THE DEVELOPMENT AND APPLICATION OF A DUAL ISOTOPE SCINTIGRAPHIC TECHNIQUE TO STUDY GASTRIC EMPTYING IN HUMANS

by

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SUMMARY

In this thesis, the development of a radionuclide technique to measure gastric emptying in humans, and its subsequent application to the study of gastric emptying in normal subjects, in pathological conditions and in the assessment of pharmacologic effects on gastric emptying are discussed, with particular reference to the physiology of gastric emptying.

The technique uses two isotopes and enables continuous measurement of gastric emptying of both solid and liquid meal components with a single scintillation camera. The solid meal is 100g of cooked, ground beef containing in-vivo labelled ^{99m}Tc-labelled chicken liver and the liquid meal is ^{113m}In-DTPA mixed in 150 ml of either water or dilute dextrose solutions.

The methodology, technical problems, advantages and limitations of this and other radionuclide techniques are described. In normal subjects, it was shown that variation in radionuclide gamma-ray attentuation caused by changes in depth of radionuclide and Compton scatter of ^{113m}In photons into the ^{99m}Tc window, account for large errors in the measurement of gastric emptying. A new technique for the correction of attenuation, which uses factors derived from a lateral image of the stomach is described and validated. Solid emptying was slower than liquid emptying and was characterised by a delay (lag period) before food entered the duodenum, which was followed by an emptying phase that approximated a linear pattern. Liquid emptying was non-linear with a slope that decreased with time and often approximated a single

exponential pattern. The effect of physiological changes induced by alterations in the caloric/osmotic content of the liquid component of the meal were assessed. Liquid emptying was slowed and the lag period was prolonged as the calorie content increased. The reproducibility of the technique was assessed and day-to-day variations in gastric emptying were not significant for any measured parameter.

Gastric emptying was examined in elderly subjects, obese patients and in normal women during both phases of the menstrual cycle. Solid and liquid emptying rates were found to be significantly slower in fit, elderly subjects. In morbidly obese subjects solid emptying is delayed due to the prolongation of the lag period and there is no evidence of abnormal duodenal regulation of gastric emptying in obese subjects. Gastric emptying does not change significantly during the normal menstrual cycle.

Gastric emptying was studied in diabetics with autonomic neuropathy and the acute and chronic effects of oral domperidone on gastric emptying, symptoms of gastroparesis and glycaemic control were assessed. Gastric emptying of both solid and liquid is significantly slower in diabetics with autonomic neuropathy than in control subjects. Acute administration of domperidone increases both solid and liquid emptying rates in diabetics. After chronic administration domperidone has no significant effect on solid emptying although its effects on liquid emptying are maintained.

The pattern of gastric emptying after gastric bypass and gastroplasty surgery for obesity was studied, with particular emphasis on the possible mechanisms of weight loss and post-operative sequelae. After gastric bypass, solid emptying is considerably slower and liquid emptying is more rapid. Both solid and liquid emptying are delayed after gastroplasty, but these changes are not marked. There is no relationship between gastric emptying rates and the extent of weight loss after either operation.

As the gastric emptying technique is reproducible, accurate, sensitive to physiological changes and measures gastric emptying of both solids and liquids simultaneously, it is concluded that there are many potential applications for its present use and further development, particularly in future research on the physiology of gastric emptying and in the assessment of disorders of gastric motility.

DECLARATION

The material in this thesis has not been previously submitted for a degree in any University, and to the best of my knowledge and belief, it contains no material previously published or written by another person except where due reference is made in the text.

M. Horowitz

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CHAPTER 1

CONTROL OF GASTRIC EMPTYING IN HUMANS

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1.1 INTRODUCTION

In this chapter the current knowledge of the physiology of gastric emptying in normal human subjects and in some pathological conditions is reviewed briefly. As there have been several excellent and comprehensive reviews of various aspects of the mechanisms and regulation of gastric emptying (Heading 1980, 1982, Hunt 1983, Kelly 1981, Malagelada 1981, Nimmo 1976, Sheiner 1975), the author has attempted to focus particularly on those aspects which provide a background to the studies of gastric emptying described in this thesis.

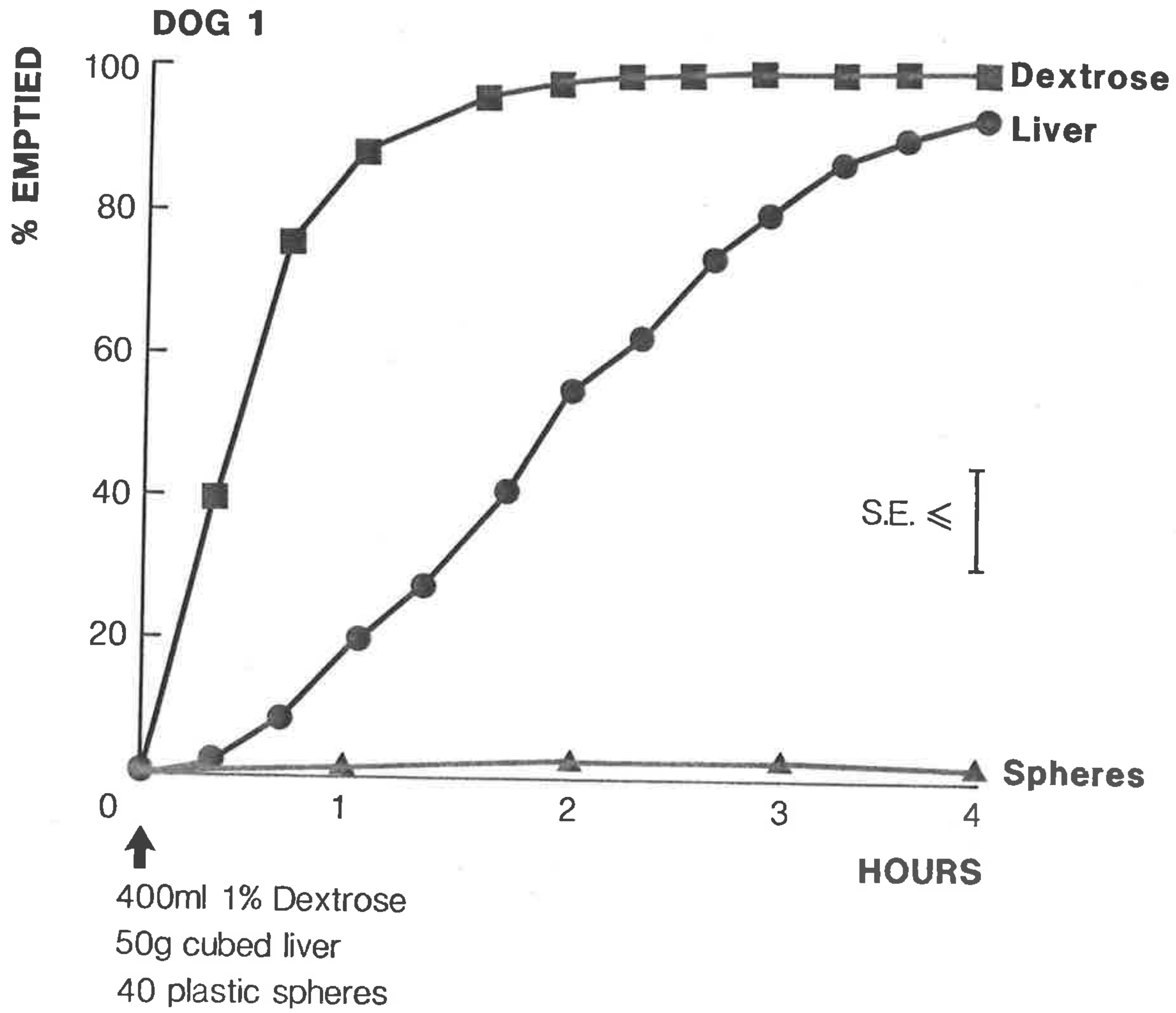
1.2 GASTRIC EMPTYING OF LIQUID, DIGESTIBLE SOLID AND NON-DIGESTIBLE SOLID FOOD

The stomach serves as a reservoir for ingested food and in normal subjects delivers into the duodenum components of the meal and gastric secretion, at rates that match the digestive capacity of the small intestine. The mechanisms mediating responses to meals of different composition and consistency are largely unknown. Much of our current knowledge is derived from the results of initial studies in experimental animals (particularly the dog), which have been subsequently applied to humans.

Hinder and Kelly (1977) demonstrated in dogs that when a liquid, a digestible solid and a non-digestible solid are simultaneously ingested, the pattern and rate of emptying of each component is different. As illustrated in Figure 1.1, when dogs consumed a meal of 400 ml of dextrose, cubed liver and plastic spheres that were 7 mm in diameter, the liquid was emptied rapidly, the digestible solid emptied more slowly and nearly all the plastic spheres were retained within the stomach, until after the digestible solid and liquid had emptied.

LEGEND FOR FIGURE 1.1

Patterns of canine gastric emptying of liquid, digestible and non-digestible solids. The liquid is emptied rapidly, the digestible solid more slowly and nearly all the plastic spheres are retained within the stomach until after the digestible solid and liquid have emptied.
(Adapted from Hinder and Kelly, 1977 and reproduced with the permission of the authors).


DOG 1
% EMPTIED
100
80
60
40
20
0
1
2
3
4
HOURS
Dextrose
Liver
Spheres
S.E. ⩽
400ml 1% Dextrose
50g cubed liver
40 plastic spheres

1.2.1 Gastric motor regions

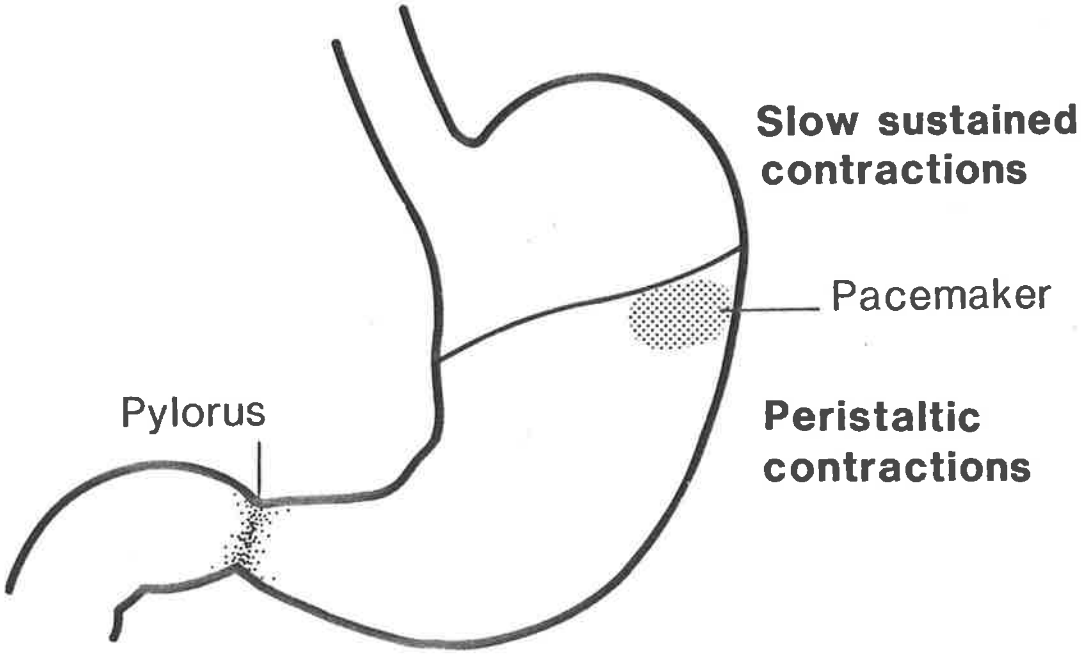
As suggested initially by Cannon (1898) the stomach can be divided into two functional motor regions (Figure 1.2). The proximal stomach consists of the fundus and the upper part of the body of the stomach. The distal stomach comprises the remainder of the corpus, the antrum and the pylorus (Hinder and Kelly 1977, Kelly 1980). The anatomy of the stomach is of functional significance. In the fundus there are longitudinal and circular muscles and a thin oblique muscle, which is in continuity with the lower oesophageal sphincter. In the antrum there is a progressively thicker circular muscle layer, which generates strong contractions. The pylorus is composed of thick circular muscles with a resting high pressure sphincter zone. The functions of the proximal and distal gastric regions in gastric emptying are now discussed briefly.

1.2.2 Functions of the proximal stomach

The proximal gastric body and fundus do not participate in the contactile activity leading to gastric peristalsis. The proximal stomach has a tonic contraction of approximately 10 cm water and exhibits two types of phasic contractions - a slow contraction with a duration of approximately three minutes and an amplitude of approximately 30 cm water and a faster contraction with a duration of 10-12 seconds and an amplitude of approximately 10 cm water. The electrical events responsible for both the phasic changes in pressure and the tonic contractions have not been identified (Kelly, 1980). Pacemaker potentials, which are found throughout the distal stomach are not present in the proximal stomach (Kelly et al, 1969).

LEGEND FOR FIGURE 1.2

Functional division of the stomach into proximal and distal motor regions. The area of the gastric pacemaker is shown.


Slow sustained
contractions
Pacemaker
Peristaltic
contractions
Pylorus

The neural control of contractile activity of the proximal stomach is mediated mainly by the non-adrenergic, non-cholinergic vagal inhibitory system. Dopamine (Valenzuela 1976) and enkephalins (Lundberg et al, 1979) may participate in this system as neurotransmitters.

Intragastric pressure and the gastro-duodenal pressure gradient are regulated primarily by the tonic contractions of the proximal stomach. The motor properties of the proximal stomach facilitate the accommodation of large volumes of food, while maintaining low intragastric pressures. Cannon and Lieb (1911) first observed that the pressure in the proximal stomach decreases during swallowing. Because of inhibition of the tonic contractions, a short-lived "receptive" relaxation of the proximal stomach occurs before the bolus of food enters the stomach from the oesophagus. This is followed by a more prolonged "adaptive" relaxation (or "accommodation") in response to gastric distension (Jahnberg 1977). Mechanoreceptors within the gastric muscle are the sensors for the adaptive relaxation reflex (Paintal, 1954). Both receptive and adaptive relaxation are mediated by inhibitory vagal neurones (Abrahamson, 1973), which are non-cholinergic, non-adrenergic and partially dopaminergic (Valenzuela, 1976) and act particularly on the oblique muscle layer of the proximal stomach (Christensen and Torres, 1975). Adaptive relaxation is impaired by proximal gastric vagotomy (Wilbur and Kelly, 1973).

The emptying of isotonic liquids from the stomach is thought to be dependent on the pressure gradient between the stomach and duodenum, which is largely controlled by the tone of the proximal stomach (Wilbur and Kelly, 1973). The observations that the emptying of isotonic liquid approximates a mono-exponential, or volume-dependent process (Hunt and Spurrell, 1951, Hunt 1956), that the rate of gastric emptying of isotonic saline increases linearly with increasing intragastric pressure (Strunz and Grossman, 1978) and that gastric emptying of liquids is more rapid after proximal gastric vagotomy (Donovan et al, 1979) are consistent with this hypothesis. In the first 5-10 minutes after consumption of a liquid meal, the rate of gastric emptying (or "early phase") may be faster or slower than the subsequent rate (Colmer et al, 1973). During this time the proximal stomach probably adapts to the distension caused by the meal.

In contrast to its major role in the gastric emptying of liquids, the proximal stomach has a minor role in the gastric emptying of solids. Proximal gastric vagotomy has minimal effects on gastric emptying of solid food (Sheiner et al, 1980).

Exogenous administration of various hormones, including gastrin, secretin, motilin, cholecystokinin, glucagon, somatostatin, gastric inhibitory polypeptide and vasoactive intestinal peptide, have been demonstrated to alter the contractions of the proximal stomach, but the physiological significance of their actions is uncertain. Gastrin inhibits the tone of the proximal stomach (Wilbur and Kelly, 1974), reduces the intragastric pressure and slows gastric emptying of liquids (Hunt and Ramsbottom, 1967). Cholecystokinin, probably in physiological doses, inhibits proximal gastric contractions (Valenzuela, 1976) and slows liquid emptying (Debas et al, 1975). Motilin stimulates proximal stomach contractions and increases gastric emptying of liquids (Debas et al, 1977).

1.2.3 Functions of the distal stomach

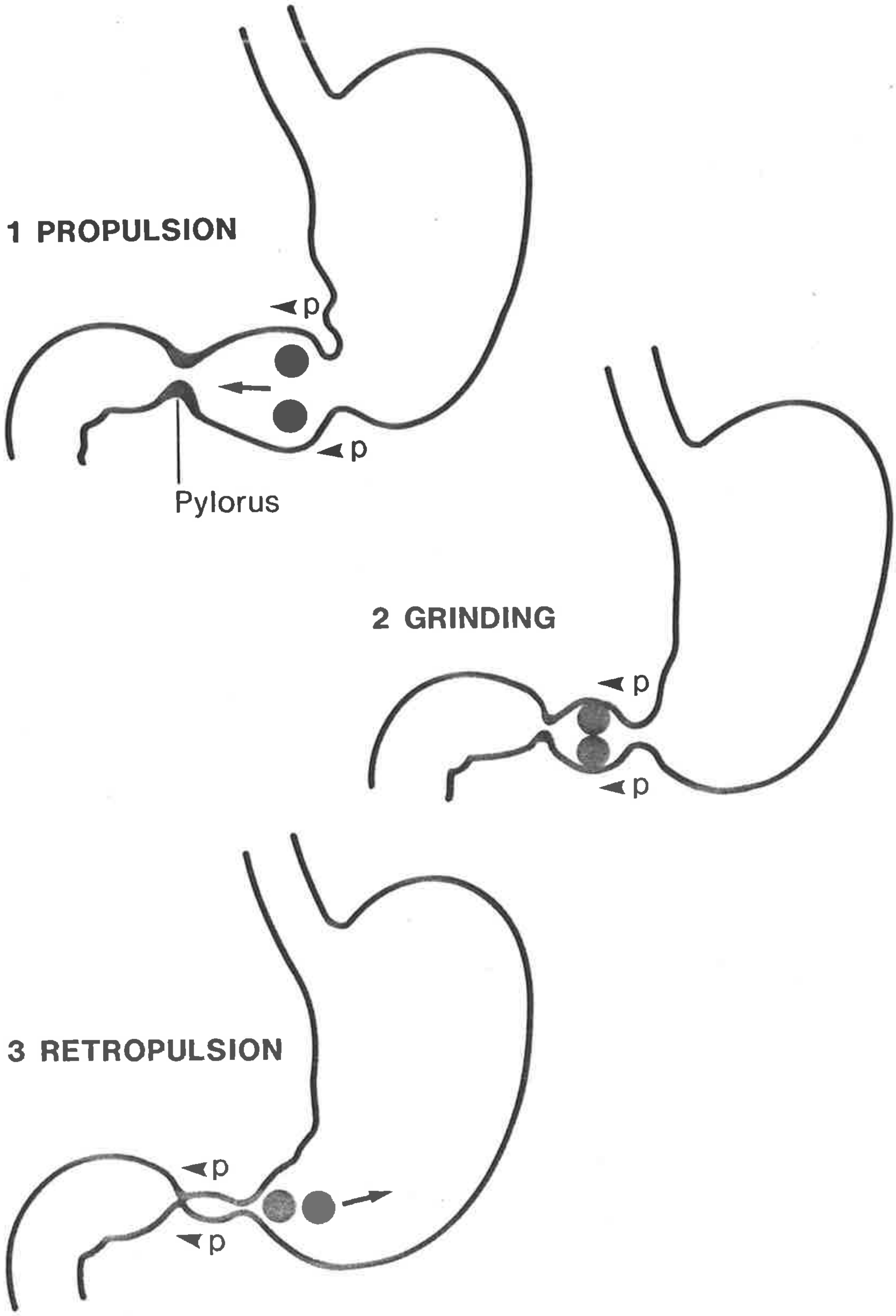
The information derived from experiments in both animals and humans suggests that the distal stomach has a major role in the gastric emptying of solid food and probably has little effect on liquid emptying. The contractions of the distal stomach are designed to retain and grind solid food. The frequency and velocity of propagation of the peristaltic waves are determined by regular cyclical changes in electrical potential called pacesetter potentials or slow waves (Kelly et al, 1969). The pacesetter potentials are generated by the muscularis of all parts of the distal stomach, but an area in the upper body of the stomach along the greater curve (Figure 1.2) depolarizes at the fastest rate, of approximately three cycles/minute, and therefore acts as a pacemaker (Kelly and Code, 1971). The pacemaker impulses are propagated both around the stomach and distally towards the pylorus. Although the pacemaker determines the frequency of distal contractions, a more rapid change in potential (action potential) is required to initiate muscular contraction. The occurrence of contraction is dependent on an intact intrinsic nerve innervation, but the various neural and hormonal influences that facilitate or inhibit muscle contraction are largely unknown.

Cholinergic vagal neurones innervate the distal stomach musculature. The distal gastric contractions increase in amplitude and velocity as they move distally and propel solid food from the body of the stomach towards the pylorus. As the peristaltic wave approaches the pylorus, the terminal antrum and pylorus close and prevent solid food entering the duodenum (Carlson et al, 1966). Thus, because of their size and the antropyloric closure, larger digestible solid particles are retained in the stomach, ground into smaller particles and retropelled into the proximal stomach (Figure 1.3). Antral pressures greater than 100 mm Hg are usually measured in humans after a mixed solid and liquid meal (Rees et al, 1979). The sequence of propulsion, grinding, retropulsion and acid-peptic digestion recurs until solids are broken down into a size small enough to pass through the pylorus into the duodenum (Meyer et al, 1976, 1979). Meyer et al (1979) have demonstrated that most digestible solid particles must be less than 1 mm in size before they pass into the duodenum. The small, solid particles are suspended in the liquid phase of the gastric contents and empty with the liquid. If a digestible solid is ingested as smaller particles, the time for trituration is less and emptying is faster (Hinder and Kelly, 1977, Holt et al, 1982, Weiner et al, 1981) and thoroughly triturated solids empty at a similar rate to liquid (Hinder and Kelly, 1977). Vagal denervation of the antrum reduces antral contractions and impairs antral trituration (Mroz and Kelly, 1977, Kelly, 1980). After antrectomy larger particles of digestible solid food enter the duodenum (Dozois et al, 1971, Meyer et al, 1979, Mayer et al, 1982).

Small inert non-digestible solid particles are emptied at similar rates to digestible solids (Malagelada et al, 1980, Holt et al, 1982). However solids which cannot be broken down to a sufficiently small size are emptied from the stomach by a different mechanism. A distinct cycle of electromechanical activity, which begins in the proximal stomach and migrates distally, occurs approximately every 100 minutes in the fasting state in both dogs and humans (Code and Marlett, 1975). This cycle, which is composed of three phases is called the migrating motor complex, or the interdigestive myoelectric complex. Phase 1 is a period of motor quiescence, with only occasional action potentials or contractions. During phase 2 there are intermittent, irregular action potentials. Phase 3 is characterized by intense bursts of regular action potentials and contractions that appear with every pacemaker potential (three contractions/minute). Phase 3 lasts approximately 5-12 minutes.

LEGEND FOR FIGURE 1.3

Propulsion, grinding and retopulsion of digestible solid food by peristaltic contractions of the distal stomach (adapted from Kelly, 1981 and reproduced with the permission of the author).


1 PROPULSION
p
p
Pylorus
2 GRINDING
p
p
3 RETROPULSION
p
p

Phases 1 and 2 constitute the remainder of the 100 minutes, but their relative duration is quite variable (phase 1 usually lasts approximately 60 minutes and phase 2 approximately 20 minutes). In contrast to the fed state, phase 3 activity appears to be associated with antropyloric relaxation, allowing larger non-digestible solid particles to be emptied. In the experiment of Hinder and Kelly (1977) (Figure 1.1), the emptying of the plastic spheres coincided with the onset of phase 3 activity. The periodicity of the migrating motor complex may be determined by central nervous system signals, but little is known about the mechanisms of these motor cycles or their regulation (Wingate, 1981). It has been postulated that gastrointestinal hormones such as motilin may play a modulating role, particularly in determining the onset of gastric cycles (Itoh et al, 1978, Thomas et al, 1980). Peaks in plasma motilin and pancreatic polypeptide concentrations have been associated with phase 3 activity (Van Trappen et al, 1978), but are probably secondary changes. Truncal vagotomy has been demonstrated to inhibit phase 3 activity (Marik and Code, 1980).

In contrast to its major role in the gastric emptying of solids, the distal stomach appears to have relatively minimal effect on liquid emptying. Vagal denervation of the distal stomach in dogs does not affect liquid emptying (Mroz and Kelly, 1977). However there is some evidence that contractions of the distal stomach, pylorus or proximal duodenum may increase resistance to the passage of liquids and slow their emptying (Stemper and Cooke, 1975, Gleysteen and Kalbfleisch, 1981), particularly if the liquid contains nutrients (White et al, 1983).

Several hormones may influence distal gastric contractions but their physiological contribution is uncertain. Gastrin increases the frequency of the gastric pacemaker (Morgan et al, 1978), stimulates distal gastric contractions and decreases gastric emptying (Hamilton et al, 1976). Pharmacologic doses of bombesin and caerulein delay gastric emptying of solids in humans (Scarpignato et al, 1981), possibly by causing antropyloric contraction (Schecter et al, 1981). Centrally administered bombesin inhibits gastric emptying in rats, probably through a vagally mediated motor pathway (Porreca and Burks, 1983).

1.2.4 Effect of meal ingestion on gastric motor activity

Ingestion of isotonic solutions such as isotonic saline does not usually affect the existing fasting motor activity (Rees et al, 1979, Malagelada, 1981). Ingestion of a liquid meal containing nutrients inhibits gastric motor activity in the proximal and distal stomach and produces an irregular pattern of motor activity in the duodenum and small bowel designated the "fed pattern". Until the majority of the liquid meal has been emptied from the stomach migratory motor complexes do not appear.

A solid, or a mixed solid and liquid meal is associated with a pattern of motor activity different from that of inert and nutrient containing liquids. Soon after the ingestion of digestible solid food or small non-digestible solid particles, vigorous contractions occur in the distal antrum and the "fed pattern" appears in the duodenum. These responses are not seen if the solid is ingested in an homogenized form (Rees et al, 1979).

1.2.5 Regulation of gastric emptying by small bowel receptors

As well as the physical nature of food, the chemical composition of a meal also influences gastric emptying. Carnot and Chassevant (1905) first suggested that the osmolarity of gastric contents strongly influenced the emptying time of the stomach. Many years later Hunt

(1960) proposed that the osmotic control of gastric emptying was a function of the duodenum. Until this time the gastric emptying of all liquids had been thought to be an exponential function, with the rate of emptying depending primarily upon gastric distention and intragastric pressure (Hunt and Spurrell, 1951). Duodenal contractions were thought to enhance or inhibit the rate of emptying, but were not believed to change the fundamental exponential pattern (Hunt and Spurrell, 1951).

As discussed previously, the gastric emptying of physiological saline or water in animals (Strunz and Grossman, 1978) and humans (Hunt and Spurrell, 1951, Weisbrodt et al, 1969, Chaudhuri, 1974, Sasaki et al, 1983) approximates an exponential process in relation to volume : that is the volume of liquid emptied per unit of time is directly proportional to the volume remaining in the stomach. However the results of many studies, which have used intubation techniques indicate that solutions which contain carbohydrate, fat, protein or are acidic, delay gastric emptying compared to solutions such as isotonic saline (Hunt and Knox, 1972, Hunt and Stubbs, 1975, McHugh and Moran, 1979), by the action of small bowel receptors on poorly characterized neural and/or hormonal pathways (Sasaki et al, 1983). In man, as distinct from the dog, these receptors are predominantly in the duodenum; and not in the gastric or jejunal epithelium (Meeroff et al, 1975). The specificity of the duodenal receptor mechanism is such that isocaloric solutions of fat, carbohydrate and protein slow gastric emptying equally (Barker et al, 1978). Hunt and Stubbs (1975) accounted for the gastric emptying rates reported for man in some 25 papers on that assumption. McHugh and Moran (1979) demonstrated in rhesus monkeys, that solutions of glucose, casein and medium chain triglycerides containing 0.5 kcal/ml emptied from the stomach at rates that were indistinguishable. Therefore the control of gastric emptying of liquid food results in a transfer of energy to the duodenum at a rate independent of the proportions of fat, carbohydrate and protein in the meal. It has also been demonstrated that although the gastric emptying of physiological saline and water approximates an exponential pattern, glucose, casein and medium chain triglycerides follow a more linear than exponential pattern of emptying (McHugh and Moran, 1979, Gulstrud et al, 1980, Sasaki et al, 1983).

Emptying of nutrient solutions is regulated by variations in the degree of inhibition mediated through duodenal receptors. Hunt and Stubbs (1975) initially demonstrated in humans that the greater the energy density of a liquid meal, the less is the volume emptied/minute, although the rate of gastroduodenal transfer of energy increased slightly with increasing energy density. Subsequent experiments in both humans (Brener et al, 1983) and primates (McHugh and Moran, 1979) have confirmed that gastric emptying slows as the nutrient content of a liquid glucose meal increases (regardless of volume), so that calories are delivered to the duodenum at a constant rate (approximately 2 kcal/min in humans and 0.4 kcal/min in primates). This constant emptying rate can be accounted for by an inhibitory control arising from the duodenum, which reduces the frequency and possibly the volume of each ejection of food into the duodenum (McHugh et al, 1982). In primates (McHugh and Moran, 1979) gastric emptying does not slow proportionately when the concentration of glucose exceeds 1 kcal/min, but no experiments have assessed this in humans yet.

The association between calories and stimulation of duodenal receptors is not essential as non calorigenic solutions such as potassium chloride slow gastric emptying (Bell and Webber, 1979). Dietary triglycerides only slow gastric emptying after digestion in the duodenum to anions of fatty acids (Hunt et al, 1983). These observations have led Hunt and McHugh (1982) to postulate that duodenal receptors are not specifically stimulated by energy, but by the osmotic effects (carbohydrate, protein) and affinity for calcium (fatty acids) of the digestion products of carbohydrate, protein and fat in the duodenal lumen, and that a reduction in the size of the lateral intercellular space between duodenal enterocytes may initiate the signal(s) that slow gastric emptying (Hunt, 1983). Although the emptying of most amino acids appears to be determined by their osmolarity, specific inhibitory receptors for L-tryptophan have been demonstrated in the dog (Stephens et al, 1975, Cooke, 1977).

While energy regulation by duodenal receptors may apply to relatively simple liquid meals, no experiments have yet attempted to assess the effects of duodenal regulation on the emptying of solid food, in either a solid or a mixed solid and liquid meal. In this situation it is possible that antral grinding of solid food plays an important role in determining the number of calories delivered to the duodenum.

1.2.6 Gastric emptying of fats

Digestible fats that are liquid at body temperature empty much more slowly than isotonic liquids, water (Cortot et al, 1981) or even digestible solids that are ingested simultaneously (Jian et al, 1982). Intragastric layering of the lipid phase on the water phase (Chang et al, 1968) does not account for the differences observed between the emptying rates of lipids and non-lipids. The observation that a non-digestible fat analogue (sucrose polyester) empties at similar rates to water (Cortot et al, 1981, 1982) suggests that duodenal receptors, stimulated by the digestion products of lipids (fatty acids and not triglycerides) are the major cause of the slow emptying of dietary fat.

1.2.7 Hormones and gastric emptying

Following ingestion of a nutrient meal a great number of intestinal hormones (cholecystokinin, gastrin, secretin, glucagon, neurotensin, somatostatin, gastric inhibitory polypeptide) are released. The amount as well as the time course of hormone release are affected by the rate of gastric emptying. As previously discussed although there is considerable evidence that intestinal peptides and hormones have the potential for influencing gastric emptying, it is unclear if these effects occur at physiological concentrations (Strunz, 1979, Sasaki et al, 1983). Cholecystokinin may be a physiological regulator of gastric motility (Valenzuela, 1976), but in general the role of intestinal hormones in gastric emptying could "best be described as modulation rather than control" (Strunz, 1979).

Recently gastrocaecal transit time has been demonstrated to be prolonged both in the luteal phase of the normal menstrual cycle (Wald et al, 1981) and during pregnancy (Wald et al, 1982, Everson et al, 1983). These effects have been attributed to changes in plasma progesterone and oestrogen concentrations. However, as these studies made no attempt to differentiate the individual effects of gastric emptying and small bowel transit, the effects of pregnancy and the menstrual cycle on gastric emptying remain uncertain.

Prostaglandins are actively generated by the gastric mucosa of many animal species and have been extracted from both human gastric mucosal tissue and gastric juice (Peskar and Peskar, 1976), but the role of endogenous prostaglandins in the modulation of gastric emptying and secretion in humans is unclear. PGI_2 decreases gastric emptying (Shea-Donohue et al, 1980), PGE_2 increases gastric emptying (Nompleggi et al, 1980) and $PGF_{2\alpha}$, the predominant prostaglandin produced by isolated parietal cells (Skoglund et al, 1980) increases gastric emptying in primates (Shea-Donohue et al, 1981), probably due to direct effects on smooth muscle contraction. PGE_2 has more potent effects than $PGF_{2\alpha}$ on gastric emptying of liquids, probably because of greater stimulation of contractions of the longitudinal smooth muscle (Hamberg et al, 1975).

1.3 PHYSIOLOGICAL VARIATIONS IN GASTRIC EMPTYING IN NORMAL SUBJECTS

1.3.1 Meal temperature and gastric emptying

The effect of meal temperature on gastric emptying has not been studied extensively in humans. Bateman (1982) observed that the early phase of gastric emptying was slightly, but significantly faster with a cold (12^{o}C) compared with a warm (37^{o}C) liquid test meal. This observation suggests that meal temperature may affect adaptive relaxation mechanisms. In dogs, increasing the temperature of a liquid meal from 5^{o}C to 45^{o}C has very little effect, but tends to increase the rate of gastric emptying (Teeter and Bass, 1982). It therefore appears likely that normal variations in meal temperature have minimal effect on gastric emptying.

1.3.2 Physical and mental stress, endogenous opiates and gastric emptying

There has been continuing interest in the effects of physical and mental stress on the function of the gastrointestinal tract for over a century (Wolf, 1981), but until recently there has been little objective data. Many of physiological effects of stress are though to be mediated by increased sympathetic nervous stimulation and the subsequent release of catecholamines (Banister and Griffiths, 1972). Some of the effects have also be attributed to other hormones and neurotransmitters such as glucagon, (Bloom et al, 1973), acetylcholine and endogenous opiates (Hartley et al, 1972), which are recognised to be released in response to experimental stress in animals. As it is probable that the physiological response to stress may depend both on the existing relative dominance of parasympathetic and sympathetic tone (Banister and Griffiths, 1972) and the nature and duration of the stimulus, the apparently contradictory results of some recent investigations are not unexpected.

β-adrenergic agents (isoprenaline, salbutamol) significantly delay gastric emptying in normal subjects and propanolol blocks these effects and increases gastric emptying (Rees et al, 1980). This latter observation suggests that the stomach is subject to some degree of adrenergic inhibition.

Morphine and other opiate substances have been demonstrated to effect gastric motility. Morphine interrupts the fed motor pattern in the stomach and induces motor pattern resembling phase 3 activity (Lewis, 1983). Gastric emptying may be delayed after administration of morphine (Feldman et al, 1980, Lamki and Sullivan, 1983), but these effects may be largely due to stimulation of receptors in the central nervous system since loperamide, a peripherally acting opiate increases gastric emptying in humans (Remington et al, 1981). Recent studies have demonstrated the presence of specific binding sites for opiates such as enkephalins in the stomach, in gastric neurones, endocrine cells and muscle layers (Linnoila and Diaugustine, 1978, Polak et al, 1977), but the role of endogenous opiates in the peripheral regulation of gastric function is uncertain. Exogenously adminstered metenkephalin inhibits gastric emptying in primates (Shea-Donohue et al, 1983) but blockage of opiate receptors with naloxone does not significantly alter (Feldman et al, 1980, Lamki and Sullivan, 1983, Shea-Donohue et al, 1983) or may delay gastric emptying (Champion et al, 1982), rather than the increase that may have been expected if the normal stomach was subject to inhibition by endogenous opiates.

Gastric emptying of liquids has been reported as being accelerated, delayed (Hellenbrandt and Tepper, 1934) or unchanged (Fortran et al, 1967) after physical exercise. Two recent studies, using more sophisticated methods of gastric emptying measurement also show conflicting results. Cammack et al (1982) reported that intermittent moderate exercise significantly increased gastric emptying of a semi-solid meal in normal subjects, while Feldman and Nixon (1982) were unable to demonstrate any effect of exercise on gastric emptying of liquids. It is likely that some of the apparent discrepancies of these studies reflect the severity of the exercise and whether it preceded or succeeded the ingestion of the meal.

Recent investigations have demonstrated that stimuli acting through the central nervous system can markedly affect gastrointestinal motor activity. Valori and Wingate (1983) and McCrae et al (1982) have demonstrated that sustained mental stress alters human jejunal motor activity, with inhibition of interdigestive motor complexes. Cann et al (1983) found that prolonged mental stress did not have any significant effect on gastric emptying, but increased small bowel transit in normal subjects. Cold pain and labyrinthine stimulation, two acute, centrally acting stimuli markedly delay gastric emptying of a liquid meal (Thompson et al, 1982, 1983) and inhibit antral motility (Strangellini et al, 1983). Both endogenous opiates and catecholamines may be involved as mediators of the gastric motor response to cold pain and labyrinthine stimulation, as these stimuli are associated with elevation of plasma levels of β-endorphin and norepinephrine and the inhibitory effect on antral motor activity is diminished both by naloxone and adrenergic blockage (Stranghellini et al, 1983).

1.3.3 Gastric emptying, appetite regulation and obesity

In primates the observations that gastric distention may interrupt feeding (Gibbs and Smith, 1978) and that some preabsorptive satiety signals also arise from the duodenum (McHugh et al, 1982), suggest that gastric emptying may be important in the regulation of food intake and possibly in the development of obesity. Differences in the rate of absorption of calories may also relate to changes in the rate of gastric emptying.

Patients with anorexia nervosa frequently complain of gastrointestinal symptoms, and the recent observations that gastric emptying of solids (Holt et al, 1981), liquids and gastric secretions (Dubois et al, 1979) is delayed in these patients, suggest that some of these symptoms may be due to delayed gastric emptying. It is possible that gastrokinetic drugs may be useful in the management of some of these patients by relieving gastrointestinal symptoms and indirectly causing weight gain. Metoclopramide (Saleh and Lebwohl, 1980) and bethanechol (Dubois et al, 1981) increase gastric emptying in patients with anorexia nervosa. The pattern of gastric emptying in obese human subjects has not been well studied.

1.3.4 Dietary changes and gastric emptying

Chronic dietary supplementation with pectin slows gastric emptying of a solid meal (Schwartz et al, 1982) and concomitant administration of pectin slows gastric emptying in normal subjects (Holt et al, 1979, Leatherdale et al, 1982). A viscosity-related delay in gastric emptying has been postulated to be partly responsible for the improved glucose tolerance observed with guar (Jenkins et al, 1977) and pectin may be useful in the treatment of patients with the dumping syndrome, by causing a delay in gastric emptying (Leeds et al, 1981).

Recently peptide substances (or "exorphins") with hormone-like activity have been isolated from the digestion products of dietary proteins such as gluten and casein. It is probable that exorphins have local effects on gastrointestinal motility (Morley et al, 1983).

1.3.5 Drugs and gastric emptying

The effects of drugs on gastric muscle activity have been determined from isolated muscle preparations and from pressure and electrical studies in animals and humans. More recently gastric emptying tests have been used to assess pharmacologic effects on gastric emptying. Anticholinergic drugs such as propantheline and hyoscine have been shown to delay (Nimmo et al, 1973) and cholinergic drugs such as bethanechol (Hamilton et al, 1976) to increase the rate of gastric emptying in normal subjects. Levodopa delays gastric emptying (Berkowitz and McCallum, 1980). As discussed (1.3.2), β-adrenergic stimulating drugs (isoprenaline, salbutamol) delay and β-adrenoreceptor blockers (propranolol) increase gastric emptying (Rees et al, 1980).

The rate of gastric emptying may be a important factor in the rate of oral drug absorption (Nimmo, 1976). Drugs such as levodopa, penicillin and digoxin are metabolised in the stomach and a delay in gastric emptying would be expected to reduce the amount of active metabolite which is available for absorption (Evans et al, 1981).

1.3.6 Effect of alteration of intragastric pH

Alteration of intragastric pH appears to have little effect on gastric emptying in humans (Deering et al, 1979) and animals (Ohashi and Meyer, 1980). Hurwitz et al (1976) reported that aluminium hydroxide delayed emptying of a water soluble radionuclide marker, but this observation probably reflected dilution of the marker by increased gastric secretion (Deering et al, 1979). Ranitidine has been reported to delay gastric emptying in man, but cimetidine, in an equivalent antisecretory dose has no effect (Scarpignato et al, 1982). A single large oral dose of omeprazole, a new drug which profoundly inhibits gastric acid secretion, has no effect on gastric emptying in patients with a past history of duodenal ulcer disease (Horowitz et al, 1984).

1.4 GASTRIC EMPTYING DISORDERS

1.4.1 Pathogenesis of delayed and rapid emptying

With the recent development and application of methods that can be used to study gastric motility there has been an increased understanding of both the diagnosis and treatment of gastric motor disorders. Abnormalities of gastric emptying may theoretically result from changes in electro-mechanical, neurohumoral and central nervous system control mechanisms and in the regulatory function of duodenal receptors. An increasing number of clinical disorders have been recognised to result in either delayed or accelerated gastric emptying. Delayed gastric emptying may be either mechanical (from narrowing of the gastric outlet lumen) or functional (due to an abnormality of gastric motility). Acute gastroparesis may develop as part of an acute gastroenteritis, and be secondary to the administration of drugs or metabolic disorders (Table 1.1). Chronic gastroparesis may occur in association with a number of (often systemic) disorders (Table 1.1). In gastroparesis a delay in the emptying of both solid and liquid meal components is usually observed, but isolated abnormalities, such as antral dysfunction reflected in delayed gastric emptying of solids and normal gastric emptying of liquids, have been documented (Soergel et al, 1980, Rees et al, 1980). Rapid gastric emptying is usually iatrogenic (Table 1.2).

Myogenic abnormalities may occur in a number of diseases which affect smooth muscle of the gut (Faulk et al, 1978). It has been recently recognised that electrophysiological rhythm disturbances such as tachygastria (characterised by an ectopic antral pacemaker firing at a faster than normal rate) may account for impaired gastric emptying in patients with unexplained upper gastrointestinal disturbances (Telander et al, 1979, You et al, 1980, Malagelada and Stranghellini, 1983). Gastric emptying of solids or liquids is delayed in more than 40% of patients with gastrooesophageal reflux (McCallum et al, 1981, 1982, Baldi et al, 1981, Hillmeier et al, 1981), indicating that the motor abnormality is not confined to the lower oesophageal sphincter and oesophageal body. This delay in gastric emptying has been postulated as a mechanism that would increase the volume of the gastric contents and contribute to reflux and provides a rationale for using agents which increase gastric emptying, such as metoclopramide (McCallum et al, 1983) and domperidone (Valenzuela et al, 1981) in the treatment of gastrooesphageal reflux.

Interruption of vagal control probably accounts for postvagotomy (Malagelada et al, 1980) and diabetic (Campbell et al, 1977) gastroparesis. Abnormalities of the intrinsic nerve plexus have been recognised histologically in some patients with gastrointestinal motility

TABLE 1.1

AETIOLOGY OF FUNCTIONAL GASTRIC STASIS

Transient delayed gastric emptying

- post-operative ileus
- acute viral gastroenteritis
- hyperglycaemia
- hypokalaemia
- drugs: morphine, anticholinergics, levodopa, β-adrenergic agonists, nicotine
- stress: labyrinthine stimulation, cold pain

Chronic gastric stasis

- diabetes mellitus
- post-surgical - truncal vagotomy with pyloroplasty or antrectomy
- gastro-oesophageal reflux
- anorexia nervosa
- progressive systemic sclerosis
- chronic idiopathic intestinal pseudo-obstruction
- amyloidosis
- myotonia dystrophica
- familial dysautonomia
- dermatomyositis
- tachygastria
- idiopathic

TABLE 1.2

AETIOLOGY OF RAPID GASTRIC EMPTYING

a. After gastric surgery

   (1) vagotomy (liquids)

   (2) antrectomy/subtotal gastrectomy

b. Zollinger-Ellison syndrome

c. Duodenal ulcer disease

disturbances (Faulk et al, 1978). Gastric stasis, or more rapid emptying secondary to inappropriate hormone release has not yet been established as a clinical entity.

As discussed previously (1.3.2) some central nervous system stimuli have been demonstrated to have profound effects on gastric emptying (Thompson et al, 1982, 1983).

The few studies which have assessed the possible role of abnormal duodenal regulation in the pathogenesis of gastric disease, have been mainly concerned with gastric emptying in duodenal ulcer disease. As discussed (1.2.5), the duodenum has pH sensitive receptors which regulate the amount of acid delivered to it in normal subjects in such a way that the duodenal contents are maintained at approximately pH 6 (Hunt and Knox, 1972). The role played by gastric emptying in the pathogenesis of duodenal ulcer disease is unclear (Heading et al, 1976). Duodenal ulcer patients (both normo- and hypersecretors) empty liquid meals more rapidly than normal individuals (Dubois and Castell, 1980, Lam et al, 1982), but there is considerable overlap with the normal range. Patients with the Zollinger-Ellison syndrome have increased gastric emptying of liquids (Dubois et al, 1977) and solids (Harrison et al, 1978). Of more interest is the observation that the ability of duodenal ulcer patients to slow gastric emptying in response to an increasing duodenal acid load is impaired (Lam et al, 1982). This finding is consistent with the hypothesis that the feeback mechanisms by which acid delays gastric emptying are impaired in duodenal ulcer disease, and implies that a greater acid load may enter the duodenum, even in the absence of gastric hypersecretion.

1.4.2 Gastric emptying after gastric surgery

Gastric surgery, such as vagal denervation (truncal or proximal), partial gastric resection or a drainage procedure may affect gastric emptying. Despite the fact that a combination of these procedures is often used, the abnormalities of gastric emptying which occur after gastric surgery are usually predictable from a knowledge of the physiology of gastric emptying. Vagal denervation of the proximal part of the stomach impairs receptive and adaptive relaxation and increases the pressure gradient across the gastroduodenal junction. Highly selective vagotomy may therefore be expected to affect gastric emptying of liquids and result in a more rapid early phase of liquid emptying. Vagotomy of the distal stomach reduces antral contractility and may delay the emptying of solid food. Pyloroplasty, or a drainage procedure, lowers the resistance across the gastroduodenal junction, disrupts the antropyloric musculature and may therefore alter the emptying of both solids and liquids.

There have been conficting reports regarding gastric emptying after gastric surgery, which may reflect variations in surgical technique, subject position and method of gastric emptying measurement. As Heading et al (1976) has previously discussed, these studies illustrate the necessity for measurement of both solid and liquid meal components for an adequate assessment of gastric emptying.

(i) Truncal vagotomy and pyloroplasty

When patients who have undergone truncal vagotomy and pyloroplasty are studied in an erect position, carbohydrate containing liquids have been demonstrated to empty faster, with a rapid initial phase of emptying, than normal persons (Colmer et al, 1973, Faxen et al, 1978, Cobb et al, 1971, Donovan et al, 1979, Gustrud et al, 1980).

Recumbency slows this fast emptying (Gulstrud et al, 1980). The rapid, early emptying of liquids probably reflects the impaired adaptive relaxation due to the denervation of the proximal stomach, and the pyloroplasty, which lowers the resistance across the gastroduodenal junction. In contrast the rate of emptying of digestible solids has been found to be variable, but is usually delayed, even when the patient is studied in the erect position (Cowley et al, 1972, Hancock et al, 1974, Howlett et al, 1976, Binswanger et al, 1978, MacGregor et al, 1977, Sheiner et al, 1980). This finding is consistent with the loss of antral function. Because the antrum is vagally denervated and the pylorus is destroyed, the antrum cannot be filled completely, and earlier emptying of solid food occurs, despite the overall slower rate of emptying (Sheiner et al, 1980).

(ii) Proximal gastric vagotomy

Proximal gastric vagotomy has only minor effects on the emptying of solids because the function of the antrum is preserved. Results of various studies have shown a normal rate of emptying for solids (Binswanger et al, 1978, Sheiner et al, 1980, Loup et al, 1981), or a delay followed by reversion to normal (Cowley et al, 1972, Howlett et al, 1974). Because of the impairment of proximal stomach receptive and adaptive relaxation, an elevation of intragastric pressure may occur and liquids empty more rapidly initially (Moberg, 1974, Clarke and Alexander-Williams, 1974, Faxen et al, 1978, Donovan et al, 1979).

(iii) Billroth II gastrectomy

Emptying of liquids is more rapid (particulary the early phase of emptying) after partial gastrectomy (antrectomy) and gastrojejunostomy in both animals (Dozois et al, 1971) and humans (Heading et al, 1976, MacGregor et al, 1977). In contrast to truncal vagotomy and pyloroplasty, the emptying of digestible solids is usually initially faster and subsequently slower than normal subjects (Meyer et al, 1979, Mayer et al, 1982). The early rapid emptying of solids is partly a "washout effect" produced by the liquid (Kroop et al, 1979). Billroth II gastrectomy results in a loss of the direct relationship and differentation between the rates of emptying of solids and liquids, which is observed in normal subjects (Heading et al, 1976). This finding is consistent with the observation that after antrectomy, antral trituration of digestible solid food is defective and a significant proportion of solid food enters the small bowel as larger particles (Meyer et al, 1979, Mayer et al, 1982).

(iv) Gastric surgery for obesity

Surgical procedures are now commonly used for the treatment of morbid obesity. Jejuno-ileal bypass promotes weight loss by causing anorexia and malabsorption, but the mortality and morbidity association with this operation have limited its use (Payne et al, 1973). Gastric operations, such as gastric bypass (Mason and Ito, 1967), gastroplasty (Gomez, 1981) and gastro-gastrostomy (Carey and Martin, 1981) are now used because they are associated with a lower incidence of complications and the achievement of a similar weight loss (Murphy et al, 1980). These operations promote weight loss by limiting the intake of food. Alterations in gastric emptying may be relevant to both the therapeutic effects and complications of these procedures, but have not yet been assessed.

(v) Relationship between gastric emptying and post-surgical complications

A relationship has been sought in many studies between various post-operative sequelae and the pattern of gastric emptying produced by an operation. It is apparent that gastric surgery may alter the normal relationship between the emptying of food and the flow of digestive secretions into the small bowel (MacGregor et al, 1977). The defects in trituration after antrectomy may be of importance in post-operative malabsorption, and the impaired antral motor function and absence of migrating motor complexes may relate to the recognised complication of gastric bezoar formation after truncal vagotomy.

The pathophysiological mechanisms of dumping and diarrhoea are poorly understood. The extensive literature on the subject has provided many aetiological factors, of which rapid emptying of carbohydrate containing liquids from the stomach may be important. The reduced incidence of dumping and diarrhoea is a distinct advantage of proximal gastric vagotomy, over vagotomy with a drainage procedure (Madsen et al, 1973, Makey et al, 1979) and has been attributed to the preservation of antroduodenal motility with maintenance of a more normal pattern of gastric emptying. The possibility that early, rapid gastric emptying of carbohydrate containing liquids may be responsible for post-operative dumping and diarrhoea has been supported by the results of some studies, demonstrating more rapid liquid emptying in symptomatic patients (Cobb et al, 1971, McKelvey et al, 1970, Madsen and Pedersen, 1968, Clarke and Alexander-Williams 1973, Ralphs et al, 1978, Mackie et al, 1982, Lawaetz et al, 1982, Blackburn et al, 1983). However, other studies have been unable to demonstrate any consistent relationship betwen symptoms and the pattern of liquid gastric emptying (Amdrup and Griffith 1969, Gulstrud et al, 1980). These discrepancies may partly relate to the technical difficulties of quantitating early gastric emptying of liquids.

1.4.3 Pharmacological treatment of gastric emptying disorders

Delayed gastric emptying may be a significant therapeutic problem, particularly in patients with diabetic (Campbell et al, 1977, Soergel et al, 1980), post-surgical (Sheiner and Catchpole, 1976, Metzger et al, 1976, Staadas and Aune, 1972) and idiopathic (Perkel et al, 1979) gastroparesis. Surgical treatment of gastroparesis is usually unsuccessful. A limited number of drugs are available for the treatment of gastroparesis. These are essentially cholinomimetic agents and/or dopamine antagonists and their effectiveness has been noted to vary considerably between patients (Perkel et al, 1979). Some of these drugs, such as metoclopramide have a central antiemetic action which may be responsible for subjective improvement. As measurement of gastric emptying before and after treatment has not usually been performed, a relationship between improvement in both symptoms and gastric emptying has often not been established.

Bethanechol is an acetylcholine analogue with a predominant effect on the gastrointestinal tract and the bladder. Bethanechol increases gastric motor activity (Malagelada et al, 1980) and gastric emptying in some patients (Sheiner and Catchpole, 1976).

Metoclopramide also increases the frequency and force of gastric contractions in patients with diminished gastric motility (Malagelada et al, 1980, Fox and Behar, 1980), but its mechanism(s) of action is unclear and probably multifactorial. Metoclopramide has a cholinergic-mediated action on gastric smooth muscle which is blocked by atropine (Hay and Man, 1979). It may also act as a dopamine antagonist and reduce the inhibitory effects of dopaminergic sympathetic transmission on gastric motility (Peringer et al, 1976). Metoclopramide also has a central action on the chemoreceptor trigger zone to inhibit nausea, and may initiate phase 3 motor activity and stimulate motilin secretion due to central dopaminergic effects (Malagelada, 1981). Metoclopramide has been demonstrated to produce subjective and objective improvement of gastric emptying in various forms of gastroparesis (Metzger et al, 1976, Frank et al, 1981, Shivshanker et al, 1983, McCallum et al, 1983).

Domperidone is a new gastrokinetic drug which has an antidopaminergic action like metoclopramide, but is believed to have a lesser effect on dopamine receptors in the central nervous system (Brogden et al, 1982). The efficacy of domperidone in the treatment of gastroparesis has not yet been assessed.

As previously discussed, opiate drugs (Remington et al, 1981), peptide hormones (Hashmonai et al, 1979) and prostaglandins may increase gastric motility (Shea-Donohue et al, 1981). However, as yet they do not have a defined therapeutic role in the management of gastric motility disorders.

CHAPTER 2

NON-RADIOISOTOPIC METHODS OF GASTRIC EMPTYING MEASUREMENT

2.1 INTRODUCTION

The present knowledge of the regulation of gastric emptying in humans has been established by investigations spanning approximately 150 years. During this time many techniques have been developed and employed to study gastric emptying (Wingate, 1981). In 1833, William Beaumont reported observations on gastric emptying and secretion in a patient with a gastric fistula. He considered that the stomach was inert in the fasting state: "After the expulsion of the last particles of chyme, the stomach becomes quiescent, and no more juice is secreted, until a fresh supply of food is presented for its action, or some other mechanical irritation is applied to its internal coat". Cannon (1902) published observations of gastric movements using x-rays and observed that the feline stomach was capable of discriminating between digestible solid and liquid contents and allowed the liquid phase to enter the intestine, while retaining the solid particles for further mixing and grinding. Boldyreff (1916) demonstrated periods of fasting motor activity in dogs. Van Leube (1883) was the first investigator to attempt to quantitate gastric emptying by aspirating the gastric contents seven hours after ingestion of a beef, potato and bread meal. Subsequently Rehfuss (1927) employed repeated sampling of gastric contents and this method was modified by other workers (Hollander and Penner, 1938). These tests only quantitated the total emptying time of one of the meal components (fractional test meal) and therefore provided little information on the pattern of gastric emptying.

In the last 30 years there have been many methodologic advances in the study of gastric emptying. The methods that have recently been applied to the measurement of gastric emptying each have advantages and limitations and are summarised in Table 2.1. The non-radionuclide methods are now briefly discussed and radionuclide techniques with be described extensively in chapter 3.

2.2 RADIOLOGIC TECHNIQUES

The first studies of the stomach using x-rays were by Cannon et al (1902), whose interest was mainly in assessment of gastric motility rather than gastric emptying. Subsequently it has been recognised that gross abnormalities of gastric emptying may be detected in a routine upper gastrointestinal radiographic assessment, with liquid barium sulphate. Although these tests have been used widely their usefulness is limited and radiographic techniques have never been adequately validated in comparison to gastric emptying methods using intubation or radioisotopes. Liquid barium is a non-physiological meal, as it is unpalatable and may irritate the gastric mucosa (Sun et al, 1959), and does not assess the emptying of solid food. Barium-coated enteric granules (Horton et al, 1965), meals incorporating barium sulphate (Van Liere and Northup, 1941, Wilkinson and Johnson, 1973) and the "barium burger" (Pelot et al, 1972) have been subsequently developed to overcome these deficiencies. All contrast studies using barium are associated with a significant radiation exposure and the inability to quantitate emptying accurately - since the volume of barium in the stomach cannot be determined accurately, only the time for complete or near-complete emptying can be assessed. Tests using solid meals impregnated with barium granules may assess only liquid emptying since rapid dissociation of the barium into the liquid phase may occur. The need for quantification of gastric emptying has prompted the use of radioopaque plastic spheres for liquid barium and barium impregnated solid meals (Carlson et al,

TABLE 2.1

METHODS OF GASTRIC EMPTYING MEASUREMENT

RADIOLOGIC

- liquid barium sulphate
- enteric coated barium granules
- "barium burger"
- radiopaque spheres

INTUBATION

- saline load test
- serial intubation and aspiration
- multiple sampling
- multilumen tube perfusion and aspiration

RADIOISOTOPIC

ULTRASOUND

ABSORPTION KINETICS OF ORALLY ADMINISTERED SOLUTES

- paracetamol
- ethanol
- glucose

FERROMAGNETIC TRACER

1966). However such markers are not representative of the emptying of solid food as they cannot be digested or mechanically fragmented and contain no food substances known to inhibit gastric emptying.

2.3 INTUBATION TECHNIQUES

There are two general types of intubation techniques - those requiring only gastric intubation and those requiring both gastric and duodenal intubation. Much of the current knowledge of the regulation of gastric emptying in normal subjects and in disease states is derived from studies utilizing intubation methods.

2.3.1 Saline load test

The "saline load test" (Goldstein and Boyle, 1965) involves nasogastric intubation, instillation of a known volume of isotonic saline (usually 750 ml) and aspiration of the gastric contents 30 minutes later. A delay in gastric emptying is a residual volume of 200 ml or greater. The test is insensitive, non-specific as it does not quantify gastric secretions and provides no information on the gastric emptying of solid food.

2.3.2 Serial intubation and aspiration

The serial test meal was developed to overcome some of the limitations of the fractional test meal and has been used extensively by Hunt and co-workers (Hunt and Spurrell, 1951, Hunt, 1956). The technique used a non-absorbable marker such as phenol red or polyethylene glycol in a specific volume of liquid test solution. At a specific time the entire gastric content was aspirated. Measurements of the volume of residual test solution and the concentration of the marker allow quantification of the amount of the marker emptied and the volume of gastric secretion. By repeating the procedure on different days, at varying time intervals after administration of the test meal, the emptying pattern of the meal can be calculated. This technique makes the questionable assumption that emptying is similar at different testing periods (Thompson et al, 1982), requires repeated nasogastric intubations which are cumbersome and impractical, takes several days to complete which limits its clinical application and permits measurement of gastric emptying of liquids only.

2.3.3 Multiple sampling

The double sampling technique (George, 1968, Hunt, 1974) was developed to overcome the need for repetitive intubations. A liquid test meal of known volume is administered in a similar way. After a sample is obtained, a small amount of nonabsorbable marker is added and soon after another sample is withdrawn. This procedure can be repeated until the stomach is empty. Since the volume and concentration of chloride and the marker in the original liquid and the subsequent samples are known, both the volume of the meal remaining in the stomach and the volume of gastric secretion can be calculated.

2.3.4 Multilumen tube perfusion and aspiration

A variation of the double sampling technique uses a triple lumen tube assembly, to allow perfusion of the duodenum with a marker to a steady state, before a test meal is introduced into the stomach and sequential aspiration of both gastric and duodenal markers is performed (Meeroff et al, 1973). Recovery of the gastric marker from the duodenum evaluates gastric emptying and recovery of the duodenal marker quantitates pancreatic and biliary secretions. Modification by

Malagelada et al (1977, 1979) have permitted application of this technique to simultaneous measurement of solid as well as liquid emptying. The liquid phase is labelled with a non-absorbable marker and the solid phase with 51-chromium.

2.3.5 Deficiencies of intubation methods

There are significant disadvantages of intubation techniques which limit particularly their clinical use. The best of these methods in the gastroduodenal intubative technique (Malagelada et al, 1979) whose accuracy depends on sampling from multiple phases, distribution of particle sizes and attainment of steady states. The complexity of this method limits its use to a research setting. As samples are obtained from multiple phases, a uniform distribution of meal marker throughout the total intragastric volume is assumed. However even with purely liquid meals containing fat, carbohydrate and protein, the distribution within the stomach has been shown to vary because of separation of fat from the aqueous phase (Lagerloff et al, 1976). There is some error in estimating duodenal flow (so that a true steady-state is not achieved), as the stomach varies its rate of emptying during the test period (Johansson and Lagerloff, 1976). The aspiration of solid particles of various sizes does not represent the ratio present in the lumen, but may be biased towards particles of smaller size (Meyer, 1979).

The effects of an intestinal tube on gastrointestinal function have not been assessed until recently. Any effect of intubation on gastric emptying could be mediated by non-specific mechanisms, such as the induction of stress or nausea, or may be directly mediated, by stimulation of mucosal mechanoreceptors (Paintal, 1957). As the effects may vary with the technique employed, contradictory results are not unexpected. A liquid meal given down a tube does not cause receptive relaxation of the proximal stomach and may empty initially faster than a swallowed meal (Hunt, 1956). Read et al (1983) have recently demonstrated that the presence of a gastrointestinal tube may be associated with a delay in gastric emptying and more rapid small bowel transit in normal subjects, but Longstreth et al (1975) and Muller-Lissner et al (1982) could not demonstrate any effect of gastric and transpyloric intubation on gastric emptying. The findings of Read et al (1983) however emphasize the advantages of non-invasive gastric emptying methods.

2.4 ULTRASOUND TECHNIQUES

Some workers have used ultrasound techniques to measure the frequency and amplitude of gastric contractions after a liquid test meal (Holt et al, 1980) and more recently gastric emptying of liquids (Bateman and Whittingham 1982, Bateman et al 1982). Bateman and coworkers initially used T-M mode recordings (Bateman et al, 1977) and subsequently real time ultrasound techniques (Bateman et al, 1982) to measure the volume of liquid in the stomach. By obtaining a series of cross-sectional images at regular (1 cm) intervals, at right angles to the long axis of the stomach, a three dimensional representation of the stomach is produced. The volume of the stomach can be computed from the measurement of areas of the cross-sectional images.

The potential advantages of this method are that it is non-invasive, readily repeatable, permits frequent measurements and is not associated with any radiation burden. Real-time ultrasound scanning of the stomach has apparently been applied successfully to study the effects of drugs on gastric emptying (Bateman et al, 1982) and physiological changes in gastric emptying (Bateman, 1982).

However the role of ultrasound techniques in the measurement of gastric emptying has yet to be determined, partly because of significant inherent deficiencies: they are unsuitable for measuring gastric emptying of solids since solid food reflects the second beam, no correction can be made for gastric secretion during the emptying of the meal and scanning may be technically difficult in obese subjects.

2.5 THE USE OF THE ABSORPTION KINETICS OF ORALLY ADMINISTERED SOLUTES AS AN INDIRECT ASSESSMENT OF GASTRIC EMPTYING

In humans, absorption of many orally administered drugs from the stomach is negligible and the rate of gastric emptying therefore controls the delivery of a drug to the maximal site of absorption in the small bowel (Nimmo, 1976, Levine, 1970). Ethanol and weakly acidic drugs, including paracetamol, barbiturates and salicylates are absorbed very much more rapidly from the small bowel than from the stomach. The dependence of oral paracetamol absorption on the rate of liquid gastric emptying was first demonstrated by Heading et al (1973) and Holt et al (1980) have subsequently shown that ethanol absorption also correlates with the rate of liquid gastric emptying. These findings have led to the use of the absorption kinetics of orally administered paracetamol and alcohol as an indirect assessment of liquid gastric emptying (Heading et al 1973, Harasawa et al, 1979, Goldstraw and Bach, 1981) and modification of paracetamol absorption by propantheline and metoclopramide has been demonstrated (Nimmo et al 1973, 1975). Thompson et al (1982) demonstrated that the results of oral glucose tolerance tests in normal subjects also correlate with the rate of liquid gastric emptying.

The use of blood concentrations of intestinally absorbed solutes, such as paracetamol, ethanol and glucose as an index of gastric emptying is potentially a simple, safe and non-invasive technique, but these methods are at present probably unsatisfactory for accurate measurement of liquid emptying. The assumption that there is insignificant drug absorption from the stomach is questionable for both alcohol and glucose and plasma glucose concentration is also dependent on many other variables, such as plasma insulin levels. These methods also have the significant disadvantage of not assessing gastric emptying of solids.

2.6 FERROMAGNETIC TRACER

Benmair et al (1977) described the use of a ferromagnetic tracer to measure gastric emptying in humans. Magnesium ferrite, in a powder form is added to a a test meal and an external transducer, sensitive to the ferromagnetic properties of the markers is used to quantitate the amount of magnesium ferrite remaining within the stomach at regular intervals. This method is non-invasive and does not involve radiation exposure, but has not found widespread use.

CHAPTER 3

MEASUREMENT OF GASTRIC EMPTYING USING RADIONUCLIDE METHODS

3.1 INTRODUCTION

The use of in-vivo radionuclide methods to study gastric emptying in humans began in 1966 when Griffith and colleagues used an orally administered ^{51}Cr-labelled meal of scrambled eggs and porridge and a scintiscanner to quantitate gastric emptying in 26 subjects. The major advantages of this technique were that it was simple, non-invasive, avoided the need for sampling of intragastric contents, and was highly acceptable to patients, unlike radiologic and intubation methods. Subsequently there have been considerable refinements in radionuclide gastric emptying techniques.

In this chapter the development, advantages and potential limitations of radionuclide gastric emptying methods are discussed. The chapter is structured to serve as an introduction to the author's studies and to be complementary to the discussion of the results of these studies (Chapters 8,9,10).

3.2 RADIOPHARMACEUTICALS

For the measurement of gastric emptying, radionuclide markers are incorporated into liquid, solid or mixed solid and liquid meals. All tests assume that the gastric emptying of the nuclide adequately represents the behaviour of the test meal. Since the liquid and solid phases of a mixed solid and liquid meal may empty at different rates (Malagelada et al 1979, Heading et al, 1976), the precise identification of each phase in necessary for accurate definition of the emptying of either phase, or of the total meal.

The ideal radiopharmaceutical for the measurement of gastric emptying should be relatively inexpensive, non-toxic, nonabsorbable and nonadsorbable from the gastric mucosa (both for purposes of limitation of radiation exposure and accuracy of measurements), homogeneously distributed within the meal, tightly bound to prevent any interaction with food particles or the gastric mucosa, and have suitable imaging characteristics for the scintillation camera, in order to achieve high count rates with relatively low radiation burdens. A variety of radioisotopic markers particularly containing ^{99m}Tc, have been used in the study of gastric emptying in an attempt to fulfill these criteria (Tables 3.1 and 3.2).

3.2.1 Markers used to label liquid meals

Liquid markers have been used to measure gastric emptying for many years. ^{131}I human serum albumin (Bromster et al, 1968) is unsatisfactory as a liquid marker, both because it is a beta emitter which has to be administered in low doses to restrict the radiation burden to both the gastrointestinal tract and the thyroid gland and the label is broken down in the duodenum, the ^{131}I absorbed and resecreted in the gastric juice. Other water soluble pharmaceuticals that have been used to measure gastric emptying of liquids such as ^{51}Cr-sodium chromate are absorbed in significant quantities onto the solid components of the meal (Heading et al, 1971) (Table 3.1).

The liquid markers that are now most often used are in a non-absorbable chelated form such as ^{111m}In- or ^{113m}In-diethylenetriaminepentaacetic acid (DTPA) (Heading et al, 1971) or ^{99m}Tc-DTPA (Chaudhuri, 1974) and their use as markers of a liquid meal seems established (Table 3.1). Delin et al (1978) have demonstrated a close correlation between measurements of emptying of a dextrose solution using ^{99m}Tc-DTPA and a non-radionuclide aspiration technique which used polyethylene glycol as an indicator. However even with these markers it is likely that in a mixed solid and liquid meal adherence to some solid foods occurs (Grimes and Goddard, 1977).

3.2.2 Markers used to label solid meals

Griffith et al (1966) first introduced a radio-isotopic method designed to measure the gastric emptying of solid food. The test meal consisted of scrambled eggs and porridge into which ^{51}Cr had been stirred during cooking, milk, butter and bread. The emptying pattern observed was exponential and similar to the liquid emptying pattern described previously with serial test meal intubative techniques (Hunt and Spurrell, 1951).

Subsequently a number of different radiopharmaceuticals have been used to label digestible solid food (Table 3.2). However, very few authors substantitated that initial labelling of the marker was high and that it remained attached to solid food in the stomach throughout the emptying study. Weakly adherent markers which dissociate from solid foods into the liquid fraction of the test meal are inadequate for assessing gastric emptying of solids (Table 3.2). For example Meyer et al (1976) demonstrated that the use of ^{51}Cr as a solid marker in the presence of non-labelled liquids (or gastric secretion), as used in the study of Griffith et al (1966) is not an accurate marker of the solid phase, because of considerable dissociation of nuclide into the liquid. This factor accounts for the observed exponential pattern and overestimation of solid emptying

TABLE 3.1

RADIONUCLIDE MARKERS USED TO LABEL LIQUID MEALS

---

1. Weakly bound labels *

^{51}Cr - sodium chromate

^{51}Cr - chloride

^{131}I - rose bengal

^{125}I - R.I.S.A.

^{131}I - human serum albumin (HSA)

2. Tightly bound labels

^{113m}In - diethylenetriaminepentaacetic acid (DTPA)

^{111m}In - DTPA

^{99m}Tc - DTPA

^{123}I - starch solution

---

rates (Griffith et al, 1966). Conversely as discussed previously ^{51}Cr as a liquid marker may be adsorbed onto solid food components (Heading et al, 1971).

The problems of labelling a digestible solid were first overcome by Meyer et al (1976). These workers described the use of intracellularly labelled chicken liver, obtained by injection of ^{99m}Tc sulphur colloid into live chickens, as a marker of solid food. This marker has a very high labelling efficiency, is resistant to peptic digestion and empties as solid particles. Some other digestible solid markers such as ^{99m}Tc-egg (Kroop et al, 1979, Malmud et al, 1982, Velasco et al, 1982) have a high labelling efficiency, which is only slightly less than <u>in-vivo</u> labelled chicken liver (Table 3.2).

As discussed previously (1.2), digestible solids are emptied as small particles, after being subjected to antral propulsive and retropulsive mincing. The emptying of non-digestible solids, which are resistant to mechanical and chemical breakdown have been studied with ^{99m}Tc sulphur colloid-filter paper (Heading et al, 1976), ^{99m}Tc-triethylenetetramine-polystyrene resin beads (Digenis et al, 1977), ^{131}I-cellulose (Carryer et al, 1982, Malagelada et al, 1980, Carlson et al, 1978) and ^{99m}Tc-bran (Sagar et al, 1983). The ^{131}I-cellulose fibre (particles 1-5 mm in length) passes virtually intact through the gastrointestinal tract and should permit the measurement of both small intestinal and colonic transit. The use of a fat marker - ^{75}Se-glycerol triether-butter has been recently described (Jian et al, 1982). Thus adequate gamma emitting markers are now available for each of the major components of an ordinary meal.

TABLE 3.2

RADIONUCLIDE MARKERS USED TO LABEL SOLID OR SEMI-SOLID MEALS

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1. Weakly bound surface labels*

^{51}Cr-eggs	^{99m}Tc-DTPA bread
^{51}Cr-porridge	^{99m}Tc-DTPA cornflakes
^{51}Cr-hamburger	

2. Tightly bound surface labels

^{99m}Tc-human albumin microspheres (H.A.M.)
^{99m}Tc-filter paper
^{99m}Tc ovalbumin eggs
^{99m}Tc-egg
^{99m}Tc-macroaggreated ferrous hydroxide (M.A.F.H.)

3. Tightly bound chemical labels

^{123}I-starch	^{99m}Tc-triethylenetetramine-polystyrene resin
^{123}I-noodles	^{75}Se-glyceroltriether butter
^{123}I-cellulose fibre	

4. Tightly bound interstitial labels

^{99m}Tc-liver (in-vivo or in-vitro)
^{113m}In-liver
^{198}Au-liver
^{51}Cr-liver
^{59}Fe-liver
^{57}Co-liver

---

* Unsatisfactory markers of solid food because of significant dissociation into liquid phase.

3.2.3 Simultaneous measurement of solid and liquid emptying

Gastric emptying of liquid and solid meals may be measured in two separate tests, but with more advanced detectors two nuclides of different energies may be used in the same meal. Heading et al (1976) were the first investigators to use a dual isotope technique for studying both solid and liquid meal components simultaneously - ^{113m}In-DTPA was used as a marker of the liquid phase together with approximately thirty small pieces of filter paper impregnated with ^{99m}Tc-sulphur colloid as a solid marker. This study demonstrated the necessity for measurement of both solid and liquid emptying for an adequate assessment of gastric emptying. Subsequently other dual isotope techniques have been described (Moore et al, 1981, Malmud et al, 1982). Such methods increase both the potential usefullness and technical complexity of the gastric emptying measurement.

3.2.4 Radiation doses

Radiopharmaceuticals which are used for the measurement of gastric emptying usually have short half-lives (that of ^{99m}Tc is approximately 6 hours and that of ^{113m}In is 100 minutes) have no particulate emissions and are administered in small doses of less than 1 millicurie. The whole body radiation burden is usually less than that of a single abdominal roentgenogram (Siegel et al, 1983) and is considerably less than fluoroscopy, or the "barium burger" test used by Pelot et al (1972). Radionuclide emptying tests are therefore usually acceptable for single or sequential studies.

3.3 ACQUISITION AND ANALYSIS OF GASTRIC EMPTYING DATA

The selection of instruments to detect gamma rays has varied in different studies and probably reflects the availability of instruments rather than experimental design. These instruments range from non-imaging probe systems to tomographic imaging devices of great sophistication. The rate of gastric emptying is determined by expressing at regular time intervals the radioactivity within the stomach as a percentage of the total activity.

The early radionuclide methods relied upon blind placement of the detector probe over the stomach. Using such fixed non imaging detectors (Bromster et al, 1968), it is impossible to separate the activity of the stomach and small intestine with any confidence and an overestimation of the rate of gastric emptying usually resulted. The problem of probe placement was resolved partially by the rectilinear scanner (both single headed and double-headed devices) which produces an image of the area scanned and allows extragastric activity to be separated satisfactorily (Heading et al 1971, 1976). Although the rectilinear scanner permits sequential quantitative measurments the long time taken to record a single observation (5-10 minutes) is a significant disadvantage, because of the resulting smaller number of data points.

Harvey and coworkers (1970) first advocated the use of the scintillation or gamma camera, which is the major instrument that is now used for studies of gastric emptying. The scintillation camera is a static imaging device by means of which a region can be viewed continuously. It has the advantage over scintiscanning of being able to record the distribution of counts in the field of view at frequent intervals, thus permitting virtually continuous quantitative imaging. Most studies have had gamma cameras interfaced with a digitial computer for rapid determination of gastric emptying. With a scintillation camera interfaced to a computer, the stomach may be recognised by its anatomical shape on a computer image screen and a region of interest may be drawn on the computer display, in an attempt to include the whole stomach, but excluding the small intestine. Changes in counts within this limited region, which reflects the gastric activity, can be monitored continously to produce curves of gastric retention against time.

3.4 SOLID AND LIQUID EMPTYING IN NORMAL SUBJECTS

In several studies of the emptying of a mixed solid and liquid meal in normal subjects, low calorie liquid components have been observed to empty more rapidly than the solid components (Heading et al, 1976, Moore et al, 1981) although there is a direct correlation between rates of solid and liquid emptying (Heading et al, 1976). The emptying of solid food approximates a linear pattern (Meyer et al, 1976, Heading et al, 1976). Some authors have in addition described a lag period, before solid food enters the duodenum (Sheiner et al, 1980) but this is a contentious point. Emptying of isotonic liquids is non-linear with a slope that decreases with time and has been described as a monoexponential or volume-dependent process (Chaudhuri, 1974, Heading et al, 1971). Meals of larger weight and calorie content are associated with longer times of emptying for both solids and liquids (Moore et al, 1981).

3.5 METHODOLOGIC PROBLEMS AND LIMITATIONS OF RADIONUCLIDE GASTRIC EMPTYING TESTS

There are several potential limitations and methodologic problems which may reduce the specificity and sensitivity of radionuclide gastric emptying tests. These problems are particularly related to the physical properties of the radionuclides and instruments and changes in radionuclide distribution within the stomach. The method of performance of an emptying test varies considerably in different centres with variations in meal composition, radionuclide markers, frequency of data sampling, subject position and correction techniques. As Sheiner (1975) wrote: "What is also needed are methods to standardise the meal, particularly with solids and an agreed expression of results" to allow comparisons between studies. - Unfortunately these wishes have not been fulfilled. Some of these potential problems are now briefly discussed.

3.5.1 Meal composition

Digestible solids empty from the stomach at rates dependent on the size and physical composition of the particles (Meyer et al 1979, 1981, Holt et al, 1982) and gastric emptying of a liquid meal is dependent on its osmotic and calcium binding properties (Hunt 1983). In view of these observations meal size and composition should be standardised in any gastric emptying method and the markers should be selected to match the properties of the meal. However this has not been the case in some studies (Moore et al, 1981, McCallum et al, 1983). The effect of alteration of the caloric or osmotic content of a mixed solid and liquid meal on the pattern of both solid and liquid emptying has not been studied.

3.5.2 Distribution of radiolabels

Since the liquid and solid phases of a meal may empty at different rates the precise identification of each phase is necessary. However, as discussed the distribution of radiolabels may not be precise, so that liquid markers adhere to solids and/or solid markers dissociate into the liquid (Heading et al, 1971, Meyer et al, 1976).

3.5.3 Intragastric dilution of solid and liquid markers

The gastric secretory response to a meal is extremely variable between normal subjects and may exceed 1000 ml of fluid in the first three hours postprandially (Malagelada et al, 1979). Because gastric secretory rates change rapidly during the post-prandial period it is impossible with external gamma counting to quantitate either the intragastric volume of gastric secretion, or the amount emptied, and both solid and liquid markers become progressively diluted by an unknown quantity of gastric secretion. This limitation applies particularly to water soluble radiolabelled markers and gastric emptying of solids may be more reliably evaluated (Meyer, 1979).

3.5.4 Subject position

As it is possible that gastric emptying may be affected by both posture and gravity (Tothill et al, 1980, Gulstrud et al, 1980, Burn-Murdoch et al, 1980) a standard subject position should be adopted. However it is not clear whether the supine (Heading et al, 1976), seated (Sheiner et al, 1980) or standing (Moore et al, 1981) positions are to be preferred for routine tests of gastric emptying.

3.5.5 Radionuclide decay

Because gastric emptying tests may extend over several hours, significant decay of radionuclides (particulary those with short half-lives such as ^{113m}In - 100 minutes) may occur.

3.6 GEOMETRICAL ERRORS OF RADIONUCLIDE METHODS

Barium radiologic techniques and many radionuclide emptying studies evaluate a three dimensional process in an essentially two dimensional manner. The stomach may however alter in shape, position and the distribution of its contents (Delin et al, 1978). Both because of this and the characteristics of the radionuclides used, the relationship between the radiation detected and the quantity of radionuclide in the stomach may not be constant and result in errors of radionuclide gamma ray attentuation, Compton scatter and septal penetration. Superposition of the stomach and small bowel may in addition prevent an absolute separation between emptied and retained meal (Chaudhuri, 1974, Tothill et al, 1978).

3.6.1 Radionuclide gamma-ray attenuation

After meal consumption anterior movement of food within the stomach (from proximal stomach to antrum) may be associated with a changing attenuation of the gamma emissions. For example, a single, posteriorly positioned camera may overestimate the rate of gastric emptying because of movement of food away from the detector (Tothill et al, 1978). The significance of this error and/or the most appropriate correction technique have been been clarified (Tothill et al, 1978, 1980, Harding et al, 1979, Rattner et al, 1981, Wright and Krinsky, 1982, Meyer et al, 1983).

3.6.2 Counting interference between multiple radionuclides (Compton Scatter)

When two nuclides of different energies are used simultaneously (such as ^{113m}In-DTPA as a liquid marker together with ^{99m}Tc as a solid marker) the number of counts in the lower energy isotope window may include some of the scattered radiation (Compton scatter) from the higher energy nuclide, which has reached the collimator as lower energy photons, indistinguishable from those emitted directly from the lower energy radionuclide (Weiner et al, 1981). If the two nuclides are of similar energies there may be scatter into both low and high energy windows (Fisher et al, 1982). The significance of this error is also disputed. Some authors have applied correction factors (Meyer et al, 1983), but not others (Moore et al, 1981).

3.6.3 Septal penetration

This technical problem reflects the characteristics of the collimator, which consists of a grid of crystal detectors separated by lead septae. Gamma rays from a large source such as the stomach strike the collimator at various angles and not just perpendicular to the collimator surface. The lead septae are designed to stop these "non-perpendicular" gamma rays reaching the crystal detectors, but may not be able to prevent this phenomenon completely (Weiner et al, 1981). Consequently it is possible that some gamma rays which originate within the stomach may be excluded when the counts within the gastric region of interest are analysed and result in an underestimation of activity within the stomach. The significance of this error is contentious (Meyer et al, 1983, Van Deventer et al, 1983, Loo et al, 1984) and most authors have not used correction factors (Heading et al, 1976).

3.7 ANALYSIS OF GASTRIC EMPTYING DATA AND INTERPRETATION OF RESULTS

With the introduction of scintiscanning techniques the entire process of gastric isotope emptying can be recorded and quantitated. There have been many methods used to enable statistical comparisons between emptying patterns after different meals, between groups of subjects or between treatments (Hopkins, 1966, Barber et al, 1974, Heading et al, 1976). The most commonly used methods, which compare the percentage emptied from the stomach at specific time intervals (McCallum et al, 1981) or the half-emptying time (Heading et al, 1976) have inherent inaccuracies (Elashoff et al, 1982) and it is not clear what quantitative parameters are most useful (Dugas et al, 1982).

The interpretation of gastric emptying data also poses significant, unresolved problems. As emptying rates depend on various factors, particularly the composition of the test meal, a large sample of normal subjects of both sexes and wide age range should be studied with the same technique by each laboratory, to obtain a control range (Brown and Malagelada, 1983). There is little information on the reproducibility, sensitivity and specificity of radioisotopic methods (Chaudhuri, 1974, Chaudhuri et al, 1975, Heading et al, 1976, Sheiner et al, 1980). It is therefore possible that inter- and intraindividual variations in gastric emptying and methodological problems may limit the application of radioisotopic tests.

3.8 COMPARISON OF RADIONUCLIDE METHODS AND OTHER GASTRIC EMPTYING TECHNIQUES

Gastric emptying of a liquid test meal may be measured relatively easily with both radionuclide methods and intubation techniques. A close correlation between the results obtained has been demonstrated by such studies (Delin et al, 1978, Blake and McKelvey, 1981, Van Deventer et al, 1983). The absorption kinetics of orally administered paracetamol also correlate with a radionuclide assessment of liquid gastric emptying (Holt et al, 1979). Intubation techniques which measure solid emptying have not been compared to radionuclide methods.

Radiologic techniques have not been adequately compared to radionuclide methods in normal subjects. Perkel et al (1981) studied a group of patients who had an abnormal barium test meal (gastric retention of barium after a meal of eggs, toast, bacon and liquid barium after 6 hours) with a radioisotopic meal and nearly half the subjects had normal half-emptying times. However as this study preselected patients with an abnormal barium test, comparative information on the sensitivity of the two tests could not be obtained. The findings of a study by Campbell et al (1977) in diabetics with autonomic neuropathy indicate that radioisotopic methods, particularly those that measure solid emptying as well as liquid, are much more sensitive than conventional barium radiologic techniques in detecting delayed gastric emptying.

3.9 CONCLUSIONS

The measurement of gastric emptying using radionuclide labelled food markers and a scintillation camera is non-invasive, quantitative and permits the simultaneous measurement of solid and liquid components of a meal. There are significant potential inaccuracies associated with these methods. The radiopharmaceuticals used must have a high labelling efficiency and stability, and meal size and composition should be standardised in routine tests. Correction techniques should be used, when necesary to compensate for errors such as radionuclide decay, radionuclide gamma-ray attenuation and Compton scatter.

CHAPTER 4

GASTRIC EMPTYING TEST METHODS

4.1 PREPARATION OF SOLID AND LIQUID MEALS.

4.2 ASSESSMENT OF STABILITY OF SOLID AND LIQUID MARKERS.

4.3 RADIATION DOSIMETRY.

4.4 PERFORMANCE OF GASTRIC EMPTYING STUDY.

4.5 DATA ACQUISITION.

4.6 DATA ANALYSIS

- 4.6.1 Correction Techniques:
  - (i) Patient movement
  - (ii) Radionuclide decay
  - (iii) Radionuclide gamma-ray attenuation
  - (iv) Compton scatter
- 4.6.2 Histogram generation and analysis.
- 4.6.3 Statistical methods.

In this chapter the methods involved in the performance and analysis of the gastric emptying test are described.

4.1 PREPARATION OF SOLID AND LIQUID MEALS

Twenty seven mCi of ^{99m}Tc sulphur colloid was injected into a wing vein of a live chicken, as described by Meyer et al (1976). After 20 minutes the chicken was killed instantly by crushing the cervical spinal cord and the liver was removed. The liver was then washed in tap water. The amount of liver containing 1-1.5 mCi of ^{99m}Tc was diced into small particles (2-4mm), and mixed into 100 g of ground beef and the resulting "hamburger" cooked on a griller (Figure 4.1). The total caloric content of the solid meal (25 g protein, 21 g fat) was approximately 270 kcal.

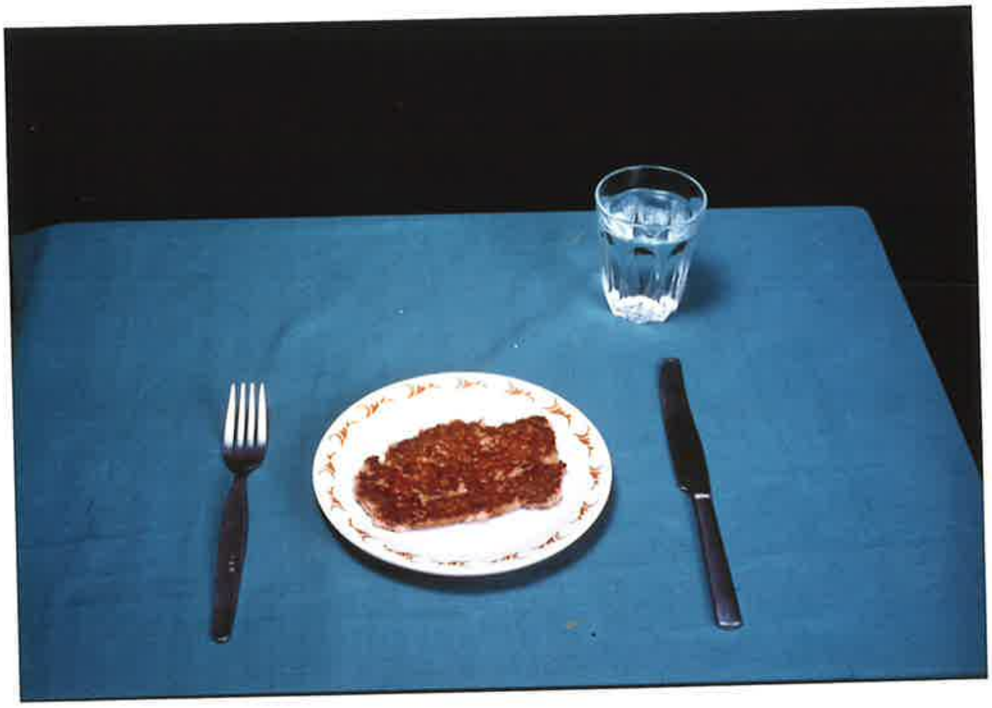
The liquid marker was 0.75-1 mCi of ^{113m}In-diethylenetriamine -pentaacetic acid (^{113m}In-DTPA) mixed in 150 ml of either tap water, 10% dextrose solution or 25% dextrose solution.

4.2 ASSESSMENT OF STABILITY OF SOLID AND LIQUID MARKERS

The stability of the ^{99m}Tc-liver was validated by in vitro testing. In two experiments (a) diced uncooked labelled liver particles, and (b) 2-4 mm particles of the cooked ^{99m}Tc chicken liver-ground beef mixture, were incubated at 37^{o}C in 50 ml of fresh gastric juice (pH = 1.3). The mixtures were gently agitated every 5 minutes. Aliquots of liquid were taken at 1 hour intervals for 5 hours and counted against a known standard. These experiments were repeated once.

LEGEND FOR FIGURE 4.1

The solid (a 100 g ^{99m}Tc-liver/beef hamburger) and liquid (150 ml of ^{113m}In-DTPA mixed in either water, 10% dextrose or 25% dextrose) meals used in the gastric emptying method.



4.3 RADIATION DOSIMETRY

The radiation burden for the stomach and whole body was calculated analytically, using values for the absorbed dose per unit cumulative actitivity (S) previously calculated by Snyder et al (1975). The dosimetry was calculated for 1 millicurie doses of each radiopharmaceutical, with a solid 50% emptying time of 80 minutes and a liquid 50% emptying time of 20 minutes, which approximated mean values in control subjects (Table 6.4). It was assumed that there was no unlabelled activity and no renal clearance of the activity.

4.4 PERFORMANCE OF TEST

The gastric emptying test was begun either at 1000 hours after the subject had fasted from 2400 hours the previous day, or at approximately 1230 hours after the subject had previously eaten a light standard breakfast (one piece of toasted bread with butter and a cup of coffee or tea) at 0730 hours. The study was performed in the sitting position with the detector behind the patient (Figure 4.2). The subject ate the solid meal gradually over a five minute period and then drank the 150 ml of liquid containing ^{113m}In-DTPA. The meal was palatable and the hamburger could be easily masticated. At approximately 30 minute intervals, data acquistion was interrupted for five minutes to allow the subject to stand or sit away from the camera if he or she wished. Each study was continued for at least two hours.

4.5 DATA ACQUISITION

A scintillation camera (Nuclear Chicago Pho-Gamma III HP; Digital Equipment Corporation) with a high energy 400 keV, 4000 parallel hole collimator interfaced to a computer (PDP 11/55) was used for data collection (Figure 4.3). Using an automatic switching device, the energy window alternated regularly between that of ^{113m}In (393 keV) and ^{99m}Tc (140 keV). The size of the energy windows were ± 10% for both ^{113m}In and ^{99m}Tc. Data collection commenced just before the beginning of food ingestion and therefore no initial data were missed. During the first 10 post-cibal minutes the energy window alternated every 5 seconds. Subsequently, this interval was increased to 50 seconds. The switching device placed switching "marks" in the data stream to allow subsequent reconstruction into frame mode images (Figure 4.4). At the end of data acquisition 100 μCi of ^{99m}Tc-DTPA in 150 ml of water was given orally and a static 1 minute left lateral image of the upper abdomen was taken. This provided a quantitative display of gastric orientation and depth from the collimator surface (Figure 4.5). Acquired counting data were stored on data discs for subsequent analysis.

4.6 DATA ANALYSIS

The study comprised at least five list mode files. Each of these files was reformated to produce separate dynamic studies for the solid and liquid components. The dynamic studies were corrected for patient movement, radionuclide decay, Compton scatter and radionuclide gamma-ray attenuation using the following methods.

4.6.1 Correction Techniques

(i) Patient movement

A cross-shaped marker containing ^{99m}Tc was taped to the subject's back before the commencement of the gastric emptying study (Figure 4.6). The dynamic studies were realigned to a single reference point using the ^{99m}Tc marker.

LEGEND FOR FIGURE 4.2

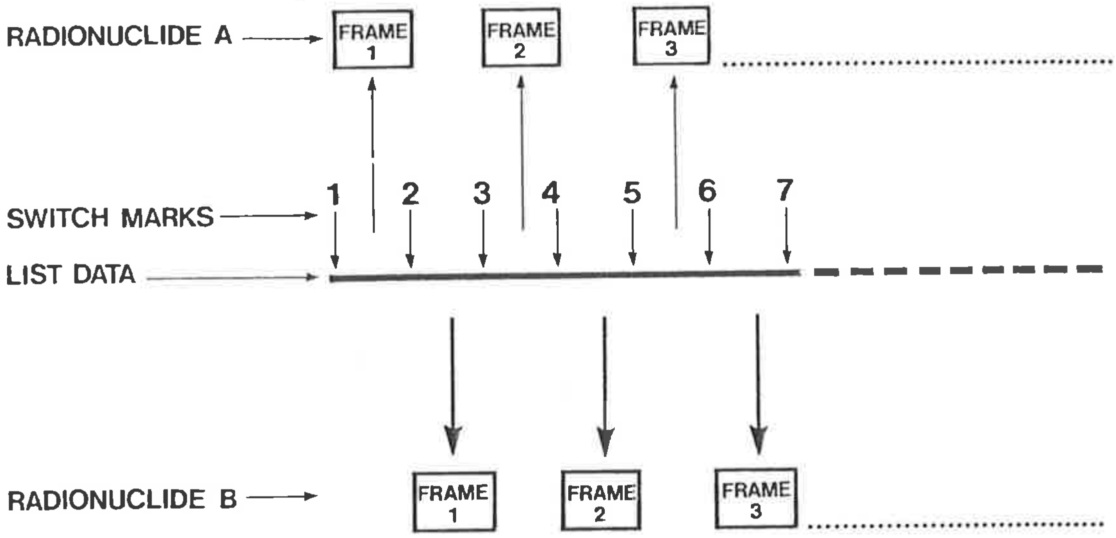
Performance of a gastric emptying study. The scintillation camera is behind the subject who is seated. Data collection commenced just before the beginning of food ingestion.

LEGEND FOR FIGURE 4.3

The computer
used in data acquisition.

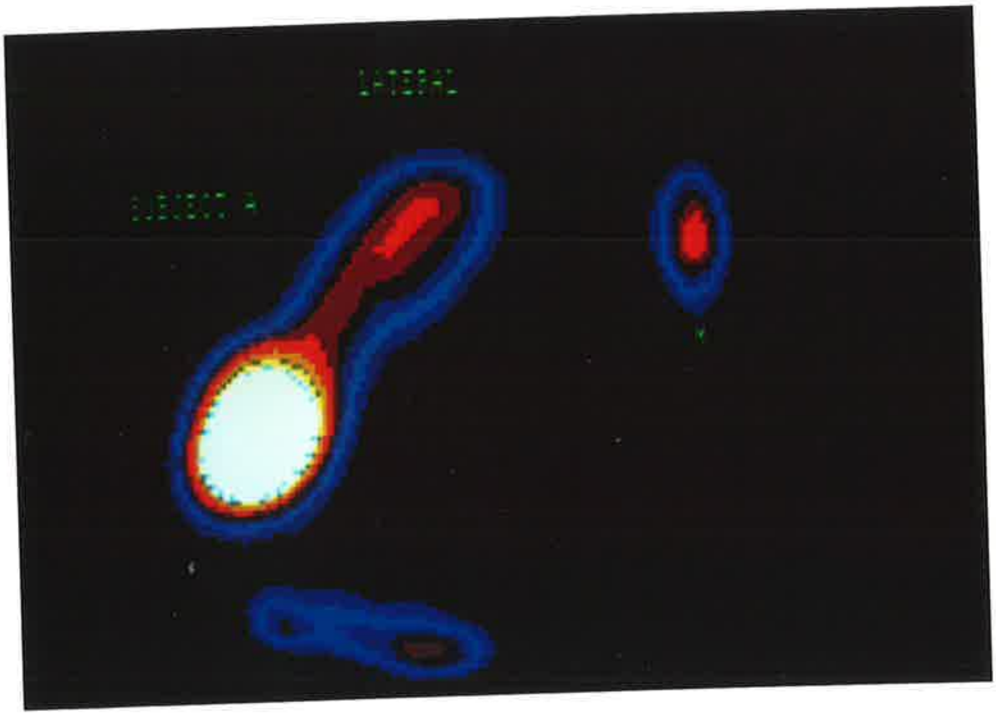
LEGEND FOR FIGURE 4.4

Diagram illustrating the alternating energy window (between that of ^{113m}In (393 keV) and ^{99m}Tc (140keV)) used in data acquisition.


RADIONUCLIDE A
FRAME 1
FRAME 2
FRAME 3
SWITCH MARKS
1
2
3
4
5
6
7
LIST DATA
RADIONUCLIDE B
FRAME 1
FRAME 2
FRAME 3

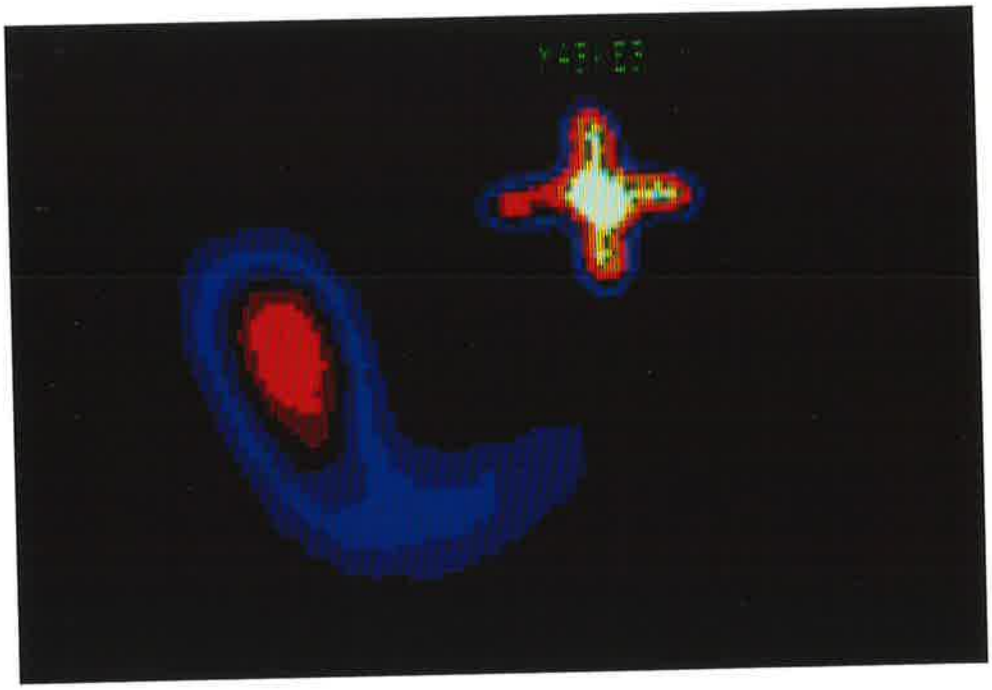
LEGEND FOR FIGURE 4.5

A lateral image of the stomach containing ^{99m}Tc-DTPA in a normal subject. "M" shows the ^{99m}Tc marker that is taped to the subject's back.



LEGEND FOR FIGURE 4.6

Scintiphotograph showing the stomach (solid meal) and the cross-shaped marker, containing ^{99m}Tc which was taped to the subject's back to allow correction for patient movement. The dynamic studies were realigned to a single reference point using this marker.



(ii) Radionuclide decay

Data were corrected for radionuclide decay using the standard formula : $C_t = C_o \exp^{-\lambda t}$ where C_t is the number of counts at time t, C_o is the number of counts at the commencement of the test and λ is the decay constant for each radionuclide. The value for λ is 0.693 divided by the half-life of the radionuclide (363 minutes for ^{99m}Tc and 100 minutes for ^{113m}In).

(iii) Radionuclide gamma-ray attenuation

(a) Attenuation coefficients

(1) Phantom study using one camera: In this phantom study (which was performed twice) attenuation coefficients for ^{99m}Tc (140 keV) and ^{113m}In (393 keV) were obtained by counting a 1mCi point source at various depths in a large water bath placed on the collimator surface (a Nuclear Chicago Pho-Gamma 111 HP with a 4000 hole collimator - PDP 11/55).

(2) Phantom study using two scintillation cameras: A 125 ml stopcock flash containing 810μCi of ^{99m}Tc was imaged at various positions in water with two opposed gamma cameras. The cameras (1-Searle LEM with a LEAP (low energy all purpose) collimator -PDP 11/34; 2-Nuclear Chicago Pho-Gamma 111 HP with a 4000 hole collimator - PDP 11/55) were separated by a distance of 32cm. The source was imaged for 2 minutes at varying positions (2 cm apart) between the cameras. The series of measurements was repeated and the mean values were used to minimize positional errors. A region of interest (ROI) was drawn automatically using Gamma-11 software based on a fixed isocount level relative to the maximum count value of each image (lower thresholds). Lower thresholds 10 (LT10) and 18 (LT18) were used to collect two sets of data, which were corrected for radionuclide decay. The radionuclide attenuation coefficent (μ) for ^{99m}Tc was estimated using least

squares analysis on the log counts versus distance curve from the two-camera data. The geometric mean of the two-camera counts was also obtained. This experiment was performed twice.

(b) Lateral image method of attenuation correction

Using the lateral image, the distance from the midpoint of the stomach to the collimator surface in cm (X_i) was calculated at all levels from the fundus to the pylorus (Figure 4.7). Two sets of line correction factors (F_i) for the solid and liquid phases of the study were generated ($F_i = \exp(\mu X_i)$ using the appropriate attenuation coefficent μ.

(c) In-vivo comparison of the lateral image method and a geometric mean method

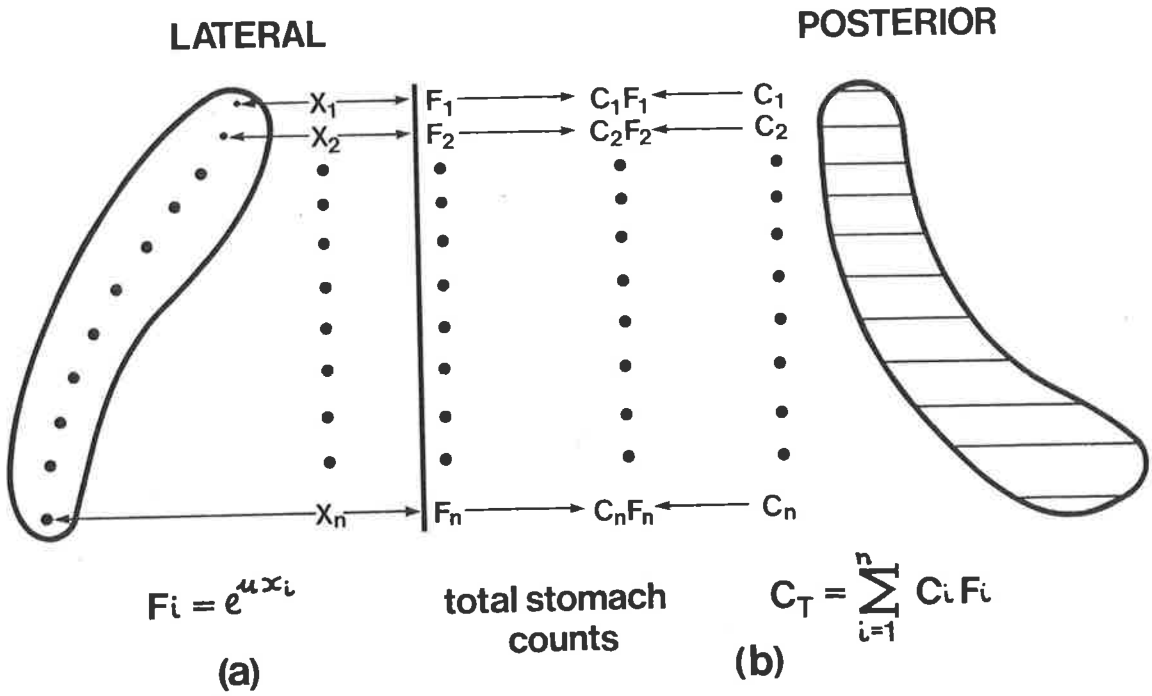
Gastric emptying studies were performed in five normal subjects (4 male, 1 female). Their median age was 31 years (range 28-35) and mean body weight 68kg (range 55-83). The solid meal was 100g of ground beef containing 810μCi of 'in-vivo' labelled ^{99m}Tc-chicken liver. After consumption of the solid meal over a 5 minute period each subject drank 150ml of (non-labelled) tap water. The subject was seated between two gamma cameras (an anterior Searle LEM with a LEAP (low energy all purpose) collimator - PDP 11/34 and a posterior Nuclear Chicago Pho-Gamma 111 HP with a 4000 hole high energy collimator - PDP 11/55) (Figure 4.8). Data acquisition commenced at the onset of food ingestion at a rate of one frame every two minutes, for at least 2 hours. At 30 minute intervals, data acquisition was interrupted briefly to allow the subject to stand or sit away from the camera. At the end of data acquisition 100μCi of ^{99m}Tc-DTPA mixed in 150ml of water was given orally and a 1 minute left lateral image of the upper abdomen was taken with the posterior detector. The lateral image was used to generate attenuation line correction factors according to the method previously described, which were applied to data obtained from the

LEGEND FOR FIGURE 4.7

Correction for tissue attenuation using a lateral image of the stomach.

(a) Generation of correction factors F_i = exponential (μX_i) where X_i is the distance from the midpoint of the stomach to the collimator surface and μ is the attenuation coefficient.

(b) Formation of the total stomach counts ($C_T = \Sigma_{i=1}^{n} C_i F_i$ where C_T is the sum, and F_i the attenuation correction factor for line i.


LATERAL
POSTERIOR
X1
X2
Xn
F1
F2
Fn
C1F1
C2F2
CnFn
C1
C2
Cn
Fi = e^{uxi}
total stomach counts
CT = Σ_{i=1}^{n} Ci Fi
(a)
(b)

LEGEND FOR FIGURE 4.8

Performance of a gastric emptying study using 2 opposed scintillation cameras.

LEGEND FOR FIGURE 4.9

Scintiphotograph showing an irregular region of interest enclosing the stomach. This method permits selective quantification of gamma emissions for this area.

posterior detector. Using the lateral image the distances of the proximal and distal stomach from the posterior detector were measured in each subject.

After correction for subject movement and radionuclide decay, four activity - time histograms were printed for each of the five studies. The value for "100% retention" of the meal was derived from the average count rate in the first 10 minutes after meal consumption. These histograms were of data obtained from (a) the anterior detector (b) the posterior detector (c) the posterior detector corrected for attenuation using the lateral image and (d) the geometric mean of anterior and posterior detectors. The following parameters were derived from these curves: the lag period before food entered the duodenum, the 50% emptying time and the average rate of linear emptying in percentage per minute (slope). The duration of the lag period was determined by the intercept of the slope with the "100% retention" value. An estimation of the lag period was also obtained by visual inspection of the images - the visual lag period (VLP). This was defined as the time point prior to when activity was first seen in the duodenum.

(d) Assessment of errors due to attenuation

In another 24 control subjects the change in solid and liquid 50% emptying times before and after correction for attenuation using the lateral image method was measured.

(iv) Compton Scatter

The solid study was corrected for ^{113m}In Compton scatter by subtracting a proportion of the ^{113m}In image from its corresponding ^{99m}Tc image. Because the solid and liquid studies were stored alternately, an image equal to the average of the two ^{113m}In images adjacent in time to the ^{99m}Tc image was used for this purpose. The correction factor for Compton scatter was derived from the following phantom study (which was performed twice) and its accuracy was validated in patient studies.

A 250 ml conical flask containing 1 mCi of ^{99m}Tc-DTPA in 200 ml of water was positioned 6 cm from the collimator surface (Nuclear Chicago Pho-Gamma 111 HP - PDP 11/55) in a water-bath and a 20 second image was taken in the ^{99m}Tc-window (image A): 0.5 mCi of ^{113m}In was then added to the flask and 20 second images were taken in the ^{99m}Tc and ^{113m}In windows. A region of interest obtained from image A was used for all three images. The increase in counts in the ^{99m}Tc window resulting from the addition of ^{113m}In was expressed as a percentage of the counts in the ^{113m}In window.

4.6.2 HISTOGRAM GENERATION AND ANALYSIS

Using the computer display, a "light-pen" attached to the computer was used to draw an irregular region of interest which included the whole stomach, but attempted to exclude the small intestine (Figure 4.9). Each frame of the study was checked to confirm that the stomach remained with the irregular region of interest. For each frame of the study, the total counts in the region of interest (C_T) was the sum of the individual line sums which had been corrected for tissue attenuation (C_i F_i), i.e., $C_T = \Sigma^n_{i=1} C_i F_i$ (Figure 4.7). The histograms for the solid and liquid components of the meal (expressed as a percentage of the total meal remaining within the stomach vs time) were printed (Figure 4.10). The value for "100% retention" of the meal was derived from the maximum count rate achieved in the first 20 minutes of the study.

Several parameters were derived from the histograms by means of curve inspection. For the solid component these parameters were: the lag period (LP) before food entered the duodenum, the time for 50% of the initial radioactivity to leave the stomach (T50), the average rate of linear emptying or slope (expressed as %/minute), and the percentage retention of tracer at 50 and 100 minutes after meal completion. For the liquid component, the T50 and the amount of tracer remaining at 5, 10 and 20 minutes after ingestion were obtained (Figure 4.10). The linear emptying rate of solid was calculated from a straight line of best fit, drawn through the data points which followed the lag period. The duration of the lag period was determined by the intercept of the slope with the 100% retention value. An estimation of the lag period was obtained by visual inspection of the images - the visual lag period (VLP). This was defined as the point preceding that at which activity was first seen in the duodenum. The deviation of the log plot of the liquid emptying curves from a straight line (Figure 4.11) precluded the use of the $T\frac{1}{2}$ to describe the entire liquid emptying process.

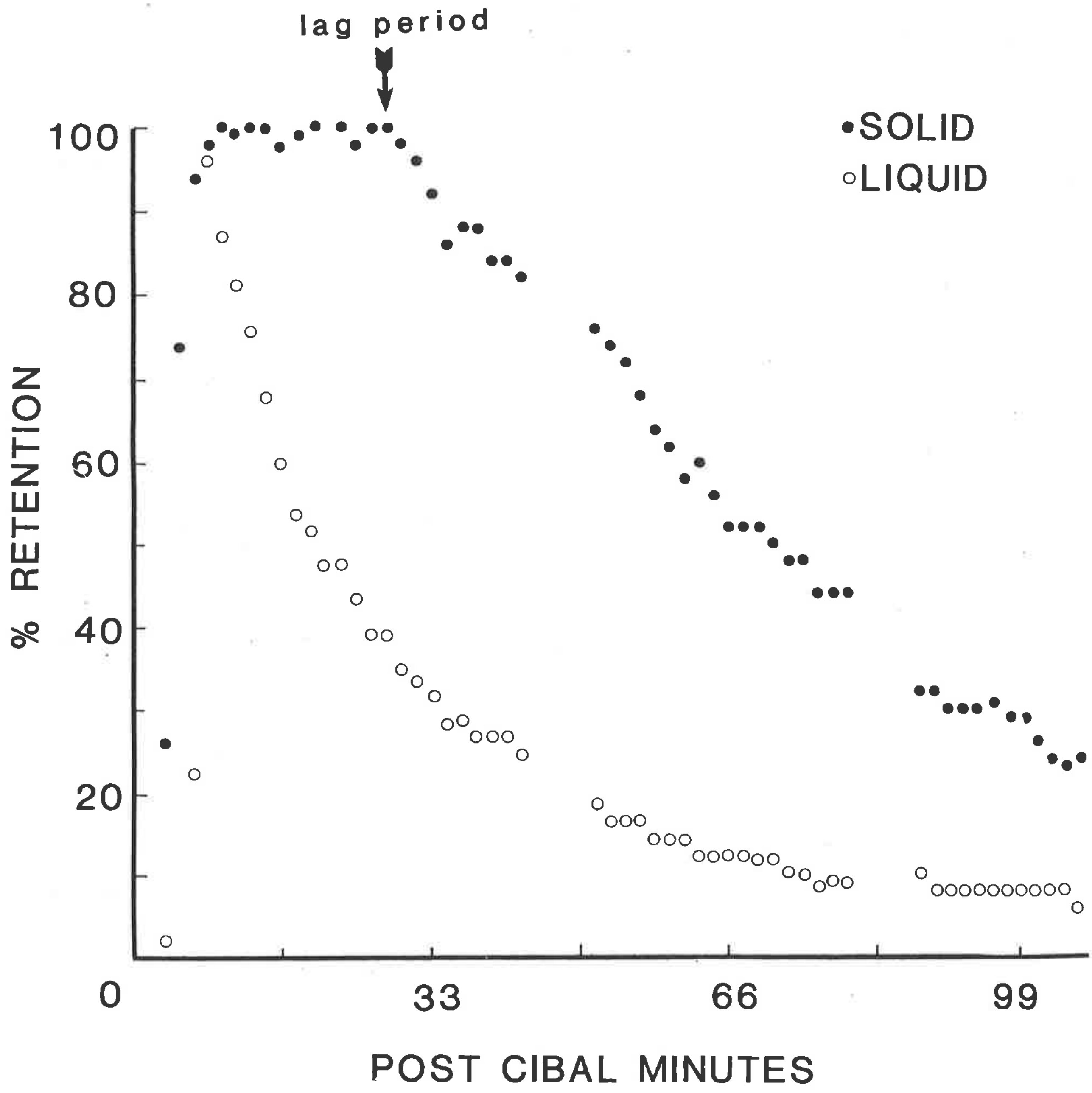
The effect of interobserver variation on the analysis of gastric emptying data was assessed in 25 randomly selected studies which were processed and analysed independently by both the author and Mr. P.J. Collins, B.App.Sci. The values for the parameters of solid lag period and solid and liquid 50% emptying times were recorded independently by both observers.

4.6.3 STATISTICAL METHODS

Data were analysed using Student's t-test, linear regression analysis and appropriate non-parametric statistical methods. The reproducibility of the technique was assessed using analysis of variance.

LEGEND FOR FIGURE 4.10

Representative histograms for solid and liquid emptying in a control subject of retention of isotope against time, after correction for radionuclide decay, Compton scatter and radionuclide attenuation. The value for "100% retention" is derived from the maximum count rate achieved in the first 20 minutes of the study. The lag period for solid is demonstrated.

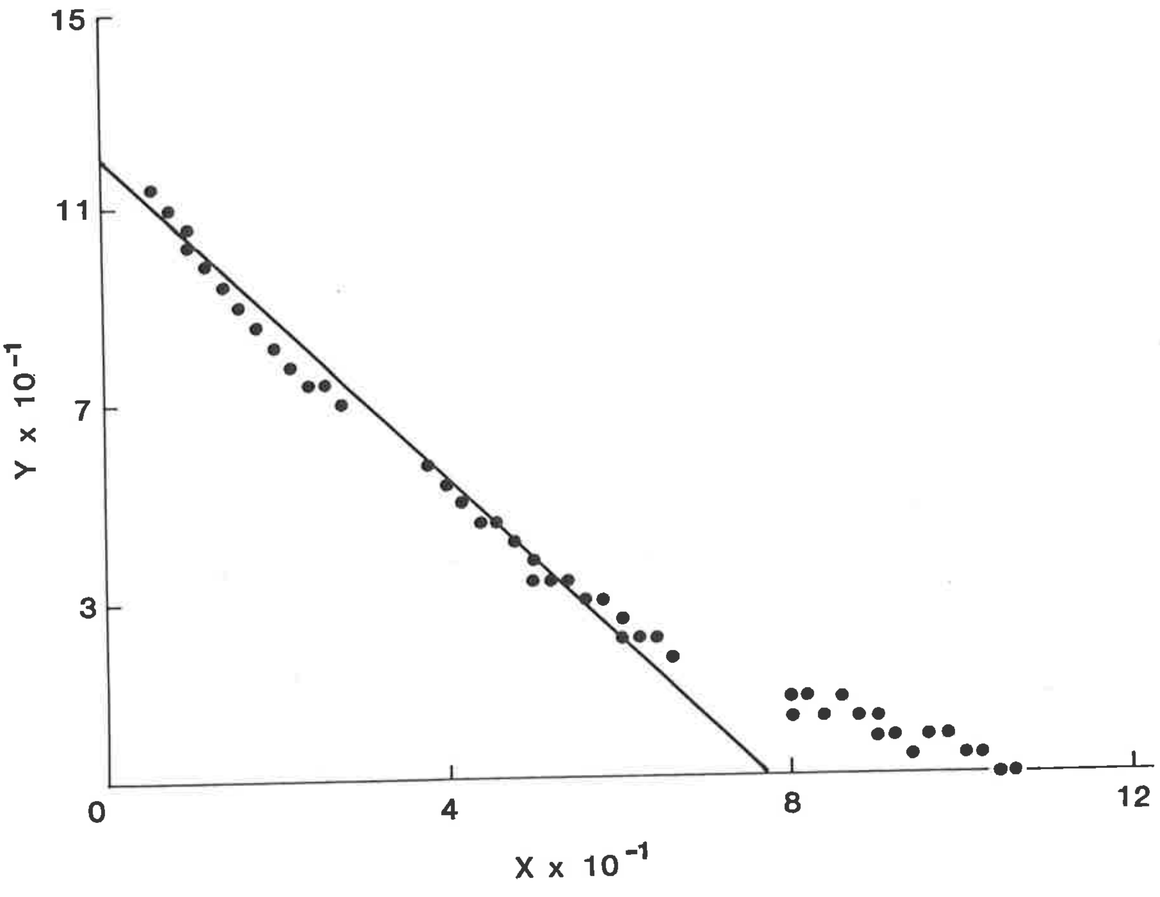


lag period
SOLID
LIQUID
% RETENTION
100
80
60
40
20
0
33
66
99
POST CIBAL MINUTES

LEGEND FOR FIGURE 4.11

Representative log plot in a control subject of retention of liquid against time. Significant deviation from a straight line is apparent.

GASTRIC EMPTYING - LIQUID PHASE



CHAPTER 5

SUBJECTS AND METHODS

5.1 GASTRIC EMPTYING IN CONTROL SUBJECTS.

5.1.1 Effect of alterations in the caloric content of the liquid meal on solid and liquid emptying.
5.1.2 Reproducibility.
5.1.3 Ranges of gastric emptying.

5.2 GASTRIC EMPTYING IN ELDERLY SUBJECTS.

5.3 ASSESSMENT OF THE EFFECT OF THE MENSTRUAL CYCLE ON GASTRIC EMPTYING.

5.4 GASTRIC EMPTYING IN OBESE SUBJECTS.

5.5 GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY AND AN ASSESSMENT OF THE EFFECTS OF ORAL DOMPERIDONE ON GASTRIC EMPTYING, SYMPTOMS OF GASTROPARESIS AND GLYCAEMIC CONTROL.

5.5.1 Assessment of gastrointestinal symptoms and symptoms of autonomic neuropathy.
5.5.2 Objective assessment of autonomic nerve function.
5.5.3 Assessment of glycaemic control.
5.5.4 Measurement of gastric emptying.
5.5.5 Assessment of the acute and chronic effects of domperidone on gastric emptying.

5.6 GASTRIC EMPTYING AFTER GASTRIC SURGERY FOR THE TREATMENT OF MORBID OBESITY.

5.6.1 Gastric emptying after gastric bypass.
5.6.2 Gastric emptying after gastroplasty.

5.1 GASTRIC EMPTYING IN NORMAL SUBJECTS

The author studied gastric emptying in several groups of subjects. The subjects and methods used in each of these studies are described in this chapter. In each study subjects were informed of the purpose of the study and were required to give their written consent to participate (in accordance with the Declarations of Helsinki and Tokyo). The study protocols were approved by the Research Review Committee of the Royal Adelaide Hospital. The test meal used in the gastric emptying studies was a 100 g ^{99m}Tc-liver beef hamburger and ^{113m}In-DTPA mixed in 150 ml of either tap water (solid and water), 10% dextrose (solid and 10% dextrose) or 25% dextrose solutions (solid and 25% dextrose).

All subjects were non-smokers, on no medication and had no gastrointestinal disease.

5.1.1 Assessment of the effect of alterations in the caloric (osmotic) content of the liquid meal on solid and liquid emptying

Three groups were studied. Group A comprised 11 subjects (7 male, 4 female) who received solid and water. In group B, 7 subjects (5 male, 2 female) were given solid and 10% dextrose and in group C, 6 subjects (5 male, 1 female) received solid and 25% dextrose (Table 5.1). The mean age in each group was similar : group A, 32 years (range 25-64); group B, 31 years (27-39); group C, 30 years (27-37). All subjects were within 20% of their ideal weight (72 ± 2 kg*, 70 ± 6 kg, 73 ± 5 kg respectively). The gastric emptying test was performed at 1230 hours in all subjects. Data were analysed using Student's t-test and linear regression analysis.

* Mean ± standard error of the mean.

5.1.2 Reproducibility

The gastric emptying study was repeated within seven days in 9 of group A, 5 of group B and 5 of group C subjects to assess reproducibility (Table 5.1). Data were analysed using analysis of variance.

5.1.3 Ranges of gastric emptying

A total of 22 control subjects (14 male, 8 female; mean age 34 years, range 21-62; mean body weight 76 $\pm$ 2 kg) received a meal consisting of a ^{99m}Tc-liver/beef hamburger and 150 ml of 10% dextrose containing ^{113m}In-DTPA. In 12 of these subjects the gastric emptying test was performed at 1230 hours (7 of these subjects were included in the studies described under 5.1.1 and in 10, at 1000 hours.

5.2 GASTRIC EMPTYING IN ELDERLY SUBJECTS

Gastric emptying studies were performed in 13 elderly subjects (6 male, 7 female) mean age 77 years (range 70-84) and body weight 66 $\pm$ 3 kg. The elderly subjects were all volunteers from an Elderly Citizens' Club. They were all non-smokers, on no medication and had no evidence of gastrointestinal or significant medical disease. In particular there was no evidence of neurological disease or history of diabetes mellitus and in all subjects the morning fasting plasma glucose level was less than 6.4 mmol/L (normal range 4.4-6.4). The gastric emptying test was performed at either 1000 or 1230 hours. The solid meal (a 100 g ^{99m}Tc-liver-beef-hamburger) was easily masticated in five minutes by all subjects. The liquid meal was 150 ml of 10% dextrose containing ^{113m}In-DTPA. Gastric emptying results were compared to those obtained in the 22 control subjects and data were analysed using Student's t-test and linear regression analysis.

TABLE 5.1

ASSESSMENT OF INCREASING THE CALORIC CONTENT OF THE LIQUID MEAL AND REPRODUCIBILITY OF GASTRIC EMPTYING IN NORMAL SUBJECTS

	Number of subjects	Number repeated
Solid and water	11	9
Solid and 10% dextrose	7	5
Solid and 25% dextrose	6	5
TOTAL NUMBER OF STUDIES	24	19

5.3 ASSESSMENT OF THE EFFECT OF THE MENSTRUAL CYCLE ON GASTRIC EMPTYING

Ten women of mean age 36 years (range 26-45) and mean body weight 65 kg (47-76), who had a bilateral ovarian tubal ligation performed from 6-120 months previously were studied. All subjects had a regular menstrual cycle and none was taking medication, or had evidence of gastrointestinal disease.

In each subject gastric emptying of a solid and 10% dextrose meal was measured on two days, at either 1000 or 1230 hours. The first test was performed during the follicular phase (day 8-10) and the second during the luteal phase (day 18-20) of one menstrual cycle (where day 1 was the first day of menstrual bleeding). After each gastric emptying study a venous blood sample was taken for subsequent determination of serum oestradiol and progesterone levels by conventional radioimmunoassay methods. Serum was obtained by allowing the blood to clot at $4^{o}C$. It was then separated, coded and stored at $-80^{o}C$ until being assayed. The samples for each steroid were run in a single assay.

Data were analysed using the Wilcoxon-matched-pairs signed-ranks test for paired data (gastric emptying data) and Student's paired-t-test (hormone levels).

5.4 GASTRIC EMPTYING IN OBESE SUBJECTS

These studies consisted of assessments of:

(a) Gastric emptying in obese subjects using a solid and water meal.

(b) The effect of increasing the caloric content of the liquid meal on gastric emptying in obese subjects.

In all of these studies the patients were non-smokers, on no medication and had no evidence of gastrointestinal disease. Data were analysed using Student's t-test and linear regression analysis.

In (a) gastric emptying studies were performed in 15 obese subjects (5 male, 10 female) who had been referred to the Obesity Clinic at the Royal Adelaide Hospital. These patients (mean age 34 years, range 20-48) were from 63-182% in excess of ideal weight according to Metropolitan Life Insurance Company tables, with a mean weight of 110 ± 17 kg and were studied prior to the commencement of dietary restriction. Gastric emptying studies were performed at 1230 hours. The meal was a ^{99m}Tc-liver-beef-hamburger and ^{113m}In-DTPA in 150 ml of water. Gastric emptying results were compared to those obtained in the 11 control subjects, who were all within 10% of their ideal weight.

In (b) gastric emptying studies were performed at 1230 hours on 2 days, separated by a maximum period of 7 days in another 7 obese subjects (1 male, 6 female; mean age 34 years, range 19-49; mean body weight 121 ± 20 kg, range 98-161), who were studied prior to the commencement of dietary restriction. On the two test days each patient received one meal of solid and 25% dextrose and one meal of solid and water. The order in which the patient received the meal was randomized. Results were compared to those obtained in 6 control subjects who had received a solid and 25% dextrose meal.

5.5 GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY AND AN ASSESSMENT OF THE EFFECTS OF ORAL DOMPERIDONE ON GASTRIC EMPTYING, SYMPTOMS OF GASTROPARESIS AND GLYCAEMIC CONTROL

Twelve patients (6 male, 6 female) mean age 43 years (range 21-61) who were ambulant outpatients, had insulin dependent diabetes mellitus for at least 10 years, and were subsequently demonstrated to have autonomic neuropathy, participated in the study. All had other complications of diabetes mellitus including nephropathy, retinopathy and peripheral neuropathy. All were non-smokers and were not taking medication known to affect gastrointestinal motility. After entering the study patients were seen at least at monthly intervals and standard adjustments were made to diabetic therapy if there had been any deterioration in glycaemic control.

All diabetic patients underwent: (a) a subjective assessment of gastrointestinal symptoms and symptoms of autonomic neuropathy unrelated to the gastrointestinal tract, (b) an objective assessment of autonomic nerve function by standard non-invasive physiological methods (c) an assessment of glycaemic control (d) measurement of gastric emptying of a mixed solid and liquid meal, (e) assessment of the acute and chronic effects of domperidone on gastric emptying and symptoms of gastroparesis.

Gastric emptying tests results were compared to those previously obtained in 22 control subjects who had received a solid and 10% dextrose meal.

5.5.1 Assessment of gastrointestinal symptoms and symptoms of autonomic neuropathy

Patients were evaluated by a standard questionnaire for symptoms of delayed gastric emptying. Each of the following four symptoms: anorexia/nausea, early satiety, epigastric fullness/upper abdominal discomfort, and post-prandial vomiting was scored as 0 = none, 1 = mild (symptom could be ignored if the patient did not think about it), 2 = moderate (symptom could not be ignored, but did not influence daily activities), 3 = severe (symptom influenced daily activities). Symptoms of dysphagia and heartburn were scored similarly. Delayed gastric emptying due to organic obstruction was excluded by upper gastrointestinal endoscopy.

Bowel habit, including the frequency, consistency and volume of stools was noted, as was the presence or absence of other symptoms of autonomic neuropathy (bladder dysfunction, impotence, abnormal sweating, postural hypotension).

Symptom scores were recorded again between days 35 and 51 after entry into the study.

5.5.2 Objective assessment of autonomic nerve function

The presence of autonomic neuropathy was determined by abnormal cardiovascular reflex tests, which have been previously demonstrated to be relatively simple to perform, non-invasive, reproducible and to require little cooperation from the patient (Ewing and Clarke, 1982). The tests that were used by the author are summarised in Table 5.2. The heart rate response to the Valsalva manoeuvre was not performed, because of the risk of intraocular haemorrhage in patients with proliferative retinopathy.

Parasympathetic function was evaluated by the heart rate variation (R-R interval) during deep breathing and the immediate heart rate response to standing ("30:15 ratio"). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. All patients were required to have definite parasympathetic damage with abnormal results on both tests of parasympathetic function, according to criteria outlined by Ewing and Clarke (1982) (Table 5.2).

The heart rate variation (R-R interval) during breathing was recorded while the patient sat quietly and breathed deeply at six breaths a minute (five seconds inspiration and five seconds expiration) for one minute. An electrocardiogram was recorded throughout the period of deep breathing and a marker was used to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals during each breathing cycle were measured and converted to beats/minute. The result was then expressed as the mean of the difference between maximum and minimum heart rates for the six measured cycles in beats/minute. An abnormal result was a maximum-minimum heart rate variation of $\leqslant$ 10 beats/minute.

The immediate heart-rate response to standing ("30:15 ratio") was performed while the patient was lying quietly on a couch and the heart rate was recorded continuously on an electrocardiogram. The patient was then asked to stand up unaided, and the point at which the patient initiated the act of standing was marked on the electrocardiogram. The shortest R-R interval at or around the 15th beat and the longest R-R interval at around the 30th beat after starting were measured. The heart-rate response was expressed by the 30: 15 ratio and an abnormal result was a ratio $\leqslant$ 1.00.

The blood-pressure response to standing was performed by measuring patient's blood pressure with a sphygmomanometer while supine and again when standing. The postural fall in blood pressure was taken as the difference between the systolic blood pressure lying and the systolic blood pressure standing. An abnormal result was a fall in systolic blood pressure of $\geqslant$ 30 mm Hg (Ewing and Clarke, 1982).

TABLE 5.2

NORMAL, BORDERLINE, AND ABNORMAL VALUES IN TESTS OF CARDIOVASCULAR AUTONOMIC FUNCTION *

	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function			
Heart-rate (R-R interval) variation during deep breating (maximum-minimum heart rate)	≥ 15 beats/min	11-14 beats/min	≤ 10 beats/min
Immediate heart-rate response to standing (30:15 ratio)	≥ 1.04	1.01-1.03	≤ 1.00
Tests reflecting sympathetic function			
Blood pressure response to standing (fall in systolic blood pressure)	≤ 10 mm Hg	11-29 mm Hg	≥ 30 mm Hg

* Criteria of Ewing and Clarke (1982).

5.5.3 Assessment of glycaemic control

All patients kept a record of their urinalysis results for glucose, their insulin doses and hypoglycaemic episodes. Plasma glucose was measured at the completion of each gastric emptying study (3 hours postprandially). Plasma glucose was not measured before or during the test because of possible effects of venepuncture on gastrointestinal motility. Haemoglobin A1c (HbA1c) levels were measured by ion exchange chromatography and the concentration determined by spectrophotometry (Schneck and Schroder, 1961) on two occasions (day 0 and between 35-51 days).

5.5.4 Measurement of gastric emptying

The solid meal was a 100g hamburger containing ^{99m}Tc-chicken liver and the liquid meal was 150 ml of 10% dextrose containing ^{113m}In-DTPA. In all diabetics the gastric emptying test was performed at approximately 1000h, after the patient had fasted from 2400h the previous day and had administered their usual morning insulin dose subcutaneously at 0930h. The solid 50% emptying time was not reached during the test period in many of the diabetics because of markedly delayed emptying.

5.5.5 Assessment of acute and chronic effects of domperidone on gastric emptying

In each patient three gastric emptying tests were performed. In the first two tests, which were separated by a maximum period of seven days, the patient was given, in double-blind fashion, a single dose of either oral domperidone 40 mg (Janssen Pharmaceutica) or placebo tablets, which were identical in appearance, one hour prior to commencement of the test. All patients then received domperidone (20 mg three times a day, 30-60 minutes prior to meals). The third gastric emptying test was performed after the administration of 40 mg domperidone when each patient had taken domperidone for 35-51 days (median 38). Gastrointestinal symptom scores were recorded again at this time. Drug compliance was assessed by tablet counts at each visit.

Statistical Methods

Gastric emptying data were evaluated using the Wilcoxon rank sum test (unpaired data), the Wilcoxon matched-pairs, signed-ranks test (paired data) and the Spearman rank correlation coefficient. The significance of other variables was assessed by Student's t-test for paired and unpaired data.

5.6 GASTRIC EMPTYING AFTER GASTRIC SURGERY FOR THE TREATMENT OF MORBID OBESITY

The pattern of gastric emptying after (a) gastric bypass and (b) gastroplasty for the treatment of morbid obesity were assessed. All patients were non-smokers and were not receiving medication. The operation had been performed by two surgeons who used identical operative techniques. Data were evaluated using the Wilcoxon rank sum test and the Spearman rank correlation coefficient.

5.6.1 Gastric emptying after gastric bypass

Two groups of patients were studied.

(i) Twelve patients (2 male, 10 female) were studied 12 months after gastric bypass. Mean age was 34 years (range 27-56) and mean weight was 80 $\pm$ 3 kg, which represented a weight loss of 28 $\pm$ 3 kg since the time of surgery. The gastric bypass surgery had involved construction of a pouch with a volume of 60-80 ml and a stoma of approximately 12 mm diameter (Figure 5.1). The emptying test (solid and water) was performed at 1230 hours. The volume of the meal produced mild abdominal discomfort in some patients. Gastric emptying results were compared to those obtained in the 11 control subjects.

Upper gastrointestinal endoscopy was performed by the same endoscopist in all patients within 10 days after the gastric emptying study. Stomal size was assessed by the passage of dilators of known diameter. The diameter of the gastric pouch was measured after its inflation with air.

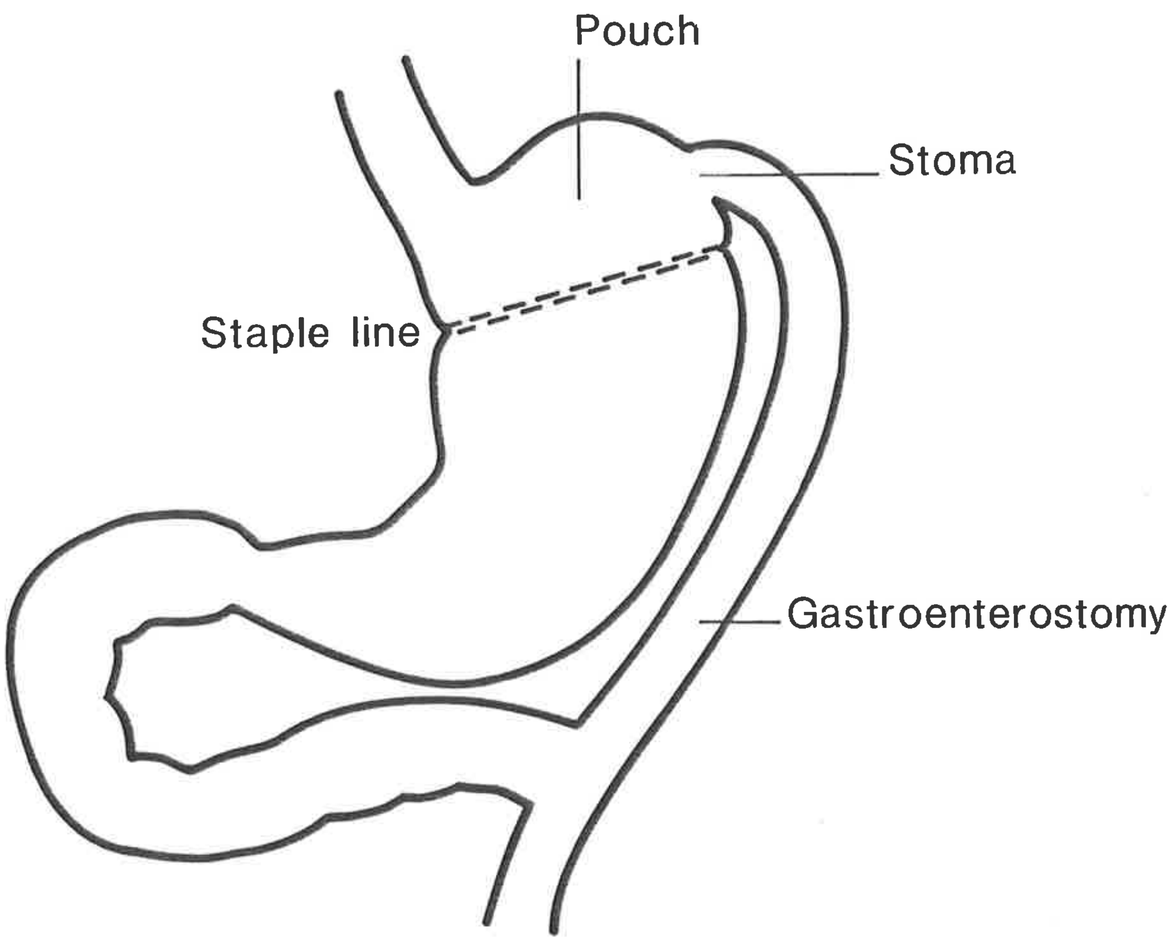
(ii) Gastric emptying was studied with a solid and 25% dextrose meal in another seven patients (1 male, 6 female; mean age 33 years, range 25-50; mean weight 83 $\pm$ kg) who had a gastric bypass 12 months previously. Gastric emptying results were compared to those obtained in the 6 control subjects who had received a solid and 25 % dextrose meal.

5.6.2 Gastric emptying after gastroplasty

Eleven patients (3 male, 8 female) were studied between 6 and 8 months after gastroplasty. Their mean age was 37 years (range 22-54) and weight at the time of the study was 86 $\pm$ 4 kg, which represented a weight loss of 29 $\pm$ 4 kg since the time of surgery. The gastroplasty surgery consisted of the creation of a 50 ml proximal gastric pouch (using a suture reinforced row of staples), with a 10 mm stoma located on the lesser curvature of the stomach. The stoma was supported with two encircling non-absorbable sutures (Figure 5.2). The gastric emptying test was performed at 1230 hours using a solid and 10% dextrose meal. The volume of the meal produced mild abdominal discomfort in some patients. Using the computer display two

LEGEND FOR FIGURE 5.1

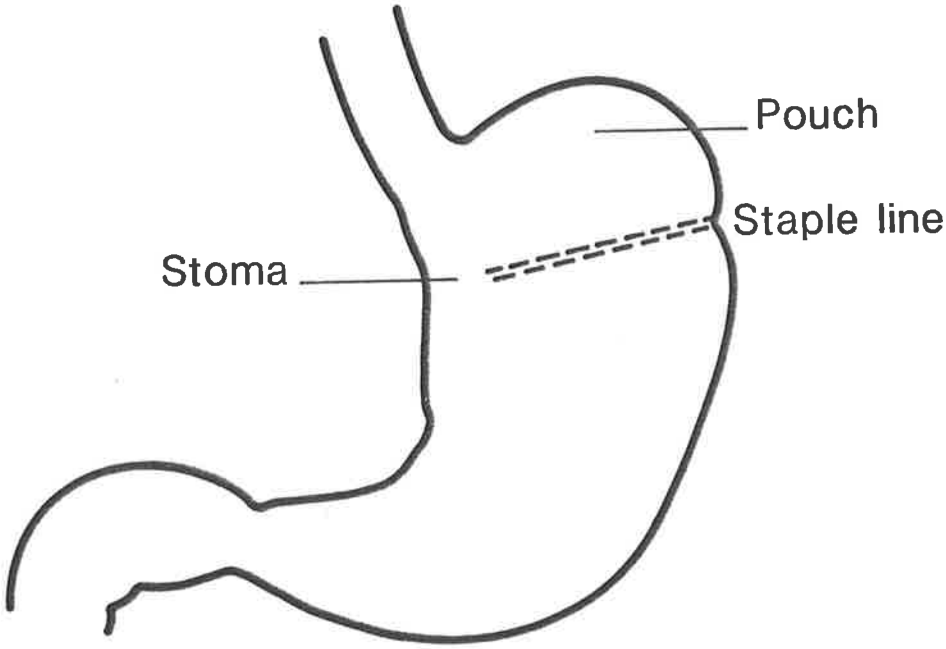
Diagram of a gastric bypass showing the pouch and gastrojejunostomy.


Pouch
Stoma
Staple line
Gastroenterostomy

regions-of-interest were drawn: one included the whole stomach (and excluded the small intestine), and the other outlined the proximal gastric pouch. In this way emptying of both the whole stomach and the proximal pouch were assessed. Results were compared to those obtained in the 22 control subjects, who had consumed a solid and 10% dextrose meal.

LEGEND FOR FIGURE 5.2

Diagram of a gastroplasty showing the proximal pouch and stoma.


Pouch
Staple line
Stoma

CHAPTER 6

RESULTS OF GASTRIC EMPTYING STUDIES IN NORMAL SUBJECTS

In this chapter the results of studies used to verify the gastric emptying methodology and those studies performed in an assessment of physiological variations in gastric emptying are presented. Gastric emptying in normal (age range 21-62), elderly (age range 70-84) and obese subjects was assessed.

6.1 STABILITY OF SOLID AND LIQUID MARKERS

The ^{99m}Tc-liver (cooked and uncooked) showed that between 98.2% and 98.6% of the ^{99m}Tc was bound to the liver after incubation in gastric juice for 5 hours.

6.2 RADIATION DOSIMETRY

The estimates for the radiation burden to the stomach and whole body for the solid and liquid markers are shown in Table 6.1. The total dose to the stomach is approximately 596 mrad (250 mrad from the ^{99m}Tc-liver, 340 mrad from the ^{113m}In-DTPA and 6 mrad from the ^{99m}Tc pertechnetate used in the lateral image). The whole body dose is approximately 6.0 mrad (3.7, 2.2, 0.1).

6.3 CORRECTION FOR TISSUE ATTENUATION

6.3.1 Attenuation Coefficients (μ)

These results were obtained from phantom studies using both one and two cameras. For both cameras there was an exponential relationship between count rate and the distance of the source from the detector. Using a point source and a single camera the attenuation coefficients in tissue were 0.12 cm^{-1} for ^{99m}Tc (140 keV) and 0.09 cm^{-1} for ^{113m}In (393 keV). The values for μ for ^{99m}Tc derived from the two camera data are shown in Table 6.2. The mean value for μ at lower

TABLE 6.1 RADIATION DOSIMETRY FOR THE STOMACH AND WHOLE BODY IN THE GASTRIC EMPTYING STUDY

---

1. Solid Tracer: Technetium-99m sulphur colloid

The average activity in the meal = 1.0 millicurie

The average 50% emptying time = 80 minutes

The absorbed dose factors S*:

(a) Stomach to Stomach Wall = 1.3 x 10 Rad/µCi-hr

(b) Stomach to Whole Body = 1.9 x 10 Rad/µCi-hr

Dose = A x t x S **

Dose from Stomach to Stomach Wall $= 1 \times 10^{-3} \times \frac{80}{60} \times 1.44 \times 1.3 \times 10^{-4}$

= 250 mR

Dose from Stomach to Whole Body $= 1 \times 10^{-3} \times \frac{80}{60} \times 1.44 \times 1.9 \times 10^{-6}$

= 3.7 mR

* "S" = Absorbed Dose per Unit cumulated activity for selected radionuclides and organs (Snyder et al, 1975).

** "A" = activity of radionuclide; t = effective half-life of radionuclide

2. Liquid Tracer: Indium-113m DTPA

The average activity in the meal = 1 millicurie

The average 50% emptying time = 20 minutes

The absorbed dose factors S*:

(a) Stomach to Stomach Wall = 7.1 x 10 Rad/µCi-hr

(b) Stomach to Whole Body = 4.7 x 10 Rad/µCi-hr

Dose = A x t x S **

Dose from Stomach to Stomach Wall $= 1 \times 10^{-3} \times \frac{20}{30} \times 7.1 \times 10^{-4}$

= 340 mR

Dose from Stomach to Whole Body $= 1 \times 10^{-3} \times \frac{20}{60} \times 4.7 \times 10^{-6}$

= 2.2 mR

TABLE 6.2

VALUES OF THE ATTENUATION COEFFICIENT (μ) FOR ^{99m}Tc OBTAINED USING TWO DIFFERENT SCINTILLATION CAMERAS AND DIFFERENT LOWER THRESHOLD VALUES FOR ROI DETERMINATION

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

threshold 10 was 0.14 cm^{-1}. The effect of the position of the source on the geometric mean value is illustrated in Figure 6.1. The maximum variation from the geometric mean value was – 4.3% for lower threshold 10 and – 3% for lower threshold 18.

6.3.2 Comparison of the lateral image and a geometric mean method

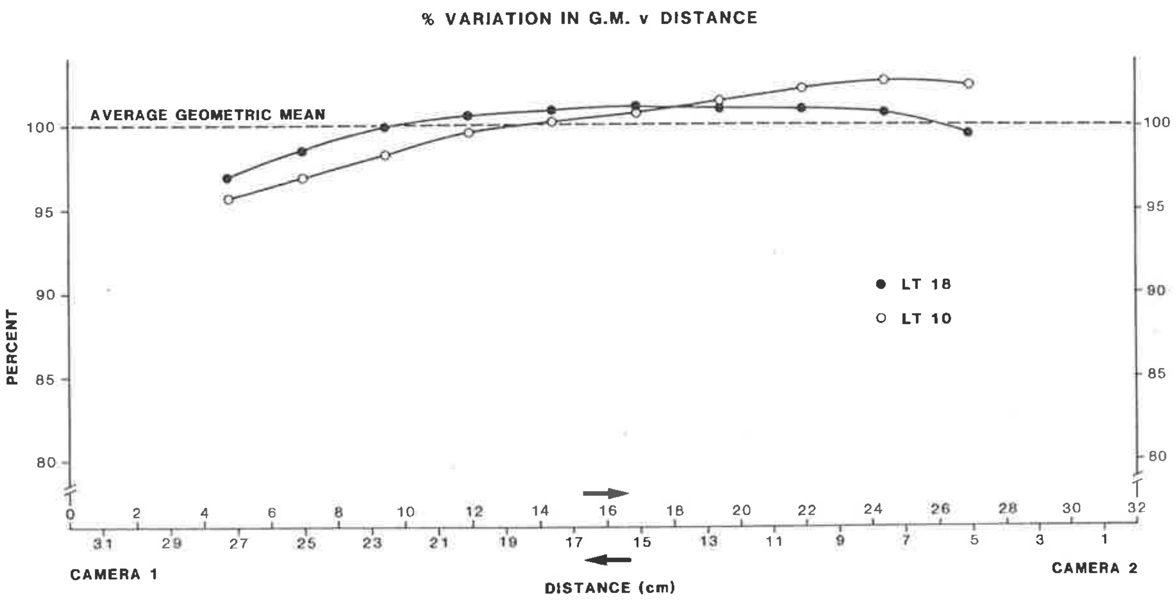
Figure 6.2A illustrates the four histograms for subject A of the anterior, posterior, geometric mean and posterior-corrected data. The count rate for the geometric mean curve remains relatively constant for the first 56 minutes and is followed by an approximately linear emptying phase. During the first 56 minutes there is a fall in count rate of approximately 36% for the anterior detector. These changes in count rate are attributable to the difference in distance of the proximal and distal stomach from the detector (Figure 6.2B). After correction for attenuation the posterior data closely approximate the geometric mean curve. The 50% emptying time value for the posterior corrected data is 103 minutes and the geometric mean value is 104 minutes.

Figure 6.3A shows the histograms for subject E. The data obtained from the posterior camera are improved after applying attenuation correction factors, but there is still a significant error in the resulting curve. For example the 50% emptying time changed from 83 minutes to 92 minutes after correction for attenuation, but this value was still 13% less than the geometric mean value of 106 minutes.

The results of the 5 subjects studied with two opposed scintillation cameras are shown in Figure 6.4 and Table 6.3. If the geometric mean is used as the standard, the anterior detector overestimated the solid 50% emptying time, slope and lag period values by 15, 13 and 48 percent, respectively, while the posterior detector underestimated these parameters by 15, 14 and 44 percent. The

LEGEND FOR FIGURE 6.1

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



% VARIATION IN G.M. v DISTANCE
AVERAGE GEOMETRIC MEAN
PERCENT
100
95
90
85
80
● LT 18
○ LT 10
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
31 29 27 25 23 21 19 17 15 13 11 9 7 5 3 1
CAMERA 1
CAMERA 2
DISTANCE (cm)

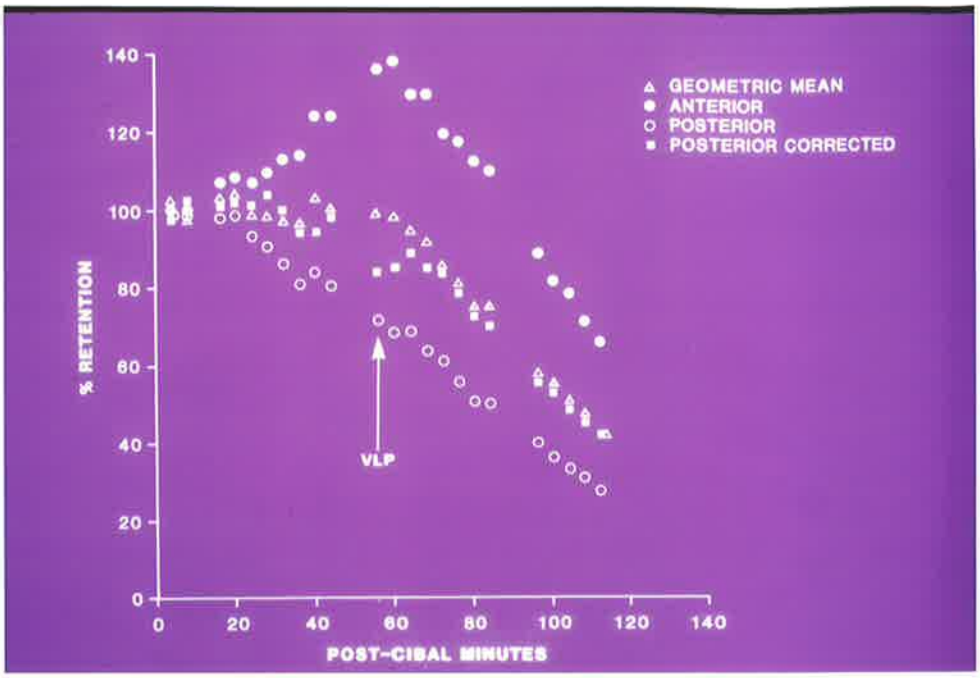
LEGEND FOR FIGURE 6.2

Data from subject A

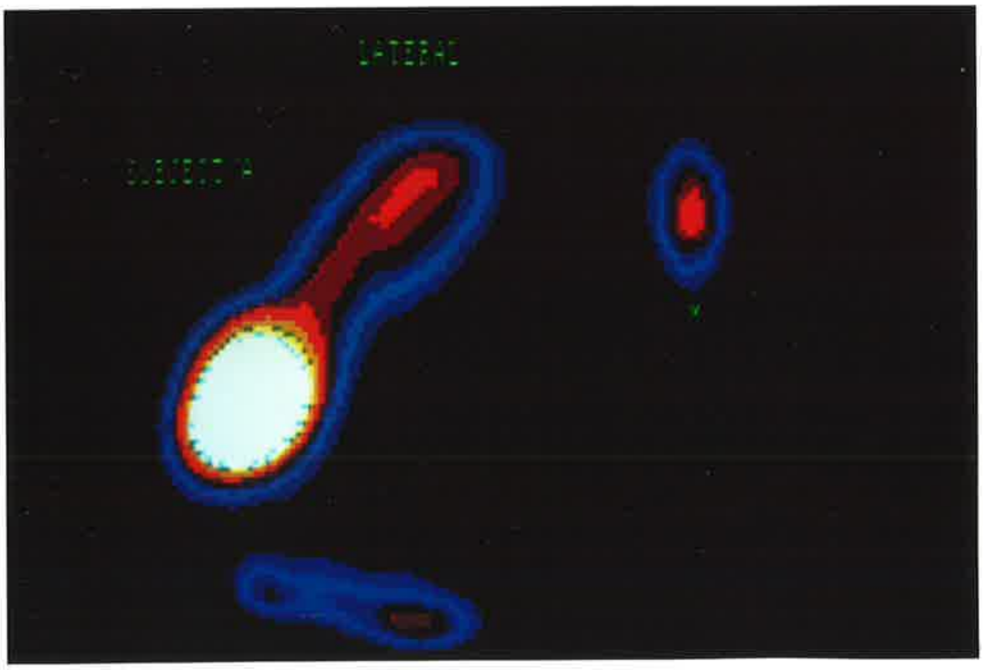
A) Histograms of retention against time for geometric mean (△), anterior detector (●), posterior detector (O) and posterior data corrected for attenuation using the lateral image method (■). One hundred percent retention is derived from the average count rate in the first 10 min. The visual lag period (VLP) is 56 min. The posterior data after correction for attenuation closely approximate the geometric mean data.

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

A


GEOMETRIC MEAN
ANTERIOR
POSTERIOR
POSTERIOR CORRECTED
% RETENTION
POST-CIBAL MINUTES
VLP
0
20
40
60
80
100
120
140

B



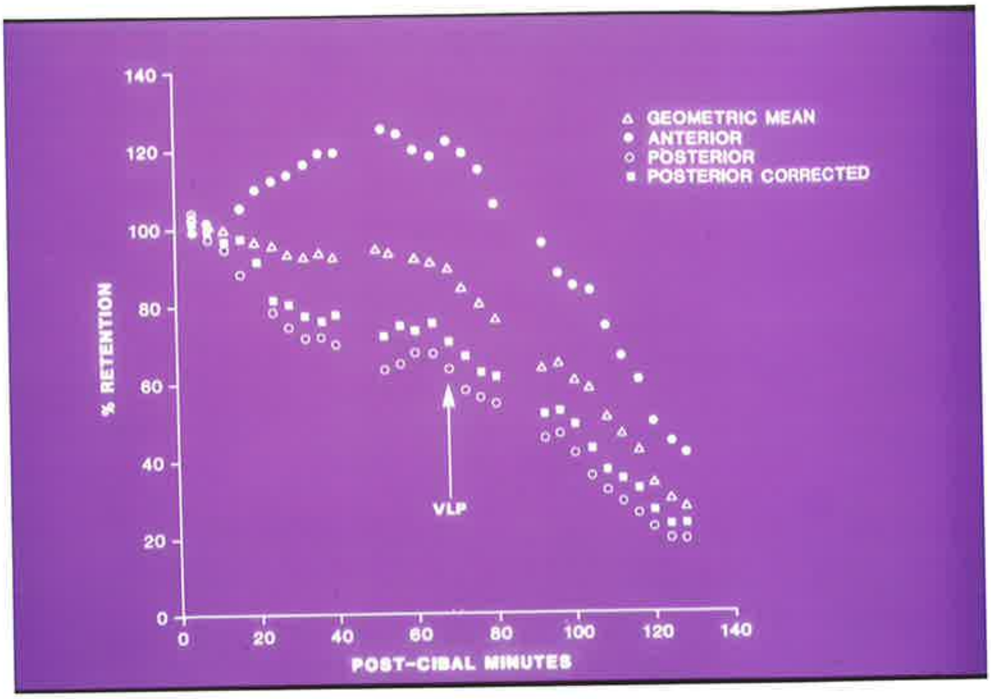
LEGEND FOR FIGURE 6.3

Data from subject E

A) Histograms of retention against time for geometric mean (△), anterior detector (●), posterior detector (O) and posterior data corrected for attenuation using the lateral image method (■). One hundred percent retention is derived from the average count rate in the first 10 min. The visual lag period (VLP) is 68 min.

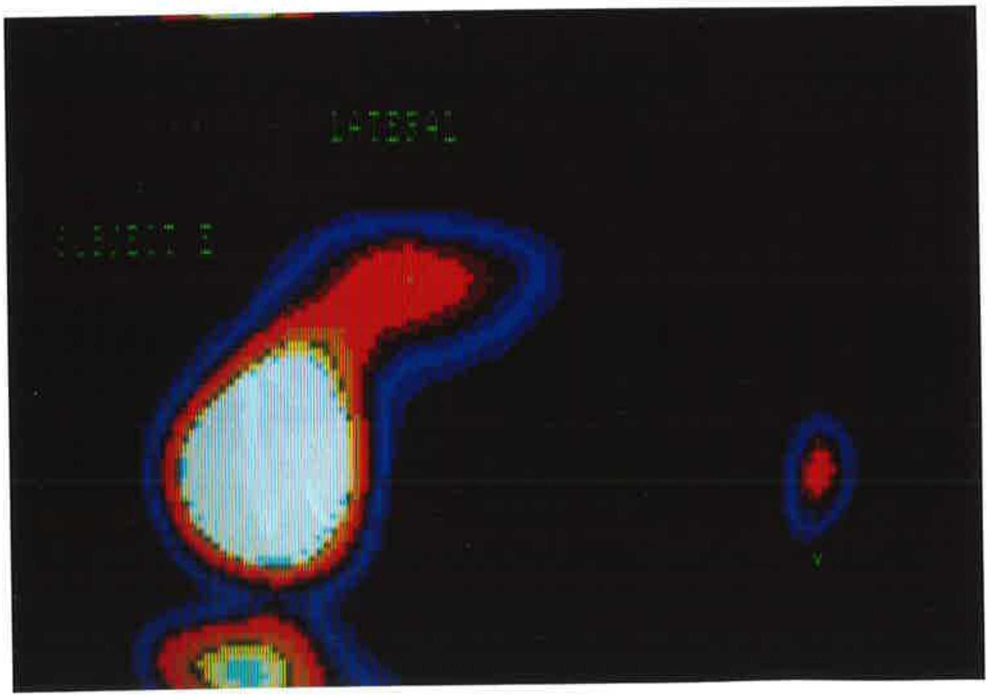
B) Lateral image of the stomach with posteriorly located marker (M). The stomach shape results in movement of food approximately perpendicular to the detector and attenuation correction is less effective.

A



140
120
100
80
60
40
20
0
% RETENTION
GEOMETRIC MEAN
ANTERIOR
POSTERIOR
POSTERIOR CORRECTED
VLP
0
20
40
60
80
100
120
140
POST-CIBAL MINUTES

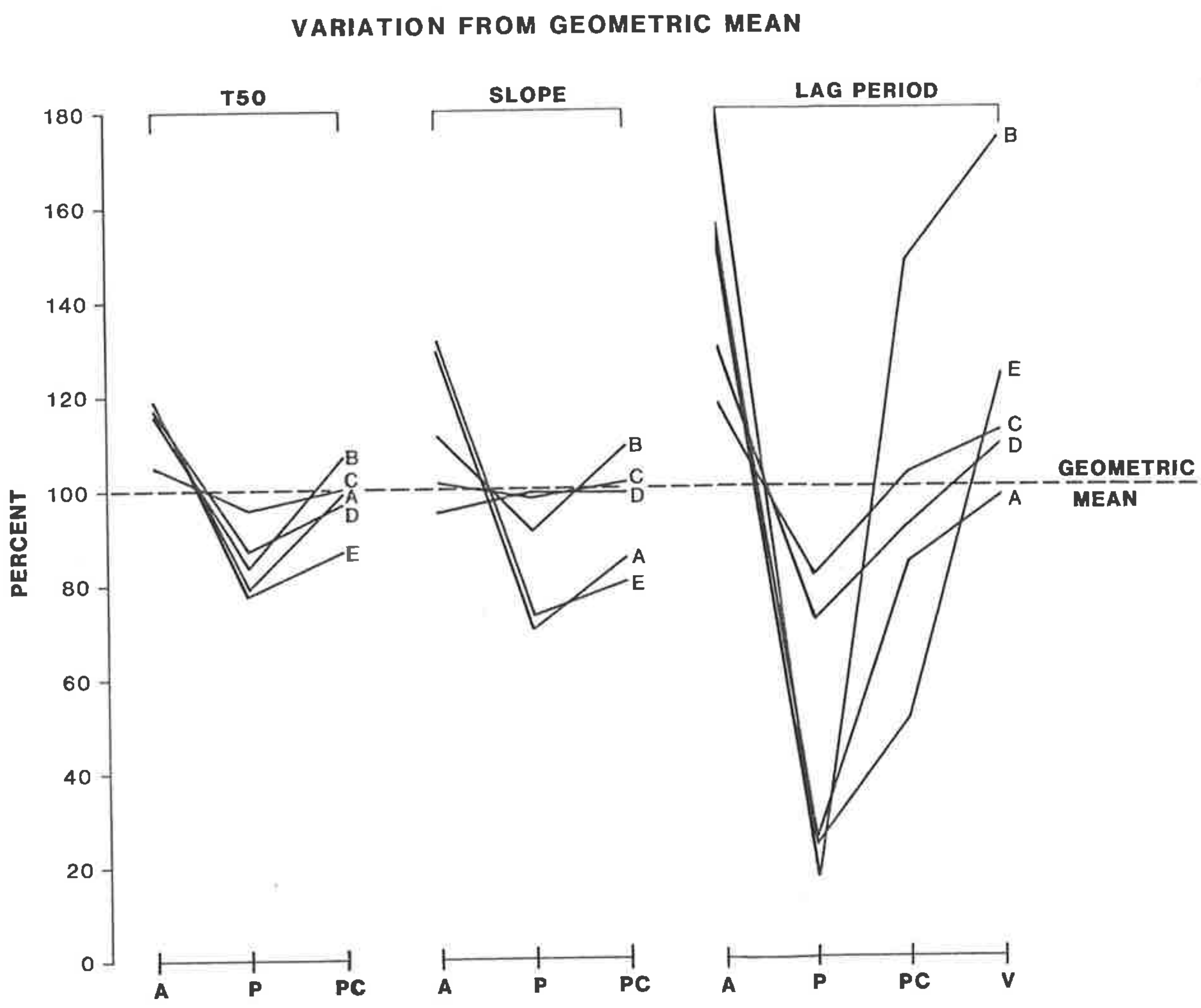
B



LATERAL

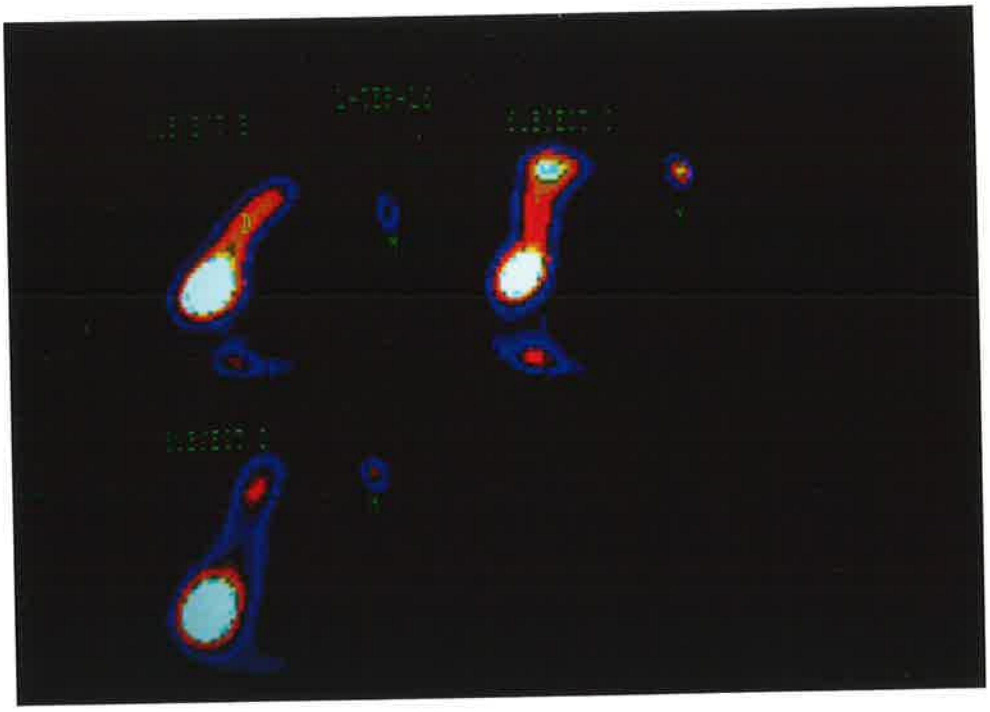
LEGEND FOR FIGURE 6.4

Values for parameters solid 50% emptying time, slope and lag period expressed as a percentage of the geometric mean value in the 5 subjects (A–E). The 50% emptying time and slope are calculated from anterior (A), posterior (P) and posterior corrected (PC) data. The lag period is determined from posterior data (P), posterior corrected data (PC), visual inspection of images (V) and the average of PC and V (VPC).


VARIATION FROM GEOMETRIC MEAN
T50
SLOPE
LAG PERIOD
PERCENT
180
160
140
120
100
80
60
40
20
0
A
P
PC
V
B
C
A
D
E
GEOMETRIC
MEAN

LEGEND FOR FIGURE 6.5

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



posterior corrected data under-estimated the 50% emptying time, slope and lag period by 2, 5 and 4 percent respectively. The visual method overestimated the lag period by 23%.

The lateral images for the 5 subjects (Figures 6.2B, 6.3B and 6.5) show considerable variations in stomach shape, and in the distance of the proximal and distal stomach from the posterior detector for all of the subjects (mean difference 5.7 cm, range 3.9 - 7.4 cm).

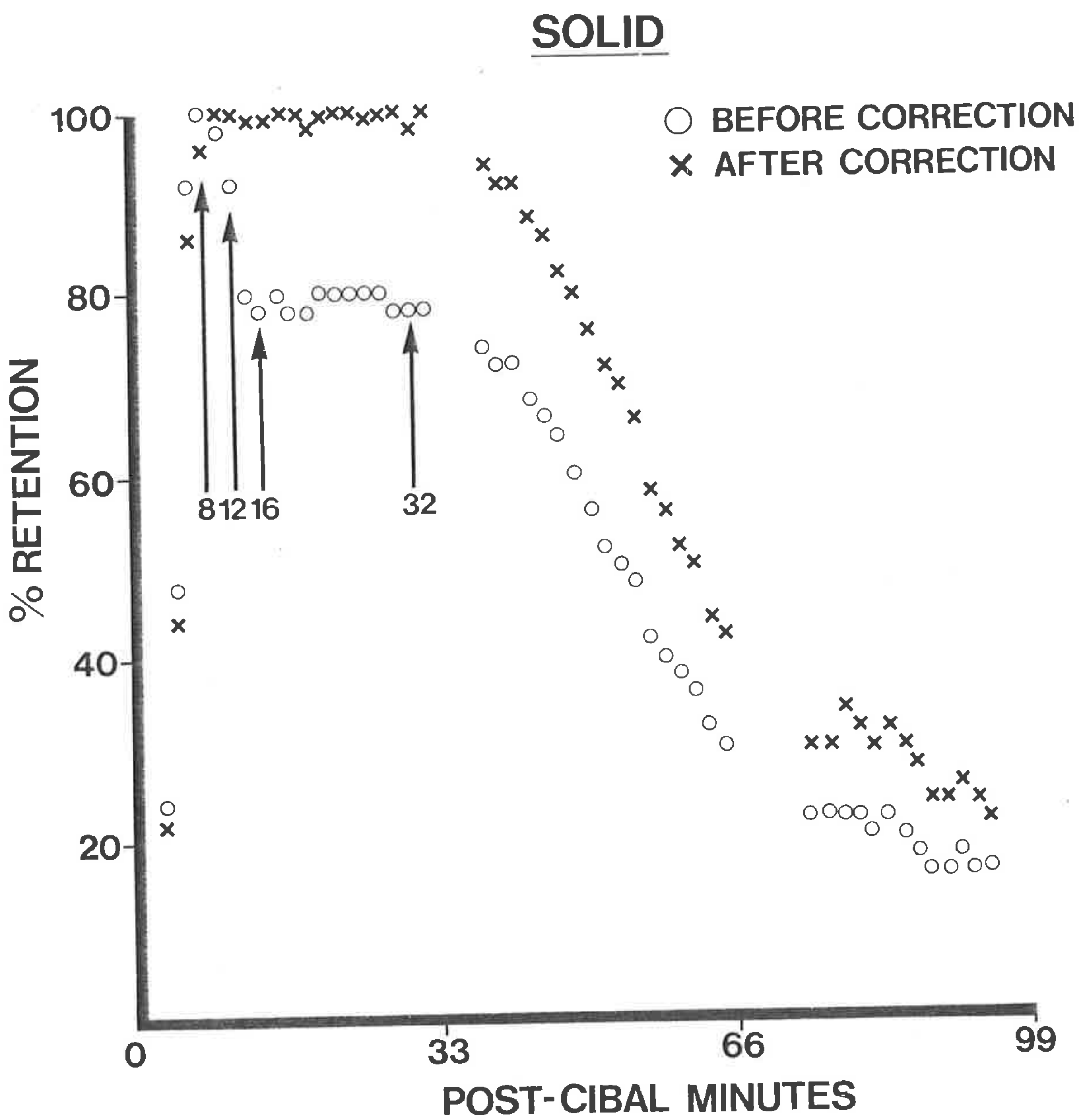
6.3.3 Assessment of errors due to attenuation using the lateral image method

Figure 6.6 illustrates typical solid retention histograms before and after correction of the data for tissue attenuation using the lateral image method. In the interval from 8 to 16 minutes there is a fall in count rate of 20% in the uncorrected data as food redistributes within the stomach. This fall is entirely attributable to radionuclide moving away from the collimator surface while remaining within the stomach (Figure 6.7). In the following 16 minutes, as there is little redistribution of solid food, the count rate remains constant. The application of line correction factors to the data eliminated the apparent emptying of food from the stomach. The resulting pattern demonstrated a lag period prior to emptying followed by a linear emptying phase. In this study 50% emptying time value changed from 49 minutes to 58 minutes (16%) as a result of correction. Tissue attenuation effects were less marked for liquids, reflecting the higher energy of ^{113m}In (Figure 6.8). Correction altered the 50% emptying time from 19 minutes to 21 minutes (10%) in this subject.

In the 24 normal controls, the mean percentage increase in 50% emptying time after correction was 22% for solid and 17% for liquid (Table 6.4).

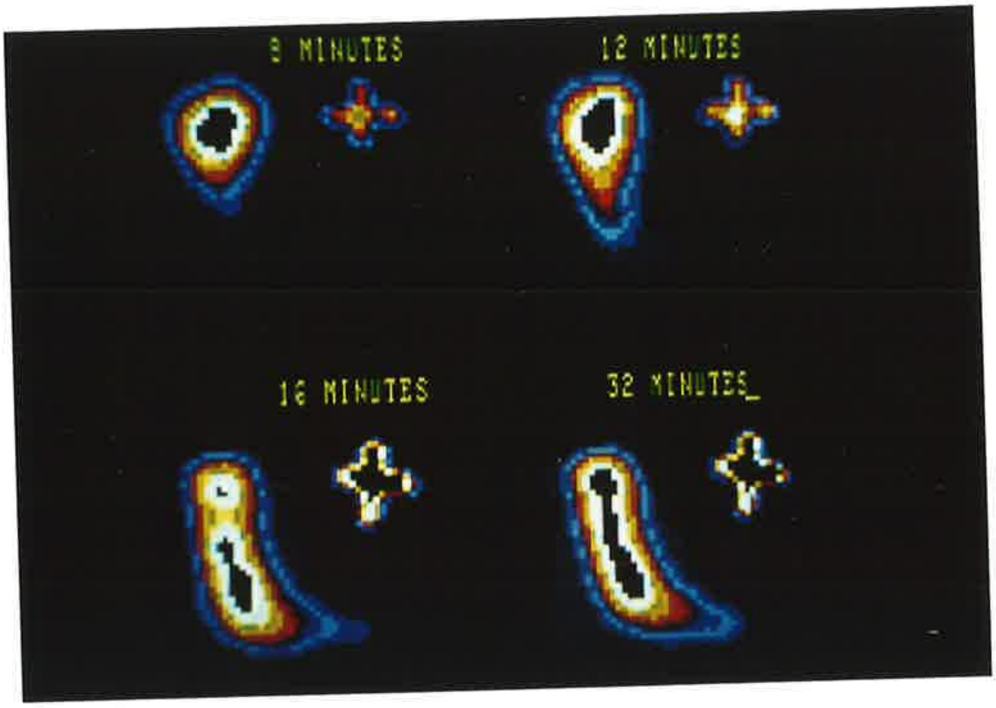
LEGEND FOR FIGURE 6.6

Gastric emptying of ^{99m}Tc-labelled liver before (0) and after (X) correction for tissue attenuation in a control subject. Arrows indicate the percentage remaining in the stomach at 8, 12, 16 and 32 minutes. One hundred per cent retention is derived from the maximum count rate achieved in the first 20 minutes of the study. A significant fall in count rate in the first 32 minutes is apparent in the uncorrected data.


SOLID
BEFORE CORRECTION
AFTER CORRECTION
% RETENTION
100
80
60
40
20
8
12
16
32
0
33
66
99
POST-CIBAL MINUTES

LEGEND FOR FIGURE 6.7

Scintiphotos showing the distribution of solid (^{99m}Tc-liver) in the stomach of a control subject at 8, 12, 16 and 32 minutes. No solid food leaves the stomach in the first 32 minutes after meal completion.


8 MINUTES
12 MINUTES
16 MINUTES
32 MINUTES

LEGEND FOR FIGURE 6.8

Gastric emptying of liquid (^{113m}In-DTPA) before (0) and after (X) correction for tissue attenuation in a control subject.

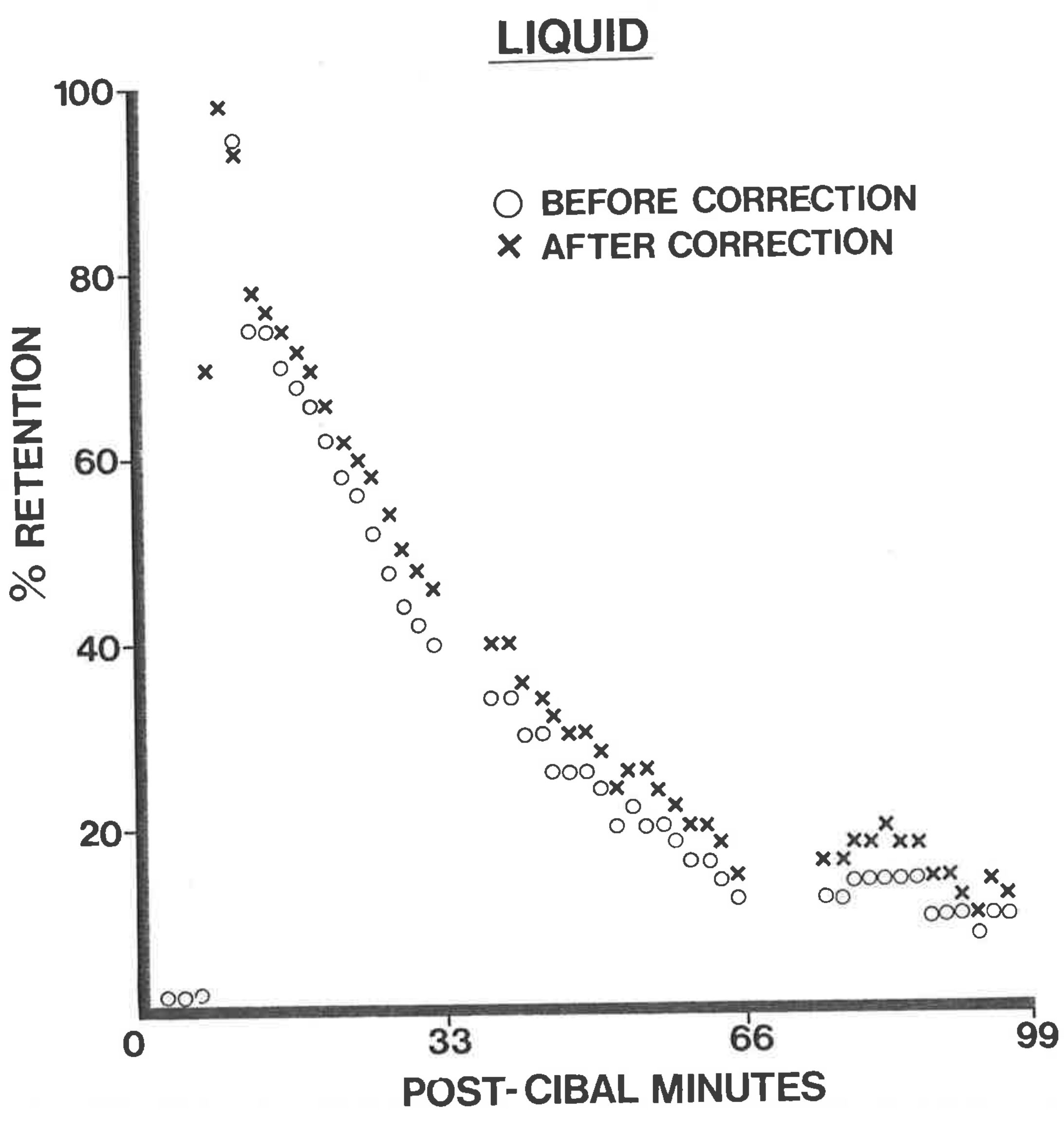

LIQUID
BEFORE CORRECTION
AFTER CORRECTION
% RETENTION
100
80
60
40
20
0
33
66
99
POST-CIBAL MINUTES

TABLE 6.3

PARAMETERS OF SOLID EMPTYING EXPRESSED AS A PERCENTAGE OF THE GEOMETRIC MEAN VALUE *

	METHOD			
Parameter	Anterior	Posterior	Posterior corrected	Visual
50% emptying time	115 (105-118)	85 (78-96)	98 (87-107)	-
Slope	113 (95-131)	86 (70-99)	95 (80-109)	-
Lag Period	148 (118-181)	45 (18-82)	96 (51-148)	123 (88-174)

* Mean value and range in parentheses of 5 subjects

TABLE 6.4

EFFECT OF CORRECTION FOR ATTENUATION USING THE LATERAL IMAGE METHOD IN TWENTY-FOUR CONTROL SUBJECTS ON THE 50% EMPTYING TIMES FOR SOLID AND LIQUID *

	Difference $= \frac{\text{Post-Pre}}{\text{Post}} \times 100\%$
Solid (^{99m}Tc)	= 22 (7-65)
Liquid (^{113m}In)	= 17 (0-59)

* Data are mean values and ranges in parentheses.

6.4 CORRECTION FOR COMPTON SCATTER

In the phantom study 21% of counts in the ^{113m}In-window scattered into the ^{99m}Tc window. Because of rapid time sampling in the first 10 minutes after commencement of meal ingestion (5 second store every 10 seconds) the adequacy of the correction for Compton scatter could be tested in patient studies. In no study was any significant change in solid count rate observed as liquid entered the stomach (Figure 6.9).

6.5 ASSESSMENT OF THE EFFECTS OF ALTERATION OF THE CALORIC CONTENT OF THE LIQUID MEAL IN CONTROL SUBJECTS

6.5.1 Solid emptying

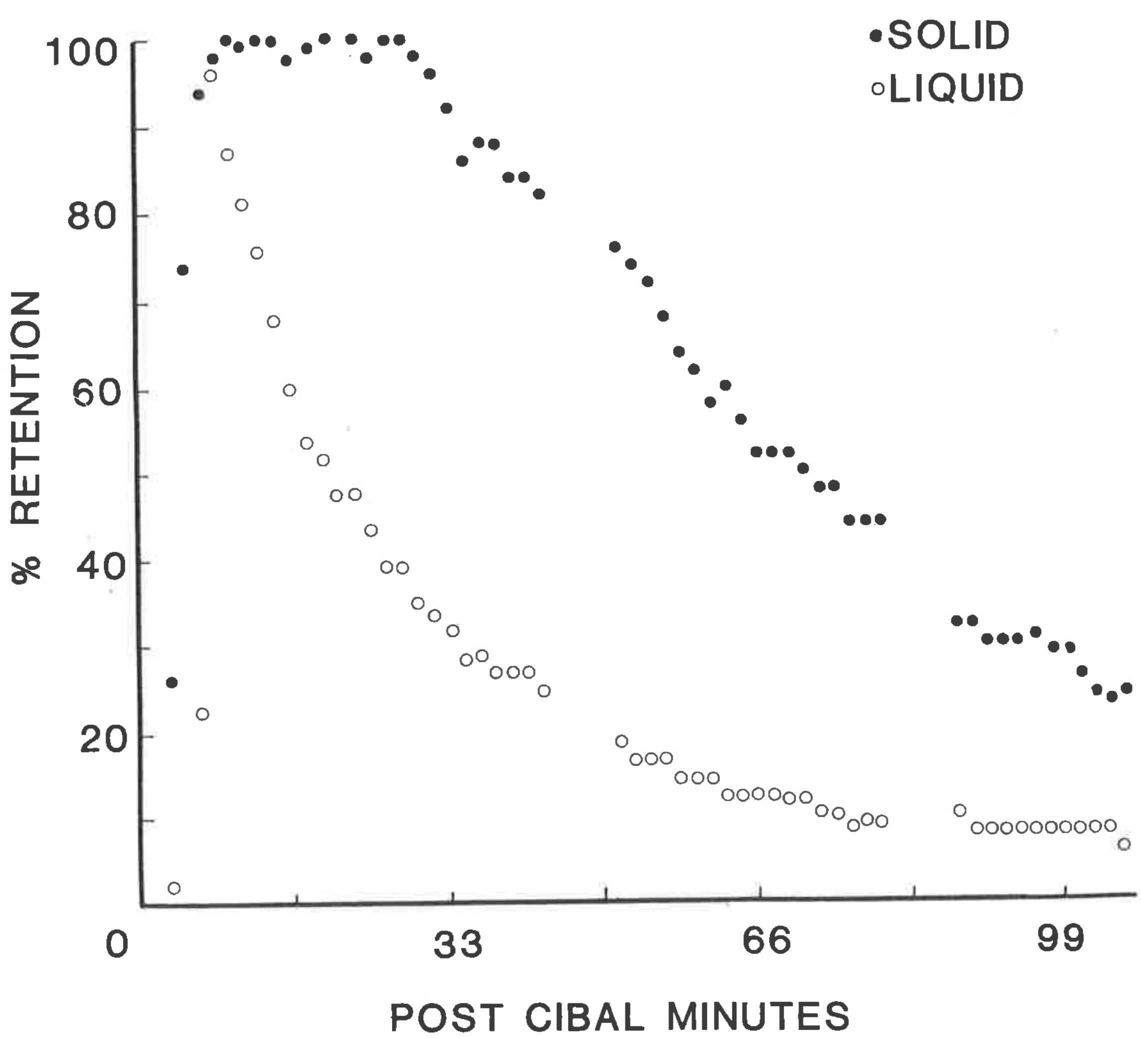
In all subjects solid emptied more slowly than liquid and was characterized by two separate phases : a lag period of variable duration followed by approximately linear emptying (Figure 6.9). The solid lag period was prolonged by the presence of both 10% and 25% dextrose in the liquid phase ($p < 0.01$). The 50% emptying time for solid was increased by 25% dextrose ($p < 0.025$), but not by 10% dextrose (Figure 6.10). There was no difference between the three groups in the rate of linear emptying after the lag period (Table 6.5) and the delay in 50% emptying time with 25% dextrose reflected lengthening of the lag period.

6.5.2 Liquid emptying

The emptying of water was non-linear with a slope that decreased with time often closely followed a monoexponential pattern. There was minimal observable lag period and with increasing caloric content liquid emptying assumed a more linear pattern (Figure 6.10). Twenty-five

LEGEND FOR FIGURE 6.9

Histograms of solid and liquid emptying in a normal subject (solid and water meal). Solid empties in an approximately linear pattern after an initial lag period. The pattern of liquid emptying is non-linear, with a slope that decreases with time.


•SOLID
○LIQUID
% RETENTION
100
80
60
40
20
0
33
66
99
POST CIBAL MINUTES

percent dextrose delayed the 50% emptying time ($p < 0.025$), while with 10% dextrose this parameter was not significantly altered (Table 6.5). The amount of liquid remaining at 10 minutes was increased by both 10% dextrose and 25% dextrose ($p < 0.025$).

6.5.3 Relationship between solid and liquid emptying

There was a relationship between the 50% emptying time for liquid and for solid in all groups ($r = 0.65$, $p < 0.005$). For the three groups the length of the lag period correlated directly with the liquid 50% emptying time ($r = 0.75$, $p < 0.01$). There was no relationship between the sex of the subject and solid or liquid emptying rates.

6.5.4 Rate of delivery of calories to the duodenum

The total number of calories (solid and liquid) delivered to the duodenum at varying time intervals in the first 50 minutes of the emptying study are shown in Table 6.6. In both the solid and 10% dextrose group and the solid and 25% dextrose group, approximately 100 kcal (2.2 kcal/min) had left the stomach at 50 minutes after meal completion. In the group of subjects who had received solid and water, the rate of delivery of calories was initially significantly slower (approximately 72 kcal at 50 minutes), but after the lag period the rate of incorporation of solid calories (mean linear emptying rate) was similar at 2.4 kcal/min).

Based on the liquid 50% emptying times (Table 6.5) approximately 30 kcal in liquid were delivered to the duodenum in the first 20 minutes in the solid and 10% dextrose group (1.5 kcal/min) and 75 kcal in 46 minutes in the solid and 25% dextrose group (1.6 kcal/min). The ratio of the mean liquid 50% emptying times (solid and 25% dextrose : solid and 10% dextrose) was 2.4. The ratio of the mean percentage of liquid

TABLE 6.5

EFFECT OF INCREASING THE LIQUID CALORIE CONTENT ON SOLID AND LIQUID EMPTYING IN CONTROL SUBJECTS *

	Water	10% Dextrose	25% Dextrose
Number of subjects	11	7	6
Solid lag period (min)	21 ± 2	37 ± 6	60 ± 9
Solid linear rate (%/min)	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
Solid 50% emptying time (min)	70 ± 7	78 ± 8	105 ± 13
Liquid 50% emptying time (min)	15 ± 2	20 ± 2	46 ± 7
Liquid retention after 10 min (%)	58 ± 4	68 ± 2	86 ± 3

* Data are mean values ± standard error of the mean

emptied after 10 minutes (solid and 10% dextrose : solid and 25% dextrose) was 2.3. Therefore in these two groups the rates of delivery of liquid calories were similar and inversely related to the caloric content of the meal.

6.5.5 Ranges of gastric emptying

The median values and ranges for solid and liquid emptying in 22 normal subjects (solid and 10% dextrose meal) are shown in Table 6.7. These values were used as a control group in other studies which will be discussed. There was no significant difference in the results of tests that commenced at 1000 h compared to 1230 h.

6.7 REPRODUCIBILITY

The reproducibility data for the parameters solid and liquid 50% emptying times solid lag period and solid linear rate in 22 control subjects are illustrated in Figure 6.11. A wide variation between the subjects exists for these parameters. There is a significant correlation between day 1 and day 2 ($p < 0.01$) for the first three parameters ($r = 0.82$, 0.76, 0.78 respectively). The correlation coefficient for the solid linear rate was of borderline significance ($r = 0.41$, $0.05 < p < 0.10$). The analysis of variance result is illustrated in Table 6.8. The day-to-day variation (day effect) was not significant ($p > 0.05$) for any of the four parameters: solid and liquid 50% emptying time, solid lag period and solid linear rate. The variation between subjects and groups was significant for all parameters ($p < 0.05$) except the solid linear rate, where the variation between subjects was of only borderline significance ($0.05 < p < 0.10$). This variability of the data implies that three paired studies would be needed to detect a difference in gastric emptying time (solid 50% emptying time) of 30%, five for a difference of 20% and 19 for a difference of 10% ($p = 0.05$).

Table 6.6

EFFECT OF INCREASING THE LIQUID CALORIC CONTENT ON THE RATE OF DELIVERY OF CALORIES (SOLID AND LIQUID) TO THE DUODENUM *

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

* Data are mean values

1 Kcal = 4.2 Kj

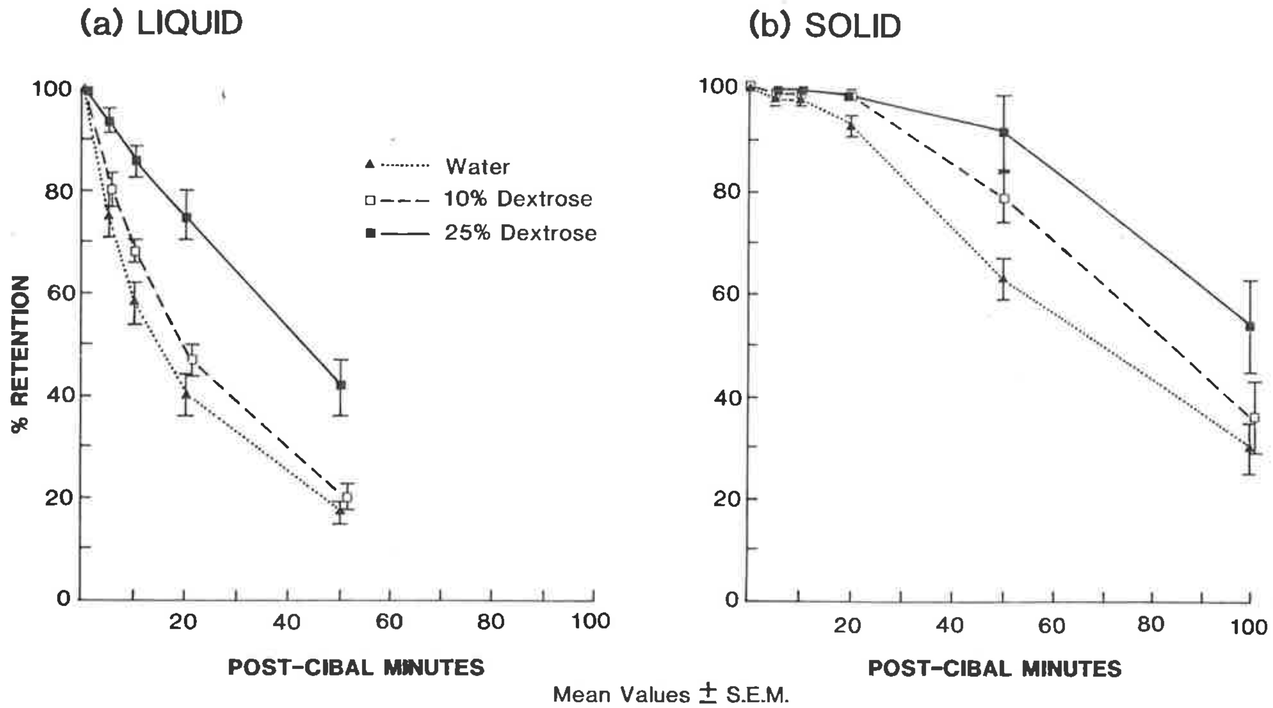
LEGEND FOR FIGURE 6.10

(a) The effect of increasing the liquid calorie content on liquid (a) and solid (b) emptying. The liquid meal was either water (▲), 10% dextrose solution (□) or 25% dextrose solution (■).

Data are mean values ± standard error of the mean.

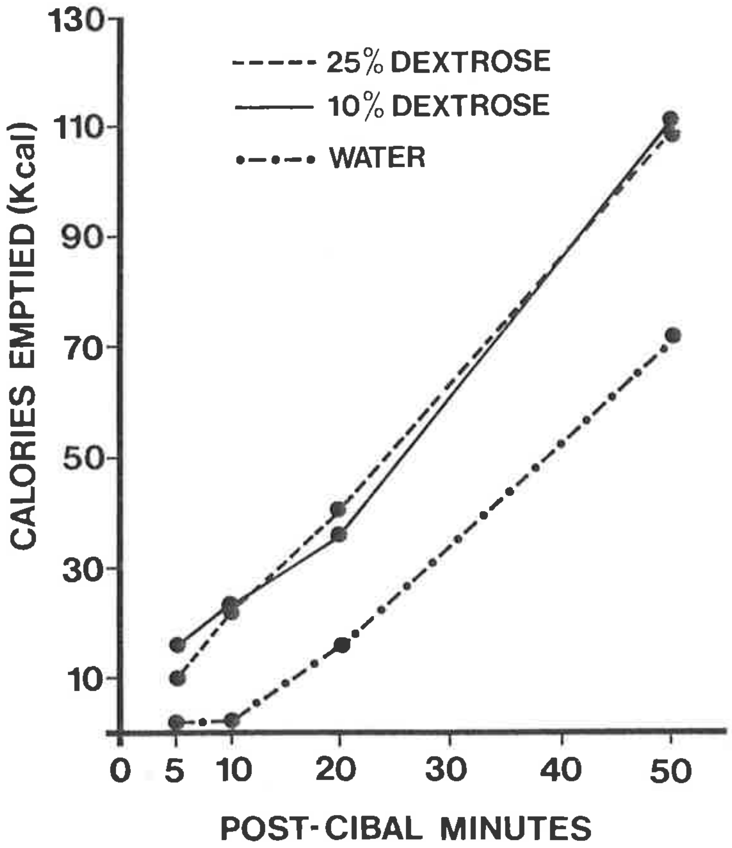
(b) Effect of increasing the liquid calorie content on the rate of delivery of calories (solid and liquid) to the duodenum .

(a)



(a) LIQUID
(b) SOLID
% RETENTION
Water
10% Dextrose
25% Dextrose
POST-CIBAL MINUTES
POST-CIBAL MINUTES
Mean Values ± S.E.M.

(b)



25% DEXTROSE
10% DEXTROSE
WATER
CALORIES EMPTIED (Kcal)
POST-CIBAL MINUTES

TABLE 6.7

SOLID AND LIQUID EMPTYING IN 22 CONTROL SUBJECTS GIVEN A SOLID AND 10% DEXTROSE MEAL *

Solid lag period (min)	35 (9-69)
Solid linear rate (%/min)	1.2 (0.7 - 2.3)
Solid 50% emptying time (min)	78 (50 - 120)
Solid retention at 100 min (%)	33 (12 - 65)
Liquid 50% emptying time (min)	19 (11 - 35)
Liquid retention after 10 min (%)	68 (56 - 93)

* Data are mean values and ranges in parentheses.

LEGEND FOR FIGURE 6.11

Reproducibility of gastric emptying in 22 normal subjects. Data are obtained on two separate days and are plotted around a line of identity (day 1 = day 2). The parameters illustrated are (a) solid lag period (b) solid linear rate (c) solid 50% emptying time (d) liquid 50% emptying time.

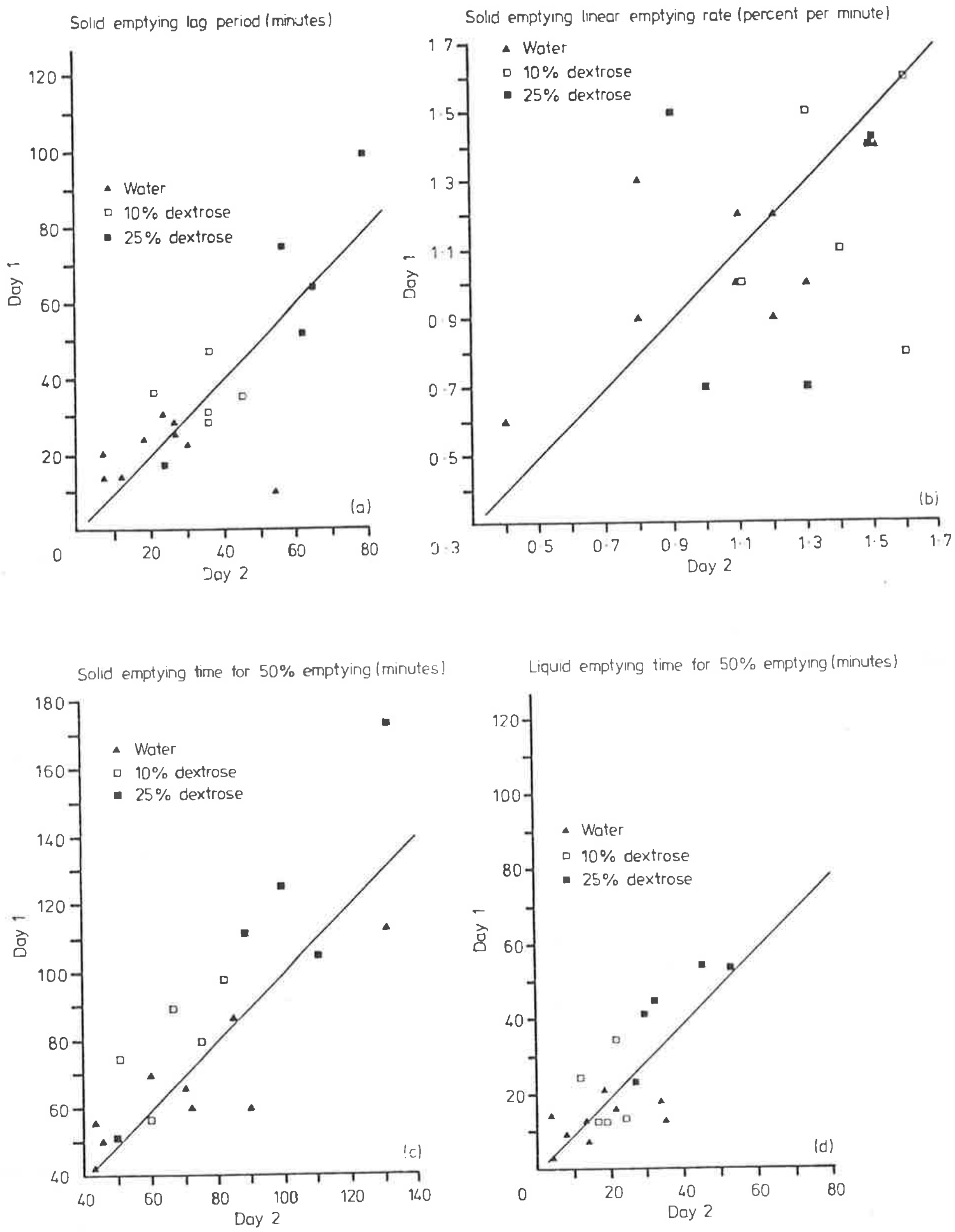

Solid emptying lag period (minutes)
Water
10% dextrose
25% dextrose
Day 1
Day 2
(a)
Solid emptying linear emptying rate (percent per minute)
Water
10% dextrose
25% dextrose
Day 1
Day 2
(b)
Solid emptying time for 50% emptying (minutes)
Water
10% dextrose
25% dextrose
Day 1
Day 2
(c)
Liquid emptying time for 50% emptying (minutes)
Water
10% dextrose
25% dextrose
Day 1
Day 2
(d)

TABLE 6.8

ASSESSMENT OF REPRODUCIBILITY OF GASTRIC EMPTYING IN 22 CONTROL SUBJECTS USING ANALYSIS OF VARIANCE

	Effect		
	Day	Subject	Group
Solid lag period (min)	n.s.*	$p < 0.05$	$p < 0.01$
Solid 50% emptying time (min)	n.s.	$p < 0.01$	$p < 0.01$
Solid linear rate (5 min)	n.s.	n.s.	n.s.
Liquid 50% emptying time (min)	n.s.	$p < 0.05$	$p < 0.01$

* Not significant ($p > 0.05$)

The variation between two observer's in the analysis of 25 gastric emptying studies (for the parameters lag period and solid and liquid 50% emptying time) was less than 5% in each of the studies. There was no significant difference between the results obtained by the two observers.

6.7 GASTRIC EMPTYING IN ELDERLY SUBJECTS

6.7.1 Solid emptying

In all subjects solid emptying was slower than liquid and was characterised by a lag period folowed by linear emptying (Figure 6.12). There was a significant delay of solid food emptying in the elderly subjects with prolongation of the solid 50% emptying time ($p < 0.0025$), increased retention of solid at 100 minutes ($p < 0.0025$) and reduction in the linear emptying rate ($p < 0.0025$) (Table 6.9, Figure 6.12).

6.7.2 Liquid emptying

The emptying of liquid was non-linear with a slope that decreased with time and usually closely followed a monoexponential pattern (Figure 6.12). Liquid emptying was delayed in the elderly subjects (50% emptying time $p < 0.05$, percentage remaining at 10 minutes $p < 0.005$) (Table 6.9, Figure 6.12). The falls in percentage retention of liquid between 10 and 20 minutes and 10 and 100 minutes were not significantly different ($p > 0.05$) between the two groups.

6.7.3 Relationship between age and solid and liquid emptying

Analysis of the gastric emptying curves of all 35 control subjects who received a solid and 10% dextrose meal, revealed a positive correlation between age and solid (50% emptying time : $r = 0.42$ p <

TABLE 6.9

SOLID AND LIQUID EMPTYING IN CONTROL (AGE RANGE 21-62 YEARS)

AND ELDERLY SUBJECTS (AGE RANGE 70-84 YEARS)

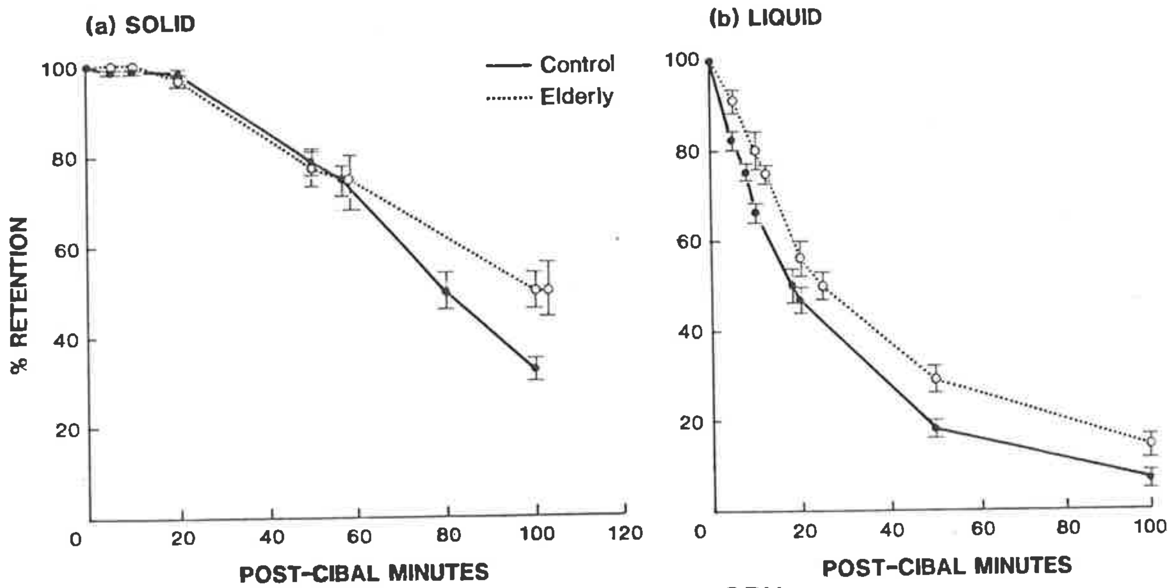
	Control	Elderly	p value
Number of subjects	22	13	
Solid lag period (min)	35 $\pm$ 3	32 $\pm$ 5	n.s. **
Solid linear rate (%/min)	1.2 $\pm$ 0.1	.78 $\pm$ 0.1	$p < .0025$
Solid 50% emptying time (min)	78 $\pm$ 5	103 $\pm$ 8	$p < .0025$
Solid retention at 100 min (%)	33 $\pm$ 3	50 $\pm$ 4	$p < .0025$
Liquid 50% emptying time (min)	19 $\pm$ 1	25 $\pm$ 3	$p < .05$
Liquid retention after 10 min (%)	68 $\pm$ 2	80 $\pm$ 4	$p < .005$
Liquid retention after 20 min (%)	47 $\pm$ 2	56 $\pm$ 4	$p < .05$

* Data are mean values $\pm$ standard error of the mean.

** Not significant ($p > .05$)

LEGEND FOR FIGURE 6.12

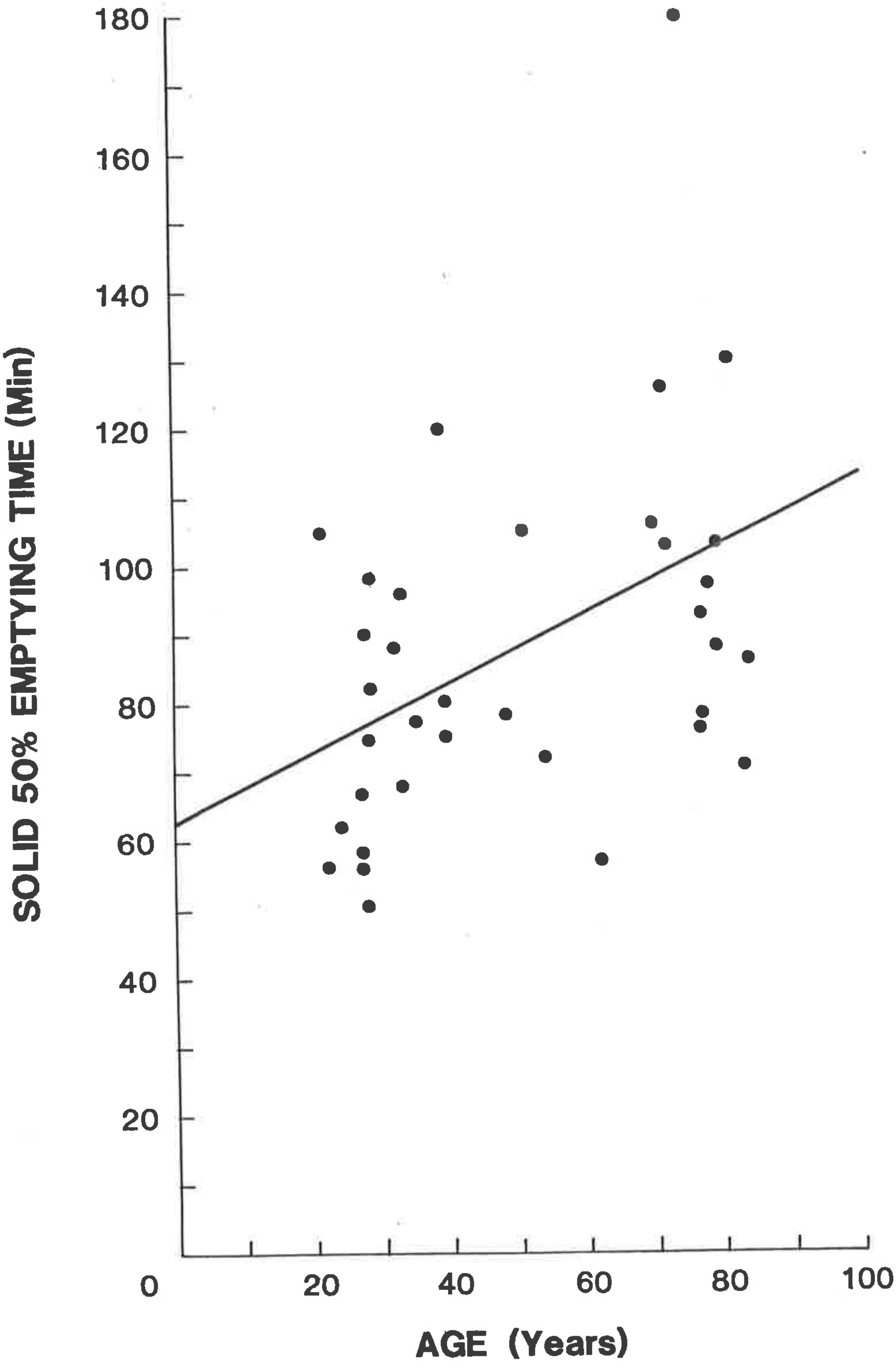
Gastric emptying curves for (a) solid and (b) liquid in control (age range 21-62 years) and elderly subjects (age range 70-84 years). Data are mean values $\pm$ standard error of the mean.



Mean Values ± S.E.M.

LEGEND FOR FIGURE 6.13

Relationship between the solid 50% emptying time and age in 35 subjects ($r = 0.42$, $p < 0.01$).



SOLID 50% EMPTYING TIME (Min)
180
160
140
120
100
80
60
40
20
0
20
40
60
80
100
AGE (Years)

0.01) and liquid emptying (percentage remaining at 10 minutes; $r = 0.36$, $p < 0.05$). The regression line indicated that the solid 50% emptying time was approximately 32 per cent greater at age 70 compared with age 20 years (Figure 6.13). A positive correlation existed between solid and liquid emptying rates in the elderly subjects ($r = 0.55$, $p < 0.05$). There was no difference ($p > 0.2$) in emptying rates between men and women and there was no correlation between subject body weight or surface area and solid or liquid emptying rates in either the elderly or control subjects. There was no correlation ($p > 0.1$) between either solid or liquid emptying rates and age in the control subjects (age range 21-62 years) alone.

6.8 THE EFFECT OF THE MENSTRUAL CYCLE ON GASTRIC EMPTYING

All 10 subjects had normal ovulatory menstrual cycles documented by a rise in progesterone levels during the luteal phase ($p < 0.005$) and onset of menstruation at the expected time (Table 6.10). Parameters of solid and liquid emptying did not change significantly ($p > 0.2$) during the menstrual cycle (Table 6.11). The values for the solid 50% emptying time in both the follicular and the luteal phase are shown in Table 6.12. The mean value for the solid 50% emptying time in these 10 subjects (105 minutes) was higher than the value obtained in 22 control subjects of 78 minutes (Table 6.7), but this difference was not statistically significant. There was also no significant difference between the solid 50% emptying time in these 10 subjects and the 14 male subjects included in the 22 control subjects. One subject had a marked delay in liquid emptying (50% emptying time of 63 minutes) for which there was no clear explanation. Otherwise the liquid emptying rates were very similar to those observed in the 22 control subjects.

TABLE 6.10

SERUM OESTRADIOL AND PROGESTERONE CONCENTRATIONS IN TEN SUBJECTS STUDIED DURING TWO PHASES OF ONE MENSTRUAL CYCLE *

	Follicular phase	Luteal phase	p value
Oestradiol (pg/ml)	557 ± 115	690 ± 293	n.s.
Progesterone (ng/ml)	2.1 ± 0.9	42 ± 11	< 0.005

* Data are mean values ± standard error of the mean.

TABLE 6.11

GASTRIC EMPTYING PARAMETERS IN TEN SUBJECTS STUDIED

IN TWO PHASES OF ONE MENSTRUAL CYCLE *

	Phase of menstrual cycle	
	Follicular	Luteal
Solid lag period (min)	34 (16-57)	31 (18-56)
Solid 50% emptying time (min)	106 (78-134)	101 (82-122)
Liquid retention at 10 minutes (%)	77 (54-87)	75 (54-92)
Liquid 50% emptying time (min)	19 (11-63)	22 (11-46)

* Data are median values and ranges in parentheses.

TABLE 6.12

SOLID 50% EMPTYING TIME (MINUTES) IN TEN SUBJECTS STUDIED IN TWO PHASES OF ONE MENSTRUAL CYCLE

	Phase of menstrual cycle	
Subject	Follicular	Luteal
1	96	82
2	109	110
3	119	122
4	134	98
5	78	100
6	98	130
7	107	102
8	107	109
9	89	100
10	105	94
Mean ± S.E.M.	104 ± 5	105 ± 5

6.9 GASTRIC EMPTYING IN OBESE SUBJECTS

The results of two studies are described:

(1) Gastric emptying in 15 obese subjects who received a solid and water meal.

(2) The effect of increasing caloric content of the liquid meal on gastric emptying in 7 obese subjects.

6.9.1 Gastric emptying in 11 obese subjects who received a solid and water meal

(i) Solid emptying

Solid emptied more slowly than liquid and was characterised by a lag period of variable duration followed by linear emptying (Figure 6.14). In obese patients solid emptying was delayed (lag period and 50% emptying time, $p < 0.025$). The delay in solid emptying was largely due to the prolongation of the lag period without any change in the rate of linear emptying (Table 6.13). In obese patients there was a direct correlation ($r = 0.61$, $p < 0.05$) between the duration of the lag period and the patient's excess weight (Figure 6.14).

(ii) Liquid emptying

The emptying of liquid was non linear and usually followed a monoexponential pattern with minimal lag period (Figure 6.13). In the obese subjects the slight slowing of liquid emptying which was evident at every counting interval after meal completion was not statistically significant (Table 6.13, liquid 50% emptying time, $0.05 < p < 0.10$).In control subjects there was no correlation between either height, weight, body surface area or lean body mass and the rate of solid or liquid emptying.

TABLE 6.13

SOLID AND LIQUID EMPTYING IN ELEVEN CONTROL AND FIFTEEN OBESE SUBJECTS GIVEN A SOLID AND WATER MEAL *

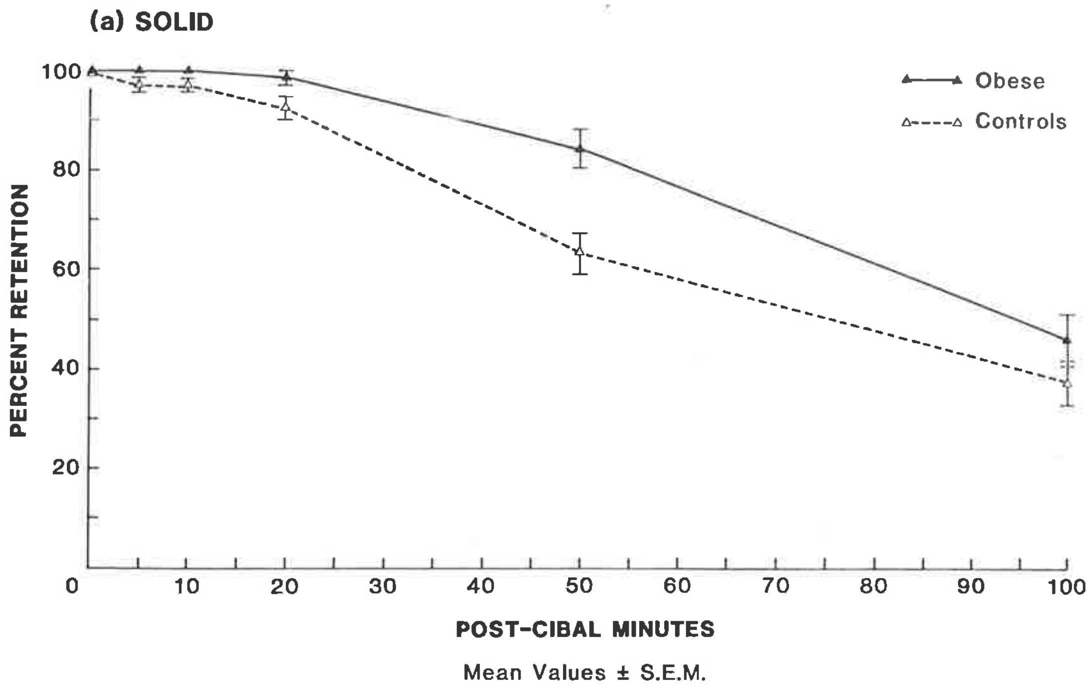
	Controls	Obese	p value **
Number of subjects	11	15	
Solid lag period (min)	21 ± 2	40 ± 5	< 0.025
Solid linear rate (%/min)	1.1 ± 0.1	1.1 ± 0.1	n.s.
Solid 50% emptying time (min)	70 ± 7	94 ± 7	< 0.025
Liquid 50% emptying time (min)	15 ± 2	21 ± 4	< 0.10
Retention of liquid at 10 min (%)	58 ± 4	69 ± 6	< 0.10

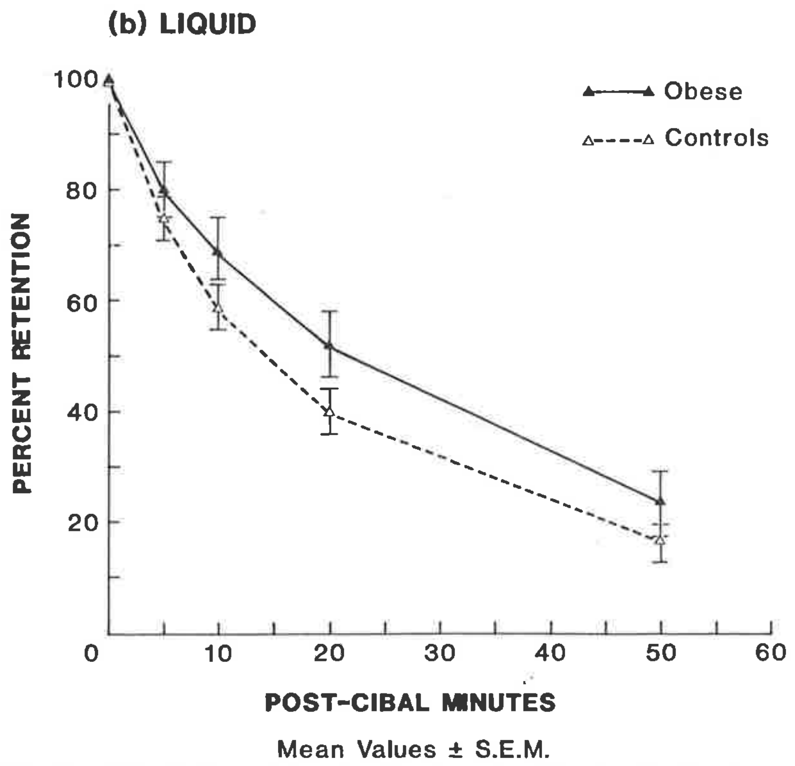
* Data are mean values ± standard error of the mean.

** n.s. - not significant $p > 0.05$

LEGEND FOR FIGURE 6.14

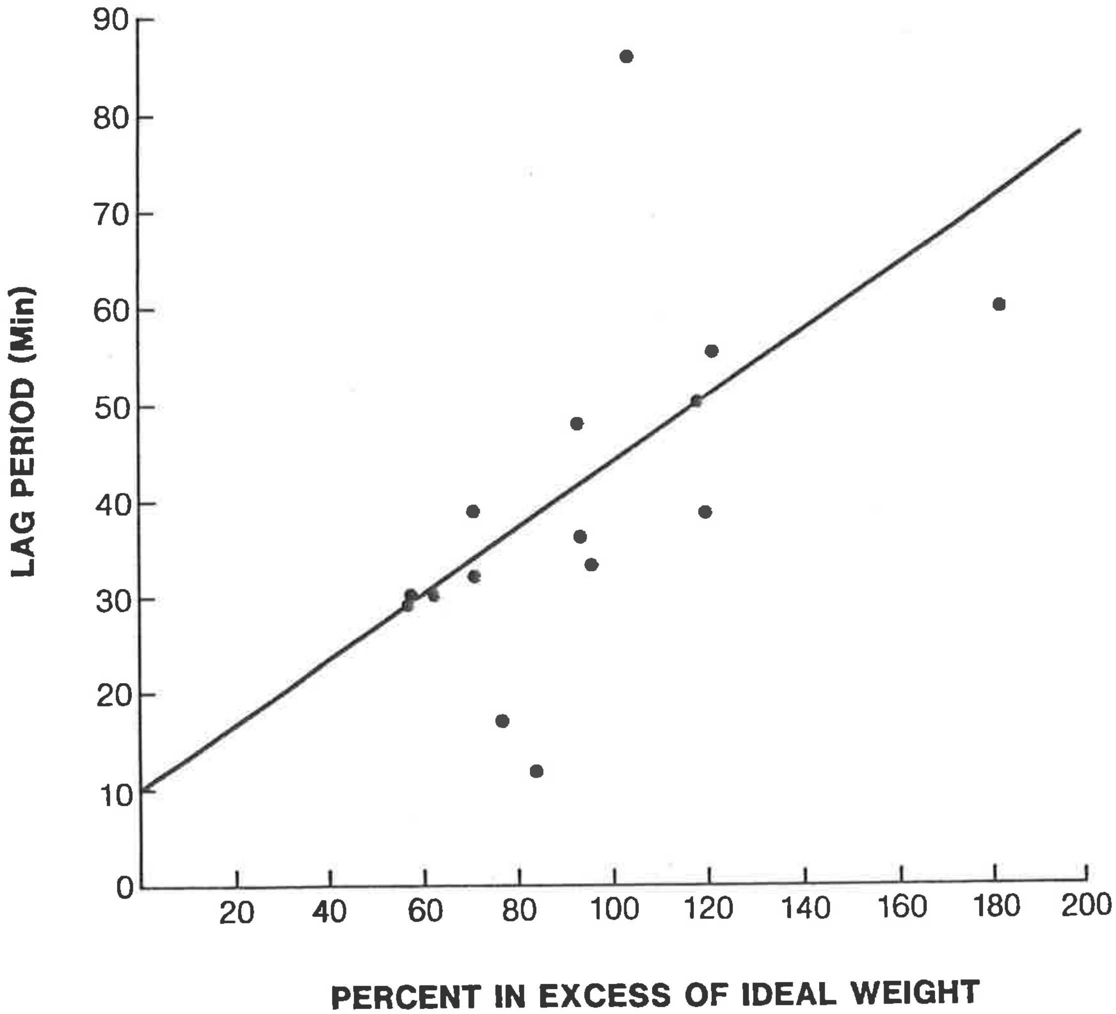
Solid (a) and liquid (b) emptying curves in 11 control subjects and 15 obese patients. There is delayed emptying of solid and a non-significant delay in liquid emptying in the obese subjects. Data are mean values $\pm$ standard error of the mean.


(a) SOLID
Obese
Controls
PERCENT RETENTION
100
80
60
40
20
0
10
20
30
40
50
60
70
80
90
100
POST-CIBAL MINUTES
Mean Values ± S.E.M.


(b) LIQUID
Obese
Controls
PERCENT RETENTION
100
80
60
40
20
0
10
20
30
40
50
60
POST-CIBAL MINUTES
Mean Values ± S.E.M.

LEGEND FOR FIGURE 6.15

Correlation between the duration of the solid lag period and excess body weight in 15 obese patients ($r = 0.61$, $p < 0.05$).



LAG PERIOD (Min)
90
80
70
60
50
40
30
20
10
0
20
40
60
80
100
120
140
160
180
200
PERCENT IN EXCESS OF IDEAL WEIGHT

(iii) Stomach size

Although stomach volume could not be accurately assessed, there was no difference in the length of the stomach between obese and control subjects in the two projections studied. The length of the stomach in its long axis (measured in reduced size on the computer display) was 5.7 $\pm$ 0.2 cm in obese patients and 5.6 $\pm$ 0.2 cm in control subjects.

6.9.2 The effect of increasing the caloric content of the liquid meal on gastric emptying in obese subjects

(i) Solid emptying

The results are shown in Tables 6.14 and 6.15. The solid 50% emptying time was prolonged by the addition of 25% dextrose ($p < 0.025$). There was no significant change in the linear emptying rate. The solid lag period was more prolonged (55 v's 43 minutes) with 25% dextrose but this difference was not statistically significant (Table 6.14). The solid 50% emptying time was delayed ($p < 0.025$) in the obese subjects compared to the 6 control subjects who received a solid and 25% dextrose meal (Table 6.15).

(ii) Liquid emptying

Liquid emptying was delayed with 25% dextrose (50% emptying time and percentage retention at 10 minutes ; $p < 0.025$) (Table 6.14). Parameters of liquid emptying for the solid and 25% dextrose meal were greater, but not significantly different from the control subjects (Table 6.15).

TABLE 6.14

EFFECT OF INCREASING THE LIQUID CALORIC CONTENT ON SOLID AND LIQUID EMPTYING IN 7 OBESE SUBJECTS *

	Water	25% Dextrose	p value
Solid lag period (min)	43 ± 6	55 ± 7	n.s.
Solid linear emptying rate (%/min)	0.9 ± 0.1	0.7 ± 0.2	n.s.
Solid 50% emptying time (min)	90 ± 6	141 ± 8	< 0.025
Liquid 50% emptying time (min)	23 ± 4	48 ± 5	< 0.005
Retention of liquid at 10 min (%)	76 ± 7	93 ± 4	< 0.025

* Data are mean values ± standard error of the mean

TABLE 6.15

SOLID AND LIQUID EMPTYING IN 6 CONTROL AND 7 OBESE SUBJECTS WHO RECEIVED A SOLID AND 25% DEXTROSE MEAL *

	Controls	Obese	p value
Number of subjects	6	7	
Solid lag period (min)	60 ± 9	55 ± 7	n.s.
Solid 50% emptying time (min)	105 ± 13	141 ± 8	< 0.025
Retention of liquid at 10 min (%)	86 ± 3	93 ± 4	n.s.
Liquid 50% emptying time (min)	46 ± 7	48 ± 5	n.s.

* Data are mean values ± standard error of the mean

6.9.3 Gastric emptying in 22 obese subjects who received a solid and water meal

The results of all subjects (included in studies 6.9.1 and 6.9.2) who received a solid and water meal are summarized in Table 6.16. The solid lag period and 50% emptying time were delayed in the obese subjects ($p < 0.005$) compared to the controls, due to prolongation of the lag period. There was no change in the linear emptying rate. The retention of water at 10 minutes was significantly greater ($p < 0.05$) in the obese subjects, but the difference in the 50% emptying time was not statistically significant.

In the 22 obese subjects the direct correlation between the solid lag period and the subject's excess weight was also evident ($r = 0.45$; $p < 0.05$).

TABLE 6.16

SOLID AND LIQUID EMPTYING IN 11 CONTROL AND 22 OBESE SUBJECTS WHO RECEIVED A SOLID AND WATER MEAL *

	Controls	Obese	p value
Number of subjects	11	22	
Solid lag period (min)	21 ± 2	41 ± 4	< 0.005
Solid linear rate (%/min)	1.1 ± 0.1	1.0 ± 0.1	n.s.
Solid 50% emptying time (min)	70 ± 7	97 ± 6	< 0.005
Liquid 50% emptying time (min)	15 ± 2	22 ± 3	n.s.
Retention of liquid at 10 min (%)	58 ± 4	72 ± 4	< 0.05

* Data are mean values ± standard error of the mean

CHAPTER 7

GASTRIC EMPTYING RESULTS IN DIABETIC AUTONOMIC NEUROPATHY AND AFTER GASTRIC SURGERY FOR THE TREATMENT OF OBESITY

7.1 GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY AND AN ASSESSMENT OF THE ACUTE AND CHRONIC EFFECTS OF ORAL DOMPERIDONE ON GASTRIC EMPTYING, SYMPTOMS OF GASTROPARESIS AND GLYCAEMIC CONTROL:

7.1.1 Gastrointestinal symptoms.
7.1.2 Glycaemic control.
7.1.3 Gastric emptying.

(i) solid emptying
(ii) liquid emptying
(iii) relationship between solid and liquid emptying and response to domperidone

7.2 GASTRIC EMPTYING AFTER GASTRIC SURGERY FOR THE TREATMENT OF OBESITY.

7.2.1 Gastric Bypass

(i) solid and water meal
(ii) solid and 25% dextrose meal

7.2.2 Gastroplasty.

In this chapter the results of studies performed in patients with diabetic gastroparesis and after gastric surgery for obesity are presented.

7.1 GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY AND AN ASSESSMENT OF THE ACUTE AND CHRONIC EFFECTS OF ORAL DOMPERIDONE ON GASTRIC EMPTYING, SYMPTOMS OF GASTROPARESIS AND GLYCAEMIC CONTROL

7.1.1 Gastrointestinal symptoms

A symptom score for delayed emptying of 4 or more out of 12 occurred in 8 of the 12 patients (Table 7.1). Four patients complained of dysphagia or heartburn (usually mild symptoms) and these symptoms were always associated with a gastroparesis score of greater than 4 out of 12. Before the study 4 patients suffered from constipation (less than 3 bowel movements each week), and 2 had nocturnal diarrhoea.

Symptoms of gastroparesis were reduced during domperidone treatment as judged by symptom scores (median 4.5, range (1-10) v's 1 (0-6), $p < 0.001$) (Table 7.1). There was no significant change in symptoms of dysphagia or heartburn. Two patients with constipation observed an increase in the frequency of bowel actions. No side effects were reported by any patient.

TABLE 7.1

SYMPTOMS OF DELAYED GASTRIC EMPTYING IN 12 DIABETIC PATIENTS BEFORE AND AFTER TREATMENT WITH ORAL DOMPERIDONE

	SYMPTOM SCORE*									
	Before treatment					After treatment				
Patient	A	B	C	D	Total	A	B	C	D	Total
1	1	2	3	0	6	1	0	0	0	1
2	2	3	3	2	10	2	1	2	1	6
3	2	2	2	2	8	0	0	0	0	0
4	0	2	2	0	4	0	0	0	0	0
5	0	1	0	0	1	0	0	0	0	0
6	2	3	3	0	7	0	2	1	0	3
7	1	0	1	0	2	0	0	0	0	0
8	2	2	0	0	4	1	2	0	0	3
9	0	0	2	0	2	0	0	2	0	2
10	0	2	0	0	2	0	0	0	0	0
11	3	2	3	1	9	1	2	1	0	4
12	1	2	2	0	5	0	2	1	0	3

Symptom*

A - anorexia/nausea

B - early satiety

C - epigastric fullness/upper abdominal discomfort

D - post prandial vomiting

Symptom score code*

0 = none

1 = mild

2 = moderate

3 = severe

7.1.2 Glycaemic control

The blood glucose level 3 hours postprandially after the first single dose of domperidone was lower than that observed after the placebo test (median 7.7 mmol/L, range (3.6-14.8) v's 12.6 mmol/L (3.8-19.0), $p < 0.005$). Five patients observed more frequent hypoglycaemic episodes while taking domperidone and reduced their total insulin dose. There was no significant change in HbA1c levels (median 8.5% range (6.8-10.9) v's 7.5 (5.6-12.1); normal range < 8.5%).

7.1.3 Gastric emptying

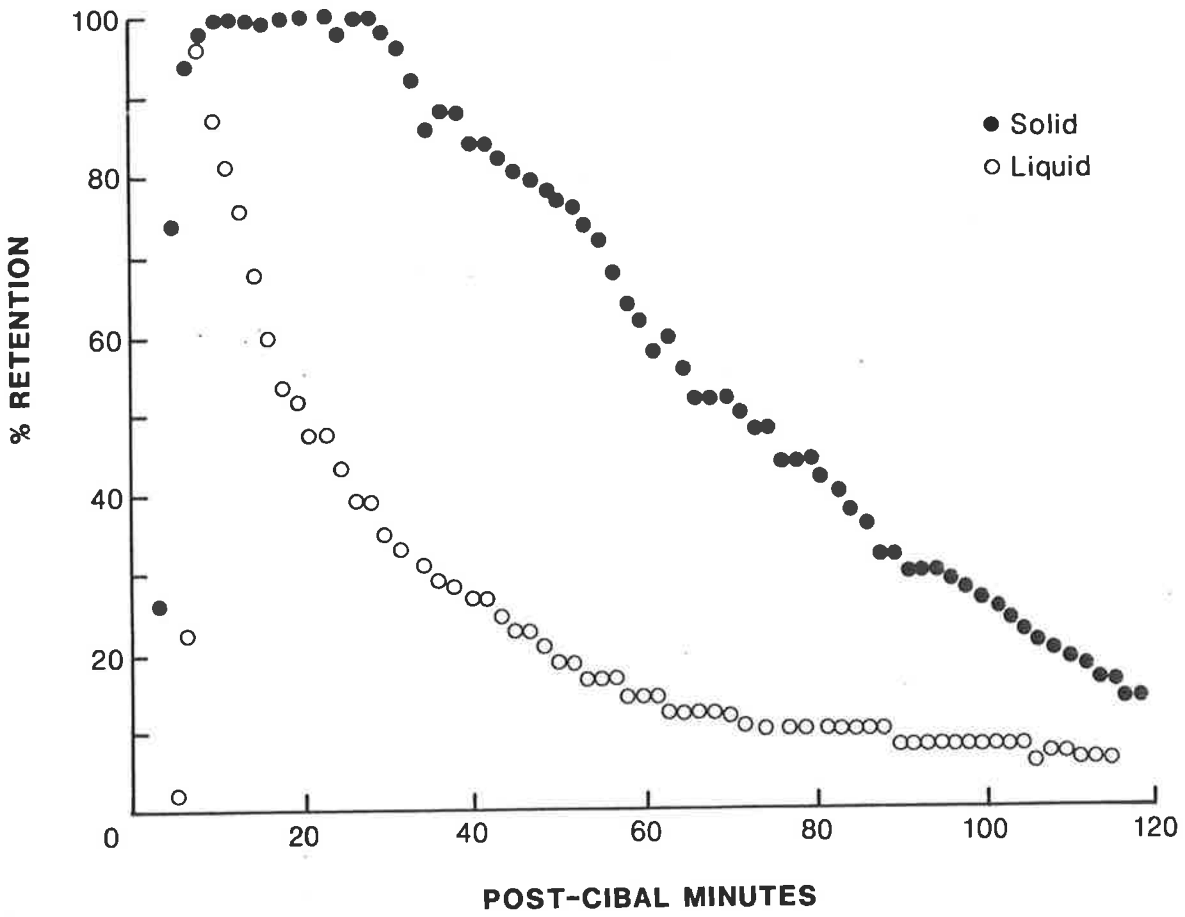
(i) Solid emptying: In patients solid emptied more slowly than liquid and was characterised by a lag period, followed by a phase of approximately linear emptying. There was a marked delay of solid food emptying in patients, with prolongation of the lag period ($p < 0.001$) and increased retention of solid at 100 minutes ($p < 0.001$) (Table 7.2, Figures 7.1 and 7.2). Acute administration of domperidone increased solid emptying rates with reduction in the duration of the lag period ($p < 0.005$) and less retention of solid at 100 minutes ($p < 0.005$) (Figure 7.3). However, after chronic administration domperidone had a less marked effect with no significant difference ($p > 0.05$) between the test with placebo and the third study (Table 7.3, Figure 7.3).

(ii) Liquid emptying: The emptying of liquid was non-linear. Liquid emptying was delayed in patients (50% emptying time; $p < 0.001$) (Table 7.2, Figures 7.1 and 7.2). Acute administration of domperidone increased liquid emptying rates (50% emptying time; $p < 0.005$) (Table

LEGEND FOR FIGURE 7.1

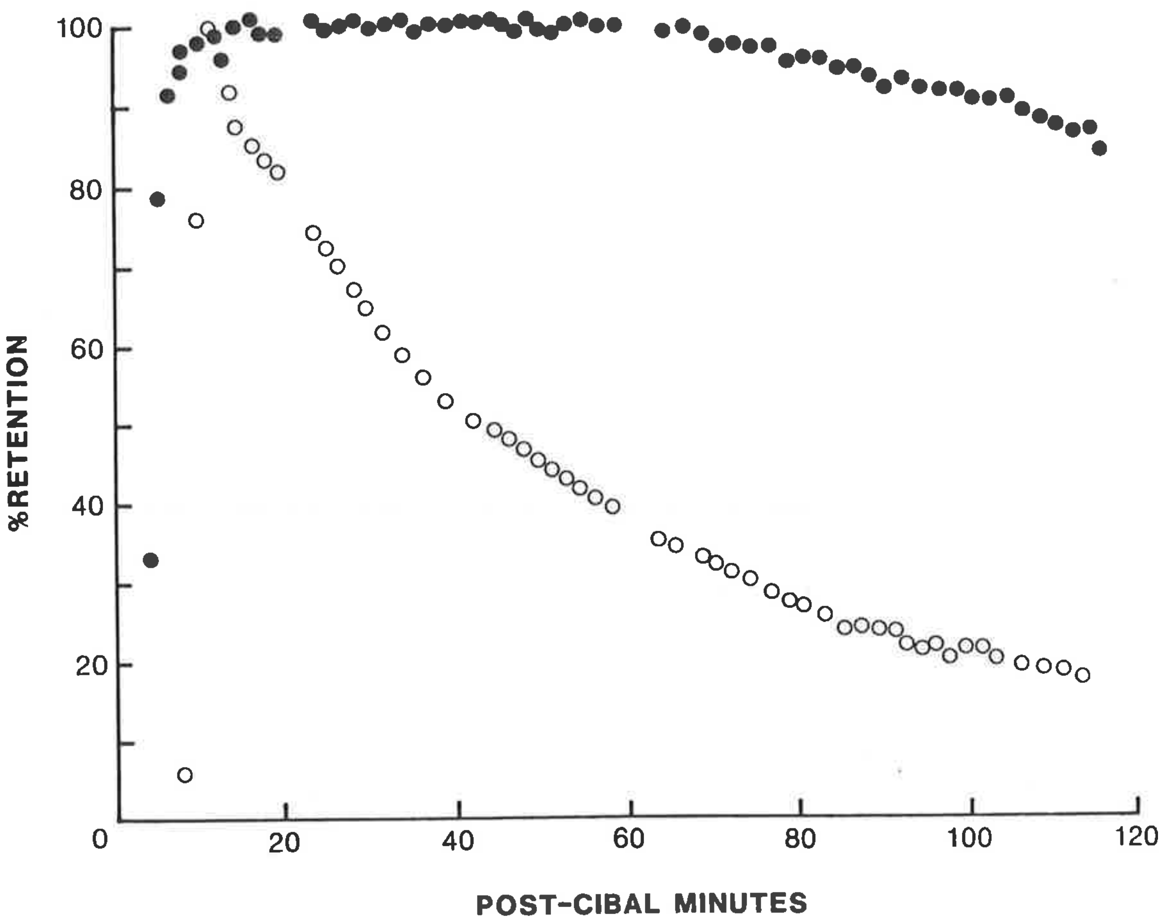
Gastric emptying curves for solid and liquid in (a) one control subject and (b) a diabetic patient with autonomic neuropathy. Both solid and liquid emptying are slower in the diabetic patient.

(a)



100
80
60
40
20
0
% RETENTION
● Solid
○ Liquid
20
40
60
80
100
120
POST-CIBAL MINUTES

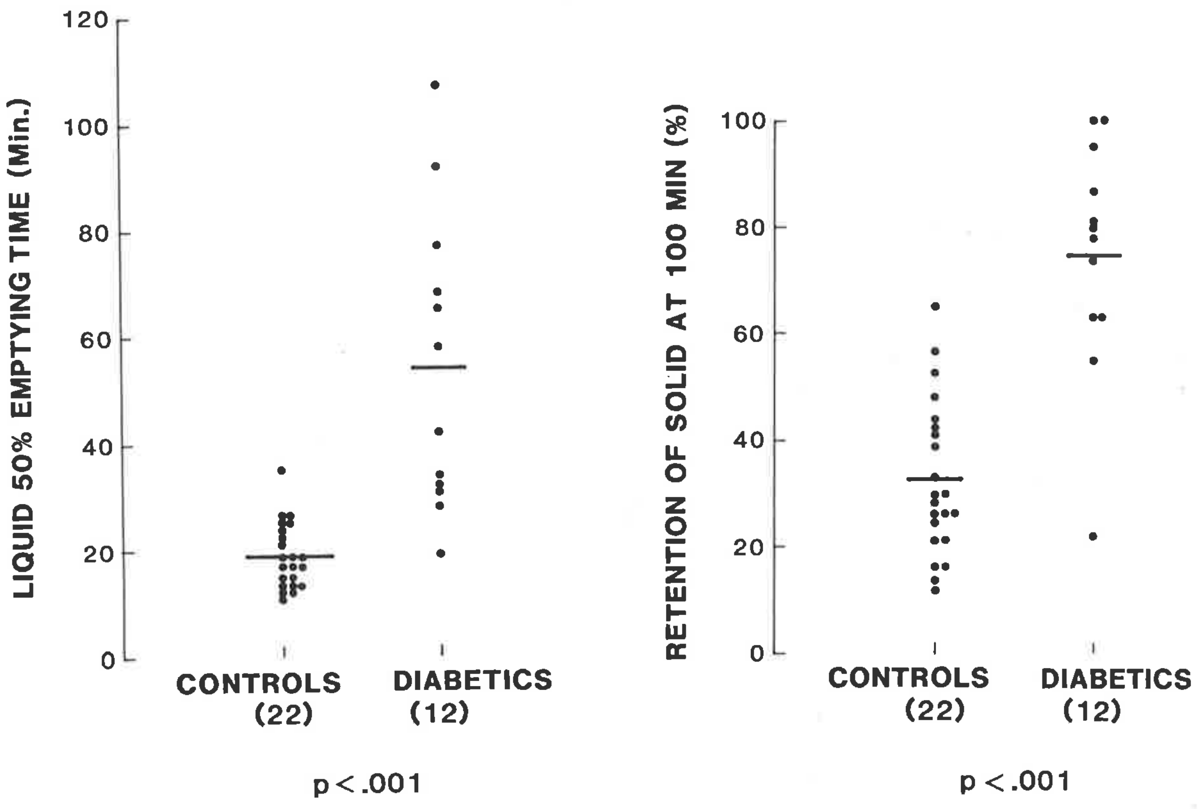
(b)



100
80
60
40
20
0
%RETENTION
20
40
60
80
100
120
POST-CIBAL MINUTES

LEGEND FOR FIGURE 7.2

Gastric emptying of solid (% retention at 100 minutes after meal completion) and liquid (50% emptying time) in 22 control subjects and 12 diabetic patients. In the diabetics there is a significant delay of both solid and liquid emptying.



LIQUID 50% EMPTYING TIME (Min.)
120
100
80
60
40
20
0
CONTROLS (22)
DIABETICS (12)
p < .001
RETENTION OF SOLID AT 100 MIN (%)
100
80
60
40
20
0
CONTROLS (22)
DIABETICS (12)
p < .001

7.3, Figure 7.4). After chronic administration, emptying rates remained significantly more rapid than when placebo was given (50% emptying time; $p < 0.025$) (Table 7.3, Figure 7.4).

If the mean and two standard deviations are used for defining the "normal range" for gastric emptying, two of the twelve diabetics had normal emptying rates for both solid and liquid meal components in the study with placebo.

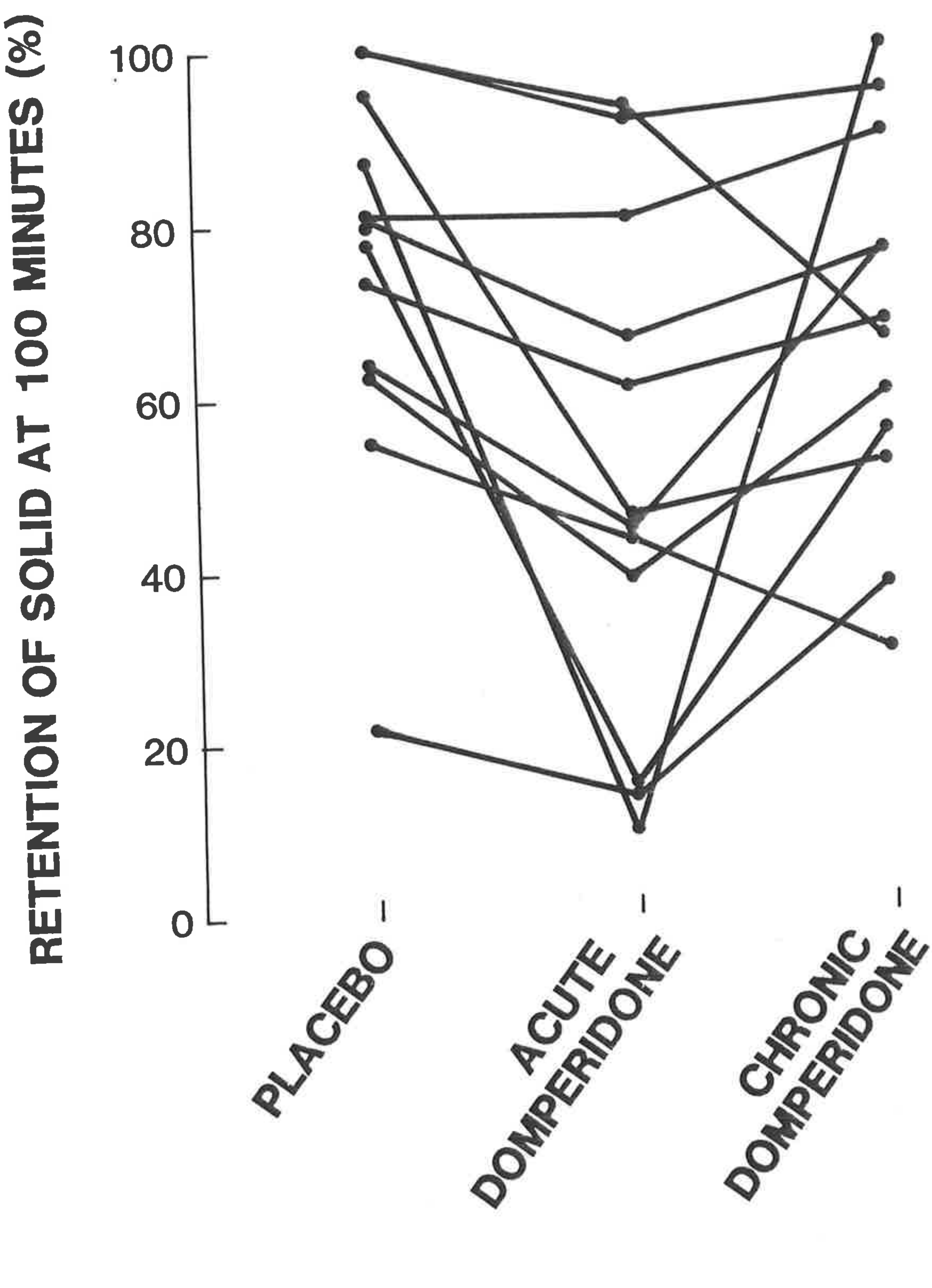
(iii) Relationship between solid and liquid emptying and response to domperidone

In the diabetic patients there was a positive correlation between solid (% retention at 100 min) and liquid (50% emptying time) emptying rates ($r_s = .58$ $p < 0.05$). In diabetics the magnitude of the improvement in both solid and liquid emptying rates in response to the initial dose of domperidone (change in lag period and change in liquid 50% emptying time) was proportional ($r_s = .73$, $p < 0.01$) to the placebo test result for these parameters. The slope of the regression line for liquid 50% emptying time was -0.52 and the zero change line was intercepted at 14 and the slope of the regression line for lag period was -0.45 the zero change line was intercepted at 14 (Figure 7.5).

After chronic administration of domperidone the change in liquid 50% emptying time also correlated with the placebo test result ($r_s = 0.77$, $p < 0.01$).

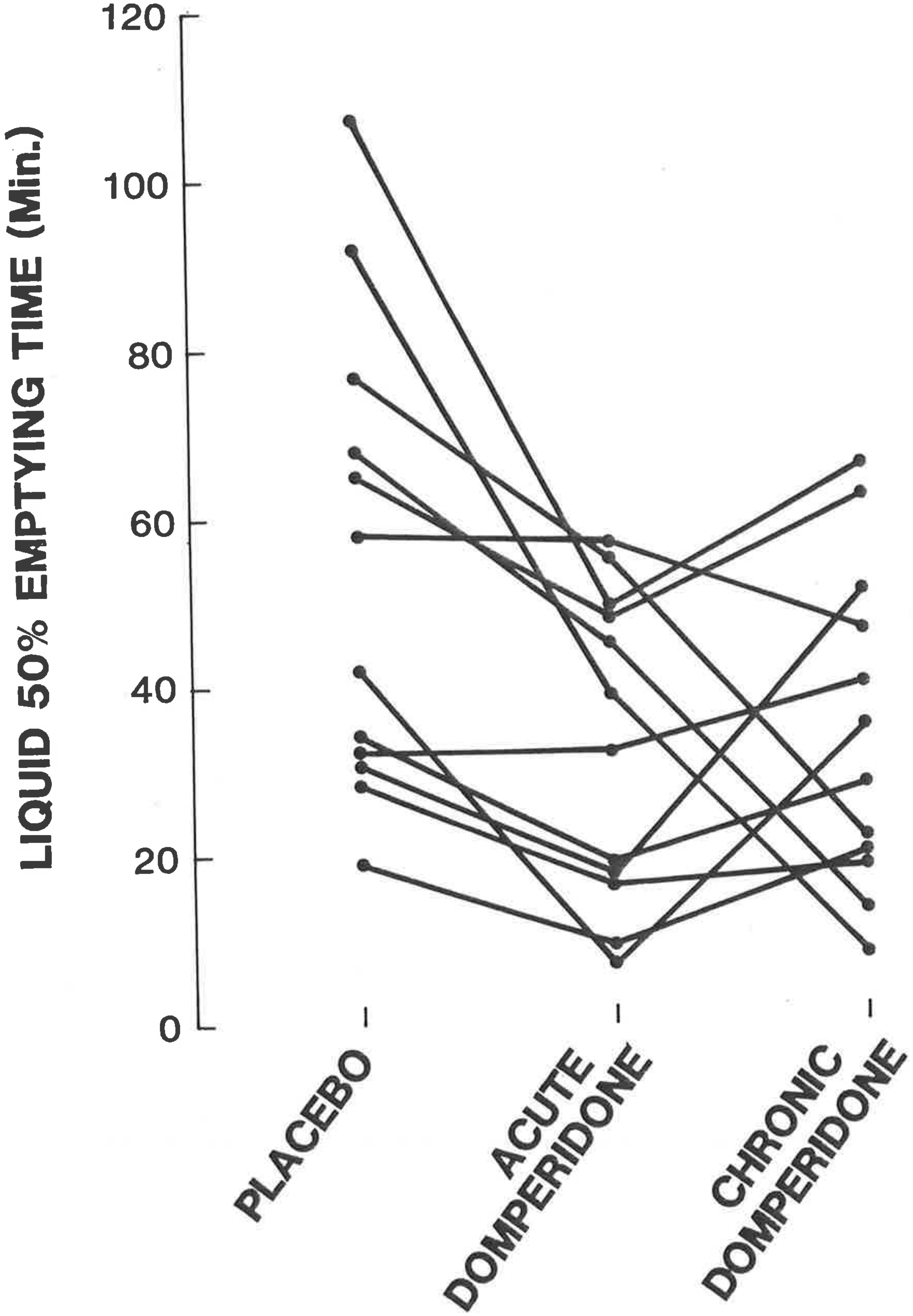
LEGEND FOR FIGURE 7.3

The effect of acute and chronic administration of oral domperidone on solid emptying (% retention at 100 minutes after meal completion) in 12 diabetics with autonomic neuropathy. Acute administration of domperidone increased solid emptying ($p < 0.001$). After chronic administration domperidone had no significant effect ($p > 0.05$) on solid emptying.


RETENTION OF SOLID AT 100 MINUTES (%)
100
80
60
40
20
0
PLACEBO
ACUTE DOMPERIDONE
CHRONIC DOMPERIDONE

LEGEND FOR FIGURE 7.4

The effect of acute and chronic administration of oral domperidone on liquid emptying (50% emptying time) in diabetics with autonomic neuropathy. Both acute and chronic administration of domperidone increased liquid emptying ($p < 0.025$).



LIQUID 50% EMPTYING TIME (Min.)
120
100
80
60
40
20
0
PLACEBO
ACUTE DOMPERIDONE
CHRONIC DOMPERIDONE

LEGEND FOR FIGURE 7.5

Regression of the response to acute administration of oral domperidone (40 mg) of the (a) liquid 50% emptying time and (b) lag period against the initial values for these parameters.

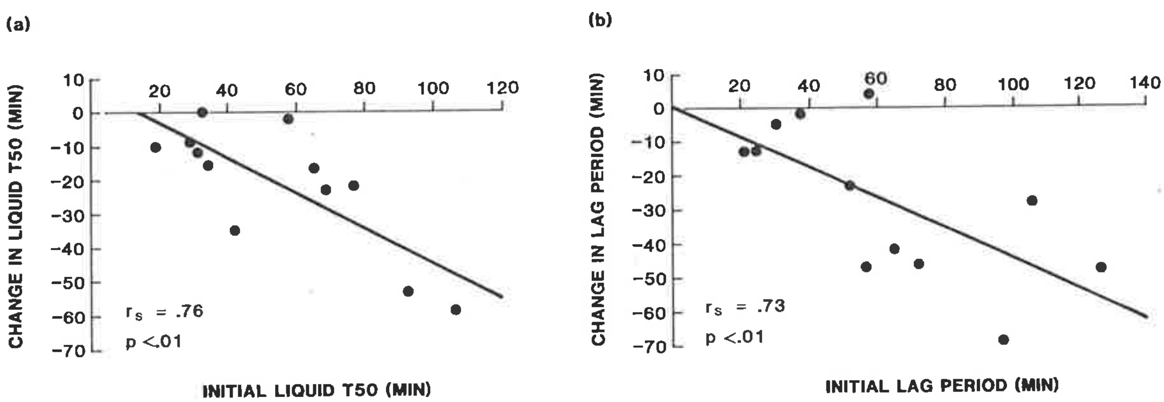

(a)
CHANGE IN LIQUID T50 (MIN)
INITIAL LIQUID T50 (MIN)
r_s = .76
p <.01
(b)
CHANGE IN LAG PERIOD (MIN)
INITIAL LAG PERIOD (MIN)
r_s = .73
p <.01

TABLE 7.2

SOLID AND LIQUID EMPTYING IN CONTROL SUBJECTS AND DIABETIC PATIENTS WHO RECEIVED A SOLID AND 10% DEXTROSE MEAL *

	Control	Diabetic	p value
Number of subjects	22	12	
Solid lag period (min)	35 (9-69)	57 (21-126)	< .001
Solid retention at 100 min (%)	29 (13-65)	79 (22-100)	< .001
Liquid 50% emptying time (min)	18 (11-35)	50 (19-107)	< .001

* Data are median values and ranges in parentheses.

TABLE 7.3

SOLID AND LIQUID EMPTYING IN DIABETIC PATIENTS *

	Placebo	Acute Domperidone	Chronic Domperidone
Solid lag period (min)	57 (21-126)	27 (10-78)	36 (18-116)
Solid retention at 100 min (%)	79 (22-100)	46 (10-94)	67 (30-100)
Liquid 50% emptying time (min)	50 (19-107)	36 (7-56)	32 (8-66)

* Data are median values and ranges in parentheses.

There was no significant correlation between gastrointestinal symmptoms and solid or liquid emptying rates, or between the change in symptoms and changes in gastric emptying after domperidone.

7.2 GASTRIC EMPTYING AFTER GASTRIC SURGERY FOR THE TREATMENT OF MORBID OBESITY

The results of gastric emptying studies in patients after: (a) gastric bypass using a solid and water meal and a solid and 25% dextrose meal, and (b) gastroplasty using solid and 10% dextrose meal, are presented.

7.2.1 GASTRIC BYPASS

(i) Results in the 11 patients who received a solid and water meal

(a) Solid emptying: In the gastric bypass (GB) subjects, solid emptied more slowly than liquid. There were three patterns of emptying in the 12 GB patients (Figure 7.6). In four, an initial rapid emptying of short duration was followed by linear emptying. In five, emptying approximated a linear pattern after an initial lag period. In three, a prolonged lag period was followed by only minimal (less than 20%) emptying of solid during the study period. There was a significant delay of solid food emptying in post-bypass patients compared with the controls (% remaining at 100 min $p < 0.005$, and rate of linear emptying $p < 0.005$) (Table 7.4, Figures 7.6 and 7.7).

(b) Liquid emptying: GB patients consistently showed two separate phases in liquid emptying. Initial emptying of water was more rapid than in controls and was followed by a slower component (Figure 7.6). The rate of liquid emptying was faster in the GB patients compared with controls (% remaining at 10 minutes $p < 0.01$, and time for 50% emptying $p < 0.005$) (Table 7.5, Figures 7.6 and 7.7). There was no correlation between solid and liquid emptying rates in gastric bypass patients.

(c) Endoscopy findings: At endoscopy, pouch diameter varied from 4 - 10 cm (mean 7 $\pm$ 0.6 cm). The four patients in whom initial rapid emptying of solid food had occurred had the smallest pouch diameters (4, 6, 6, 6 cm). Stomal size varied from 12-20 mm (mean 16 $\pm$ 2).

In GB patients there was no correlation between the extent of weight loss produced by the operation and (1) the observed rate of solid or liquid emptying or (2) the stoma or pouch size assessed endoscopically.

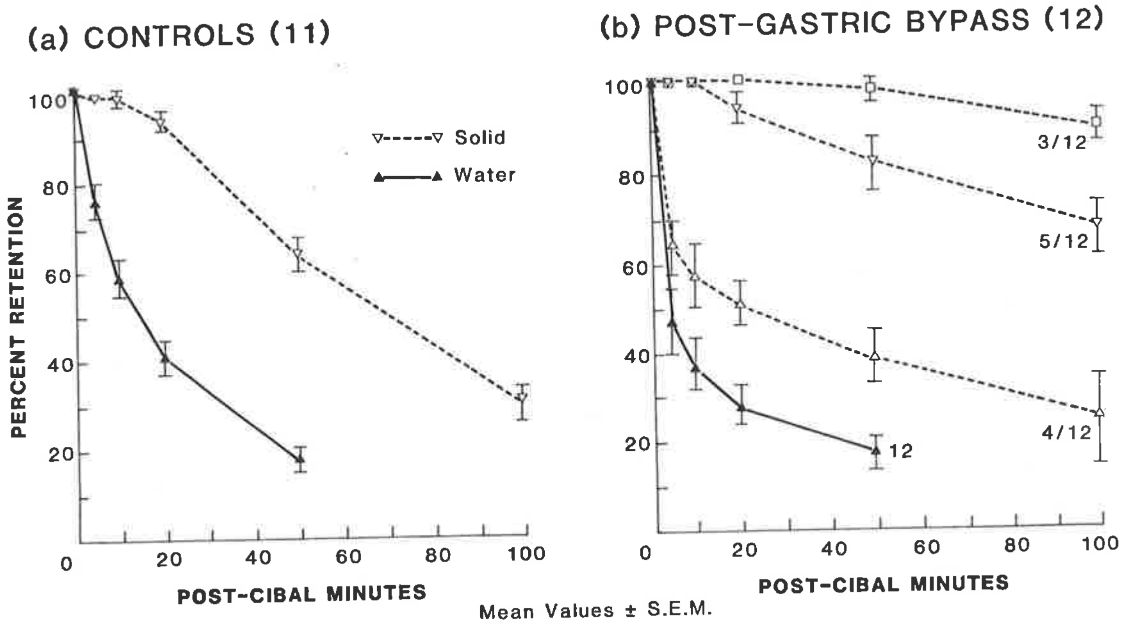
(ii) Results in 7 patients who received a solid and 25% dextrose meal

(a) Solid emptying: There was a significant delay of solid food emptying in GB patients compared to controls (% remaining at 100 minutes $p < 0.05$). In 2, initial rapid emptying of solid food occurred; in 3, emptying approximated a linear pattern after an initial lag period and in 2, minimal emptying of solid food occurred (Table 7.6). Solid emptying rates were not significantly different from the previously described gastric bypass patients who received a solid and water meal.

LEGEND FOR FIGURE 7.6

Solid and liquid emptying curves in 12 gastric bypass patients (solid and water meal).

Data are mean values $\pm$ standard error of the mean.



Mean Values ± S.E.M.

LEGEND FOR FIGURE 7.7

Scintiphotos showing the distribution of solid (^{99m}Tc-liver) and liquid (^{113m}In-DTPA in water) in a gastric bypass patient at 5 (left) and 100 (right) minutes. More rapid emptying of liquid and retention of solid are evident in the gastric bypass patient.

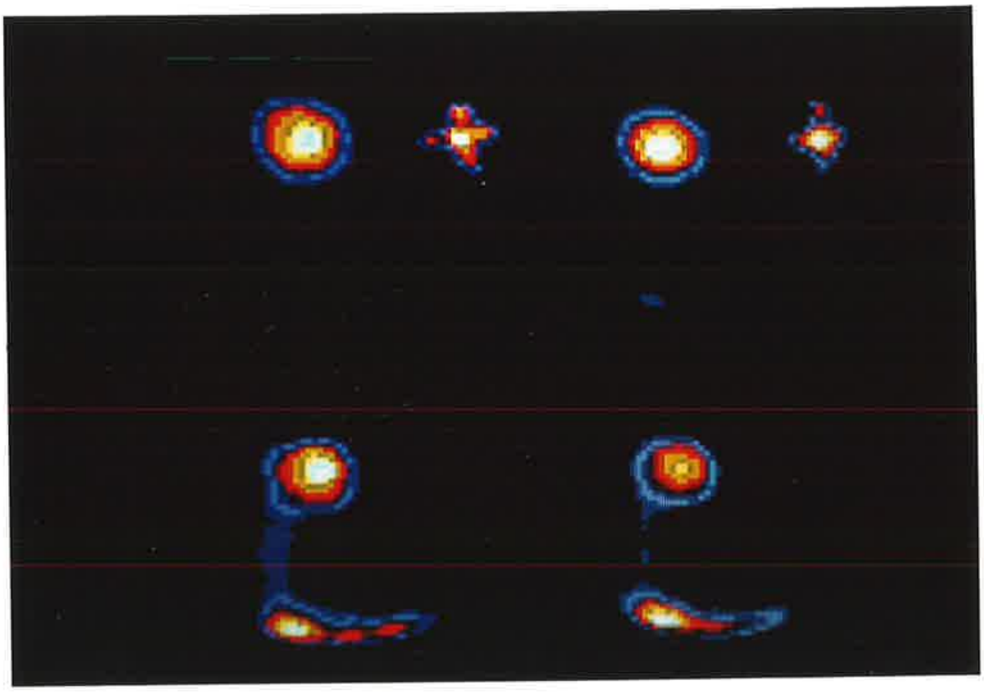


TABLE 7.4

SOLID EMPTYING IN GASTRIC BYPASS PATIENTS WHO RECEIVED A SOLID AND WATER MEAL *

	Controls	Gastric bypass **		
		Group 1	Group 2	Group 3
Number of subjects	11	4	5	3
Lag period (min)	22(10-31)	0	13(10-48)	60(50-70)
Retention at 50 min %	62(38-86)	49(24-49)	78(65-95)	100
Retention at 100 min %	25(14-64)	27(20-40)	56(52-81)	83(78-95)
50% emptying time (min)	66(42-120)	22(6-46)	130(70-180)	200
Linear emptying rate (%/min)	1.1(0.5-1.2)	0.3(0.2-0.8)	0.3(0.1-0.5)	0.1

** Group 1 : initial rapid emptying then linear, group 2 : initial lag then linear : group 3 : prolonged lag (see text).

* Data are median values and ranges in parentheses - solid and water meal.

Table 7.5

LIQUID EMPTYING IN GASTRIC BYPASS PATIENTS WHO RECEIVED A SOLID AND WATER MEAL

	Control	Gastric bypass
Number of subjects	11	12
Retention at 5 min (%)	80 (43-88)	39 (14-82)
Retention at 10 min (%)	68 (32-75)	35 (12-74)
50% emptying time (min)	16 (4-26)	3 (1-24)

* Data are median values and ranges in parentheses.

TABLE 7.6

SOLID AND LIQUID EMPTYING IN 7 GASTRIC BYPASS PATIENTS WHO RECEIVED A SOLID AND 25% DEXTROSE MEAL*

	Control	Gastric bypass
Number of subjects	6	7
Lag period (min)	65 (20-88)	60 (0-90)
Solid retention at 100 min (%)	57 (15-82)	50 (28-90)
Solid linear rate (%/min)	1.3 (0.9-1.5)	0.1 (0.1-1.2)
Liquid retention at 10 min (%)	85 (76-99)	28 (15-58)
Liquid 50% emptying time (min)	46 (25-74)	3 (1-11)

* Data are median values and ranges in parentheses.

(b) Liquid emptying: Emptying of liquid was faster in gastric bypass patients than controls (time for 50% emptying, $p < 0.005$) and was not significantly different from the patients who received a solid and water meal (Table 7.6).

7.2.2 GASTROPLASTY

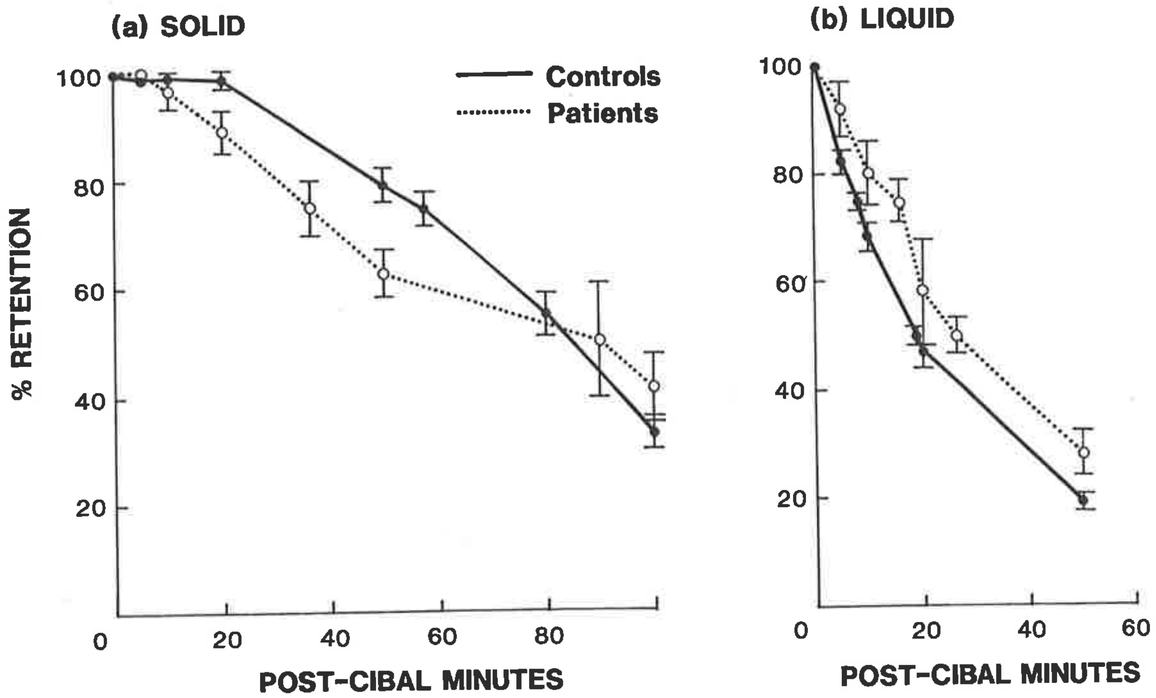
(a) Solid emptying - whole stomach: In gastroplasty patients solid emptied more slowly than liquid and was characterised by a lag period followed by linear emptying (Figure 7.8). In gastroplasty patients the lag period was shorter ($p < 0.001$) and more solid was emptied in the first 50 minutes of the test than in the controls ($p < .01$) (Figure 7.8) but the linear emptying rate was reduced ($p < 0.001$) (Table 7.7). Three patients had solid 50% emptying times of 130, 135 and 138 minutes; the remaining 8 falling within the control range (50-120 min).

(b) Liquid emptying - whole stomach: The emptying of liquid was non-linear and usually approximated a monoexponential pattern. Liquid emptying was delayed after gastroplasty (% retention at 10 minutes ; $p < 0.05$) (Figure 7.8, Table 7.8).

(c) Pouch emptying: Liquid emptied faster from the pouch than solid. For both solid and liquid the 50% emptying times for the pouch were significantly shorter than for the whole stomach ($p < 0.001$) (Table 7.9). Visual examination of the computer images indicated that when the fluid was consumed, 5-90% of solid was immediately washed from the pouch into the main body of the stomach (Figure 7.9).

LEGEND FOR FIGURE 7.8

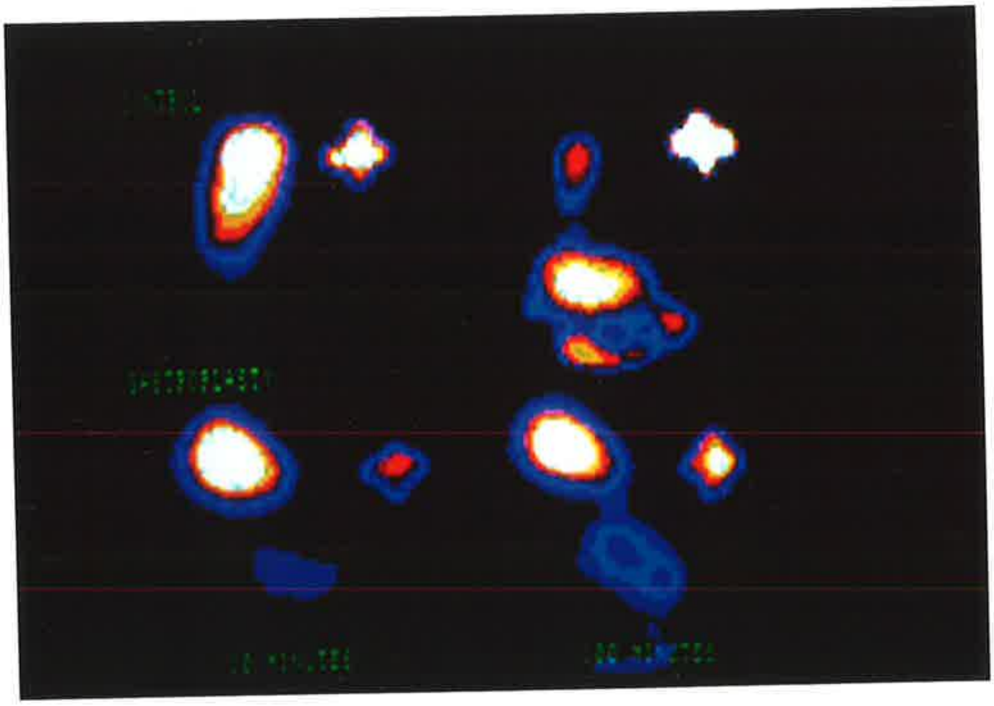
Solid (a) and liquid (b) emptying curves in 11 gastroplasty patients and in 22 control subjects. Data are mean values $\pm$ standard error of the mean.



Mean Values ± S.E.M.

LEGEND FOR FIGURE 7.9

Scintiphotos showing the distribution of solid food (^{99m}Tc-liver) in the stomach and intestine at 10 and 100 minutes after meal ingestion in a control subject and a gastroplasty patient. Earlier emptying of solid food and subsequent retention of solid in the partitioned pouch are evident in the gastroplasty patient.



(d) Relationships between solid and liquid emptying: A positive correlation existed between the whole stomach solid and liquid emptying rates in patients (50% emptying time, $r_s = .59$, $p < 0.05$). Solid and liquid emptying rates for the pouch were also directly related (50% emptying time, $r_s = .83$, $p < 0.01$). The whole stomach solid 50% emptying times and solid % retention at 100 minutes correlated directly with the solid % retention in the pouch at 100 minutes ($r_s = .75$, $p < 0.01$).

In patients there was no correlation between the extent of weight loss produced by the operation and the observed rates of solid or liquid emptying.

TABLE 7.7

SOLID EMPTYING IN CONTROL SUBJECTS AND GASTROPLASTY PATIENTS WHO RECEIVED A SOLID AND 10% DEXTROSE MEAL *

	Control	Gastroplasty	p value **
Number of subjects	22	11	
Lag period (min)	35 (9-69)	21 (7034)	< .001
25% emptying time (min)	55 (33-90)	37 (6-68)	< .005
50% emptying time (min)	76 (50-120)	94 (42-138)	n.s.
Retention at 50 min (%)	81 (50-100)	68 (43-83)	< .02
Retention at 100 min (%)	29 (13-65)	46 (10-69)	n.s.
Linear emptying rate (%/min)	1.2 (0.7-2.3)	0.4 (0.3-1.2)	< .001

* Data are median values and ranges in parentheses.

** n.s. - not significant p > 0.05.

TABLE 7.8

LIQUID EMPTYING IN CONTROL SUBJECTS AND GASTROPLASTY PATIENTS WHO RECEIVED A SOLID AND 10% DEXTROSE MEAL *

	Control	Gastroplasty	p value **
Number of subjects	22	11	
Retention at 10 min (%)	65 (56-93)	76 (50-100)	< .05
25% emptying time (min)	7 (1-17)	10 (6-34)	< .01
50% emptying time (min)	18 (11-35)	29 (10-49)	n.s.

* Data are median values and ranges in parentheses.

** n.s. - not significant p> 0.05

TABLE 7.9

SOLID AND LIQUID EMPTYING FOR THE WHOLE STOMACH AND THE POUCH IN GASTROPLASTY PATIENTS *

	Whole stomach	Pouch
Solid 50% emptying time (min)	94 (42-138)	15 (2-103)
Solid retention at 100 min (%)	46 (10-69)	25 (2-50)
Liquid 50% emptying time (min)	20 (10-49)	3 (1-28)

* Data are median values and ranges in parentheses.

CHAPTER 8

PERFORMANCE AND ANALYSIS OF THE GASTRIC EMPTYING TEST

8.1 SOLID AND LIQUID RADIONUCLIDE MARKERS.

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- 8.6.5 Assessment of the intragastric distribution of solids and liquids.

In this chapter the methods involved in the performance and analysis of the gastric emptying test are discussed.

8.1 SOLID AND LIQUID RADIONUCLIDE MARKERS

A variety of labelled food markers have been used to study liquid, semi-solid or solid phases of gastric emptying (Tables 3.1 and 3.2). Radionuclide markers should have a high labelling efficiency and must be stable throughout the duration of a study. In addition ideally they should be relatively inexpensive, have an energy suitable for imaging and be associated with a low radiation dose when administered. The selection of radionuclides to be used in the author's studies was based on these points. ^{113m}In (or ^{111m}In) bound to DTPA is water soluble, not absorbed from the gastrointestinal tract, stable and equilibrates rapidly with a liquid meal, making it an ideal liquid phase marker (Heading et al 1971, Wright et al 1981).

Many solid foods have been labelled with radionuclide markers (Table 3.2). The use of chicken liver labelled in-vivo with ^{99m}Tc-sulphur colloid was first described by Meyer et al (1976). After injection of ^{99m}Tc sulphur colloid into the wing vein of a live chicken, between 60-80% of the administered technetium is incorporated intracellularly into the Kupffer cells of the liver. In-vitro and in-vivo studies have previously demonstrated that the marker is tightly bound, resistant to peptic digestion and empties as solid particles (Meyer et al 1976, Christian et al 1980). In the author's in vitro study, the chicken liver also showed excellent (greater than 98%) stability as a solid food marker, in the presence of gastric juice. In-vivo labelled chicken liver is therefore an ideal solid phase marker.

Some laboratories have found it inconvenient to handle and inject live chickens and recently chicken liver has been surface labelled with ^{99m}Tc sulphur colloid by in vitro techniques involving injection of either fresh, commercial chicken liver at multiple sites (Wright et al 1981) or cubes of precooked liver (McCallum et al 1980, Christian et al 1981, Malmud et al, 1982). This form of chicken liver is less stable in the presence of gastric juice (Christian et al 1981, Malmud et al 1982), but some authors have claimed that it may be acceptable for routine gastric emptying tests (Wright et al 1981, Malmud et al 1982). ^{99m}Tc sulphur colloid incorporated into pureed meat (paté) may be more suitable (Christian et al 1981). The use of in vitro labelled chicken liver needs to be clarified by further studies.

Since solids and liquids are emptied from the stomach by different mechanisms in normal subjects, tests that can separately measure solids and liquids would be expected to provide a better assessment of gastric emptying than measurement of either solid or liquid alone. In some pathological states the advantages of tests which can measure gastric emptying of solids and liquids are already accepted. Delayed emptying of solid food and normal (Soergel et al 1980, Loo et al, 1984) or rapid emptying of liquids (Gulstrud et al 1980) may occur in some forms of gastroparesis and after gastric surgery.

Gastric emptying of liquid and solid meals may be measured in two separate tests, but with more advanced gamma cameras two nuclides of different energies may be used in the same meal. Since the original description by Heading et al (1976) several techniques have been used to measure simultaneously solid and liquid emptying (Moore et al 1981, Malmud et al 1982).

If the solid phase of the meal is labelled with ^{99m}Tc, the liquid marker for simultaneous use must have an energy different to ^{99m}Tc. In addition, because the liquid and solid phases of a meal may empty at very different rates, the precise definition of each phase is necessary for the accurate definition of the emptying of either phase or of the total meal.

As well as the studies by the author, several studies have utilized ^{99m}Tc and ^{113m}In simultaneously as solid and liquid markers respectively (Heading et al 1976, Tothill et al 1978). The combination of ^{99m}Tc and ^{111m}In has also been used (Moore et al 1981). <u>In vitro</u> experiments indicate that ^{113m}In or ^{111m}In-DTPA can be used simultaneously with ^{99m}Tc-chicken liver, without significant transfer of the liquid markers to the solid food (Moore et al 1981).

B. RADIATION DOSIMETRY

The calculated radiation burden for the author's gastric emptying study was approximately 596 millirads for the stomach and 6.0 millirads for the whole body (Table 6.4). These results are similar to those calculated by Siegel et al (1983), Wright et al (1981) and Heading et al (1976). This radiation burden is approximately the same as a single roentgenogram of the abdomen. Fluoroscopy results in a radiation dose of approximately 5000 millirads per minute of exposure. In this context the radiation dose from radionuclide gastric emptying studies is acceptable for single or sequential studies (3.2.4). The stomach, which is relatively radioresistant, has the highest absorbed dose. The radiation burden to other organs (small and large intestine, ovaries, testes and gallbladder) is considerably less (Siegel et al, 1983).

8.3 MEAL SIZE, COMPOSITION AND TIME FOR MEAL CONSUMPTION

Most meals are composed of both solid and liquid foods, containing protein, carbohydrate and fat. The test meal used by the author in all studies (a 100 g chicken liver/beef hamburger and usually 150 ml of 10% dextrose solution) was palatable and relatively representative of an ordinary meal. The temperature of the test meal was not standardised, but as discussed previously, slight variations probably have no significant effect on gastric emptying (1.3.1) (Teeter and Bass 1982, Bateman 1982). A test meal which is ingested orally should be appetizing, as the cephalic phase may be an important factor in the gastric motor response to a meal (Hunt, 1956). However in some other studies subjects have consumed unpalatable "foods" such as starch balls (Gulstrud et al 1980).

The meal size used by the author was standardized and relatively small, at approximately 250 g, unlike the large meals (up to 1700 g) used by some workers (Moore et al 1981), to allow gradual consumption by all subjects over a 5 minute period. The meal composed of both solid and liquid components and contained each of the essential nutrients : carbohydrate, protein and fat.

In radionuclide emptying studies the assumption is made that the labelled food also reflects the rate of emptying of the unlabelled meal contents. ^{113m}In-DTPA equilibrates rapidly in a liquid meal and is therefore representative of liquid emptying (Heading et al 1971).

Solid food is subjected to antral grinding before emptying as small particles (Meyer et al 1976). It is apparent from the results of recent studies (Holt et al 1982, Weiner et al 1981) in which the simultaneous emptying of two different radiolabelled solid foods in the same meal has been measured, that the various solid components of a meal empty at different rates, which are determined by both particle size and composition (1.2.3). Solid particles empty more slowly if they are larger and/or more resistant to fragmentation (Meyer et al 1981, Weiner et al 1981, Hinder and Kelly 1977). Therefore noodles, which are larger, but more easily triturated, empty more rapidly than cubes of chicken liver (Weiner et al 1981). Higher caloric density liquid meals empty more slowly than low calorie meals (Hunt and Stubbs, 1975). Therefore, in addition to standardizing meal composition for all studies, the solid meal was selected by the author to have similar properties to the solid marker i.e. the ground beef had a similar particle size and composition to chicken liver. The choice of a meat stew meal by other workers is also appropriate (Meyer et al 1976, Malmud et al 1982). However, because of different handling by the stomach, labelled chicken liver particles would not be expected to empty at the same rate as the bread, applesauce, salad or fruits with which it has been combined in some studies (Moore et al 1981, McCallum et al 1983), although the rate of emptying of the liver would be affected by these other non-labelled foods. It is possible that larger particles of nuclide labelled foods may more sensitively detect antral dysfunction, since they would require more grinding by the antrum than small particles such as ^{99m}Tc-polystyrene resin (Digenis et al, 1977) and human albumin macroaggregates (Calderon et al, 1971).

Variations in the extent of mastication also affect the particle size of the radiolabel and the rate of gastric emptying (Carlsson, 1974). This is a error inherent in all radionuclide methods, using digestible solids as markers, which may possibly be minimized by giving subjects strict instructions as to how thoroughly they should chew their food (as in the author's study on elderly subjects). The use of a uniform particulate, non-digestible tracer such as ^{99m}Tc-triethylenetetramine polystyrene resin (Digenis et al, 1977) or ^{99m}Tc-filter paper (Heading et al 1976) would have prevented this dependance on degree of mastication. From this discussion the difficulties of comparing studies when test meals differ in volume or composition, even when the same radionuclide markers are used are apparent.

The importance of standardizing the test meal composition is further highlighted by the recent isolation of peptide hormone-like substances from various foods (Zioudrou et al, 1979, Morley, 1982), which may act as exogenous regulators of gastrointestinal motility and hormone release. Peptic digestion of a variety of dietary proteins, such as casein and wheat gluten, results in the production of substances that have opiate-like activity (Zioudrou et al, 1979). Hydrolyzed gluten prolongs gastro-cecal transit time and increases plasma somatostatin-like activity in normal subjects and these effects are reversed by concomitant administration of naloxone (Morley et al, 1983). A peptide with thyrotropin-releasing hormone (TRH) activity is present in alfalfa and TRH has documented effects on gastrointestinal motility in experimental animals (Morley, 1982). The effects of dietary peptides on gastric motility in humans have not yet been investigated and are an exciting area of future research.

Solid foods can be either digestible or non-digestible. The emptying of non-digestible solids (usually dietary fibre derived from vegetables, grains or fruit), which are resistant to mechanical and chemical breakdown, was not assessed with the author's method. As discussed previously (3.2.2) an ^{131}I fibre marker (radiolabelled cellulose) has recently been developed (Carlson, 1978) and ^{99m}Tc-filter paper (Heading et al, 1976), ^{99m}Tc-bran (Sagar et al, 1983) and ^{99m}Tc-polystyrene resin (Digenis et al, 1977) have been used. Thus adequate γ-emitting markers are now available for each of the major components of an ordinary meal. As discussed previously, these studies have suggested that the rate of emptying of small particles of non-digestible solids is slightly different to that of digestible solids (Holt, et al, 1982, Carryer et al, 1982)

The time between commencement of meal ingestion and completion should be standardized in any gastric emptying study. In the author's study the solid meal was eaten during a 4-5 minute period, before all the liquid was consumed rapidly. This methodology attempted to ensure that the entire meal (solid and liquid) was present in the stomach before food entered the duodenum. Scanning was commenced before the onset of meal ingestion in order to determine accurately the maximum gastric isotopic content. In other studies inaccuracies have been introduced because ingestion times have been prolonged or variable (Moore et al, 1981), liquid has been consumed with the solid food (Christian et al, 1980) and scanning has been commenced only after meal completion (Heading et al, 1976). Prolongation of the time for meal consumption may be reflected in a delay for maximum count rates to be achieved (and a consequent alteration in the estimation of other parameters derived from this), and may preclude an accurate measurement of the "100% retention" value for liquid, because of rapid emptying of this part of the meal. For this latter reason it is essential that scanning is commenced at least at the time of initiation of meal ingestion and it is suggested that liquids are consumed after solids. Another reason for restricting the period of meal ingestion to as short a time as practicable is because it is clear that emptying responds to feedback inhibition from prior emptying, probably mediated by duodenal receptors (1.2.5).

8.4 DATA ACQUISITION

Gastric emptying tests should preferably be performed at a fixed time when the subject's stomach does not contain food. In the author's study, tests were performed at either 1000 hours, after the subject had fasted overnight or at 1230 hours after the subject had consumed a light, standard breakfast at 0730 hours. There was no difference between the gastric emptying rates at 1000 and 1230 hours in control subjects. Ideally the pattern of upper gastrointestinal motor activity at the time of commencement of meal ingestion should be known, as gastric emptying may be more rapid when a test meal is ingested during a period of motor activity than motor quiescence (Thompson et al, 1982), but clearly this is impractical for routine tests. The observed rate of gastric emptying depends on many variables and in the author's studies attempts were made to eliminate factors such as anxiety, vénepuncture and nicotine, which may all slow gastric emptying (Grimes and Goddard, 1978, Harrington and Ippoliti, 1979, Thompson et al, 1983). No subjects were receiving drugs known to influence gastrointestinal motility. These factors have apparently been neglected by some workers who have studied subjects taking medications which may have affected gastric emptying (Evans et al, 1981) and performed venepuncture throughout gastric emptying studies (Wright et al, 1983).

8.4.1 Subject position

In normal subjects gastric emptying (particularly of low calorie liquids) may be affected by the position of the subject (3.5.4). Slight variations in emptying may occur between the upright and supine positions (Tothill et al, 1980) and liquids may empty more rapidly when subjects lie on their right sides than on their left sides (Burn-Murdoch et al, 1980). In a meal containing liquid and fat, some separation of the fatty component may occur to form an upper layer on the gastric contents. This may contribute to slower emptying (Chang et al, 1968). In pathological states the effect of posture may be more marked. For example, after vagotomy and pyloroplasty, liquid meals empty abnormally rapidly when subjects are erect, but this is not apparent in the supine position (Gulstrud et al 1980). Since gastric emptying may be affected by posture and gravity, a standard and reproducible imaging position must be maintained in gastric emptying studies. Radionuclide emptying studies have been performed with the subject standing (MacGregor et al 1977, Christian et al 1980, Moore et al 1981, Weiner et al 1981), supine (Heading et al 1976, Tothill et al 1978, Malmud et al 1982, McCallum et al 1983) and seated, either upright (Hamilton et al 1980, Sheiner et al 1980, Dugas et al 1982) or at an angle (Jacobs et al 1982). These methodological differences may contribute to the discrepancies in results between groups of workers.

The author feels that the sitting or standing positions are more physiological and to be preferred for routine tests of gastric emptying. The seated upright position was used by the author (Figure 4.2) because, unlike the standing position it could be comfortably adopted for prolonged periods, even by patients who were unwell (subjects were able to read during the study), thereby reducing subject movement and permitting virtually continuous monitoring of both solid and liquid gastric emptying. At regular intervals (approximately every thirty minutes) data acquisition was interrupted to allow subjects to stand or sit away from the camera if they wished. This was designed to minimise any possibility of subject discomfort, due to prolonged sitting.

8.4.2 Position of detector

In the author's studies data were collected using a scintillation camera that was located behind the subject. The choice between the anterior (MacGregor et al 1977, Sheiner et al 1980, McCallum et al 1983) or posterior position (Dugas et al 1982) for a single detector is probably empirical, providing that adequate correction is made for radionuclide γ ray attenuation. The use of both anterior and posterior detectors (Tothill et al 1978, Jacobs et al 1982) confers some advantages in the accuracy of correction for depth changes but clearly it is much more expensive to employ two γ-cameras. These points are considered further in the discussion on attenuation correction (8.5.3).

8.4.3 Frequency and duration of data sampling

The frequency and times of data sampling should be the same for every subject and chosen with the expected emptying pattern in mind. Accurate definition of the shape of an emptying curve depends on frequent measurement during periods of rapid emptying and when alterations in the emptying pattern are likely to occur, and ideally on taking measurements until emptying is nearly complete. In the author's studies data were sampled at very frequent intervals (every 5 seconds) for the first ten minutes and thereafter at 50 second intervals for at least 2 hours. This methodology was designed particularly to permit an accurate estimation of liquid emptying (which was much more rapid than solid) the value for "100% retention", and the lag period for solids. As discussed previously many previous studies may be criticised because of infrequent data sampling (Moore et al 1981). In nearly all subjects the study was continued until at least 50% of the solid food had emptied but in some subjects with markedly delayed gastric emptying (as in diabetic gastroparesis (Figures 7.1 and 7.2), the solid 50% emptying time was not reached despite prolongation of the test.

8.5 CORRECTION FOR ERRORS IN GASTRIC EMPTYING STUDIES

8.5.1 Subject movement

In the author's studies a cross-shaped marker containing ^{99m}Tc was taped to the subject's back. Using the ^{99m}Tc marker the dynamic studies were realigned to a single reference point. This method facilitated determination of the region of interest and sometimes a single region of interest could be used for all parts of the study. Similar methods have been employed by other workers (Moore et al 1981).

8.5.2 Radionuclide decay

Because the gastric emptying studies were of at least 2 hours duration, correction of data for radionuclide decay (3.5.5) was required (Heading et al 1976, Christian et al 1980). This was particularly important for ^{113m}In, because of its shorter half life (approximately 100 minutes compared to 6 hours for ^{99m}Tc) and in subjects with markedly delayed gastric emptying.

8.5.3 Radionuclide gamma ray attenuation

(a) Errors due to attenuation

The need for correction for radionuclide gamma ray attenuation in gastric emptying studies is disputed (3.6.1). Although some workers agree that attenuation effects can be considerable in some subjects (Tothill et al 1978, 1980, Christian et al, 1980), others have stated that this effect is minimal (Harding et al, 1979, Rattner et al, 1981, Wright and Krinsky, 1982, Meyer et al, 1983, Van Deventer et al, 1983). The author's studies indicate that large errors in the measurement of gastric emptying can occur if correction for attenuation is not made. Using the geometric mean as the standard, the anterior detector overestimated the solid 50% emptying time by a mean of 15% (range 5-18) in 5 subjects, while the posterior detector underestimated this parameter by 15% (range

4-22) (Table 6.3). In 24 normal subjects the mean increase in 50% emptying time after correction for attenuation, using the lateral image method was 22% for solid and 17% for liquid (Table 6.4).

The information obtained from the lateral images explains the significant errors when using a single detector without correction (Figures 6.2, 6.3, 6.5). In 5 subjects the difference in the distance of the proximal and distal stomach from the posterior detector was large (mean difference 5.7 cm). These differences are significantly larger than those reported by other workers. Tothill et al (1978, 1980) used the ratio of the counts in the anterior region of interest (ROI) to the counts in the posterior ROI (A : P ratio) and found that a mean forward movement of the solid phase of one cm was exceeded in three of eight subjects studied. However the parameter these authors measured was the mean depth of food in the stomach as a whole and some food will have moved considerably more anteriorly than this mean value. Furthermore the first scan was taken approximately 10 minutes after food ingestion and some anterior movement of food would have already occurred. Meyer et al (1983) used both the anterior : posterior ratio method and the peak-to-scatter ratio method (P : S) to detect posterior-anterior movement of food. These workers reported up to 2-3 cm of anterior movement during the three hours of the test, confirming that significant anterior movement occurs in many studies. The use of the lateral image allows direct measurement rather than an indirect estimation of this movement.

Errors due to attenuation are less when higher energy nuclides such as ^{113m}In are employed (Tothill et al 1978). In the author's phantom studies the attenuation coefficients (μ) were 0.14 cm^{-1} for ^{99m}Tc and 0.09 cm^{-1} for ^{113m}In. The effects of radionuclide attenuation may be more marked with large meals (Christian et al 1980, Rattner et al 1981) but this was not assessed by the author. However as Tothill et al (1980), Christian et al (1980) and Meyer et al (1983) each incorporated ^{99m}Tc in the solid phase marker and used a meal size (185-455 g) similar to that used by the author, these factors are unlikely to account for discrepancies in the amount of anterior movement measured.

The author used posterior rather than anterior imaging as this was found to be a more comfortable position for the subject to adopt, if data were collected continuously for a prolonged time period. With posterior as opposed to anterior detection the distance of the stomach from the collimator is greater and it is theoretically possible that attenuation due to the spine may produce additional errors. However, as the errors obtained with anterior of posterior detection alone were very similar (mean error of 15% for the parameter of solid 50% emptying time) these factors do not appear to have significantly influenced the results (Table 6.3).

(b) Methods of attenuation correction

The most widely accepted method for correcting for depth attenuation has used the geometric mean of anterior and posterior data (Tothill et al 1978, 1980, Christian et al 1980, Jacobs et al, 1982) and a peak : scatter method has recently been applied (Meyer et al 1983, Van Deventer et al, 1983). As most Nuclear Medicine departments cannot afford to dedicate two camera/computer systems for 2-3 hours, the geometric mean method will require rotation of either the patient, or a single scintillation camera. This technique does not lend itself to frequent data sampling and rapid sequential anterior and posterior imaging is cumbersome and impractical. Tothill et al (1978) scanned the subject at regular intervals (10, 30, 60, 90 and 120 minutes) with a dual detector rectilinear scanner, while Christian et al (1980) imaged at 30 minute intervals with a single scintillation camera). Important information may be lost or measured inaccurately. This includes determination of the value for "100% retention", analysis of distribution changes within the stomach (Sheiner et al 1980, Jacobs et al 1982), estimation of the lag period (Jacobs et al, 1982) and monitoring the rapid emptying rates that may occur in liquid emptying, particularly in patients after gastric surgery (Heading et al, 1976).

The peak : scatter (P : S) method suffers from two sources of error when using ^{99m}Tc as the radionuclide (Meyer et al, 1983). As the gradient of the P : S ratio versus depth curve is small, particularly in the depth region typical for gastric emptying studies, small shifts in the P : S ratio can result in large changes in the distance estimate. Also the P : S ratio is potentially influenced by scattered radiation from activity in the small bowel into the gastric region of interest. These two factors probably limit the use of the P : S ratio in the measurement of depth in gastric emptying studies, using a lower energy nuclide such as ^{99m}Tc. As the P : S technique requires an additional image (either for posterior photopeak counts or for anterior scatter counts), its application to dual isotope studies is associated with infrequent data sampling.

(c) Lateral method of attenuation correction

The use of a lateral image to derive attenuation correction factors is a new technique which permits continuous monitoring of both solid and liquid gastric emptying using a single camera/computer system. This method requires the use of the tissue attenuation coefficents (μ) for the radionuclides used. The results of the phantom studies raise two important points that warrant discussion. These are the size of the phantom and the method used to determine the region of interest from which the counts are taken. If a point source of ^{99m}Tc and the total field of view counts were used a μ value of 0.12 cm^{-1} was obtained, but using an "extended" source and a region of interest based on a threshold method, the calculated value of μ ranged from 0.137 cm^{-1} to 0.146 cm^{-1}, depending on the lower threshold and the camera used (Table 6.2). Tothill et al (1980) used an extended volume and obtained a value of μ = 0.12 cm^{-1} for ^{99m}Tc. Although it is not clear in the text, it appears that these workers used the counts in the total field of view. If this is correct, the lower value for μ obtained by these authors is attributable to an increase in the proportion of scattered radiation accepted at depth. As a threshold method was used in the author's "in-vivo" studies the value of μ = 0.14 cm^{-1} for ^{99m}Tc is probably more appropriate. The lateral method of attenuation correction and other methods of attenuation correction assume μ to be constant within the subject. However, as the imaged area may contain significant amounts of air and bone, the potential limitations of this assumption must be recognised.

In the two camera studies the difference in characteristics of the two collimators resulted in significantly more scatter being collected in camera 1 at larger depths (and therefore a lower value of μ) than with camera 2 (Table 6.2). These different values of μ resulted in the geometric mean versus distance curve being non-symmetrical about the midpoint (Figure 6.1). This asymmetry decreased as the lower threshold was increased from 10 to 18 and the small variability of the geometric mean value (maximum variation from mean of – 4.3%) was considered to be acceptable for the validation study.

The lateral method for attenuation correction does not duplicate exactly the results obtained using the geometric mean but a much closer estimate is achieved than would be obtained with the posterior data without correction (Figures 6.2 and 6.4). Table 6.3, which gives the average values for the five subejcts shows improvements for the parameter of solid 50% emptying time, slope and lag period of 13%, 9% and 51% respectively.

The correction was less effective in one of the five subjects (E) studied with two cameras (Figure 6.3). This error can be attributed to the shape of the stomach in the lateral position (Figure 6.3B). Initial movement of food in the proximal stomach will be approximately perpendicular to the detector surface. Because of the direction of this movement there was a decrease in count rate of approximately 20% in the first 30 minutes in the posterior data after correction for attenuation, before any food was seen to leave the stomach (visual lag period = 68 minutes). This error can be reduced if small changes in count rate in the early part of the study are ignored. For example, in subject E (Figure 6.3) if the count rate at 20 minutes is used as the "100% retention" value, a 50% emptying time of 106 minutes is obtained, which is identical to the geometric mean value. In approximately 15% of the subjects studied the shape of the stomach resulted in movement of food perpendicular to the camera and small falls in count rate in the early part of the study occurred.

In the two camera studies for the posterior data the lag period was determined from both curve analysis of the posterior corrected data (LP) and also visually from the images (VLP). In three of the five subjects both the LP and VLP were similar results to that of the geometric mean value for lag period. In subject E the VLP approximated the geometric mean value, but the LP was much less (Figure 6.4). The data of this subject, as discussed earlier, were not adequately corrected for attenuation using the lateral method and this probably accounts for the discrepancy. In subject B, the VLP and the LP were similar, but were larger than the value obtained with the geometric mean method. The explanation for this finding is not clear.

It is apparent from these studies that attenuation correction is essential if an accurate measurement of gastric emptying is to be obtained with radionuclide methods. Despite some limitations, the lateral image method significantly reduces the errors due to attenuation in most subjects.

8.5.4 Correction for Compton scatter

Because of scatter, some gamma rays which originate within the stomach reach the collimator as lower energy photons. The magnitude of this error will be greater with increasing distance, but the author accounted for this by using attenuation correction factors derived from phantom studies, which incorporated correction for depth. In dual isotope radionuclide studies Compton scatter of the higher energy isotope into the lower energy window may occur (3.6.2), and if the two radionuclide energies are similar (such as ^{111m}In and ^{99m}Tc) there may be interference into both the low- and high-energy windows (Fisher et al 1982). The magnitude of this error is dependent on various factors : the relative quantities and energies of each radionuclide used, the properties of the scintillation camera and collimator, the width of the energy windows and possibly the anatomic shape of the stomach and the size of the gastric region of interest. The contribution of Compton scatter to the lower energy isotope can be minimized by using relatively lower quantities of the higher energy tracer. However in many gastric emptying studies larger amounts of high energy nuclides (such as ^{113m}In) are used to achieve good temporal resolution (Heading et al, 1976) and correction factors must be applied. The appropriate correction factor may be derived from studies with phantoms (Weiner et al, 1981), although a peak : scatter method has recently been used (Van Deventer et al, 1983).

The author found that approximately 21% of the ^{113m}In counts were scattered into the ^{99m}Tc window and this percentage was subtracted from the counts in the ^{99m}Tc window. The effects of changes in depth on Compton scatter were not assessed. Weiner et al (1981) found in phantom studies that the percentage of down-scatter from ^{113m}In into the ^{99m}Tc window ranged from 39% (fixed ROI) to 74% when down-scatter was considered in the whole field of view. This latter figure is of interest only if the percentage remaining in the stomach is calculated as a fraction of the total abdominal activity. The discrepancy in the figures for downscatter into a fixed ROI is likely to be accounted for by methodologic differences in the performance of the phantom studies; particularly in the characteristics of the collimator and the size of the phantom used. However both studies confirm the significant errors due to downscatter occur with the simultaneous use of ^{113m}In and ^{99m}Tc. Other published reports of gastric emptying of solid and liquid meal components labelled with two different radionuclides have provided no details on how correction for Compton scatter were made (Heading et al, 1976, Moore et al, 1981)

In view of the interaction of various factors in Compton scatter the potential limitations of the author's methods were recognised. Rapid time sampling (five second store every ten seconds) in the first ten minutes of the gastric emptying study, enabled the correction to be tested in patient studies. No significant change in the solid count rate was observed as liquid entered the stomach (Figure 6.9). Because of the faster emptying of the liquid meal (higher energy radionuclide) from the stomach, correction for Compton scatter was mainly required during the lag period of the solid study.

Van Deventer et al (1983) and Meyer et al (1983) used a P : S technique to correct for Compton scatter and attenuation. The probable deficiences of the P : S method have previously been discussed (8.5.3).

8.5.5 Septal penetration

As discussed previously (3.6.3), septal penetration may arise because some gamma rays which arise from the stomach may reach the collimator surface outside the gastric region of interest, to result in a degradation of the resolution of the image and possibly an underestimation of intragastric activity. The magnitude of this error is dependent on the characteristics of the collimator and is larger with higher energy radionuclides. This latter point is consistent with the author's observation that the region of interest was slightly larger with ^{113m}In, compared with a similar size ^{99m}Tc source.

The significance of septal penetration is uncertain and remains to be quantified by future studies. Attempts have been made to derive correction factors from phantom studies (Weiner et al, 1981, Meyer et al, 1973, Loo et al, 1984). Using a ^{113m}In- and ^{99m}Tc-labelled solid meal Meyer and coworkers (1983) have claimed that the combined error for Compton scatter and septal penetration was 30-40%. As previously discussed, the methods of derivation of these correction factors may be criticised and in addition these studies provided no direct information on the error due to septal penetration alone. A more recent study (Loo et al, 1984) indicates that the amount of septal penetration is a small and relatively constant percentage, with the variations in depth from the collimator and in the size of the gastric region of interest found in radionuclide gastric emptying tests. Consequently, if the counts in the region of interest at time zero are taken as 100% (as in the author's studies) the amount of septal penetration, which is constant throughout the study will not be a significant factor in the analysis, and correction will not be required.

8.6 ANALYSIS OF GASTRIC EMPTYING DATA

With the use of scintiscanning techniques the entire process of gastric isotope emptying can be recorded and quantitated. Some other methods of measurement of gastric emptying e.g. radiographic, are only capable of estimating the total emptying time (2.2).

The use of a "light pen" to identify the gastric region of interest is designed to allow selective quantification of γ emissions from this area, with ideally no overlap of duodenal or small bowel activity. The limitations of this attempted anatomical separation must be recognised, but the small interobserver variation indicates that this error was small. The observations of Van Deventer et al (1983) also suggest that the error from overlap using this technique is small. There have been many approaches to the analysis of gastric emptying data and results have been expressed in diverse ways. It is unclear which quantitative parameters are the most useful and valid to allow comparisons of emptying between meals or groups of subjects within a study and to facilitate comparisons between studies. Ideally a method of analysis should take into account the whole emptying curve and be used to derive one or two parameters which can be computed statistically. There is as yet no standard way of deriving meaningful numerical expressions to allow statistical comparisons between curves of different shapes.

8.6.1 Parameters of gastric emptying for liquids and solids

In the author's studies parameters of isotopic emptying were mainly obtained for curve inspection. For both solid and liquid the percentage of meal remaining in the stomach at varying times after meal completion was used to derive the times for 50% emptying (solid and liquid), the percentage retention at 100 minutes (solid) the lag period (solid), the linear emptying rate or slope (solid) and the percentage retention at 10 and 20 minutes (liquid) (Figure 6.9). This approach has been utilized in other studies (Delin et al 1978, McCallum et al 1981). The linear emptying rate of solid was calculated from a line of best fit drawn through the data points which followed the lag period (Figure 6.9). The duration of the lag period was checked by visual inspection of the computer images. The reason for selection of these parameters will now be discussed.

8.6.2 Liquid emptying

A major factor controlling the gastric emptying of liquids is the pressure gradient across the gastroduodenal junction which is largely dependent on fundal tone (1.2.2) (Wilbur and Kelly 1973, Kelly 1980). Based on this postulate liquid emptying may be expected to be a simple exponential or volume-dependent process and it has been represented as such by many workers (Hunt and Spurrell 1951, Griffith et al 1966, Harvey 1970, Tothill et al 1978, Sheiner et al 1980, Moore et al 1981). If this were the case, knowledge of the half-time would allow complete characterization of the entire emptying process and be an ideal quantitative parameter.

The author observed that liquid emptying was non-linear, with minimal lag period and a slope that decreased with time (Figure 4.10). However even in normal subjects, consuming water as the liquid meal, there was often significant deviation of the log plot of the entire emptying curve from a straight line; particularly because of differences at the beginning and end of the curve (Figure 4.11). With increasing caloric content of the liquid meal, liquid emptying assumed a more linear pattern (Figure 6.10). Previous workers who have defined liquid emptying as a monoexponential process have often sampled data infrequently (Hunt and Spurrell 1951) and/or used liquid meals with a low caloric/osmotic density (Chaudhuri 1974, Heading et al 1976). With liquid meals of low osmotic density liquid emptying is closer to a monoexponential pattern (Chaudhuri, 1974). Therefore the half-time derived from curve inspection as used by the author is a useful parameter for statistical comparisons, which has some physiological basis (particularly in normal subjects studied with low caloric liquid meals), but its use to confidently characterize the entire emptying process is inappropriate. Another error in the use exponential curves to describe liquid emptying (McHugh and Moran, 1979) has been the failure to extrapolate the derived curve to go through 100% at the time of maximum counts. If this is not done the estimated $T\frac{1}{2}$ (from the exponential fit) will not correspond to the time at which 50% of the meal has emptied (as derived from curve inspection). In pathological situations the variations in liquid emptying from a simple exponential may be even more marked. For example after truncal vagotomy and pyloroplasty (1.4.2) (Heading et al 1976, Gulstrud et al 1980, Sheiner et al 1980) and gastric bypass surgery (10.2) there may be very rapid initial emptying followed by a longer period of slow emptying. Therefore, despite having obviously different emptying patterns, half-emptying times may be similar to normal subjects (Sheiner et al 1980). To improve discrimination between normal and abnormal, some authors have used methods of analysis to describe early and late emptying components (Heading et al 1976). Like Colmer et al (1973) and Hinder and Bremmer (1978), the author recorded the amount emptied in the first 10 minutes as an arbitrary definition of the length of the early phase. Mackie et al (1982) and Gleysteen and Kalbfleisch (1981) have quantitated liquid emptying as a discontinuous, double-exponential process. With this method intermediate times of emptying are not quantitated.

8.6.3 Solid emptying

The author found that solid emptied in two distinct phases in control subjects: an initial lag period, followed by an emptying phase which approximated a linear pattern for at least the first 80 minutes

(Figure 4.10). These findings are in accordance with those of other workers (Sheiner et al 1980, Jacobs et al 1982, Meyer et al, 1983). The lag period, before food enters the duodenum reflects both redistribution of solid food from proximal stomach to antrum and the time taken to reduce some solid food to small particles. It is therefore dependent on fundal tone, stomach volume and antral motility. It has been demonstrated that the length of the lag phase depends on the consistency of the ingested food, being shorter with semi-solid than with solid meals due to a shorter time for antral filling (Jacobs et al 1982). Abnormalities of antral motility can be reflected in alterations in length of the lag phase (Sheiner et al 1980, Jacobs et al 1982) and after truncal vagotomy with antrectomy the duration of the lag phase is reduced (Mayer et al, 1982). Other authors (Wright et al 1983) however have not observed a lag period for solids. This probably reflects variations in meal composition, infrequent data sampling (McCallum et al, 1983), prolonged meal ingestion times (Moore et al, 1981) and lack of correction for changes in depth when a single detector is used (Wright et al, 1983). Linear emptying of solid after the lag period has been observed by many authors (Moore et al 1981, Heading et al 1976, Meyer et al, 1983) and probably occurs because of the ability of the antrum to maintain a relatively constant volume during emptying (Sheiner et al 1980, Moore et al 1981, Jacobs et al 1982).

Therefore the model of gastric emptying of solids being linear, after an initial lag period in normal subjects has some physiological basis. However its application to a description of gastric emptying of solids in pathological situations, such as markedly delayed or rapid emptying is less satisfactory. For example in some subjects with diabetic gastroparesis (Figure 7.1) the solid 50% emptying time was often not reached and it was often uncertain if the emptying phase fitted as well into a linear pattern.

8.6.4 Other models and parameters for solid and liquid emptying

In many gastric emptying studies (including the author's) in which emptying curves have been plotted by averaging values across subjects for specified time points it is possible that the shape of the mean curve may vary significantly from the shapes of individual curves. This was apparent when the linear emptying phase was not clearly evidence in the mean curves (Figure 6.12). Computation of t-tests betwen groups of meals for specified time points is also associated with some inaccuracies (Elashoff 1981). The limitations of the single or double exponential models for liquid emptying have previously been mentioned (8.6.2). Therefore, parameters derived in this way may not convey subtle abnormalities of gastric emptying. For these reasons many authors have attempted to fit a mathematical curve to gastric emptying data and used the estimated parameters of the curve in subsequent statistical comparisons between test meals or groups of subjects. Such models should ideally have parameters with a physiological basis, but this is clearly difficult in view of the complex and uncertain interaction of various factors i.e. propulsive and inhibitory forces and the anatomic structure of the stomach, in the determination of gastric emptying. Many models have been simplistic and unsatisfactory. For example Hopkins (1966) used the square root of the volume remaining in the stomach and Barber et al (1974) applied principal component analysis to the examination of gastric emptying curves.

Recently Elashoff et al (1982) recommended the use of the power exponential curve to describe gastric emptying of both solids and liquids. This is an empirical equation, which provides a reasonable fit to restricted parts of gastric emptying curves exhibiting either a monoexponential pattern, a pattern of initial slow and then later rapid emptying, or a pattern of initially rapid and then slower emptying. However, deficiences of the fit of the empirical curve to the data occur during meal ingestion when a rise to a peak occurs, or when a post-peak delay prior to emptying occurs.

Dugas et al (1982) have suggested that the area under the residue curve represents a more objective and quantifiable parameter for the testing of significant differences than values obtained by curve inspection or exponential half-emptying times for liquid.

The most appropriate measure(s) for quantitating gastric emptying can only be solved by future comparisons between methods. At present it is uncertain whether either the power exponential or residue areas method have significant advantages over the techniques used by the author.

8.6.5 Assessment of the intragastric distribution of solid and liquids

It is clear from the preceding discussion that the liquid and solid emptying patterns of net retention of isotope for the whole stomach against time, are more complex than theoretical mathematical curves. In addition, because of the large interindividual variations in gastric emptying rates, if whole stomach emptying times are relatively normal, abnormalities of the intragastric distribution of contents may not be appreciated. For example duodenogastric reflux or retropulsion of gastric contents from antrum into the proximal stomach may not be detected by these methods.

With radionuclide methodology a quantitative assessment of the intragastric distribution of solid and liquid meal components during gastric emptying is possible (Jian et al, 1982). Preliminary studies have indicated that this approach may be valuable in increasing the understanding of the roles of different parts of the stomach in the redistribution and emptying of food. Regions of interest may be selected to include the whole stomach, the stomach body and the antrum to obtain time-activity curves for all three areas. Such subdivision of the stomach on a computer screen may be useful despite not being anatomically accurate. A mid-gastric transverse band (which was frequently observed in the author's studies) has been used to separate gastric body and antrum (Sheiner et al 1980, Moore et al 1981). In normal subjects total gastric emptying parallels emptying from the body of the stomach, while antral activity, particularly for solids remains relatively constant (Moore et al 1981) and the lag period for solid reflects redistribution of contents between proximal stomach and antrum (Sheiner et al 1980). After vagotomy and pyloroplasty, antral filling and volume is reduced and proximal gastric vagotomy is associated with a delay in the redistribution of contents between proximal stomach and antrum (Sheiner et al 1980). Retropulsion of food from the antrum into the proximal stomach may occur in patients with systemic sclerosis (Barker et al 1979).

Recently, Jacobs et al (1982) were able to indirectly assess the frequency of gastric contractions (fundal and antral) by studying the changes in isotope activity within small regions of interest over the stomach.

CHAPTER 9

ASSESSMENT OF PHYSIOLOGICAL CHANGES IN GASTRIC EMPTYING

9.1 GASTRIC EMPTYING IN NORMAL SUBJECTS

9.1.1 Rates of solid and liquid emptying.

9.1.2 Effect of alterations in the calorie content of the liquid meal on solid and liquid emptying.

9.1.3 Reproducibility.

9.2 GASTRIC EMPTYING IN ELDERLY SUBJECTS

9.3 ASSESSMENT OF THE EFFECT OF THE MENSTRUAL CYCLE ON GASTRIC EMPTYING.

9.4 GASTRIC EMPTYING IN OBESE SUBJECTS.

9.4.1 Possible relationship between gastric emptying and obesity.

9.4.2 Gastric emptying in morbidly obese subjects.

9.4.3 Results of other studies assessing the relationship between gastric emptying and body weight.

9.4.4 Duodenal regulation of gastric emptying in obesity.

9.4.5 Conclusions.

In this chapter the results of gastric emptying studies performed by the author in control (age range 21-62 years), elderly (age range 70-84 years) and obese subjects are discussed. All of these studies have assessed the application of the radionuclide method to the study of physiological variations in gastric emptying.

9.1 GASTRIC EMPTYING IN CONTROL SUBJECTS

9.1.1 Rates of solid and liquid emptying

There was a large interindividual variation in both solid and liquid emptying rates in control subjects. For the solid and 10% dextrose solution meal, the mean times for 50% emptying were 78 minutes for solid (range 50-120) and 19 minutes for liquid (range 11-35). In Table 9.1, the results of the author's and some other dual isotopic studies are summarized. In accordance with the author's results, in mixed solid and liquid meals, liquids have been observed to empty more rapidly than digestible solids and a correlation between rates of solid and liquid emptying has been noted (Heading et al, 1976, Moore et al, 1981). Probably the slower emptying of solids relates to the prevention of the passage of larger food particles into the duodenum, by the mincing action of the antropyloric musculature (Meyer et al, 1976). However, the osmotic density of the food components is another factor of importance (which is discussed further under 9.1.2) and solid starch balls and isocaloric glucose solutions empty at similar rates (Gulstrud et al, 1980). In general, meals of larger weight and caloric density are associated with longer times of emptying for both solids and liquids (Table 9.1).

TABLE 9.1

SOLID AND LIQUID GASTRIC EMPTYING IN NORMAL SUBJECTS ASSESSED BY DUAL ISOTOPIC RADIONUCLIDE METHODS *

Author(s)	Meal size	Solid T50	Liquid T50	Meal composition
1. Fisher et al (1982)	380 g	100 min	30 min	Chicken liver, chicken stew, water
2. Heading et al (1976)	185 g	120 min	45 min	Cornflakes, sugar, milk, filter paper
3. Horowitz	250 g	78 min	19 min	Chicken liver, ground beef, dextose solution
4. MacGregor et al (1977)	425 g	107 min	25 min	Chicken liver, beef stew, water
5. Moore et al (1981)	300 g	77 min	38 min	Chicken liver, beef stew, orange juice
	900 g	146 min	81 min	Chicken liver, beef stew, applesauce, orange juice
	1692 g	277 min	178 min	Chicken liver, meats, fruits, vegetables, soup, wine (non-standardized)
6. Wright et al (1983)	410 g	87 min	63 min	Chicken liver, beef stew, "kool-aid"

* Data are mean values

As gastric emptying rates depend on numerous factors such as the size and composition of the test meal, normal ranges must be obtained by performing the same test on healthy subjects of a wide age range. As all the subjects studied by the author were ambulant outpatients, on no medication, the selection of this control group was appropriate. There is no reported study of gastric emptying in "disease controls" - hospitalized patients who have non-gastrointestinal disease. Such a study may be useful to increase the reliability of abnormal results in a patient population.

The relationship between gastric emptying rates and body weight is to be discussed further (9.4). Like Moore et al (1981), the author was unable to demonstrate any relationship between gastric emptying rates and body weight or surface area in normal subjects who were all within 20% of ideal weight. Lavigne et al (1978) have previously reported a slower rate of solid food emptying (^{99m}Tc-liver) in heavier subjects. Johansson and Ekelund (1976) used an indicator dilution technique and found that emptying of liquid was more rapid in heavier non-obese subjects.

Wright et al (1983), have recently reported, apparently for the first time that gastric emptying (^{99m}Tc-liver) is slightly slower in women (of all ages), compared to men. The author however could not demonstrate any difference in gastric emptying rates between men and women.

9.1.2 Effect of alterations in the caloric content of the liquid meal on solid and liquid emptying

The rate of gastric emptying for both solids and liquids is determined in part by the composition of the duodenal content (1.2.5) (Hunt and Stubbs, 1975, McHugh and Moran, 1979). Gastric emptying slows with increasing caloric content of a liquid meal and this delay is mediated by receptors in the duodenum that are sensitive to the osmotic effects and calcium binding properties of the digestion products of food (Hunt and McHugh, 1982, Hunt, 1983). The lateral intercellular space between duodenal enterocytes may be the site which initiates signals which slow gastric emptying (Hunt 1983) by poorly understood neural and/or hormonal mechanisms (Strunz, 1979, Valenzuela and DeFilippi, 1981). In primates (McHugh and Moran 1979) and humans (Brener et al, 1983) solutions of carbohydrate, protein and fat (0.2 - 1 kcal/ml) slow gastric emptying in direct proportion to their caloric concentration, so that the rate of delivery of energy to the duodenum is maintained at a constant level. In the majority of these studies (Hunt and Stubbs, 1975, McHugh and Moran, 1979, Brener et al, 1983) gastric emptying has been assessed with the serial test meal method of Hunt and Spurrell (1951). This intubation method provides information about the emptying of the liquid meal instilled and should be distinguished from the indicator-dilution method of George (1968) that gives information about the total volume of gastric contents (meal and secretions) (2.3). Emptying of solid meals or assessment of the intragastric distribution of the meal cannot be performed.

It is not clear what alterations in the mechanical activation of the proximal stomach, antrum or duodenum occur during gastric emptying (Rhodes et al, 1966). Stimulation of the duodenal receptors apparently decreases gastric propulsive activity and increases the resistance of the duodenum to filling (Weisbrodt et al, 1969).

The author's study was designed to assess the effect of alterations in the caloric/osmotic content of the liquid meal on the pattern of both solid and liquid emptying. The progressive increase in the calorie content of the liquid meal from 0 to 0.4 to 1 kcal/ml resulted in a delay in both solid and liquid emptying. For liquids a generalized slowing of the entire emptying curve was evident and emptying assumed a more linear pattern. The delay in solid emptying reflected a lengthening of the lag period, with no alteration in the rate of linear emptying (Figure 6.10, Table 6.5). This is the first study that has used radioisotopes to demonstrate that meals of approximately the same weight, but of different caloric density empty from the stomach at different rates. Previously, Moore et al (1981) have shown that meals of larger weight (300 G, 900 G, 1700 G) and calorie content (approximately 0.6 - 1.1 kcal/ml) are associated with longer emptying times for both solids and liquids, but the methodology used made it impossible to conclude whether these changes were due to the increased volume or caloric/osmotic density of the meals (or both).

In the author's study the observations of a delay in liquid emptying with increasing caloric/osmotic content of the liquid meal and the observation that the magnitude of the delay was inversely related to the caloric concentration are consistent with an inhibitory effect on gastric emptying mediated by duodenal receptors. Because water is a minimal stimulus to duodenal receptors, it's emptying closely approximated an exponential or volume-dependent process. Initial emptying of the two other liquid meals (10% dextrose, 25% dextrose) may have occurred before inhibition by duodenal receptors, but the initial rapid emptying of these meals was followed by a more linear phase (Figure 6.10) which presumably reflected regulation by duodenal receptors. These findings are consistent with observations in primates (McHugh and Moran, 1979) and humans (Brener et al, 1983) made with liquid meals and the use of intubation techniques.

The prolongation of the solid lag period with increasing calorie content of the liquid meal has not previously been demonstrated and may reflect either a delay in the redistribution of solid food from fundus to antrum and/or an alteration in the mixing function of the antrum. The author suggests that the delay in both solid and liquid emptying with increasing caloric content of the liquid meal probably reflected a reduction in proximal stomach tone mediated by the osmotic effects of the digestion products on duodenal receptors. The direct relationship that was observed between the liquid 50% emptying time and the duration of the lag period supports this hypothesis. A significant reduction in antral motility would be likely to have affected the linear emptying rate of solid. However, analysis of the distribution of solid and liquid food within the stomach, which is feasible with radionuclide methods (8.6.5) (Moore et al, 1981, Sheiner et al, 1980, Jacobs et al, 1982) would clarify this point. Previously, Fisher et al (1982), on the basis of the results of radionuclide studies have stated that gastric emptying of solid is not affected by the simultaneous ingestion of liquid, although gastric emptying of liquid is slowed by solid. Clearly this conclusion is incorrect as a general statement, and merely reflects the use of tap water as the liquid meal in their study, which was a minimal stimulus to duodenal receptors.

In the author's study the rate of delivery of calories to the duodenum (solid and liquid) was approximately 2.2 kcal/min in the two groups in which liquid calories were given with the solid food (Table 6.6, Figure 6.10). This result is similar to that obtained with liquid meals in humans of 2 kcal/min (Brener et al, 1983) In the group of subjects who received water, calories entered the duodenum only after the solid lag period, at least partly accounting for the slower initial delivery of calories in this group. After the lag period the rate of incorporation of solid calories (linear emptying rate) in this group was approximately 2.4 kcal/min. These values may be overestimations of the caloric density of food emptied into the duodenum, because of dilution, particularly of the liquid meal, by gastric secretion. This may explain why the derived values were slightly greater that those of Brener et al (1983).

It is clear that there is considerable variation between individuals in the rate of incorporation of calories. The possible implications of duodenal regulation in appetite and weight control will be discussed further (9.4.4). It also remains to be demonstrated whether major abnormalities in duodenal regulation occur in disease states. Preliminary studies in duodenal ulcer patients (Lam et al, 1982, Dubois and Castell, 1981) have suggested that this warrants further study.

9.1.3 Reproducibility

To the author's knowledge there have been no previous reproducibility studies using ^{99m}Tc-chicken liver and ^{113m}In-DTPA to measure gastric emptying, despite the previous use of these radionuclides in a number of published studies. Reproducibility studies using other radionuclides (Calderon et al, 1971, Chaudhuri, 1974, Heading et al, 1976, Sheiner et al, 1980) have shown a day-to-day variation in gastric emptying rates within normal subjects, as well as wide variations in rates between subjects. The implications of this variability have not been clarified, although it is clearly of major importance in assessing the sensitivity and specificity of gastric emptying tests - particularly in individual subjects where it may have restricted detection to only very abnormal emptying. The author assessed reproducibility during physiological studies to determine the effect of increasing the calorie content of the liquid component of the meal. In this study, the day-to-day variation in gastric emptying within individual subjects was not significant compared to the variation between subjects in each group and did not affect the sensitivity of the technique in its ability to discriminate between the three groups studied (Table 6.11). Also a small number of paired studies would be required to detect relatively minor changes in gastric emptying. Three paired studies would be needed to detect a difference in the solid 50% emptying time of 30%, five for a difference of 20% and 19 for a difference of 10% ($p = 0.05$).

Reproducibility of gastric emptying in pathological conditions (fast or slow emptying), in which variations in gastric emptying may be larger or smaller than in control subjects has not yet been studied and warrants further assessment. This point is discussed further with reference to the study of gastric emptying in diabetic autonomic neuropathy.

Differences in the results of studies in the same subject may reflect both technical problems (many of which have been previously discussed) and variations in gastric emptying. For this latter reason attempts were made to minimize stress or discomfort to the subjects, who were selected to be non-smokers and on no medication. Part of the within individual variability, particularly in the emptying of the liquid meal in the first few minutes, may be related to the existing pattern of gastric motor activity at the time of ingestion of the test meal. Although some studies (Rees et al, 1979, Gulstrud et al, 1980) have failed to show a clear relationship between gastric emptying and gastric motility, Thompson et al (1982) have recently demonstrated with a double sampling method, that the results of repeated oral glucose tolerance tests in normal subjects vary with the phase of fasting upper gut motor activity occurring at the time of glucose ingestion and that this difference is probably the result of variations in rates of gastric emptying; so that after fasting gastric emptying of liquids increases with the preexisting motor activity of the stomach. Clearly with current methods it is impractical to define the phase of upper gastrointestinal motor activity at the commencement of a gastric emptying study. Non-invasive external electrogastrographic techniques have recently been reported (Abell et al, 1983). Such techniques are technically challenging, particularly when attempting to obtain continuous recordings for extended periods and/or after eating. It is possible that further development of these methods may permit their clinical application.

9.2 GASTRIC EMPTYING IN ELDERLY SUBJECTS

The subjective impression that many physiological functions are retarded with age has been confirmed with direct measurements of function from the immune system (Nagel et al, 1981) to the musculoskeletal system (Nordin 1980). There is a paucity of information on the effect of ageing on the gastrointestinal tract. A reduction in oesophageal peristalsis in patients over 70 years of age has been documented (Hollis and Castell 1974). The absorption of nutrients such as 3-methylglucose, galactose, calcium and iron is reduced (Bender 1968, Montgomery et al, 1978) suggesting that some small intestinal transport processes may be less functional in the elderly. Transit time in the large intestine increases with age in some laboratory animals (Varga, 1976)

Most of the available data concerning age-related changes in the structure and function of the stomach pertain to the gastric mucosa. Atrophic changes in the gastric mucosa are common with increasing age (Andrews et al, 1967) and both basal and maximal (histamine stimulated) acid secretion are reduced (Baron, 1963). There is conflicting information, both on the effects of age on gastric emptying and the clinical implications of any change. Reviews of pharmacokinetics in the elderly have suggested that there is a significant delay in gastric emptying with increasing age (Bender, 1968, Crooks et al, 1976, Richey and Bender, 1977), mainly as a conclusion from the results of indirect studies reporting a delay in the rate of absorption of drugs in aged subjects (Nimmo 1976). However the validity of these studies has been questioned (Divoll et al, 1982, Greenblatt et al, 1979, Ochs et al, 1982). Some investigators who have directly measured the influence of age on gastric motility have found no change either in laboratory animals (Varga, 1976) or humans (Halvorsen et al, 1973, Van Liere and Northup, 1941, Wright et al, 1983) while others (Evans et al, 1981) have reported a marked delay in the emptying of liquids. Some of these studies have used subjects who were hospitalized (Van Liere and Northup 1941) or taking drugs (Evans et al 1981), or have employed relatively inaccurate methods to measure gastric emptying (Halvorsen et al, 1973, Van Liere and Northup, 1941) and it is therefore probable that variations in subject selection and gastric emptying techniques have contributed to the contradictory results.

An understanding of gastric emptying is of particular relevance to the selection of control subjects for gastric emptying studies and the study of drug absorption in the elderly. The author therefore studied the effect of age on gastric emptying using an accurate, physiological technique and appropriate subjects, in an attempt to clarify the discrepancy in these findings.

This study demonstrates that increasing age is associated with a reduction in gastric emptying of both solid and liquid meal components (Table 6.9, Figure 6.12). The delay in liquid emptying is in the early phase of gastric emptying. These findings did not relate to differences between the two groups in subject sex or body weight. The solid meal could be easily masticated over a 5 minute period by all elderly subjects and variations in the extent of mastication would be unlikely to have affected the results.

The emptying of solid and liquids is dependent on different portions of the stomach (1.2). A major factor controlling the emptying of liquids is the pressure gradient across the gastroduodenal junction, which is dependent on the tone of the proximal stomach (Wilbur and Kelly 1973). In contrast, digestible solids are emptied by a dual process : a grinding and mixing function of the antrum which reduces solid food to small particles and an emptying process by which the small particles are emptied with the liquid (Meyer et al 1976). The emptying process for solids may be dependent on propulsive forces mainly dependent on fundal tone. The delay of solid emptying in elderly subjects may therefore reflect either a reduction in mixing function of the antrum and/or a reduction in proximal stomach tone. The findings suggest that changes in function of the proximal stomach and possibly the antropyloric musculature accompany the ageing process.

A deficiency of all radionuclide methods, already discussed, (3.5) is that gastric emptying of the solid and liquid marker is measured and the effects of dilution by gastric secretion cannot be quantitated. This limitation applies particularly to water soluble radiolabelled markers and it is thought that gastric emptying of solids is more reliably evaluated and largely independent of the volume of intragastric liquid (Meyer et al, 1979). Therefore differences in gastric secretion rates could theoretically have influenced the results. However the delay in liquid emptying observed in the elderly subjects was apparent soon after meal completion when the effect of gastric secretion would be minimal. Also a reduction in gastric secretion may produce an apparent increase in gastric emptying rates - that is the percentage of the meal contents emptied in a given time (particularly liquid) would be greater. Therefore it is possible that the delay in gastric emptying in the elderly may have been underestimated.

Some previous investigators have found no change in gastric emptying with increasing age. Van Liere and Northup (1941) used fluoroscopy to measure gastric emptying of a high carbohydrate meal into which barium sulphate had been incorporated in 12 patients (mean age 71 years, range 58-84). It is not surprising that these authors found no correlation between gastric emptying and age, as contrast studies using barium have limited usefullness in determining even major alterations in gastric emptying because of their inability to quantitate emptying accurately (2.2). Halvorsen et al (1973) studied gastric emptying of water using an intubation technique in 19 subjects (age range 22-63 years). The small changes in liquid emptying may not have been apparent, both because of the non-physiological nature and inherent inaccuracies of the technique used and the smaller age range of the subjects studied.

More recent studies have used radioisotopes to measure gastric emptying. Wright et al (1983) found no correlation between solid or liquid gastric emptying rates and age in 31 control subjects, but the maximum age of any subject was 62 years. Evans et al (1981) found that gastric emptying of a liquid meal was considerably delayed in elderly patients, (mean 50% emptying time was 123 minutes, compared with 50 minutes in controls), but these findings must be viewed with uncertainty, as all of their elderly patients had multiple pathological conditions (6 out of 11 had Parkinson's disease) and the patients' physical illness(es) and the medications they were taking may have affected gastric emptying. For this reason the author selected a subject group which had no significant medical illness and was not taking any medication. The results of a study by Moore et al (1983) were recently published. These workers used a similar radionuclide method (the meal size was larger (900G) and the caloric density of the liquid meal was greater) and reported a delay in liquid emptying in fit, male elderly subjects. A smaller group consisting of 10 "elderly" and 10 control subjects was studied and perhaps because of this no change in solid food emptying was observed. In addition these authors observed a loss of liquid-solid differential emptying in elderly subjects, which clearly was not apparent in the present study (Table 9.2).

The author's results indicate that the effect of ageing should be taken into account when defining normal ranges, or in selecting control subjects for gastric emptying studies (Figure 6.13). For this reason in all other studies the majority of subjects studied were between 21 and 45 years of age (a range in which there is no significant variation in emptying rates).

The rate of gastric emptying is an important determinant of gastrointestinal drug absorption. In humans, absorption of drugs from the stomach is usually slow, irrespective of pH and whether the drug is acidic, basic or neutral. Most drugs are absorbed by passive diffusion in the proximal small bowel (Levine 1970). Consequently the rate of absorption of orally administered drugs and the time of onset and duration of a pharmacologic response, depend on the rate at which drugs are passed from the stomach to the proximal small bowel (Heading et al, 1973, Prescott et al, 1976). Delayed gastric emptying is most

TABLE 9.2

OTHER STUDIES EXAMINING THE RELATIONSHIP BETWEEN GASTRIC EMPTYING AND AGE

Investigators	Method	Age range of subjects	Results
1. Val Liere and Northup (1941)	Radiologic	58-84 yr	No change.
2. Halvorsen et al (1973)	Intubation	22-63 yr	No change.
3. Evans et al (1981)	Radionuclide ^{99m}Tc-liver ^{111m}In-DTPA	22-86 yr	Slower emptying of liquid in older subjects.
4. Wright et al (1983)	Radionuclide ^{99m}Tc-liver ^{111m}In-DTPA	20-62 yr.	No change in solid or liquid emptying.
5. Moore et al (1983)	Radionuclide ^{99m}Tc-liver ^{111m}In-DTPA	24-88 yr	Slower emptying of liquid in older men. No change in solid emptying.

likely to be significant clinically when a rapid onset of action of a drug is required, or with drugs such as methyl digoxin and penicillin, which are metabolized or degraded in the stomach (Nimmo, 1976).

Divoll et al (1982) noted that elderly subjects (mean age 71 years) have a slight, but significant reduction in oral paracetamol (acetaminophen) absorption. This observation is consistent with the delay in liquid emptying the author demonstrated, as paracetamol absorption correlates with the rate of gastric emptying (Heading et al, 1973). However there appears to be no significant alteration in the absorption kinetics of oral oxazepam, lorazepam (Greenblatt et al, 1979), diazepam (Ochs et al, 1982), tetracycline (Kramer et al, 1978) or levodopa (Evans et al, 1981) in elderly subjects and apart from paracetamol it seems likely that the slight delay in gastric emptying does not significantly affect drug absorption.

It must therefore be emphasized that the demonstrated changes in gastric emptying are small and unlikely to be of clinical significance. In fit, elderly subjects gastric emptying rates for solids and liquids are usually within the "normal" range found in younger control subjects, and the previously reported major delay in gastric emptying of liquid in elderly patients (Evans et al, 1981) was likely to be due to associated disease, stress and/or drug effects, rather than ageing itself.

As has been previously discussed, stress has been demonstrated to delay gastric emptying (Malagelada, 1982, Thompson et al, 1982) in normal subjects (1.3.2). From basic pharmacology it seems likely that many drugs: particularly anticholinergics, antihistamines, phenothiazines, sedatives, narcotics and antihypertensive agents may delay gastric emptying (Nimmo, 1976) and this has been supported by some studies in normal subjects (Gothoni et al, 1972, Nimmo et al, 1975, Hurwitz et al, 1982, Gibbons and Lant, 1975, Rees et al, 1980, Champion et al, 1982, Berkowitz and McCallum, 1980) (1.3.5). The effects of stress, illness and pharmacological agents on gastric emptying in the elderly have not been investigated and it is possible that these effects may be different from those demonstrated in younger subjects. The present study demonstrates that a radionuclide method can be easily applied to the study of gastric emptying in geriatric subjects.

9.3 THE EFFECT OF THE MENSTRUAL CYCLE ON GASTRIC EMPTYING

There has been considerable interest in the effects of sex steroid hormones on gastrointestinal function (Van Thiel et al 1976, 1977, Schultze and Christensen 1977, Wald et al 1981, 1982). Symptoms of constipation, abdominal distension and heartburn are common in pregnant women, but little objective information is available concerning the effects of steroid hormones (particularly progesterone and oestradiol) on the gastrointestinal tract.

A reduction in lower oesophageal sphincter pressure and an increased prevalence of gastrooesophageal reflux have been reported to occur in pregnancy (Van Thiel et al 1977), and may be mediated by smooth muscle inhibitory effects of progesterone and/or oestradiol (Bruce and Behsudi 1979, Fisher et al 1978, Schultze and Christensen, 1977). However, in humans Nelson et al (1983) could not demonstrate any effect of the normal menstrual cycle on oesophageal contractions, or lower oesophageal sphincter pressure.

Gall-bladder stasis has been demonstrated in pregnancy (Braverman 1980, Everson et al 1982) and Nilsson and Stattin (1967), using oral cholecystography, reported that gallbladder emptying may be impaired in the luteal phase of the normal menstrual cycle. However this latter observation could not be confirmed by recent workers (Everson et al 1982) who used ultrasound techniques.

It has been recently demonstrated (by breath hydrogen analysis of expired air after oral administration of lactulose) that gastro-caecal transit time is prolonged, both in the luteal phase of the normal menstrual cycle (Wald et al, 1981) and in pregnancy (Wald et al 1982, Everson et al 1983). The prolongation of transit time in pregnancy is most marked in the third trimester (Everson et al, 1983). As these studies have made no attempt to differentiate between the individual effects of gastric emptying and small intestinal transit, the effects of the menstrual cycle and pregnancy on gastric emptying were not known.

In the author's study, normal subjects who had previously been sterilized by ovarian tubal ligation were studied in order to eliminate the possibility of pregnancy occurring during radiation exposure. All these subjects had regular menstrual cycles prior to the study and an ovulatory cycle during the study documented by a rise in serum progesterone concentrations (Table 6.10) and onset of menstruation at the expected time. Parameters of solid and liquid emptying did not change between the follicular and luteal phases (Table 6.11), indicating that the normal menstrual cycle has no significant effect on gastric emptying and that the previously demonstrated prolongation of gastro-caecal transit time, reflected a delay in small intestinal transit.

It is possible that the stomach is less sensitive to sex steroids than the small intestine and some change in gastric emptying may be evident in pregnancy, (particularly in the third trimester) when progesterone and oestradiol levels are considerably higher. However Wald et al (1982), have observed that the prolongation of gastro-caecal transit in pregnancy is only slightly greater than in the luteal phase of the normal menstrual cycle, indicating that the effect of sex steroids may be relatively independent of the magnitude of the circulating levels. With radionuclide methods it is unethical in most circumstances to study normal pregnant subjects, because of the radiation exposure and because of this limitation no studies were performed by the author in pregnant subjects.

9.4 GASTRIC EMPTYING IN OBESE SUBJECTS

The pathophysiology of obesity is complex and poorly defined. Genetic, metabolic and neuropsychiatric factors have all been implicated (Soll et al 1975, DeLuise et al 1980). It is not clear whether gastrointestinal abnormalities can be implicated in the pathogenesis of obesity.

9.4.1 Possible relationship between gastric emptying and obesity

The close relationship between ingestion of food and satiety suggests that the long-term regulation of food intake is mediated partly through complex neural and hormonal reflexes resulting from the presence of food in the gastrointestinal tract (Gibbs and Smith 1978, Moran and McHugh 1982, Hunt 1980) (1.3.3). The gastric distension theory of post-prandial satiety emphasizes the importance of peripheral factors in appetite regulation and is based on the close association between fullness, stomach distension and cessation of feeding (Gibbs and Smith, 1978). This observation was made many years ago by Cannon and Washburn (1912). The theory was initially strengthened by the discovery of receptors in the wall of the stomach that were activated by distension (Paintal, 1954) and has been supported by recent studies (Smith et al, 1981). Some satiety signals have been demonstrated to arise from the duodenum (McHugh et al, 1982), but since gastric emptying is slowed by duodenal receptors (1.2.5) these effects could be mediated by indirect activation of the gastric distension mechanism.

Gastric distension is dependent on the rate of ingestion of food, intragastric pressure and the rate of gastric emptying. As discussed (1.2.2), the muscle of the proximal stomach is responsible for facilitating the accommodation of large volumes of ingested food within the gastric lumen, while maintaining low intragastric pressures. A short-lived receptive relaxation occurs prior to the arrival of the bolus of food and is followed by a more prolonged adaptive relaxation (Jahnberg, 1977). Both these receptors are mediated by non-cholinergic, non-adrenergic, partially dopaminergic vagal innervation (Valenzuela, 1976). Some gastrointestinal hormones released during a meal (1.2.2), such as cholecystokinin, pancreatic polypeptide, glucagon and gastrin may affect proximal stomach tone (Strunz, 1979). Cholecystokinin, glucagon, bombesin and somatostatin have been shown to have specific satiety effects when administered exogenously (Smith et al, 1981) and since the blood-brain barrier largely excludes circulating peptides (Morley et al, 1983), it is likely that the primary site of action of gut peptides with a satiety effect is in peripheral tissues. A recent study (Moran and McHugh, 1982) has suggested that cholecystokinin may produce its satiety effect by inhibiting gastric emptying and increasing gastric distension. Vagal efferent fibres probably provide the pathway by which the visceral effects of gut hormones are carried to the brain (Kral, 1981). The integration of visceral impulses caused by gastric distension takes place mainly in the hypothalamus and it is likely that opioid peptides and neuropeptides (calcitonin, bombesin, cholecystokinin) are involved in the central control of appetite (Morley and Levine, 1983).

It is possible that part of the anoretic action of appetite suppressants such as fenfluramine (Davies et al, 1983) and amphetamine (Bridges et al, 1976) is due to inhibition of gastric emptying.

Gastric emptying may therefore be important in the regulation of food intake and possibly in the development of obesity, through its effects on gastric distension. It has been postulated that retention of food may serve as a signal for satiety and that abnormally rapid gastric emptying may predispose to obesity (Johansson and Ekelund, 1976).

9.4.2 Gastric emptying in morbidly obese subjects

It is uncertain whether changes in gastric emptying could be contributory to the development of obesity. The author's study was initiated to determine whether gastric emptying in morbidly obese subjects is different from that in non-obese control subjects. In 15 obese subjects, who consumed a solid and water meal it was demonstrated that there is a delay in gastric emptying of solid due to prolongation of the lag period (Table 6.13, Figure 6.14) and that the duration of the lag period correlates directly with excess body weight (Figure 6.15). Similar results were apparent when data from all 22 subjects who received a solid and water meal were analysed (Table 6.16). In control subjects there was no relationship between gastric emptying rates and body weight parameters. The solid 50% emptying time was also prolonged in 7 obese subjects compared to 6 control subjects who received a solid and 25% dextrose meal, but significant prolongation of the lag period was not evident, perhaps because of the small number of subjects studied (Table 6.15).

The liquid 50% emptying time was greater in obese subjects (for both solid and water and solid and 25% dextrose meals) but this difference was statistically significant . The retention of liquid at 10 minutes after meal completion was greater in the obese subjects and this difference was statistically significant in the 22 subjects who received a solid and water meal (Table 6.16).

The delay of solid food emptying in obese subjects probably predominantly reflects a slower redistribution of solid food from proximal stomach to antrum, mediated by a reduction in proximal stomach tone. The suggestion of a delay in liquid emptying, particularly in the early phase of gastric emptying, is consistent with this postulate. An alternative explanation would be the occurrence of a significant increase in volume of the stomach in obese subjects. Although objective measurement of stomach volume could not be made with the author's method, stomach length was measured and was not significantly different between obese and control subjects. Finally it remains possible that the prolonged lag period could be due to a reduction in mixing function of the antrum ; the author's technique would not detect such changes.

9.4.3 Results of other studies assessing the relationship between gastric emptying and body weight

Previous studies on the relationship between gastric emptying and body weight have produced variable results (Table 9.3). Lavigne et al (1978) measured gastric emptying of ^{99m}Tc-liver in 9 control subjects who were within 20% of their ideal weight, and found an inverse linear relationship in which gastric emptying of solid food was slower in subjects with greater body weight or surface area. Other investigators (Moore et al, 1981) who studied 10 normal subjects and Wright et al (1981) who studied 46 obese patients have used similar radionuclide methods and found no correlation between gastric emptying rates of solid or liquid and body weight. Johansson and Ekelund (1976) used a liquid test meal and multiple indicator dilution technique to study gastric emptying in 10 normal subjects and found a more rapid rate of gastric emptying in heavier subjects and that emptying was directly proportional to body weight. Lavigne et al (1978) studied one morbidly obese patient and found an abnormal (non-linear) pattern of gastric emptying. Apart from this subject, in all four of these studies the subjects studied were within the normal range of body weight (Lavigne et al 1978), Moore et al 1981, Johansson and Ekelund, 1976) or only moderately obese (Wright et al 1981, 1983). All the author's subjects were very obese (> 60% in excess of ideal weight) and demonstrated a linear pattern of solid emptying after the prolonged lag period.

The author's results contradict the findings of a recent study by Wright et al (1983). These workers used a similar dual isotope technique and reported more rapid emptying of a solid meal in obese patients, in contrast to their earlier report (Wright et al, 1981). They studied a larger number (46 obese, 31 control) of subjects. The obese subjects were from 30-107% in excess of ideal weight and were therefore a less obese group than those studied by the author.

However methodologic criticisms of the studies by Wright et al 1981, 1983) and Lavigne et al (1978) raise questions as to the validity of their conclusions and probably contribute to the discrepancy in the results. For example, in the study by Wright et al (1983), corrections for radionuclide attenuation and Compton scatter were not made, data were sampled relatively infrequently, venepuncture was performed throughout gastric emptying studies, and a lag period for solid was not observed (probably because of the lack of correction for attenuation and infrequent data sampling). As discussed previously (8.5.3) errors due to attenuation may be more marked in obese subjects. It also remains possible that posture (supine, seated or erect position) may affect gastric emptying in obese subjects and account for some of the discrepancy in the results of different workers.

9.4.4 Duodenal regulation of gastric emptying in obesity

As discussed (9.1.2), previous investigators using non-isotopic fluid meals and repeated aspiration of gastric contents have demonstrated a duodenal response to dietary carbohydrate, fat and protein with resultant slowing of gastric emptying (Hunt and Stubbs, 1975). The regulatory function of these postulated duodenal receptors is such that gastric emptying slows in proportion to the caloric content of a liquid meal (McHugh and Moran, 1979, Brener et al, 1983). In primates the direct relationship between calorie content and gastric emptying is lost after energy density exceeds 1 kcal/ml, so that food leaves the stomach

TABLE 9.3

OTHER STUDIES EXAMINING THE RELATIONSHIP BETWEEN GASTRIC EMPTYING AND BODY WEIGHT

Investigators	Method	Weight range of subjects	Results
1. Johansson & Ekelund (1976)	Indicator dilution technique	58-95 kg	Faster emptying of liquid in heavier subjects.
2. Lavigne et al (1978)	Radionuclide ^{99m}Tc-liver	59-93 kg	Slower emptying of solid in heavier subjects. Liquid emptying not measured.
3. Moore et al (1981)	Radionuclide ^{99m}Tc-liver ^{111m}In-DTPA	62-106 kg	No change.
4. Wright et al (1981)	Radionuclide ^{99m}Tc-liver ^{111m}In-DTPA	Not stated	No change.
5. Wright et al (1983)	Radionuclide ^{99m}Tc-liver ^{111m}In-DTPA	75-209 kg	Faster emptying of solid in obese subjects. No change in liquid emptying.

relatively more rapidly (McHugh and Moran, 1979). Hunt et al (1975) examined the dietary records of subjects of various weights and suggested that obese subjects ate a more energy dense meal, which may increase the rate of transfer of calories from the stomach to the duodenum. Relatively rapid gastric emptying could also be secondary to abnormal duodenal regulation. This latter possibly was assessed by the author in preliminary studies in 7 obese subjects who received both a solid and water and a solid and 25% dextrose meal. In these subjects solid and liquid emptying (50% emptying times) were delayed by the 25% dextrose and solid meal (Table 6.14). The solid lag period was prolonged by 25% dextrose (mean 55 minutes v's 43 minutes), but this difference was not statistically significant, probably because of the small number of subjects studied. There was no change in the linear emptying rate of solid. These changes are therefore very similar to those demonstrated in control subjects (Table 6.9) and, as discussed previously, are likely to represent a delay in gastric emptying mediated by duodenal receptors. These preliminary findings suggest that the duodenal osmoreceptor mechanisms are not defective in obesity.

It is not clear from the author's studies, or from previous data whether the abnormal emptying pattern in the morbidly obese is intrinsic to the obese or secondary to weight gain. Wright et al (1983) found no change in emptying rates in 4 obese subjects who were studied before and after significant weight loss. The author has attempted to address this question by studies currently in progress on patients who have undergone jaw-wiring for the treatment of morbid obesity. To date no patient has lost weight to within the normal range and paired studies have been performed in only 5 subjects.

9.4.5 Conclusions

The author has demonstrated significant abnormalities of gastric emptying in morbidly obese subjects. This was a tendency for slower, rather than the more rapid emptying that may have been expected. These findings differ from those of other workers (Wright et al 1983, Johansson and Ekelund, 1976) probably due to methodological discrepancies. The demonstrated delay in gastric emptying was relatively small and in most obese subjects emptying rates lay within the range of emptying rates observed in control subjects. It therefore seems unlikely that changes in gastric emptying (primary or secondary) are a significant factor in the pathogenesis of obesity.

CHAPTER 10

GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY AND AFTER GASTRIC SURGERY FOR MORBID OBESITY

The author studied gastric emptying in two situations of pathological gastric emptying - diabetic autonomic neuropathy and after gastric surgery for obesity. In the diabetics the acute and chronic effects of domperidone on gastric emptying and symptoms of gastroparesis were assessed. The effects on gastric emptying of two operations - gastric bypass and gastroplasty, which are widely performed for the treatment of morbid obesity were studied. The results of these studies are discussed in this chapter.

10.1 ACUTE AND CHRONIC EFFECTS OF DOMPERIDONE ON GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY

Gastrointestinal symptoms such as vomiting, constipation, diarrhoea and faecal incontinence occur frequently in diabetes mellitus. A reduction in gastric motility in diabetes was first clearly described by Rundles (1945). Later Kassander (1958) introduced the term "gastroparesis diabeticorum" to describe gastric atony and delayed emptying in diabetes mellitus. In one survey of diabetic outpatients, 29% suffered from nausea and vomiting (Feldman and Schiller, 1983).

Diabetic gastroparesis is most often found in longstanding insulin-dependent diabetes and is frequently associated with evidence of autonomic nerve dysfunction, including impairment of cardiovascular reflexes, bladder and sexual function (Campbell et al 1977, Ewing and Clarke, 1982) and complications of peripheral neuropathy, nephropathy and retinopathy (Feldman and Schiller, 1983). Delayed gastric emptying is usually attributed to vagal damage, occurring as part of a generalized autonomic neuropathy (Fox and Behar, 1980, Malagelada, et al 1980), although other contributory factors such as hyperglycaemia

(MacGregor et al, 1976) and hormonal changes (Aylett, 1962) have been suggested. On cardiovascular reflex tests 20-40% of all diabetics have abnormalities of autonomic nerve function (Ewing and Clarke, 1982). Parasympathetic damage probably occurs earlier than sympathetic damage.

There is little data regarding the proportion of diabetics who have delayed gastric emptying, partly because of the previous lack of sensitive (Zitomer, 1968) and simple tests (Dotevall, 1961, Fox and Behar, 1980, Malagelada et al, 1980) with which to investigate patients and the fact that asymptomatic patients may have abnormalities (Kassander, 1958, Feldman and Schiller, 1983, Goyal and Spiro, 1971, Wooten and Meriwether, 1961). Asymptomatic gastroparesis may contribute to poor glycaemic control (Wooten and Meriwether, 1961).

The treatment of diabetic gastroparesis is unsatisfactory. Drugs such as metoclopramide and bethanechol have been shown to stimulate gastric motor activity (Fox and Behar, 1980, Malagelada et al, 1980), probably through a cholinergic mediated action on gastric smooth muscle (Hay and Man, 1979), but while the acute stimulatory effects of these drugs on gastric motility are well established, their efficacy in the long-term is uncertain and mainly based on the results of uncontrolled trials (Brownlee and Kroopf, 1974, Longstreth et al, 1977). Metoclopramide, which has been the most extensively studied of these drugs also has a central antiemetic effect which may be responsible for improvement in symptoms (Hay and Man, 1979). In many studies (Brownlee and Kroopf, 1974, Longstreth et al, 1977, Perkel et al, 1979) measurement of gastric emptying before and after a treatment period has not been performed and consequently a relationship between improvement in symptoms and alterations in motility has not been established. Up to 10% of patients given metoclopramide develop significant neurological side effects (Hay and Man, 1979).

Domperidone is a new gastrokinetic drug which is a potent peripheral dopamine antagonist like metoclopramide, but lacks cholinergic activity and does not cross the blood-brain barrier in significant amounts; consequently neurological side effects are rare (Brogden et al, 1982). Reports have indicated that domperidone is effective in the treatment of a variety of gastrointestinal disorders such as nausea and vomiting (Brogden et al, 1982) oesophageal reflux (Valenzuela et al, 1981) and dyspepsia (Nagler and Miskovitz, 1981).

Radionuclide gastric emptying tests have been recently applied in a small number of studies (Campbell et al, 1977, Domstad et al, 1980, Kim et al, 1981, Scarpello et al, 1976, Snape et al, 1982, Soergel et al, 1980) to both the diagnosis of diabetic gastroparesis and the objective assessment of the response to pharmacologic treatment, because of their distinct advantages over the previously used radiologic (Zitomer, 1968) and intubation methods (Dotevall, 1961, Fox and Behar, 1980, Malagelada et al, 1980). These studies have produced conflicting results - Scarpello et al (1976) reported no change in solid food emptying in diabetics with or without autonomic neuropathy, while other workers (Campbell et al, 1977, Domstad et al, 1980, Kim et al, 1982, Snape et al, 1982, Soergel et al, 1980) who have mainly assessed symptomatic patients, have demonstrated a delay in either solid and/or liquid emptying. Both objective improvement in gastric emptying after metoclopramide (Campbell et al, 1977, Domstad et al, 1980, Kim et al, 1980, Snape et al, 1982, Loo et al, 1984) or no significant change, despite an improvement in symptoms (Soergel et al, 1980) have been reported, suggesting that both local and centrally mediated effects of the drug may be important. Most of these studies have examined acute administration only. Snape et al (1982) recently demonstrated an improvement in both symptoms and gastric emptying of liquids in diabetics after treatment with oral metoclopramide for three weeks, but there was a poor correlation betwen improvement in symptoms and gastric emptying.

In any normal or diabetic subject glycaemic control depends both on the precision of insulin delivery and the rate of absorption of calories. Gastric emptying is likely to be of major importance in glycaemic control. In normal individuals, variations in glucose tolerance correlate with the inherent periodicity of gastric motor activity and gastric emptying, and administration of both metoclopramide or hysocine butylbromide reduces the intraindividual variation in glucose tolerance tests (Thompson et al, 1982). If changes in gastric emptying in normal subjects can cause significant variations in glucose tolerance, it is probable that gastric emptying in diabetics is of major importance in glycaemic control. Diabetics may develop unexplained hypoglycaemia as a manifestation of delayed gastric emptying (Wooten and Meriwether, 1961) and treatment with metoclopramide may improve diabetic control in uncontrolled insulin dependent diabetes associated with gastroparesis (Longstreth et al, 1977, Muls and Lamberigts, 1981). It has been suggested (Jenkins et al, 1982, Ray et al, 1983) that the demonstrated delay in gastric emptying produced by guar gum in normal subjects (Holt et al, 1979, Leatherdate et al, 1982) may be one of the mechanisms responsible for the observed beneficial effect of gel-fibre on glycaemic control in non-insulin dependent diabetics. Guar may also reduce the rate of intestinal glucose absorption partly by causing an increased viscosity of the luminal contents (Gassull et al, 1976, Leatherdale et al, 1982). As these patients have delayed insulin release (Jenkins et al, 1982), these observations are consistent with the hypothesis that glycaemic control in both normal and diabetic subjects will be improved if glucose absorption correlates with insulin delivery. By contrast, insulin dependent diabetics are unable to regulate plasma insulin levels in response to variations in blood glucose. It is therefore possible that glycaemic control will also be improved in these patients when variations in gastric emptying are diminished, so that gastric emptying (and the resulting energy absorption) is synchronized with the action of insulin absorbed from the injection site. The effect of gastrokinetic drugs on glycaemic control has however not previously been studied.

Delayed gastric emptying in diabetes mellitus is therefore a relatively common form of symptomatic chronic gastoparesis (1.4) in which : (1) radionuclide methods may have particular diagnostic application and (2) the efficacy of previously used gastrokinetic drugs is uncertain. Gastoparesis may also be a factor in glycaemic control in both symptomatic and asymptomatic patients. With specific reference to these points, the author studied gastric emptying in diabetics with autonomic neuropathy and assessed the acute and chronic effects of oral domperidone on gastric emptying, symptoms of gastroparesis and glycaemic control.

This study demonstrated that gastric emptying of solid and liquid was slower in diabetics than controls. Although the diabetics were not selected on the basis of gastrointestinal symptoms, in the majority gastric emptying rates for both solids and liquids lay outside the range of values found in control subjects (Figure 7.2, Table 7.2). This reaffirms recent evidence on the sensitivity of scintigraphic gastric emptying techniques in diabetic gastroparesis (Campbell et al, 1977, Snape et al, 1982, Soergel et al, 1980, Loo et al, 1984). Previously, a delay in liquid emptying in small number of symptomatic patients with diabetic gastroparesis had been demonstrated by radiologic or intubation methods (Aylett, 1962, Zitomer et al, 1968, Dotevall, 1961). It is possible, but unlikely (because of the 10 hour fast), that the observed delay of liquid emptying in the diabetics may have reflected a greater gastric residual volume at the time of the study. Determination of the gastric residual volume by aspiration was not performed because of potential effects on gastric motility.

Previous studies in diabetic gastroparesis (Fox and Behar, 1980, Malagelada et al, 1980) have demonstrated that during fasting there is a marked reduction in antral motor activity and an absence of interdigestive myoelectric complexes. The latter may lead to the accumulation of non-digestible solids in the stomach of these patients (Feldman and Schiller, 1983). The findings in this study of a delay in solid and liquid emptying in most diabetic patients implies that both proximal stomach and antropyloric motor acitivity are diminished in diabetic autonomic neuropathy, even in patients without upper gastrointestinal symptoms. Campbell et al (1977) have reported that in diabetics without gastric stasis the normal differentation between solid and liquid emptying is impaired,so that solid emptying is relatively faster and they suggested that an abnormality of antral motility, not attributable to a vagal neuropathy may have been responsible. In the author's study however, the relationship between solid and liquid emptying was maintained, and in all diabetics solid emptied slower than liquid.

The evidence favouring a neural regulatory disorder rather than primary smooth muscle defect as the aetiology of diabetic gastroparesis is supported by the fact that contractile activity can be restored in part by gastrokinetic drugs such as metoclopramide and bethanechol (Fox and Behar, 1980, Malagelada et al, 1980). In the treatment of symptomatic gastroparesis, metoclopramide, which has both central and peripheral effects, has been the most closely studied drug. In the gastrointestinal tract its mechanism of action is probably related to local release of acetylcholine, or by sensitizing smooth muscle cells to this transmitter (Hay and Man, 1979), but it may also act as a dopamine antagonist and reduce the inhibitory effects of dopamine on gastric motility (Peringer et al, 1976). The possible dependency of metoclopramide on tissue acetylcholine stores, or on sympathetic tone has been postulated as the explanation for the observed variability of the symptomatic response to the drug (Hay and Man, 1979). Perkel et al (1979) showed that symptoms of gastric stasis were improved with metoclopramide, but did not differentiate the antiemetic effect from the effect on gastric emptying.

The precise mechanism of action of domperidone on the gastrointestinal tract is uncertain. Dopamine receptors are thought to be present in the stomach and dopamine inhibits gastric motility, particularly the adaptive relaxation of the proximal stomach which occurs in response to ingestion of a meal (Shuurkes and Van Neuten, 1981, Valenzuela, 1976). Acute administration of domperidone decreases adaptive relaxation (Bateman et al, 1982), increases gastric emptying of liquid meals in normal subjects (Baeyens et al, 1979, Broekart, 1979, DeShepper et al, 1978) and in subjects with gastro-oesophageal reflux (Valenzuela et al, 1981). The minimal data on its effects on the emptying of solid meals suggests that it may be less effective in increasing gastric emptying of solids (Valenzuela et al, 1981, Akkermans et al, 1983). Heer et al (1980) successfully treated a diabetic with gastroparesis and colonic dilatation with intravenous domperidone and have subsequently demonstrated that acute administration of intravenous domperidone to 6 patients with gastroparesis, increased gastric emptying of the liquid (^{99m}Tc-DTPA) component of a mixed solid and liquid meal (Heer et al, 1983). Two of 3 diabetics treated with oral domperidone by Nagler and Miskovitz (1981) experienced improvement in symptoms with domperidone, but objective measurement of gastric emptying was not performed.

In the author's study, acute administration of oral domperidone increased both solid and liquid gastric emptying in diabetics with autonomic neuropathy (Figures 7.3 and 7.4, Table 7.3) and the response to domperidone was most marked in those patients with the greatest delay in gastric emptying. The regression lines of change in lag period and liquid 50% emptying time indicate that domperidone improved gastric emptying rates towards a basal value which lay within the normal range (Figure 7.5). The lag period for solid which reflects redistribution of solid food from proximal stomach to antrum and the time taken for the antrum to reduce some solid food to small particles, was markedly reduced by domperidone. After chronic admininstration, domperidone had no significant effect on solid emptying but was still effective in increasing liquid emptying (Figures 7.3 and 7.4). The reason for this diminished effect is uncertain. The present results concur with the recent suggestion (Akkermans et al, 1983) that the drug acts predominantly by increasing proximal stomach tone and that secondary to this more rapid redistribution of solid food and an increased volume of the antral contents results. The increase in tone of the proximal stomach results in faster emptying of liquids. A possible way of investigating the importance of the tolerance of the antral smooth muscle to domperidone, would be the addition of bethanechol after the chronic administration of domperidone.

The author's study confirmed the poor correlation between symptoms of gastroparesis (Table 7.1) and gastric emptying abnormalities in diabetics with autonomic neuropathy (Loo et al, 1984). Symptoms of gastoparesis were significantly improved during domperidone treatment, probably reflecting the improvement in gastric emptying. However, this result should be interpreted with caution in the absence of a placebo control. A possible beneficial effect on constipation has also been reported with metoclopramide (Snape et al, 1982). It is also possible that domperidone has a central antiemetic effect, but the lack of correlation between symptoms and gastric emptying rates after domperidone was not unexpected, since it probably has less central effects than metoclopramide.

The observations that the 3 hour post-prandial blood glucose level was lower after gastric emptying had been increased with domperidone, and that insulin requirements were diminished in some patients on chronic domperidone therapy are consistent with a change in rates of glucose absorption secondary to more rapid gastric emptying. As blood glucose concentrations were not measured before or during the gastric emptying study, and 24 hour blood glucose profiles were not performed, the effects of domperidone on glycaemic control are difficult to assess. For example it is possible that some patients may have required a compensatory increase in short acting insulin to counter an earlier (1-2 hour) post-prandial peak in blood glucose levels. In normal subjects, Thompson et al (1982) have demonstrated that plasma glucose levels between 20 and 50 minutes (50 g oral glucose tolerance test) are significantly greater for glucose tolerance tests performed during gut activity than for those during quiescence. It is therefore theoretically possible that gastrokinetic drugs could be used in insulin dependent diabetics to improve gastric emptying, reduce intraindividual variations in gastric emptying and improve the coordination between glucose absorption and insulin delivery.

There are therefore clear extensions and limitations of this study. Blood glucose levels were not measured before or during the gastric emptying study, because of possible effects of venepuncture on gastric emptying, which would have precluded a comparison with the control subjects. Hyperglycaemia has been demonstrated to delay gastric emptying in normal subjects (MacGregor et al, 1976). It is not known whether this effect occurs in diabetic subjects and whether any action is additive to the effects of autonomic neuropathy. It is therefore possible that high preprandial blood glucose levels may delay gastric emptying. Possible variation in drug absorption due to changes in gastric emptying were not assessed because of the necessity for venepuncture. In healthy volunteers peak plasma concentrations of domperidone are attained within 30 minutes after oral adminstration (Heykants et al, 1981). In normal subjects domperidone does not accumulate on repeated administration, or induce its own metabolism and because renal clearance of the drug is small compared to the total plasma clearance, accumulation should not occur in renal dysfunction (Brogden et al, 1982). It is therefore unlikely that the lack of response to domperidone in some patients (both after acute and chronic administration) was due to reduced bioavailability of orally administered domperidone. This point could be clarified by studies using intravenous administration of the drug, or by incorporating measurement of plasma drug concentrations. In the chronic phase of the study a placebo control would have been required for valid assessment of both symptoms and glycaemic control. The main emphasis of this study was the objective gastric emptying measurements, and a placebo was not used because of the larger number of patients required and ethical limitations on the number of gastric emptying studies that could be performed on each patient because of radiation exposure. The reproducibility of gastric emptying in diabetics has not yet been assessed. It has previously been suggested (Scarpello et al, 1976) that there may have been a greater intraindividual variation in gastric emptying in diabetics than in normal subjects. Clearly this has implications for glycaemic control and the possible use of gastrokinetic agents in diabetic gastroparesis.

The diagnostic usefulness of the technique and its application to the assessment of the effects of pharmacological agents on gastric emptying has been clearly demonstrated in this study. It would be possible to compare the potency of varying doses of one drug or different drugs on increasing or inhibiting emptying by comparing the slopes of the regression lines of change against initial value (Nordin et al, 1980).

10.2 GASTRIC EMPTYING AFTER GASTRIC SURGERY FOR MORBID OBESITY

Morbid obesity (a body weight in excess of 200% of ideal weight) is associated with increased mortality, morbidity from cardiopulmonary disorders, hypertension, diabetes and osteoarthritis and problems with psychosocial adjustment (Lew and Garfinkel 1979). A variety of non-operative approaches have therefore been used in an attempt to control morbid obesity, but these rarely lead to permanent weight reduction (Bothe et al, 1979). These failures have led to the development and widespread use of surgical means of controlling obesity (Alden, 1977, Payne et al, 1973, Griffen et al 1977, Mason et al, 1981, Hocking et al, 1983). The role of operation in the treatment of obesity remains uncertain and controversial.

These surgical procedures can essentially be divided into jejunoileal bypass operations and gastric operations, although recently truncal vagotomy (Kral and Gortz, 1981) and pancreatic-biliary bypass operations (Scopinaro et al, 1981) have been proposed . The jejunoileal bypass, which was pioneered euthusiastically by Payne and DeWind (1969) may no longer be justified, because of long-term metabolic complications such as electrolyte imbalance, nephrolithiasis, cholelithiasis and hepatic dysfunction (Halverson et al, 1980, Hocking et al, 1983). The gastric operations can be separated into gastric bypass, with closure of the fundic pouch and anastomosis to a segment of small bowel, gastroplasty, with separation of the stomach into a small upper pouch, communicating by a small orifice to the remainder of the stomach and gastric partitioning, the simplest variation of gastroplasty, consisting of a cross-stapling of the stomach with omission of several central staples. All three operations employ a small gastric reservoir

(50-80 ml) and a small orifice of communication (approximately 10 mm diameter) with the remainder of the gastrointestinal tract. Gastroplasty and gastric partitioning procedures are technically simpler than gastric bypass and therefore may be associated with lower mortality and morbidity (Gomez, 1981, Carey and Martin, 1981). All these operations promote weight loss by limiting the intake of food and the majority of patients eat both less food at meals and reduce their frequency of eating during the day (Halmi et al, 1981). Satiety and fullness are usually achieved very early during eating, and if the morbidly obese patient continues to overeat, vomiting may occur.

In contrast to jejuno-ileal bypass procedures there has been a low incidence of nutritional and metabolic complications following gastric operations (Halverson and Koehler, 1981). The extent of weight loss is extremely variable, comparable with all three operations and approximates 30% of the initial body weight at 1 year, with a plateau of weight loss at 18-24 months post-operatively (Griffen et al, 1981). However, the prolonged follow-up that is required to demonstrate that rebound weight gain does not occur has not yet been reported.

The mechanisms involved in satiety after gastric operations for obesity have not been investigated in detail. As discussed previously (1.3.3) it is possible that the long-term regulation of food intake is mediated partly through short-term effects of the presence of food in the gastrointestinal tract (Gibbs and Smith, 1978, Strunz, 1979). The gastric distension theory of appetite regulation is based on the close association between fullness, stomach distension and cessation of eating (Gibbs and Smith, 1978). As gastric distension is dependent on the rate of ingestion of food, intragastric pressure and the rate of gastric emptying, a slowing in the rate of gastric emptying with subsequent gastric retention could be an important factor in the mechanisms of satiety produced by gastric operations (Mason et al, 1981). Satisfactory weight loss apparently depends on the construction of a small volume gastric pouch and a small stoma (Mason et al, 1978) and a progressive increase in size of the proximal pouch, dilatation of the gastroenterostomy or staple line dehiscence may be associated with a loss of satiety and weight gain (Murphy et al 1980, Griffen et al 1981). In addition some patients apparently fail to lose weight because they drink high calorie liquids or consume small quantities of food very frequently (Peltier et al, 1979).

The author studied gastric emptying of solid and liquid meal components after both gastric bypass and gastroplasty procedures in a small group of patients. Methodologic difficulties unfortunately prevented a direct comparison of pre- and post-operative gastric emptying. In the gastric bypass patients the size of the pouch and stoma were assessed endoscopically. This measurement of pouch diameter should only be considered as an estimate, as even an operative assessment of pouch capacity is inaccurate (Villar et al, 1981).

After gastric bypass, gastric emptying of a solid meal is slowed considerably but the emptying of water is more rapid than in controls (Figure 7.6, Table 7.5). There is a loss of the normal relationship between solid and liquid emptying. High calorie liquids (25% dextrose) also emptied as rapidly as water (Table 7.6). The study reinforces the need for measurement of both solid and liquid emptying for adequate assessment of gastric emptying after gastric surgery. This pattern of emptying would favour rapid absorption and shorter satiety periods with liquid calories and is consistent with the clinical observation that some patients can maintain weight by consuming large quantities of high calorie liquids. There was no correlation between the stoma size and rates of solid and liquid emptying, or the weight loss produced by the operation and the rates of solid and liquid emptying, stoma or pouch size.

Vagal innervation of the excluded stomach is intact after gastric bypass (Printen and Owensby, 1978) and fullness is probably secondary to receptive relaxation of the upper pouch, rather than to an increase in upper pouch pressure (Villar et al, 1981). The observed slow rate of solid emptying may be attributed to the absence of the antrum, which has an important role in regulating the emptying of solid food, and the small size of the stoma. An initial rapid emptying of solid food occurred in four patients with smaller pouch diameters (Figure 7.6) probably because the oesophagus had delivered a greater volume of food into the pouch than could be accommodated. Emptying of water may have been faster than in normals because the stoma is a fixed opening, unlike the pyloric region of the normal stomach. In addition, as the duodenum has been bypassed in gastric bypass, a loss of the inhibitory effect on gastric emptying (Hunt 1983) and satiety signals (Gibbs and Smith 1978) produced by the action of liquid calories on duodenal receptors would be predicted. The rapid emptying of high calorie liquids may contribute to the dumping syndromes sometimes seen after gastric bypass (Mason et al, 1981) and explain the observation that high calorie beverages are less frequently consumed after gastric bypass (Halmi et al, 1981).

The pattern of gastric emptying after gastric bypass is similar to that observed after truncal vagotomy and antrectomy (1.4.2), in which a variable initial rapid emptying followed by slower emptying of solid food and more rapid emptying of liquids have been observed (MacGregor et al 1977, Mayer et al 1982). After antrectomy, gastric sieving of solid food is impaired, so that a significant proportion of solid food enters the small bowel as larger and less easily digested particles (Meyer et al 1979, Mayer et al 1982) and it is likely that this would occur after gastic bypass. The effects of the operation on gastric emptying and probably gastric trituration of digestible solid food would clearly alter the normal relationship between gastric emptying and the flow of pancreatic and biliary secretions into the proximal small bowel and may contribute to the mild post-operative malabsorption observed after gastric bypass (Griffen et al, 1981).

After gastroplasty, liquid emptying is slower than in control subjects. The emptying of a solid meal is faster than in control subjects for the first few minutes and thereafter becomes slower (Figure 7.8, Table 7.7). As the solid in the author's study was consumed before the liquid, the slower rate of liquid emptying may have reflected mechanical obstruction by the bolus of solid food. Conversely, the liquid caused some solid food to be transferred more rapidly from proximal to distal stomach, probably because a greater volume had been delivered into the pouch than could be readily accommodated. The slower rate of solid emptying which subsequently occurred, reflected retention of food in the partitioned pouch (Figure 7.9, Table 7.8). However, unlike the study in gastric bypass patients, the changes in gastric emptying produced by gastroplasty were relatively small and gastric emptying rates overlapped considerably with the range of emptying rates found in normal subjects.

The satiety effects of both gastroplasty and gastric bypass may partly depend on retention of solid food in the proximal pouch. It is probable that radionuclide methods could be used to identify patients with unduly delayed gastric emptying due to stenosis of the pouch outlet and that those patients who have excessively large stomas due to an inadequate surgical procedure will demonstrate more rapid emptying of both solids and liquids from the pouch. In this latter group surgical reduction of the size of the stoma may be indicated if weight loss is not adequate. Drane et al (1983) recently studied gastric emptying of a solid meal (^{99m}Tc sulphur colloid egg) in 14 patients who had a gastroplasty. In most of these subjects delayed emptying of solid food from the pouch was also evident and there was a significant inverse correlation between emptying rates and weight loss. This correlation probably only existed because some patients with technically inadequate surgical procedures (excessively large stomas), who had very much more rapid emptying were included. Villar et al (1981) have reported a slower rate of solid food (^{99m}Tc-liver) emptying after gastrogastrostomy (another gastric partition procedure), compared to gastric bypass. This finding is surprising in view of the author's results. However interpretation of the results of their study is difficult as patients were not compared to a control group, the solid meal was smaller and the time of administration of the liquid meal was not stated.

The gastric bypass and gastroplasty patients studied by the author all had technically satisfactory operations followed by a satisfactory weight loss. There was no correlation in these patients between the weight loss following the operation and rates of either solid or liquid emptying. It is possible that some correlation may have been evident is greater numbers of patients had been studied, but this seems unlikely as gastric bypass and gastroplasty produce a comparable weight loss despite different effects on gastric emptying. Marked alterations in eating behaviour are necessary to achieve weight loss after gastric surgery for obesity and it is clear that dietary intake is enormously variable among patients who have technically successful operations and is strongly influenced by psychogenic factors (Halmi et al, 1981).

Other mechanisms apart from abnormal gastric emptying may also be responsible for mediating gastric distension and satiety signals after gastric surgery for obesity. Villar et al (1981) have demonstrated that after gastric bypass and gastrogastrostomy the normal distension-stimulated fundic contractile activity is absent, possibly due to interruption of antral and body motor activity by the staple line. Because of both the anatomical changes (e.g. the duodenum is bypassed in gastric bypass) and alterations in gastric emptying a change in the secretion of gastrointestinal hormones, which may possibly alter proximal stomach tone and gastric emptying may occur after gastric surgery for obesity. Recently it has been reported that the pancreatic polypeptide response to a meal is diminished after both gastroplasty and gastric bypass although gastrin responses are normal (Shulkes et al 1982, Schrumpf et al 1981). Meal stimulated neurotensin release is diminished after gastroplasty (Shulkes et al, 1983). As neurotensin is released predominantly from the mucosa of the terminal ileum (Polak et al 1977) these changes are likely to reflect a reduced overall rate of delivery of food to the distal small intestine, secondary to the demonstrated delay in gastric emptying.

APPENDIX

Published papers and abstracts based on material presented in this thesis

PUBLICATIONS

Papers

1. Collins, P., Horowitz, M., Cook, D., Harding, P. and Shearman, D.J.C. (1982). The effects of increasing liquid calories on gastric emptying in normal subjects. Nuclear Medicine and Biology 3: 2415-8.

2. Horowitz, M., Collins, P., Cook, D., Harding, P. and Shearman, D.J.C. (1982). Gastric emptying after gastric bypass surgery. Nuclear Medicine and Biology 1:273-6.

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6. Collins, P.J., Horowitz, M., Cook, D.J., Harding, P.E. and Shearman, D.J.C. (1983). Gastric emptying in normal subjects – A reproducible technique using a single scintillation camera and computer system Gut 24 : 1117-1125.

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9. Collins, P.J., Horowitz, M., Shearman, D.J.C., Chatterton, B.E., (1984). Correction for tissue attenuation in radionuclide gastric emptying studies : a comparison of a lateral image method and a geometric mean method. British Journal of Radiology (accepted for publication).

10. Horowitz, M., Maddern, G.J., Chatterton, B.E., Collins, P.J., Harding, P.E., Shearman, D.J.C. (1984). Changes in gastric emptying rates with age. Clinical Science (accepted for publication).

Abstracts and Letters

1. Horowitz, M., Collins, P., Cook, D.J., Harding, P. and Shearman, D.J.C. (1982). The effect of variation of the concentration of dextrose on the emptying of a mixed liquid and solid meal. Gastroenterology, 82:1087.

2. Horowitz, M., Collins, P., Cook, D.J., Harding, P. and Shearman, D.J.C. (1982). The effect of gastric bypass surgery on gastric emptying. Gastroenterology 82:1087.

3. Collins, P.J., Cook, D.J., and Horowitz, M. (1982). A correction technique for depth attenuation in gastric emptying studies using a single detector system. Aust. N.Z. J. Med. 12:662.

4. Horowitz, M., Collins, P.J., Cook, D.J., Harding, P.E. and Shearman, D.J.C. (1982). Gastric emptying studies in normal and obese subjects. Aust. N.Z. J. Med. 12:662.

5. Maddern, G.J., Jamieson, G.G., Shearman, D.J.C., Horowitz, M., Chatterton, B.E. and Collins, P. (1983). Gastric emptying in gastro-oesophageal reflux - does it correlate with other parameters of severity of disease? Aust. N.Z. J. Med. 13:320-1.

6. Horowitz, M., Maddern, G.J., Chatterton, B.E., Collins, P.J., Harding, P.E., and Shearman, D.J.C. (1983). Gastric emptying in the elderly. Gastroenterology 84:1191.

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