DB:
        Pathogenesis of oesophagitis in patients with gastroesophageal
        reflux: Surgery 88: 101-107, 1980

(194)   Little AG, Martinez EI, DeMeester TR, Blough RM, Skinner DB: Duodenogastric reflux and reflux esophagitis: Surg 96: 447-454, 1984

(195)   Louckes HS, Quigley JP, Kersey J: Inductograph method for recording muscle activity, especially pyloric sphincter physiology: Am J Physiol 199: 301-310, 1960

(196)   Ludwick JR, Wiley JN, Bass P: Pyloroplasty and Vagotomy: early effects on antral and duodenal contractile activity: Arch Surg 99: 553-559, 1969

(197)   Ludwick JR, Wiley JN, Bass P: Gastric emptying following finney pyloroplasty and vagotomy: Dig Dis Sci 15: 347-352, 1970

(198)   Lutz H, Rettenmaier G: Sonographic pattern of tumors of the stomach and the intestine: Exc Med Int Cong Ser 277: 67, 1973 (Abst)

(199)   Lutz H, Petzoldt R: Ultrasonic patterns of space occupying lesions of the stomach and the intestine: Ultr Med Biol 2: 129, 1976

(200)   Mackie GR, Wisbey M, Cuschieri A: Milk 99mTc-EHIDA test for enterogastric bile reflux: Br J Surg 69: 101-104, 1982

(201)   Makey DA, Tovey FI, Heald RJ: Results of proximal gastric vagotomy over 1-5 years in a district general hospital: Br J Surg 66: 39-42, 1979

(202)   Malagelada JR, Longstreth GF, Summerskill WH, Go VLW: Measurement of gastric functions during digestion of ordinary solid meals in man: Gastroenterol 70: 203-210, 1976

(203)   Malagelada JR: Quantifiation of gastric solid-liquid discrimination during digestion of ordinary meals: Gastroenterol 72: 1264-1267, 1977

(204)   Malagelada JR: Physiologic basis and clinical significance of gastric emptying disorders: Dig Dis Sci 24: 657-661, 1979

(205)   Malagelada JR, Go VLW, Summerskill WHJ: Different gastric, pancreatic and biliary responses to solid, liquid or homogenised meals: Dig Dis Sci 24: 101-110,1979

(206)   Malmud LS, Long WB: Radionuclide studies of gastric emptying: in Multiple Imaging Proceedings, 1982

(207)   Marbaix O: Le passage pylorique: Cellule 14: 249-232, 1898

(208)   Martinson J: Studies on the efferent vagal control of the stomach: Acta Physiol Scand 255: suppl, 1-24, 1965

(209)   Mascatello VJ, Carrera GF, Telle RL, Berger M, Holm HH, Smith EH: The ultrasonic demonstration of gastric lesions: J Clin Ultrasound 5: 383-387, 1977

(210)   Matikainen M, Taavitsainen M, Kalima TV: Duodenogastric reflux in patients with heartburn and oesophagitis: Scand J Gastroent 16: 253-255, 1981

(211)   Mearin F, Camilleri M, Malagelada JR: Pyloric dysfunction in diabetics with recurrent nausea and vomiting: Gastroenterol 90: 1919-1925, 1986

(212)   Meeroff JC, Go VLW, Phillips SF: Gastric emptying of liquids in man: quantification by duodenal recovery marker: Mayo Clin Proc 48: 728-732, 1973

(213)   Meeroff JC, Go VLW, Phillips SF: Control of gastric emptying by osmolality of duodenal contents in man: Gastroenterol 68: 1144-1151, 1975

(214)   Menguy R: Role of biliary and pancreatic secretions in the inhibition of gastric motility by fat in the intestine: Am J Dig Dis 5: 792-800, 1960

(215)   Meyer JH: Gastric emptying of ordinary food: effect of antrum on particle size: Am J Physiol 239: G133-G135, 1980

(216)   Meyer JH, MacGregor IL, Gueller R, Martin P, Cavalieri R: 99m-Tc-tagged chicken liver as a marker of solid food in the human stomach: Am J Dig Dis 21: 296-304, 1976

(217)   Meyer JH, Thompson JB, Cohen MB, Shadchehr A, Mandiola SA: Sieving of solid food by the canine stomach and sieving after gastric surgery: Gastroenterol 76: 804-813, 1979

(218)   Meyer JH, Ohashi H, Jehn D, Thomson JB: Size of liver particles emptied from the human stomach: Gastroenterol 80: 1489-1496, 1981

(219)   Millar HD, Baker CE: A stable ultraminiature catheter tip pressure transducer: Med Biol Eng 11: 86-89, 1973

(220)   Moberg S, Carlberger G, Barany F, Lundh G: Gastric emptying in peptic ulcer patients before and after partial gastrectomy and selective proximal vagotomy: Rendic Gastroenterol 4: 1-7, 1972

(221)   Moffat RC, Berkas EM: Bile esophagitis: Arch Surg 91: 963-966, 1965

(222)   Mroz CT, Kelly KA: The role of the extrinsic antral nerves in the regulation of gastric emptying: Surg Gynae Obst 145: 369-377, 1977

(223)   Muller-Lissner SA, Fimmel CJ, Will N, Muller-Duysing W, Heinzel F, Blum A: Effect of gastric and transpyloric tubes and gastric emptying and duodenogastric reflux: Gastroenterol 83: 1276-1279, 1982

(224) Muller-Lissner SA, Sonnenberg S, Hollinger A, Schattenmann G, Siewert JR, Blum AL: Gastric emptying and postprandial duodenogastric reflux in dogs with Heineke-Mikulicz pyloroplasty: Br J Surg 69: 323-327, 1982

(225) Muller-Lissner SA, Fimmel CJ, Sonnenberg A, Will N, Muller-Duysing W, Heinzel F, Muller R, Blum AL: Novel approach to quantify duodenogastric reflux in healthy volunteers and in patients with type I gastric ulcer: Gut 24: 510-518, 1983

(226) Muller-Lissner SA, Fraass C: Dissociation of duodenogastric marker relux and bile salt reflux: Dig Dis Sci 30: 733-738, 1985

(227) McCallum RW: Diagnosing motility disorders of the upper gastrointestinal tract: S Med J 77: 947-955, 1984

(228) McCallum RW, Berkowitz DM, Lerner E: Gastric emptying in patients with gastroesophageal reflux: Gastroenterol 80: 285-291, 1981

(229) McCallum RW, Mensh R, Lange R: Definition of the gastric emptying abnormality present in gastroesophageal reflux patients: in Motility of the Digestive tract, Ed Weinbeck: Raven Press, New York, 1982

(230) McDicken WN: Diagnostic ultrasonics - principles and use of instruments: London: Crosby Lockwood Staples, 1976

(231) MacGregor I, Parent J, Meyer JH: Gastric emptying of liquid meals and pancreatic biliary secretion after subtotal gastrectomy or truncal vagotomy and pyloroplasty in man: Gastroenterol 72: 195-205, 1977

(232) Mackenzie I, Kennedy F, Mackay C, Kay AW: A prospective controlled trial of truncal vagotomy and drainage for chronic duodenal ulcer: Br J Surg 64: 292, 1977

(233) McHugh PR, Moran TH, Barton GN: Satiety: a graded behaviour phenomenon regulating calorie intake: Science 190: 167-169, 1975

(234) McHugh PR, Moran TH: Calories and gastric emptying: a regulatory capacity with implications for feeding: Am J Physiol 236: R254-R260, 1979

(235) McShane AJ, O'Morain CO, Lennon JR, Coakley JB, Alton BG: Atraumatic non-distorting pyloric sphincter pressure studies: Gut 21: 826-828, 1980

(236) Nelson TS, Kohatsu S: The stomach as a pump: Rend R Gastroenterol 3: 65-70, 1971

(237) Nimmo J, Heading RC, Tothill P, Prescott LF: Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption: Br Med J 1: 587-589, 1973

(238) Nimmo WS, Heading RC, Wilson J, Tothill P, Prescott LF: Inhibition of gastric emptying by narcotic analgesics: Br J clin Pharmac 2: 509-513, 1975

(239) Oberhelman HA, Dragstedt LR: New physiologic concepts related to the surgical treatment of duodenal ulcer by vagotomy and gastroenterostomy: Surg Gynaecol Obst 101: 194-200, 1955

(240) Ogilvie AL, James PD, Atkinson M: Impairment of vagal function in reflux oesophagitis: Q J Med 54: 61-74, 1985

(241) Olbe L, Jacobson B: Intraluminal pressure waves of the stomach in dogs studied by endoradiosondes: Gastroenterol 44: 787-796, 1963

(242) Oliva L, Biggi E, Derchi LE, Cicio GR: Ultrasonic anatomy of the fluid-filled duodenum: J Clin Ultras 9: 245-248, 1981

(243) Ormsbee HS, Bass P: Gastroduodenal motor gradients in the dog after pyloroplasty: Am J Physiol 230: 389-402, 1976

(244) Ouyang A, Cohen S: Effects of hormones on gastrointestinal motility: Med Clin North Am 65: 1111-1127, 1981

(245) Paintal AS: A study of gastric stretch receptors. Their role in the peripheral mechanism of satiation of hunger and thirst: J Physiol 126: 255-270, 1954

(246) Pope CE: A dynamic test of sphincter strength: Its application to the lower esophageal sphincter: Gastroenterol 52: 779-786, 1967

(247) Prove J, Ehrlein H-J: Motor function of gastric antrum and pylorus for evacuation of low and high viscosity meals in dogs: Gut 23: 150-156, 1982

(248) Read NW, Al Janabi MN, Bates TE, Barber DC: Effect of gastrointestinal intubation on the passage of a solid meal through the stomach and small intestine in humans: Gastroenterol 84: 1568-1572, 1983

(249) Rees WDW, Malagelada JR, Go VLW: Human interdigestive motor activity: Effect of saline and liquid nutrient meals: Gastroenterol 74: 1083, 1978

(250) Rees WDW, Go VLW, Malagelada JR: Antroduodenal motor response to solid-liquid and homogenised meals: Gastroenterol 76: 1438-1442, 1979

(251) Rees WDW, Go VLW, Malagelada JR: Simultaneous measurement of antroduodenal motility, gastric emptying, and duodenogastric reflux in man: Gut 20: 963-970, 1979

(252) Rehfuss ME: Diagnosis and treatment of diseases of the stomach: Saunders, Philadelphia, 1927

(253)   Reichsman F, Engel GL, Segal HL: Behaviour and gastric secretion:
        the study of an infant with a gastric fistula: Psychosom Med 17:
        481, 1955

(254)   Reiser SB, Holle GE: Motor and electrical activity of the
        gastroduodenal junction before and after submucosal pyloroplasty:
        World J Surg 6: 231-235, 1982

(255)   Richet C: Souvenirs d´un physiologist: Paris. J Peyronnet & Cie,
        1944

(256)   Richter CP: Action currents from the stomach: Am J Physiol 67:
        612-633, 1924

(257)   Richter CP: Total self-regulatory functions in animals and human
        beings: Harvey Lectures Ser 38: 63-103, 1942-43

(258)   Rock E, Malmud L, Fisher RS: Motor disorders of the stomach: Med
        Clin N Am 65: 1269-1289, 1981

(259)   Rokkjaer M: Some aspects of intestino-gastric reflux: Dan Med Bul
        27: 185-202, 1980

(260)   Sagar S, Grime JS, Little W, Patten M, Gulliford P, Critchley M,
        Bennet R, Sheilds R: Technetium-99M labelled bran: A new agent
        for measuring gastric emptying: Clin Rad 34: 275-278, 1983

(261)   Sample WF, Po JB, Gray RK, et al: Gray-scale ultrasonography,
        techniques in pancreatic scanning: Appl Radiol 4: 63, 1975

(262)   Sarna SK, Daniel EE: Vagal control of gastric electrical control
        activity and motility: Gastroenterol 68: 301-308, 1975

(263)   Sarna SK, Daniel EE, Kingma YJ: A simulation of the electrical
        control activity of the stomach by an array of relaxation
        oscillators: Am J Dig Dis 17: 299-310, 1972

(264)   Schapiro H, Woodward ER: Pathway of enterogastric reflux: Proc
        Soc Exp Biol Med 101: 407-409, 1959

(265)   Siegel M, Lebenthal E, Topper W, Krantz B, Li PK: Gastric
        emptying in prematures of isocaloric feeding with differing
        osmolalities: Paediatr Res 16: 141-147, 1982

(266)   Sheiner HJ: Gastric emptying tests in man: Gut 15: 235-247, 1975

(267)   Sheiner HJ, Quinlan MF, Thompson IJ: Gastric motility and
        emptying in normal and post-vagotomy subjects: Gut 21: 753-759,
        1980

(268)   Smith AWM, Code CF: The effect of an ordinary and of an
        excessively fatty breakfast on human gastric antral motility:
        Gastroenterol 35: 398-405, 1958

(269)   Smith AWM, Code CF, Schlegel JF: Simultaneous cine-radiographic
         and kymographic studies of human gastric antral motility: J Appl
         Physiol 11: 12-16, 1957

(270)   Somer JC: Electronic sector scanning for ultrasonic diagnosis:
         Ultrason 6: 153-159, 1968

(271)   Sonnenberg A, Muller-Lissner SA, Weiser HF, Muller-Duysing W,
         Heinzel F, Blum AL: Effect of liquid meals on duodenogastric
         reflux in humans: Am J Physiol 243: G42-47, 1982

(272)   Stadaas J, Aune S: Intragastric pressure/volume relationship
         before and after vagotomy: Acta Chir Scand 136: 611-615, 1970

(273)   Stadaas J: Intragastric pressure/volume relationship. A clinical
         and experimental study: Thesis: Universitets-forlaget, Oslo: 1974

(274)   Stadaas J: Gastric motility 1 year after proximal gastric
         vagotomy: Scand J Gastroent 15: 799-804, 1980

(275)   Stadaas JO, Schrumpf E, Hanssen KF: Somatostatin inhibits gastric
         motility in response to distention: Scand J Gastroent 13:
         145-148, 1978

(276)   Stanghellini V, Malagelada J-R: Gastric manometric abnormalities
         in patients with dyspeptic symptoms after fundoplication: Gut 24:
         790-797, 1983

(277)   Stemper TJ, Cooke AR: Gastric emptying and its relationship to
         antral contractile activity: Gastroenterol 69: 649-653, 1975

(278)   Stemper TJ, Cooke AR: Effect of a fixed pyloric opening in the
         cat and dog: Am J Physiol 230: 813-817, 1976

(279)   Stoddard CJ, Waterfall WE, Brown BH, Duthie HL: The effects of
         varying the extent of the vagotomy on the myoelectrical and motor
         activity of the stomach: Gut 14: 657-664, 1973

(280)   Stoddard CJ, Smallwood R, Brown BH, Duthie HL: The immediate and
         delayed effects of different types of vagotomy on human gastric
         myoelectrical activity: Gut 16: 165-170, 1975

(281)   Stoddard CJ, Vasilakis JS, Duthie HL: Highly selective vagotomy
         or   truncal vagotomy and pyloroplasty for chronic duodenal
         ulceration: a randomised, prospective clinical study: Br J Surg
         65: 793-796, 1978

(282)   Stol DV, Murphy GM, Collis JL: Duodeno-gastric reflux and acid
         secretion in patients with symptomatic hiatal hernia: Scand J
         Gastroent 9: 97-101, 1974

(283)   Stordy SN, Greig JH, Bogogh A: The steak and barium meal: Am J
         Dig Dis 14: 463-469, 1969

(284)   Stratmeyer ME: Research in ultrasound bioeffects: A public health
         view: Birth Fam J 7: 92-100, 1980

(285) Strunz UT, Grossman MI: Effect of intragastric pressure on gastric emptying and secretion: Am J Physiol 235: E552-555, 1978

(286) Sun DCH, Shay H, Woloshin HJ: Effect of tricyclamol on gastric emptying and intestinal transit: Am J Dig Dis 4: 282-288, 1959

(287) Thomas WEG: Effect of truncal vagotomy on functional and morphological changes produced by duodenogastric reflux: Dig Dis Sci 27: 609-614, 1982

(288) Thomas JE, Crider JO, Mogan CJ: A study of reflexes involving the pyloric sphincter and antrum and their role in gastric evacuation: Am J Physiol 108: 683-700, 1934

(289) Thomas JE, Baldwin MV: Pathways and mechanisms of regulation of gastric motility: ch 95, in Handbook of Physiology, sect 6: Alimentary Canal, vol 4. Ed CF Code, Washington DC, American Physiological Society, 1968, 1937-1968

(290) Thompson DG: Duodenogastric reflux: is there any progress: Br Med J 284: 845-846, 1982

(291) Thompson DG, Wingate DL, Thomas M, Harrison D: Gastric emptying as a determinant of the oral glucose tolerance test: Gastroenterol 82: 51-53, 1982

(292) Thompson DG, Richelson E, Malagelada JR: Peturbation of gastric emptying and duodenal motility through the central nervous system: Gastroenterol 82: 1200-1206, 1982

(293) Thompson DG, Richelson E, Malagelada JR: Peturbation of upper gastrointestinal function by cold stress: Gut 24: 277-283, 1983

(294) Tolin RD, Malmud LS, Stelzer F, Menin R, Makler PT, Applegate G, Fisher RS: Enterogastric reflux in normal subjects and in patients with Billroth II gastroenterostomy: Gastroenterol 77: 1027-1033, 1979

(295) Tothill P, McLaughlin GP, Heading RC: Techniques and errors in scintigraphic measurements of gastric emptying: J Nucl Med 19: 256-262, 1978

(296) Valenzuela JE, Defilippi C, Csendes A: Manometric studies on the human pyloric sphincter: Effect of cigarette smoking, metoclopramide, and atropine: Gastroenterol 70: 481-483, 1976

(297) Valori RM, Collins SM, Daniel EE, Reddy SN, Shannon S, Jury J: Comparison of methodologies for the measurement of antroduodenal motor activity in the dog: Gastroenterol 91: 546-553, 1986

(298) van Dam APM: The gamma camera in clinical evaluation of gastric emptying: J Nucl Med 110: 371-374, 1971

(299) Von Leube: Beitrage zur diagnostik der magenkrankheiten: Dtsch Arch Klin Med 33: 1-21, 1883

(300) Walker GD, Stewart JJ, Bass P: The effect of parietal cell and truncal vagotomy on gastric and duodenal contractile activity of the unanaesthetized dog: Ann Surg 179: 853-858, 1974

(301) Walls W: The evaluation of malignant neoplasms by ultrasonic B-scanning: Radiology 118: 159, 1976

(302) Warren PS, Garrett WJ, Kossoff G: The liquid filled stomach: An ultrasonic window to the upper abdomen: J Clin Ultras 6: 315, 1978

(303) Warshaw AL: Bile gastritis without prior gastric surgery: contributing role of cholecystectomy: Am J Surg 137: 527-530, 1979

(304) Weems WA: The intestine as a fluid propelling system: Annu Rev Physiol 43: 9-19, 1981

(305) Weems WA: Intestinal wall motion, propulsion, and fluid movement: trends towards a unified theory: Am J Physiol 243: G177-G188, 1982

(306) Weighall SL, Wolfman NT, Watson N: The fluid-filled stomach: A new sonic window: J Clin Ultras 7: 353-356, 1979

(307) Weiner K, Graham LS, Reedy T, Elashoff J, Meyer JH: Simultaneous gastric emptying of two solid foods: Gastroenterol 81: 257-266, 1981

(308) Weisbrodt NW, Wiley JN, Overholt BF, Bass P: A relation between gastroduodenal muscle contractions and gastric emptying: Gut 10: 543-548, 1969

(309) White CM, Poxon V, Alexander-Williams J: A study of motility of normal gastroduodenal region: Dig Dis Sci 26: 609-617, 1981

(310) White CM, Poxon V, Alexander-Williams J: Effects of nutrient liquids on human gastroduodenal motor activity: Gut 24: 1109-1116, 1983

(311) Wilbur BG, Kelly KA: The effect of proximal gastric, complete gastric and truncal vagotomy on canine gastric electric activity, motility and emptying: Ann Surg 178: 295-302, 1973

(312) Wilkinson AR, Johnston D: Effect of truncal, selective and highly selective vagotomy on gastric emptying and intestinal transit of a food-barium meal in man: Ann Surg 178: 190-193, 1973

(313) Windsor CWD: Gastroesophageal reflux after partial gastrectomy: Br Med J 2: 1233-1234, 1967

(314) Wolf S: The psyche and the stomach: A historical vignette: Gastroenterol 80: 605-614, 1981

(315) Wolf S, Wolf HG: In: Human gastric function: 1st Ed. New York: Oxford Univ. Press, 1943

(316) Wormsley KG: Aspects of duodeno-gastric reflux in man: Gut 13: 243-250, 1972