# UPPER GASTRO-INTESTINAL MOTILITY AND GASTRO-OESOPHAGEAL REFLUX

Thesis submitted in February 1985 for
the degree of Doctor of Philosophy
in the University of Adelaide

by

Guy John Maddern, M.B., B.S. (Adel).

The work described was performed within
the Department of Surgery of the
University of Adelaide.



Awarded 7 August, 1985

## TABLE OF CONTENTS

Page No.

Page No.

# TABLE OF FIGURES

Page No.

## SUMMARY

In this thesis upper gastro-intestinal motility and its relationship to patients with gastro-oesophageal reflux has been investigated.

Current methods of assessment of gastro-oesophageal reflux have been used and where necessary validated. In addition new techniques have been developed to investigate upper gastro-intestinal motility. A technique of solid bolus radionuclide oesophageal emptying has been validated in normal volunteers and applied to patients. The use of plasma and salivary paracetamol levels to determine gastric emptying has also been explored. A technique for assessing antropyloroduodenal motility and duodenogastric reflux as determined by antral pH changes has been developed in an animal model and adapted to normal human volunteers.

Patients with primary gastro-oesophageal reflux have been assessed by some of these techniques. Oesophageal emptying in these patients was found to be significantly slower than controls. Following anti-reflux surgery no improvement was seen in the ability of the oesophagus to clear itself of a solid bolus.

Gastric emptying was significantly delayed in patients with gastro-oesophageal reflux, showing a delay in both solid and liquid emptying. No significant correlation was found between resting lower oesophageal sphincter pressures and the gastric emptying results. However a significant correlation existed between the delayed solid emptying and the presence of oesophagitis.

A double blind cross over trial of the drugs metoclopramide, domperidone and placebo was also conducted in a group of these patients. Patients clinically improved during all three treatment periods, but active treatments were not significantly better than placebo. Pre-existing delay of gastric emptying appeared to be of no significance, nor was a significant alteration in gastric emptying found after one months treatment with domperidone.

A further group of patients with gastro-oesophageal reflux was assessed by gastric emptying studies performed six months following a standardised fundoplication. This group showed more rapid solid and liquid gastric emptying. A group of patients who presented with recurrent gastro-oesophageal reflux following anti-reflux surgery was also investigated and found to have significantly slower gastric emptying.

Two additional groups of patients with secondary gastro-oesophageal reflux were also studied. Patients with progressive systemic sclerosis displayed a delay of oesophageal emptying and solid and liquid gastric emptying. Oesophageal emptying was also delayed in a group of diabetic patients with autonomic neuropathy.

This thesis confirms the abnormalities of oesophageal function described in gastro-oesophageal reflux disease. Further it demonstrates a significant proportion of such patients have delay in both solid and liquid gastric emptying. Agents that promote gastric emptying were not significantly superior to placebo in symptomatic control, however, surgery was associated with both symptomatic and objective improvement in gastric emptying.

A new technique for the assessment of antropyloroduodenal motility has been developed and is now being applied to patients. It is hoped it may clarify some of the questions unanswered by these studies.

## DECLARATION

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any University and that to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis. I further consent to the thesis being made available for photocopying and loan if applicable if accepted for the award of the degree.

GUY MADDERN

## ACKNOWLEDGEMENTS

The work which is reported in this thesis was made possible by support from the Clive and Vera Ramaciotti Foundations, the E.R. Dawes, L.C. Hughes and A.R. Curren Research Fellowships of the Royal Adelaide Hospital and a medical post graduate research scholarship awarded by the National Health and Medical Research Council of Australia.

The studies described involved a number of departments within the Royal Adelaide Hospital, Flinders Medical Centre and University of Adelaide. Within the Royal Adelaide Hospital, the Department of Nuclear Medicine, and in particular Dr. B. E. Chatterton and Mr. P.J. Collins were generous with both their facilities and guidance. Professor Giles Stevenson performed the radiological assessment of oesophageal emptying during his sabbatical stay in the Department of Radiology. The Flinders Medical Centre permitted much of the animal work to be performed within their animal housing facilities under the care of Mr. R. Yeats. Mr. B. Bridger in the Department of Biomedical Engineering provided many hours of his time in helping to solve the complex potential difference problems in the duodenal studies. Within the University of Adelaide, a number of departments provided staff and facilities including the Physiology Department which lent space and equipment to permit conclusion of the animal studies. The Statistics department's Statistical Consultant, Mr. P. I. Leppard, was invaluable in guidance and assistance in much of the data analysis. Dr. M. Horowitz and Professor D.J.C. Shearman from the Department of Medicine co-operated on a number of aspects of the work. Development of the normal range for gastric emptying was formed from pooled data with Dr. M. Horowitz. Within the Department of Surgery a number of individuals ensured the conclusion of the thesis. Invaluable Technical assistance was provided by Mrs. Jenny Kelly, Miss Sharon Colquhuon and Miss Jenny Myers, all of whom contributed far beyond the call of duty. Mr. Neville DeYoung was called on and solved countless logistic and laboratory problems during the three years. Tribute must also be paid to Ms Margaret Madsen and Miss Fiona Matthews for their patience and constructive advice in typing this thesis.

The most important contributor to the final success of the study was Professor Glyn Jamieson, who supervised the study throughout its duration. Not only did he contribute to the scientific dimension of the work, but shouldered the administrative and funding burdens that ensued. His supervision was supplemented in 1984 by Dr. John Dent of the Flinders Medical Centre, who was responsible for supervision of the animal and human duodenal studies.

## PREFACE

Part of the work described in this thesis has been published or accepted for publication. These publications are listed below in the order in which they were submitted.

### REFEREED PAPERS

1. Kiroff, G.K., Maddern, G.J., Jamieson, G.G. (1984) A study of factors responsible for the efficacy of fundoplication in the treatment of gastro-oesophageal reflux. Aust. N.Z. J. Surg. 54:109-12.

2. Horowitz, M., Maddern, G.J., Chatterton, B.E., Collins, P.J., Harding, P.E., Shearman, D.J.C. (1984) Changes in gastric emptying with age. Clin. Sci. 67:213-218.

3. Maddern, G.J., Horowitz, M., Jamieson, G.G., Chatterton, B.E., Collins, P.J., Roberts-Thomson, P. (1984) Abnormalities of esophageal and gastric emptying in progressive systemic sclerosis. Gastroenterology 87:922-6.

4. Maddern, G.J., Miners, J., Collins, P.J., Jamieson, G.G. (1984) Liquid gastric emptying assessed by direct and indirect techniques: radionuclide labelled liquid emptying compared with a simple paracetamol marker method. Aust. NZ. J. Surg. (in press)

5. Maddern, G.J., Jamieson, G.G. (1985) Fundoplication enhances gastric emptying. Ann. Surg. 201:42-45.

6. Maddern, G.J., Horowitz, M., Hetzel, D.J., Jamieson, G.G. (1984) Altered solid and liquid gastric emptying in duodenal ulcer disease. Gut (in press).

7. Maddern, G.J., Jamieson, G.G. (1984) Alteration in oesophageal emptying in gastroesophageal reflux. Surg. Gastroenterol. (in press).

8. Maddern, G.J., Chatterton, B.E., Collins, P.J., Horowitz, M., Shearman, D.J.C., Jamieson, G.G. (1984) Solid and liquid gastric emptying in patients with gastro-oesophageal reflux. Br. J. Surg. (in press).

9. Maddern, G.J., Horowitz, M., Jamieson, G.G. (1984) The effect of domperidone on oesophageal emptying in diabetic autonomic neuropathy. Br. J. Clin. Pharmacol. (in press).

10. Horowitz, M., Maddern, G.J., Chatterton, B.E., Collins, P.J., Petrucco, O.M., Seamark,R., Shearman, D.J.C. (1985). The normal menstrual cycle has no effect on gastric emptying. Brit. J. Obstet. Gynaecol. (in press).

11. Maddern, G.J., Chatterton, B.E., Collins, P.J., Jamieson, G.G. (1985). Is there an association between failed anti-reflux surgery and delayed gastric emptying? Ann. Surg. (in press).

# SECTION I

## AIMS

### 1.1 TO EXAMINE AND DEVELOP METHODS OF USE IN THE ASSESSMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE

An array of investigations is available to investigate gastro-oesophageal reflux disease. The reproducibility and reliability of these methods has been little studied. Further, technology for the assessment of physiology and its derangements in gastro-oesophageal reflux disease has been limited. This study aims to answer a number of questions.

(i) Is oesophageal manometry reproducible?

(ii) Is measurement of oesophageal acid clearance useful in the clinical situation?

(iii) Can radionuclide techniques be used to measure oesophageal function, and if so is that function disordered in gastro-oesophageal reflux disease?

(iv) Are tests of gastro-oesophageal reflux by acid loading of the stomach useful in determining the presence or absence of reflux disease?

(v) What relationship exists between gastric emptying and gastro-oesophageal reflux?

(vi) Is there a simple alternative to radionuclide assessment of gastric emptying which would be applicable to patients with gastro-oesophageal reflux disease?

(vii) Can an accurate method of measuring antropyloroduodenal function be developed and applied in humans?

(viii) Is measurement of duodenogastric reflux possible by ulitising pH changes in the gastric antrum and duodenum?

(ix) What is the relationship of antropyloroduodenal function and duodenogastric reflux to gastro-oesophageal reflux disease?

## 1.2 <u>TO USE THESE METHODS IN THE ASSESSMENT OF UPPER GASTROINTESTINAL MOTILITY IN PATIENTS WITH PARTICULAR REFERENCE TO GASTRO-OESOPHAGEAL REFLUX</u>

New investigations or novel combinations of more traditional methods of investigation will be used in patients with gastro-oesophageal reflux. These are used with the aim of gaining a greater understanding of the underlying abnormalities of upper gastro-intestinal motility present in such patients. There remain several unanswered questions which will be investigated.

(i) What is the pattern of gastric emptying in patients with gastro-oesophageal reflux?

(ii) Are solids and liquids equally involved?

(iii) Do the gastric emptying findings relate to other measures of reflux disease such as presence of oesophagitis or hypotensive lower oesophageal sphincter?

(iv) Is oesophageal emptying of a solid bolus impaired in these patients?

(v) How reliable are symptoms as an indicator of abnormal motility in these patients?

(vi) In conditions known to be associated with gastro-oesophageal reflux (e.g. scleroderma and diabetes) are the motility disturbances similar to patients with primary gastro-oesophageal reflux?

## 1.3 TO INVESTIGATE THE EFFECTS OF EITHER PHARMACOLOGICAL OR SURGICAL TREATMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE ON MOTILITY IN THE OESOPHAGUS, STOMACH AND DUODENUM

Management of gastro-oesophageal reflux has been largely empirical. Decisions are made without complete documentation of the motility disorder present. A number of pharmacological and surgical options are in current vogue yet questions about their impact on underlying motility disturbances remain largely unresolved:

(i) Does stratification of patients by their gastric emptying status predict response to drugs such as metoclopramide and domperidone?

(ii) What is the extent of the placebo effect in patients managed medically?

(iii) Is response to therapy with chronic treatment of gastro-kinetic drugs due to improved gastric emptying?

(iv) Is oesophageal function improved by domperidone?

(v) Does surgical correction of gastro-oesophagel reflux alter gastric and oesophageal function?

(vi) Can patients with a poor outcome after anti-reflux surgery be classified on the basis of their upper gastro-intestinal motility?

(vii) If so, can these disorders be identified pre-operatively?

(viii) What possible developments may improve the surgical management of such patients?

# SECTION II

## INTRODUCTION

2.1 Definition of Gastro-oesophageal Reflux

2.2 Normal Control of Gastro-oesophageal Reflux

2.3 Assessment of Reflux and Upper Gastrointestinal Motility.

- (i) Symptoms.
- (ii) Radiology.
- (iii) Manometry
  - a. Gastro-oesophageal
  - b. Gastro-duodenal
- (iv) pH Studies.
- (v) Radionuclide Techniques.
- (vi) Endoscopy
- (vii) Histopathology

2.4 Treatment of Gastro-oesophageal Reflux

- (i) Medical
- (ii) Surgical

## 2.1 DEFINITION OF GASTRO-OESOPHAGEAL REFLUX

The reflux of gastric contents into the oesophagus occurs intermittently in everyone during their waking hours.

Gastro-oesophageal reflux occurring in normal people and producing neither the symptoms nor histological changes in the oesophagus is called physiological gastro-oesophageal reflux. Gastro-oesophageal reflux which causes symptoms or complications is pathological gastro-oesophageal reflux. This term embraces reflux oesophagitis (gastro-oesophageal reflux with unequivocal evidence of inflammation of the oesophagus) and reflux disorder (reflux proven by pH probe testing or other objective means, without inflammatory changes being demonstrated). In the older literature the term symptomatic sliding hiatus hernia was also used as an all embracing term for gastro-oesophageal reflux.

The commonest symptom to be associated with pathological gastro-oesophageal reflux is the retro-sternal pain known as heartburn. However, symptoms cover a wide spectrum from severe pain without evidence of oesophagitis to no pain with severe oesophagitis even to the point of stricture formation. This makes any study of the natural history of the disorder dependent on where a patient falls in this spectrum, when they are being evaluated. As far as is known there have been no long-term studies of the whole spectrum of gastro-oesophageal reflux disease.

Flood and Hennig (1958) followed 100 patients with symptomatic hiatus hernia treated medically for a mean of 4 years. They found symptoms became mild or disappeared in about half of the patients, and that symptoms generally did not worsen with the passage of time. Rex et al (1961) reported 301 patients with symptomatic sliding hiatus hernia who were evaluated by a follow-up letter or re-examination after a 10-year period. They found also that more than half the patients were improved or asymptomatic regardless of whether endoscopic oesophagitis had been present initially or not. In one of the few other studies which attempted to look at the disease complex over many years, Palmer (1968) reported on 1011 patients with a hiatus hernia/oesophagitis/oesophageal stricture complex. In 142 patients examined endoscopically over periods up to 9 years, he reported that oesophagitis appeared for the first time in 13% of the patients, remained unchanged or worsened in 35% and improved or disappeared in 52%. He also noted that 45 of 413 patients with oesophagitis developed a stricture. On the other hand, in a series of 400 patients, Allison et al (1972) made the observation that "where patients have been observed repeatedly (endoscopically) over a long period, the degree of oesophagitis has not been seen to alter much". Perhaps the best study available in the literature because of its prospective nature is that of Behar et al (1975) in their randomized trial of surgery v. medical therapy for reflux oesophagitis. Although not a study of untreated patients, their medical therapy group received only simple symptomatic measures such as elevation of the head end of the bed at night and liquid antacids after meals and before retiring. Their patients were carefully followed for 2 or more years with an assessment of symptoms and manometry, oesophagoscopy, histology of the oesophagus, and pH probe evaluation. They found only 3 patients out of 16 had a good to excellent result with simple medical therapy. (This included symptoms and objective testing). Many patients remained symptomatic with objective evidence of persisting reflux disease.

Therefore, it is apparent that this disease can wax and wane and results of studies will often depend on which phase the patient is in regardless of the therapy being used. It is also apparent that in many patients once they have developed reflux disease it is likely to be a continuing problem lifelong. However, major progression occurs in a minority only.

## 2.2 NORMAL CONTROL OF GASTRO-OESOPHAGEAL REFLUX

The mean pressure in the lumen of the thoracic oesophagus is negative, varying from -15 mmHg to +5 mmHg, reflecting intrapleural pressures (Goyal and Cobb, 1981). The mean pressure in the fundus and proximal body of the stomach is positive and varies from 7 to 50 mmHg. During fasting, the pressures in the stomach can rise to even higher levels (Kelly, 1981). Therefore in quiet inspiration the head of pressure tending to force gastric contents back into the oesophagus varies from 5 to 15 mmHg, while with maximal inspiration, abdominal straining or coughing, the head of pressure can exceed 75 mmHg (Marchand, 1957; Morgan, 1962). With pressure gradients such as these gastric contents would continually pass back into the oesophagus, unless mechanisms existed to prevent such reflux.

Such mechanisms exist and can be broadly classified as physiological and anatomical.

### PHYSIOLOGICAL MECHANISM - THE LOWER OESOPHAGEAL SPHINCTER

The presence of a sphincter at the lower end of the oesophagus had been hypothesized ever since Magendie's observation that food tended to be held up at this point (Magendie, 1822).

In 1897, Meltzer recorded high pressures occurring in the lower oesophagus after swallowing and then in 1906, Tileston put forward some views, remarkably in line with current thoughts, on the cardia and its role in the prevention of peptic ulceration of the oesophagus. For instance, he noted that the cardia is normally closed and relaxes with swallowing, belching or vomiting. He also noted that relaxation of the cardia occurs normally in some animals allowing free reflux of gastric contents. As well he noted that pyrosis (heartburn) could lower cardiac tone and that chronically low cardiac tone could be due to either organic or functional causes.

In 1909, Fischer demonstrated an anatomical lower oesophageal sphincter in the bat. This was a nice demonstration of evolution at work, as the animal spent much of its life hanging upside down: but the observation probably had little relevance to man. The advent of more sophisticated techniques for measuring oesophageal pressure verified that there was a high pressure zone in the lower oesophagus (Sanchez et al, 1953; Butin et al, 1953; Dornhorst et al, 1954) and then Fyke et al (1956) first clearly identified this region as a physiological sphincter. Botha et al (1957) and Atkinson et al (1957b) also demonstrated the physiological nature of this sphincter, which maintained a basal tone above that of intra-gastric pressure and relaxed as a swallowing wave was initiated and contracted when the wave passed.

Introduction of perfused manometry systems by Pope (1967) and Winans and Harris (1967) led to greater fidelity in recording of pressures in the lower oesophageal sphincter region. However perfused side hole systems continued to be open to the criticism that movement of the oesophagus relative to the side hole introduced problems in fidelity of recordings (Dodds et al, 1976a). The introduction of the pressure sleeve (Dent, 1976) resolved this difficulty and allowed long term recording of pressure events in the lower oesophageal sphincter region to take place.

It had been known since the 1960's that reflux sometimes occurred in normal individuals. Such reflux was difficult to understand when basal lower oesophageal sphincter tone was measured as normal. Studies in normal people using the pressure sensor sleeve across the lower oesophageal sphincter have shown that intermittent transient relaxations occur and such relaxations occur more frequently after a meal (Dent et al, 1980). A subsequent study in ten normal controls revealed transient relaxations of the lower oesophageal sphicter, 5% followed a transient increase in intra abdominal pressure and 1% were without an obvious cause (Dodds et al, 1982).

The level of basal tone recorded in the lower oesophageal sphincter is variable and is influenced by catheter orientation within the sphincter, oesophageal movement with respiration and swallowing, the method of measuring sphincter pressure, the fed state of the patient and the recording equipment which is being used. (Pope, 1981; Meyer and Castell, 1981; Duranceau et al, 1983).

The role of the lower oesophageal sphincter in preventing reflux when intra abdominal pressure is increased is a disputed one.

Lind et al (1966) and Cohen and Harris (1970) found that increases in intra abdominal pressure of either a passive or active nature led to an increase in lower oesophageal sphincter pressure - regardless of whether the lower oesophageal sphincter was in the abdomen or in the chest (sliding hiatus hernia). Since the response was attenuated by vagotomy (Crispin et al, 1967) and atropine (Lind et al, 1968) it was suggested that this effect was a cholinergic reflex mediated via the vagus nerves. Support for this theory was also provided by Laitinen and Larmi (1981) with a study of dogs.

However, others have argued that the pressure changes are transmitted ones only. Gastric distension may also influence the pressure in the lower oesophageal sphincter although the mechanisms await elucidation.

Ahtaridis et al (1981) studying intra gastric acid infusions in both normal controls and patients, concluded that the lower oesophageal sphincter resting pressure correlated linearly with the propensity to reflux. They did not address themselves to the mechanism of reflux in the subjects however.

## The anatomical lower oesophageal sphincter

In 1909, Fischer demonstrated an anatomical lower sphincter in the bat, but subsequent studies in humans were unable to unequivocally demonstrate such a sphincter anatomically (Lendrum, 1937; Byrnes and Pisko-Dubienski, 1963; Higgs et al, 1965; Bombeck et al, 1966). Liebermann-Meffert et al (1979; 1983) have used both human and feline specimens to examine the muscular equivalent of the high pressure zone in the lower oesophagus. They found that an oblique gastro- oesophageal ring of muscle fibres was the site of greatest muscular thickness in man and the thickness tapered off from this point in both an oesophageal and gastric direction. Subsequent studies in a feline model have established that this area of muscle thickening corresponds with the high pressure lower sphincter demonstrated manometrically.

## ANATOMICAL AND MECHANICAL FACTORS

Abolition of lower sphincter tone by atropine was carried out by Skinner and Camp (1968) and did not lead to an increase in gastro-oesophageal reflux.

Dodds et al (1976b) and Edwards (1982) reported in an anecdotal way that when normal volunteers were placed in a steep head down position no reflux occurred even when the lower sphincter was relaxed following swallowing. In a more physiological study Dodds et al (1982) noted that when sphincter pressure fell to 0 in normal people reflux events occurred on only 34% of occasions. It seems that factors other than intrinsic lower oesophageal sphincter tone must play a role in preventing gastro-oesophageal reflux.

Mechanical and physical factors of significance in the region of the oesophageal hiatus, have been the subject of speculation and investigation for centuries. Willis (1679) described muscle fibres of the diaphragm which "do compass about and as occasion serves being contracted, do shut up".

Gubarroff (1886) noted that when pressure was exerted on the stomach of a cadaver it proved difficult to force fluid back into the oesophagus, suggesting that physical as opposed to physiological factors were exerting an action. Factors which have been regarded as important will be considered in turn.

## The acute angle of entry and valve mechanism at gastro-oesophageal junction

The sling of muscle fibres maintaining the acute angle of entry of the oesophagus into the stomach was first drawn by Willis in 1679 and then described by Helvetius in 1719. However, the acute angle is named after His following the studies he published in 1903. The acute angle of entry of the oesophagus and its importance in preventing reflux was also commented on by Dick and Hurst (1942), Barrett (1954) and Creamer (1955). Atkinson and Sumerling (1959) noted that the acute angle lessened or even disappeared in cadavers suggesting that active processes were involved in maintaining the angle in life. Not withstanding this, Wald and Polk (1983) in an autopsy study of 36 fresh cadavers found great variability in the acute angle ranging from $7^{o}$ to $60^{o}$ (with a mean angle of $21^{o}$).

Donnelly (1953) used barium studies, Leigh Collis et al (1954) used cadaver dissections in situ and outside the body and Adler et al (1958) used dog studies to support the theory that the acute angle of the oesophagus and the pinch cock action of the diaphragmatic crura act in co-ordination to prevent reflux. As the diaphragm descends in deep inspiration - it forces the gastric fundus downward and reduces the acute angle of His. The right crus of the diaphragm contracts, along with the rest of the diaphragm, thereby occluding the oesophageal lumen.

The mechanism of the acute insertion of the oesophagus forming a "flap valve" was demonstrated in a further study in dogs in which the oesophagus was divided and joined to the posterior stomach in such a way that a long mucosal lip anteriorly was the only mechanism capable of preventing reflux. This maintained competence even in the face of induced gastric hypersecretion (Tocornal et al, 1968).

The diaphragm

Ramond et al (1921) and Mosher (1923) both commented on the angulation of the oesophagus passing through the diaphragm acting as a valve mechanism. The oesophagus passed rather obliquely through the diaphragmatic hiatus which was usually made up of fibres from the right crus. Leigh Collis et al (1954) found that 98% of the muscle fibres of the hiatus were from right crus and in only 2% of dissections were the fibres predominantly from the left crus. A band of tissue (the muscle of Low), containing either muscle (infrequently) or fibrous tissue (frequently) was found in 36% of cases. It passed from the left crus behind the oesophagus across the inferior vena caval hiatus.

The tunnel of the diaphragm is approximately 3 cms in length (Milstein, 1961). Jackson (1922) suggested that the diaphragm acted as a pinch cock on the oesophagus and Allison (1948) initially subscribed to the view that deficiency in this pinch cock action was the most important factor leading to reflux disease. Allison also noted that contraction in the hiatus with inspiration could be felt at operation (Allison, 1948; 1951), an observation extended by Wooller to include contraction in the hiatus on stimulation of the right phrenic nerve (Wooler, 1952). The radiological counterpart of this was suspension of the barium column in the oesophagus above the diaphragm observed in deep inspiration (Mosher, 1930; Lawler and McCreath, 1951).

### The intra-abdominal oesophagus

When a length of intra-abdominal oesophagus is present then this part of the oesophagus is exposed to the same pressure changes as occur in the rest of the abdominal cavity. Thus increased intra-abdominal pressure will not only be transmitted to the gastric cavity but to the lower oesophagus, tending to keep it shut. This physical effect as an explanation of pressure rises within the lower oesophagus, during transient abdominal pressure increases has been reported by Dodds et al (1975), Kaye et al (1976b), Csendes et al (1979), De Meester et al (1979) and Wernly et al (1980).

### The phreno-oesophagaeal ligament (membrane)

This is a fibro elastic membrane which arises as a condensation of the endo-abdominal fascia on the under surface of the diaphragm. Roux (1939) called it the 'lame de Laimer' after the man who is said to have first described it in 1883. Anders and Bahrmann (1932) described its elastic structure and Harrington (1940) believed that atrophy of the ligament was important in the increased incidence of hiatus hernia with age. Allison (1951) considered the structure to be of considerable importance but Barrett (1952) thought the ligament too insubstantial to play any role in hiatus hernia development. Peters (1955) undertook anatomical and histological sections of the region and showed it splitting into an ascending thoracic limb and a descending and stronger abdominal limb. He believed the membrane not only prevented the cardia passing up into the chest, but when forces did lead to such an event then the elastic fibres in the membrane gave the area some 'recoil'.

In an autopsy series Friedland et al (1966) showed attenuation of the phreno-oesophageal membrane in 7 cases where a hiatus hernia was present but not in 125 cases without a hiatus hernia. Similarly Bombeck et al (1966), in an autopsy series, claimed that the upper leaf of the phreno-oesophageal membrane was displaced caudad in its insertion on the oesophagus in those cases where oesophagitis was present. The most marked caudad displacement was seen in hiatus hernia with oesophagitis. However, it is impossible to know if this latter finding was cause or effect. They defined the gastro-oesophageal junction as the squamo columnar junction. And this, taken with the variability of this latter and its upward movement in some cases of oesophagitis, throw some doubt on their conclusion that the displacement of the phreno-oesophageal ligament caused the oesophagitis.

Eliska (1973) undertook an autopsy study in 163 human cadavers, from the foetal period to age 75. He found that the upper layer of the phreno-oesophageal membrane became thinner with age and that patients with hiatus hernia had the insertion of the lower leaf displaced craniad at least in part associated with an increase in sub-peritoneal fat in the region of the hiatus.

Wolf (1973) used radiological anatomy in patients to reinforce his belief in the phreno-oesophageal ligament as an important anti-reflux mechanism. Whilst his arguments are persuasive there is no way of substantiating his thesis from the data he presents.

Bremner et al (1970) carried out a study in dogs of re-attaching the phreno-oesophageal membrane at various points and they could not prove a relationship between its insertion and gastro-oesophageal reflux.

There is no question that the phreno-oesophageal ligament is a definable anatomic stucture which inserts into the lower oesophagus. As such it presumably plays a role in maintaining the normal anatomy in this hiatal area.

There is also no question that the ligament is attenuated and displaced (both upwards and downwards have been reported) in patients with a sliding hiatus hernia. However, the role of the ligament in the development of gastro-oesophageal reflux has not been worked out, and its attenuation and displacement in patients is just as likely an effect of sliding hiatus hernia as a cause of it.

Saliva

Salivary flow occurs only during waking hours and virtually ceases during sleep (Schneyer et al, 1956). In resting circumstances human salivary flow occurs at the rate of about 0.5 ml/min (Helm et al, 1982), and this saliva is transmitted into the oesophagus by spontaneous swallows which occur at the rate of about once a minute in the waking state (Lear et al, 1965; Dent et al, 1980).

Saliva functions as a weak base and is capable of neutralising acid - this capacity being linearly related to its bicarbonate concentrations (Helm et al, 1982).

Aylwin (1953) recognised the possible importance of saliva in the oesophagus in its buffering role against acid and spoke of '... an extreme form of universal oesophagitis ... when dehydration from severe illness suppresses salivation completely'. In spite of this, changes in salivary flow and composition have not been much studied in patients with gastro-oesophageal reflux. Agents which stimulate salivary flow and bicarbonate secretion by the salivary glands have the potential to increase acid clearance, e.g. cholinergic drugs such as Bethanecol and oral lozenges (Helm et al, 1983). Agents which decrease flow and bicarbonate secretion have the potential for slowing oesophageal clearance and thus allowing prolonged contact of refluxed contents with oesophageal mucosa. Agents which have been shown to act in this way are anti-cholinergic drugs, which dry up salivary secretion (Helm et al, 1982) and alcohol which when taken orally initially stimulates salivary flow (Martin and Pangborn, 1971) and thereafter depresses flow for 60-90 minutes (Kissin and Kaley, 1974).

The importance of saliva in the clearance of acid from the oesophagus was demonstrated in a study of 27 normal subjects reported by Helm et al (1983). They found that stimulation of salivary flow led to more rapid clearance of acid from the oesophagus and diminution in, or removal of, salivary secretion and greatly prolonged acid clearance.

<u>Oesophageal emptying</u>

This was initially assessed by the instillation of an acid load into the oesophagus and recording how many swallows were required before the oesophagus emptied itself of the acid (Booth et al, 1968). A Beckman pH probe was positioned 5 cm above the lower oesophageal sphincter and 15 mls of 0.1 N HCl was instilled into the oesophagus, 10 cms proximal to the probe. Seven subjects free of upper gastrointestinal symptoms were instructed to carry out dry swallows at one minute intervals, 7 subjects at 30 second intervals and 7 were allowed to swallow when they felt like it. In all subjects the pH was raised to 6.0 or more within 10 swallows.

Stanciu and Bennett (1974a) found that all normal controls cleared their oesophagus of an acid load with 12 swallows, Heil et al (1981) found some normal people who took 23 swallows to clear, Sonnenberg et al (1982) found normal people who took more than 20 swallows to clear their oesophagus and Krejs et al (1976) found that 20 normal controls took a mean of 38 swallows to clear their oesophagus of acid.

Acid clearance is not a quantitative or even semi-quantitative test of oesophageal emptying, and the number of swallows taken to bring the pH of the oesophagus back to normal (i.e. clearance) is different from the number of swallows required to empty the body of the oesophagus of the bulk of its contents (Helm et al, 1984). An oesophageal emptying test was introduced by Tolin et al (1979) when they used radionuclide labelled sulphur colloid diluted in 15 mls of water to calculate the time it took for the radioactive counts to pass from oesophagus to stomach. In 15 normal subjects in the supine position they found that 93% of the counts had been emptied from the oesophagus after eight swallows at 15 second intervals. Russell et al (1981a) also have used radioactively labelled liquid to study transit through the oesophagus and oesophageal emptying.

## Oesophageal mucosal resistance

The oesophagus consists of a similar structure to the rest of the alimentary tract with a mucosa, a submucosa, a muscle layer and an adventitial outer coat (Geboes and Desmet, 1978). The mucosa consists of an epithelial layer of squamous cells, a subjacent lamina propria, and a muscularis mucosa. The epithelial layer consists of an outer layer of flat and non-keratinised squamous cells (the stratum spinosum), and a basal layer is usually less than 15% of the total thickness of the epithelial layer. Conical papillae containing blood vessels of the lamina propria reach into the epithelial layer but not usually to a point more than two-thirds of the epithelial thickness. Basal cells undergo mitotic activity and then migrate to the superficial layers. This process takes about 11 days in the lower oesophagus of the rat (Bertalanffy, 1960) although the rate of migration is not known in man.

Chronic irritative stimulation of the oesophageal mucosa leads to increased cell turnover in the basal layers and eventually basal cell hyperplasia (Schulze-Delrieu et al, 1978; Livstone et al, 1977).

In spite of the relative paucity of mucous secreting oesophageal glands in the mucosa and lamina propria (Ham, 1974) large amounts of mucopolysaccharide are found in the interstitial spaces between the squamous cells of the oesophagus (Hopwood et al, 1977).

Vagal stimulation in the dog leads to an outpouring of viscous, alkaline mucus (Vineberg and Komarov, 1933) but whether such control occurs in man is not known.

Oesophageal mucosa is normally impermeable to hydrogen ions. However, when acid of low pH comes in contact with the mucosa particularly when the acid is mixed with bile salts and/or pepsin then the mucosa loses its impermeability and back diffusion of hydrogen ions occurs (Safaie-Shirazi et al, 1975; Chung et al, 1977; Harmon et al, 1981).

Studies of saliva and the clearance of acid from the oesophagus suggest that mucus, mixed with alkaline saliva, may give some protection to oesophageal mucosal cells. Such a system has some resemblance to the 'unstirred alkaline fluid layer' on the surface of gastric mucosal cells.

GASTRODUODENAL MOTILITY

The stomach is divided into two functionally distinct compartments. The fundus and upper body acts as a reservoir for food while the lower body and antrum is responsible for the mixing and breakdown of solids. Liquid gastric emptying is thought to be due to the pressure gradient between stomach and duodenum, generated mainly by the proximal stomach. Deglutition and gastric distention results in prompt relaxation of the proximal stomach wall (Code and Carlson, 1968; Jahnberg, 1977) which permits the fundus and upper body of the stomach to act as a "hopper" for a large volume of food while maintaining low intragastric pressures.

Liquid emptying is reported to be under the influence of slow sustained contractions in the proximal stomach (Wilbur and Kelly, 1973) and that the rate of liquid emptying from the stomach increases linearly with increasing intragastric pressure (Strunz and Grossman, 1978). This contractile activity of the proximal stomach is under neural and hormonal control. The main neural influence is thought to be through the inhibitory vagal system. The transmitter of this nonadrenergic, noncholinergic system is not known. Of the hormones implicated in control of gastric function, cholecystokinin only, has been shown to inhibit proximal gastric contractions in physiological doses (Debas et al, 1975).

In contrast to liquids, solids are emptied from the stomach only when they have been changed to an essentially liquified form. Although some small solid particles will empty in parallel with liquids (Heading, 1982), normally particles are retained until less than 2 mm in size (Meyer et al, 1979b). 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 the pacesetter potentials or slow waves (Kelly et al, 1969). These 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 depolarizes at the fastest rate (Kelly and Code, 1971).

The pacemaker impulses are propagated both around the stomach and distally towards the pylorus at a rate of 3 to 4 cycles per minute in the human. Although the pacemaker determines the frequency of distal contractions, a more rapid change in potential (action potential) is required to initiate muscular contraction. 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. Through this grinding action along with acid-peptic digestion, most solid particles are reduced to chymous-like consistency allowing outflow into the duodenum. Several hormones can influence distal gastric contractions (Strunz, 1979), but only gastrin may have a physiologic role (Strunz et al, 1979; Morgan et al, 1978). Gastrin appears to increase the frequency of the gastric pacemaker and facilitates generation of action potentials (Morgan et al, 1978) however the net effect of gastrin is to retard gastric emptying. Neural pathways are poorly understood but involve both vagal and sympathetic fibres.

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 120 minutes in the fasting state in both dogs and humans (Code and Marlett, 1975). This cycle which is composed of four phases is called the migrating motor complex or interdigestive myoelectric complex. Phase 1 is a period of motor inactivity with only rare action potentials or contractions and lasts 45-60 minutes. During phase 2 there are intermittent peristaltic contractions that increase in frequency and amplitude over a

30-45 minute period. Phase 3 lasts approximately 5-15 minutes and is characterised by intense bursts of regular action potentials and contractions that appear with every pacemaker potential. In the fasting state the pylorus remains open as a phase 3 interdigestive contraction approaches and the contraction sweeps indigestible solids out of the stomach. Phase 4 is the short transition period between the vigour of phase 3 and the inactivity of phase 1.

Inco-ordination of any or all of these factors involved in solid and liquid emptying can lead to delay in gastric emptying. Although delayed gastric emptying of liquids or solids may be one of the mechanisms that predisposes to gastro-oesophageal reflux by increasing the volume of the gastric contents available for reflux into the oesophagus, investigation of this relationship have been conflicting. Behar and Ramsby (1978) found normal liquid emptying in patients with reflux oesophagitis but antral contractility and cumulative antral activity were observed to be decreased. Baldi et al (1981) found delay of liquid emptying in patients with oesophagitis. Other studies (McCallum et al, 1981; Donovan et al, 1977) reported mixed solid/liquid meals were significantly delayed in such patients but were not able to descriminate between solid and liquid emptying. Little et al (1980) documented solid gastric emptying in a group of 50 patients with pH probe documented reflux - 26 with endoscopic evidence of oesophagitis and 24 without. They reported that patients with oesophagitis as a group had delayed emptying. Patients without oesophagitis did not have significantly delayed emptying although their data suggests that some patients in this group probably fell outside their normal range. A poor correlation between symptoms such as nausea and vomiting and delay of gastric emptying as been reported in such patients (McCallum et al, 1981). Whether delay in gastric emptying in the presence of gastro-oesophageal reflux is a primary or secondary phenomenon remains to be determined.

## 2.3 ASSESSMENT OF GASTRO-OESOPHAGEAL REFLUX AND UPPER GASTRO-INTESTINAL MOTILITY.

(i) SYMPTOMS

The reflux of gastric contents into the oesophagus is a common event probably occurring daily in normal people (Dodds et al, 1982). Such reflux does not cause symptoms. On the other hand, even in normal people, reflux of gastric contents into the oesophagus does cause symptoms sometimes (Richter and Castell, 1982). Recent reviews of the subject have emphasised that many factors are involved in the development of symptoms from gastro-oesophageal reflux (Dodds et al, 1982). The severity of symptoms bears little relationship to the degree of inflammation of the oesophagus as assessed endoscopically and/or histologically. Also, just as endoscopy diagnoses some patients as having oesophagitis who do not have histological confirmation of this, occasionally it diagnoses some patients as normal who do have histological evidence of oesophagitis (Breen and Whelan, 1978).

The patient's symptoms will usually lead the clinician to diagnose the oesophagus as the origin of the problem and in typical cases a diagnosis is not difficult to make. Nevertheless, one cannot rely solely on symptoms. In one report of patients having anti-reflux surgery on the basis of their symptoms, operation worsened their condition.

Further investigation indicated that motor disorders such as primary diffuse spasm and achalasia were the real basis of their problem (Leonardi et al, 1981). However, it seems that in practice clinical decisions are really made on whether or not the patient has significant and serious symptomatic heartburn (DeMeester et al, 1974). Such statements avoid the question of whether the symptoms are due to reflux in the first place and also tend to ignore two important features of symptoms vis-a-vis reflux. The first is that severe oesophagitis, even causing stricture formation, can occur whilst the patient remains totally asymptomatic (Skinner, 1966; Leigh Collis, 1966). In similar fashion, others have found a lack of correlation between objective assessments of oesophagitis with endoscopy and histology, and severity of patients's symptoms (DeMeester et , 1976; Henderson, 1980). The actual amount of reflux which occurs similarly failed to correlate with patient's symptoms (Woodward, 1970).

Older methods of classification such as the Visick Classification are unsatisfactory and techniques such as analogue scoring are perhaps more useful (Kiroff et al, 1984). The best method of scoring may be found in combination analogue scoring (deDombal and Hall, 1979). In this method, several different symptoms are taken and graded on an analogue scale for severity, the points are then added or multiplied giving an overall grading of the severity of the disease. Several authors have used this approach with different numbers of symptoms for their scoring. For example Moran et al used 4 symptoms with a maximum score of 10 (1971), De Meester and Johnson used 2 symptoms with a maximum score of 6 (DeMeester et al, 1974), and Henderson used 9 symptoms with a maximum score of 14 (1976). There is general agreement that a complication of reflux such as overt bleeding or stricture formation should be given a maximum score. In large series of patients it is apparent that the commonest symptoms of reflux are heartburn, regurgitation and dysphagia, and these may be the most important symptoms to record. Henderson's suggestion that duration of symptoms should also be recorded is a reasonable one.

(ii) RADIOLOGY

Radiological methods of investigation have played an important role in defining the structure and function of the oesophagus. The conventional barium swallow has provided a standard means of diagnosis of hiatal hernia and is useful to exclude other diagnoses such as peptic ulcer disease or to identify possible complications of chronic reflux, e.g. Barrett's oesophagus. This test is available using a single or double contrast technique (Stewart, 1981).

Cine-radiography or fluoroscopy after gastric loading with barium provides a simple method for assessing gastro-oesophageal reflux that can be incorporated into a barium meal. The weakness of this test lies in the fact that many patients with gastro-oesophageal reflux show no abnormality. Kantrowitz et al (1969) compared the pH reflux test with radiological techniques in 29 subjects. In this study the radiologist was either unable to demonstrate reflux at all or identified it less frequently than the pH electrode in the five tests positive for reflux. Furthermore, Ritcher and Castell (1982) found that fluoroscopy had an average sensitivity of 40% and specificity of 85%. Attempts to increase the sensitivity of radiography with the acid barium (Donner et al, 1966) and water syphon tests (Linsman, 1965) have been disappointing. The water syphon test is largely unsuccessful because the lower oesophageal sphincter normally relaxes during swallowing and thus a high percentage of normal subjects will reflux (Crummy, 1966). The use of acid barium (pH 1.7) in an attempt to combine an acid clearance test with a normal barium swallow was also unsuccessful (Benz et al, 1972). They discovered a large variation in individual oesophageal sensitivity with 62% false positive and 40% false negative results.

Fluoroscopic observation of oesophageal motility has been available for many years. Cine-radiography, if properly performed, (Wolf and Khilnani, 1966; Stewart, 1981) compares favourably with oesophageal manometry, and may be used to provide functional information about the oesophagus. Concurrent recording of intraluminal pressures and x-ray appearances allow recognition of motor events visually and more confident interpretation in light of simultaneously recorded pressure events.

Radiological procedures are of use in investigating anatomical hiatus hernia and to a lesser degree reflux. Primary motility disorders such as achalasia may be very obvious or quite subtle with the characteristic oesophageal dilation becoming more prominent as the disease progresses. Diffuse oesophageal spasm usually needs manometric confirmation.

Secondary motility disorders associated with gastro-oesophageal reflux such as those encountered in systemic lupus erythematosis, Raynaud's disease; dermatomyositis and scleroderma may be elucidated radiologically.

(iii) MANOMETRY

a. Gastro-oesophageal

The earliest studies of oesophageal motility were done by Kronecker and Meltzer in 1883 using balloons. Fyke et al (1956) first identified the lower oesophageal sphincter manometrically and in 1957a, Atkinson et al noted the correlation between low lower oesophageal sphincter pressure and gastric reflux. In the first years of this new mode of investigation water filled, non infused catheters were used but they were not accurate enough to allow distinction of subjects with normal sphincter pressures from patients with severe reflux symptoms.

In the 1960's Pope (1967) developed an infused catheter system and found a clear separation between controls and reflux patients on the basis of lower oesophageal sphincter pressure. Later and larger studies had success to a lesser degree and revealed considerable overlap between normal subjects and those with reflux (Winans and Harris, 1967). In their review Richter and Castell (1982) concluded that poor sensitivity (58%) but good specificity (84%) was obtained if a lower oesophageal sphincter pressure less than 10 mmHg was used to distinguish between normal and refluxing patients. Thus a single value had little diagnostic value unless it resides at one end of the spectrum.

At this time there were two general methods for recording resting lower oesophageal sphincter pressure. The first introduced was the station pull through technique in which the recording sensors were intermittently withdrawn across the lower oesophageal sphincter in 0.5 to 1 cm increments. A pause of 20 seconds or more was made at each station. As a result, the pressure curve obtained was stepped and had respiratory oscillations at each step. The oscillations were probably attributable to movement of the lower oesophageal sphincter relative to the catheter system and bear little relation to pressure changes extrinsic to the oesophagus. Many scoring methods have been used (e.g. peak pressure, mean pressure, highest minimum pressure) but they were associated with considerable inaccuracy due to the pressure oscillations. The rapid pull through technique was performed by continuously (hand or motor) withdrawing a pressure sensor at the rate of 0.5 to 1.0 cm per second across the lower oesophageal sphincter with the patient's breath held. This latter procedure was simpler, saved time but was found to give values which seemed to have a much higher co-efficient of variation than pressures recorded using the slow pull through technique (Welch and Drake, 1980)

In 1979 Hay et al reassessed the reproducibility of lower oesophageal sphincter pressure as measured by the station pull through technique. Values obtained from time to time on the same day showed good reproducibility ($r = 0.88$) but were poorer ($r = 0.74$) from day to day. They concluded that measurement of lower oesophageal sphincter pressure as recorded by station pull through was more reproducible using a water infused catheter system and pointed out the enormous variation encountered if different recording systems are compared. In a comparison of station pull through and rapid pull through methods Welch and Drake

(1980) found that the rapid pull through method varied significantly more than the former. Peak pressures were also recommended as the easiest way to score station pull through pressures.

According to Dodds (1976a) the fidelity achieved in recording oesophageal pressure waves was inversely related to the wave amplitude and directly related to wave duration. When using infusion manometry the fidelity was related to the infusion rate and inversely proportional to the total complicance of the system, the major source of error. Understanding of these facts led Arndorfer et al (1977) to introduce an improved catheter infusion system in order to correct the excessive compliance of the then conventional syringe pumps. In order to achieve a reasonable degree of recording accuracy infusion rates of approximately 6 ml/min had been required. The new system, a minimally compliant hydraulic capillary infusion system enabled infusion rates of less than 1 ml/min.

In 1971, Kaye and Showalter demonstrated that the manometric tracing from a continuously perfused side hole catheter was greatly influenced by the orientation of the recording opening within the lower oesophageal high pressure zone. The problem posed by an asymetric lower oesophageal sphincter was solved by Dent (1976), who proposed a solution in the form of a 5 cm long perfused sleeve. It provided a continuous measurement of maximal lower oesophageal sphincter pressure in spite of sphincter or catheter movement.

Techniques of oesophageal manometry have greatly aided the understanding of normal and diseased oesophageal function. This investigation provided information about the length, location and pressure of the lower oesophageal sphincter. In addition it measured the speed and amplitude of the peristaltic wave and also its timing with sphincter opening. As such manometry has been used to screen for abnormalities of the lower oesophageal sphincter and in excluding other conditions such as achalasia, scleroderma or oesophageal spasm. This investigation may also provide a guide to the location of the lower oesophageal sphincter so that a pH electrode can be positioned in order to conduct other oesophageal function tests.

In the clinical field, however, considerable debate has arisen concerning the usefulness of manometric techniques. Pope (1981) concluded that the intrinsic variability of the lower oesophageal sphincter and the inaccuracies of recording techniques make pressure measurements useless unless they are at an extreme. On the other hand, Castell (1982) considered this investigation of relevance in evaluating patients with reflux oesophagitis and in assessing the potential for acid reflux in a clinical setting.

Meshkinpour et al (1982) stated that manometry is of benefit to patients with chest pain, dysphagia and those in whom achalasia is suspected but is of little benefit in patients with chronic heartburn. It was also noted that the clinical diagnosis was changed as a result of manometry in only 6% of the patients and the treatment altered in only 4%. Manometry can be of use in a clinical setting if its use is restricted to a carefully selected group of patients. Inability to demonstrate a high pressure zone at all in a patient is probably highly significant and any such patient can be presumed to have gastro-oesophageal reflux until proven otherwise. However, any value of lower oesophageal pressure above zero has some predictive value of the likelihood for reflux occurring but tells nothing about the actuality of reflux.

b. Antropyloroduodenal

The antropyloroduodenal region although easily defined anatomically provides considerable problems to assess functionally. The pylorus has been alleged to have a resting pressure by some workers (Fisher and Cohen, 1973; Valenzuela et al, 1976; Brink et al, 1965; Ehrlein, 1981; Pantoja et al, 1979) while others have been unable to demonstrate a resting tone (Atkinson et al, 1957b; Andersson and Grossman, 1965; Kaye et al, 1976a; McShane et al, 1980; White et al, 1981). The difficulties in interpreting these divergent findings of antropyloroduodenal manometry probably can be explained by two fundamental factors, the inadequacy of the recording systems used (Winans, 1976), and insufficient periods of recording (Vantrappen et al, 1977). The mainstay of manometric measurement of this region has been a side hole perfused manometric system, utilising a station pull through technique to identify the pyloric pressure (Fisher and Cohen, 1973; Kaye et al, 1976a). Others (Andersson and Grossman, 1965) have used a water filled balloon drawn across the pylorus. Both techniques have methodological problems similar to those encountered in assessment of the lower oesophageal sphincter prior to the introduction of the Dent Sleeve (Dent, 1976). Further the cyclical changes seen in the interdigestive motor complex make short term recording of the pylorus an unacceptable method of assessment. It may well be that all patterns currently observed in the pylorus existed in any one subject and their appearance depends on the phase of the interdigestive motor complex or hormonal status of the subject. Whatever the answer this area of enquiry remains in its infancy.

## (iv) pH STUDIES

### Acid perfusion test

In 1958 Bernstein and Baker introduced the acid perfusion test as a means of better defining the cause of typical symptoms of oesophagitis and in particular to distinguish between pains of cardiac and oesophageal origin. In this test 0.9% NaCl was administered at a rate of 6-7.5 ml/min for 15 to 30 minutes. Without the knowledge of the patient the test solution (0.1N HCl) was given at the same rate. The test was considered positive if the HCl caused pain, burning or other persistent symptoms of that nature. Sensations experienced should stop soon after cessation of acid administration. Bernstein found 9 out of 10 patients with endoscopically demonstrable oesophagitis had positive results and that 20 out of 21 patients without history or endoscopic findings of oesophagitis had negative findings. These results imply an excellent sensitivity and specificity. The acid perfusion test has little application to phenomena other than reflux, for example, no correlation with hiatus hernia has been found (Skinner and Booth, 1970).

Subsequent studies (Benz et al, 1972; Skinner and Hendrix, 1972) have brought into question the high specificity observed by Bernstein when a number of asymptomatic patients were found to have an acid sensitive oesophagus. For example, in 1976, Behar et al found that the acid perfusion test was positive in 88% of patients with chronic reflux symptoms but was also positive in 15% of normal subjects. In yet another study (Skinner and Booth, 1970) 100% of symptomatic subjects had positive results and 14% of asymptomatic subjects had positive results. Another problem was the incidence of false positive results in symptomatic patients without reflux. For the above reasons the acid perfusion test seemed of litte use in diagnosis of gastro-oesophageal reflux and should be confined to determining if a patient's oesophagus is symptomatically sensitive to acid. If reflux can be demonstrated, for example with the pH reflux test then there is a high probability that symptoms observed are due to gastro-oesophageal reflux.

Acid clearance test

The ability of the oesophagus to clear itself obviously plays a role in the prevention of prolonged gastro-oesophageal reflux. Booth et al (1968) first introduced the acid clearance test. Skinner and Booth (1970) have also suggested the value of the acid clearing test in discriminating between patients with or without visible oesophagitis by oesophagoscopy. In their paper 70% of patients with visible oesophagitis and 36% of patients without visible oesophagitis had abnormal acid clearance. In 1976 Krejs et al concluded that acid clearance was the best test to diagnose gastro-oesophageal reflux. Two years later Kjellen and Tibbling (1978), and others (Sonnenberg et al, 1982; Helm et al, 1984) proposed that the outcome of the acid clearing test was dependent on salivary production, the state of the oesophageal musculature and body position (supine or upright).

The presence of acid in the oesophagus has been implicated in the production of motor abnormalities in people who have significant gastro-oesophageal reflux (Stanciu and Bennett, 1974a). Since efficient peristalsis initiated by swallowing is important if normal clearance is to be achieved, the presence of acid may slow oesophageal clearance. Alternatively, motor defects may lead to greater acid exposure worsening the inefficient peristalsis in a positive feedback fashion.

One of the deficiencies of this test lies in the fact that the pH probe records the pH in its immediate vicinity but has no method of distinguishing between small and large acid volumes (Dodds et al, 1981). While attractive in its simplicity, this test does not appear to be presently worthwhile performing in the assessment of patients.

pH reflux test

Imprecise correlation between manometry results and abnormal gastro-oesophageal reflux has led to attempts to demonstrate reflux directly. The pH reflux test first introduced in 1958 by Tuttle and Grossman has been widely used and provides a way of directly and qualitatively measuring gastro-oesophageal reflux even if the tube system alters the normal physiologic state.

In general, the test features gastric loading with approximately 300 ml of 0.1 n HCl and positioning of a pH probe 5 cm above the manometrically localized lower oesophageal sphincter. If no spontaneous reflux occurs the subject then undergoes a number of manoeuvres (e.g. coughing, Valsalva and Muller) to reduce lower oesophageal sphincter pressure and any reflux events are recorded. A decrease in oesophageal pH to less than 4 on at least 3 occasions is considered to evidence gastro-oesophageal reflux.

In its original form the acid reflux test had a number of false positive and negative results. To reduce these, Skinner and Booth (1970) developed the standard acid reflux test (SART) in which the number of drops in pH and the proportion of the study during which oesophageal pH is less than 4 are combined into a score ranging from 0 to 3+. Zero and 1+ are values considered consistent with normal oesophageal function. In their study, from 91 normal subjects a false positive rate of 2.2% was found. The results of their test correlated significantly with radiographic and symptomatic evaluations of 306 patients who had some upper abdominal or chest symptoms and/or a hiatal hernia.

It is highly probably that false negative tests do occur in subjects who have intermittent reflux present on the day of testing (Ismail-Beigi et al, 1970) but this cannot be detected efficiently unless 24 hour pH monitoring is used.

In 1972, Benz et al found that 26 out of 29 symptomatic patients refluxed acid into the oesophagus as defined by their test. Twenty out of twenty one asymptomatic subjects had no demonstrable reflux. These results implied an excellent sensitivity (89%) and specificity (95%). They also compared radiological evidence of reflux (acid barium swallow) with the pH probe. The pH reflux test was positive in 27 subjects but only 16 were seen to reflux during radiological examination. In a later study Thurer et al (1974) scored patients for symptoms of heartburn, regurgitation, dysphagia and bleeding with a total range of 0 to 12. Seventy five per cent of strongly symptomatic patients (scores greater than 4) showed abnormal reflux during the SART. Of the 63 asymptomatic subjects 13% had abnormal reflux. These figures are less favourable than those of Benz et al (1972). Further evidence supporting the data of Thurer et al (1974) was provided by Richter and Castell (1982) who reviewed a number of studies. The acid reflux test had an overall sensitivity of 84% and a specificity of 83%.

The pH reflux test is simple, takes about 60 minutes to complete and has acceptable sensitivity and specificity but it requires intubation and special equipment. It is not a first line investigation.

24 hour pH

The logical extention of studies designed to induce reflux in patients suspected of having gastro-oesophageal reflux was to actually measure naturally occurring reflux events. This is achieved initially by placing a pH probe into the distal oesophagus and leaving it in position for 24 hours (Johnson and DeMeester, 1974). During this time the patient was able to have a normal diet, sit and lie down as required. The disadvantage was that measurements required the patient to be connected to a recording instrument which was usually bulky and restricted movement. More recently this problem has been overcome by modern technology in developing ambulent 24 hour pH systems (Weiser and Siewert, 1982; Breedijk and Akkermans, 1984). These still require a pH probe to be inserted but the recording device can be worn on a belt. This not only enables the patient to go home and enjoy a normal diet, but also to reproduce normal activity which may include bending or straining.

Studies in a large number of controls has lead to a normal range for 24 hour studies being developed (DeMeester et al, 1980). It is stated that if more than 4% of the 24 hour period has a pH of less than 4 then the patient lies outside the normal. Prolonged pH monitoring has been found to have the best sensitivity (88%) of any clinical test of gastro-oesophageal reflux as well as excellent specificity (98%) (DeMeester et al, 1980; Richter and Castell, 1982). This investigation may offer the current "gold standard" in assessment of gastro-oesophageal reflux however it is not always well tolerated by patients and relies on patients accurately recording their food consumption over the period. It may be particularly valuable in patients with atypical symptoms or in patients who have clear cut symptoms of reflux but in whom other studies have failed to show any objective evidence of reflux.

### (v) RADIONUCLIDE TECHNIQUES

#### Oesophageal

Although radiography and endoscopy provide accurate anatomic information about the oesophagus and manometry defines its motor functions, they all induce a change in the normal physiological state. Manometry and endoscopy require introduction of foreign bodies and radiography uses a foreign material such as barium as a test medium. For these reasons, the techniques of radionuclide labelled substances to assess oesophageal function was first introduced by Kazem (1972). The new investigation was called a "radioesophagram" and it entailed patients drinking 0.5 - 1 mCi $^{99m}$Tc pertechnetate dissolved in a total volume of 10 - 20 ml water or tea. During passage of the fluid bolus from the mouth to the stomach a gamma camera linked to a computer was used to digitally record positional information about each event. It was found that a time delay of 1 - 2 seconds occurred in the vicinity of the aortic arch and the lower third of the oesophagus produced a delay of about 5 seconds. Kazem also applied his test to patients with mechanical or functional obstruction of the oesophagus and hence started to define the types of abnormality this test can detect.

Four years later, Fisher et al (1976) evaluated a similar technique in 30 patients with heartburn and a positive acid reflux test in 20 normal subjects. One hundred micro-Ci $^{99m}$Tc-sulphur colloid was diluted with isotonic saline and instilled into the stomach using a nasogastric tube. The gastro-oesophageal pressure gradient was increased using an abdominal pressure cuff in 5 mmHg steps from 5 to 35 mmHg with a 30 second scintiscan being taken at each level. If no reflux was demonstrated the procedure was repeated using acid instead of saline. A gastro-oeophageal reflux index was calculated which was an expression of radioactive counts over the oesophagus as a percentage of gastric counts. A reflux index value of 4% or greater enabled visualisation of the oesophagus. The patients with gastro-oesophageal reflux were also investigated using conventional methods, namely barium oesophagography, fluoroscopy, oesophagogastroscopy, fluoroscopy, oesophageal biopsy, acid perfusion testing and oesophageal manometry. Scintiscanning detected reflux in 90 % of patients, a greater sensitivity than any of the above tests. Ten per cent of normal controls exhibited reflux only at the highest gastro-oesophageal pressure gradient after the instillation of acid. However, such a technique still suffers from the non-physiological increase in abdominal pressure. This test is semi-quantitative only and such factors as a hiatus hernia and poor oesophageal emptying will undoubtedly influence the result.

The excellent sensitivity and specificity found by Fisher et al (1976) was challenged by Hoffman and Vansant (1979) who obtained positive results in only 4 out of 29 reflux patients. More support for the sensitivity of this new investigation has been provided (Rudd and Christie, 1979; Malmud and Fisher, 1981) and it is now considered a viable method of quantitating gastro-oesophageal reflux and oesophageal transit. Later, Menin et al (1980) attempted to determine the utility of scintiscanning in predicting which patients would benefit from anti-reflux surgery. A linear relationship was found between the gastro-oesophageal reflux index and the severity of clinical symptoms as assessed by a symptom score (r = 0.7). The reflux index was greater than 10% in all patients with severe clinical symptoms and in 11 out of 12 patients who underwent anti-reflux surgery. Since the reflux index is a measure of oesophageal clearance as well as the quantity of reflux, it reflects the contact time betwen refluxed gastric contents and the oesophageal mucosa. It is not suprising that this could correlate with symptomatic severity.

In 1979 Tolin et al used scintigraphy to quantitate oesophageal transit in a total of 62 normal subjects and patients. Subjects ingested 150 micro-Ci of $^{99m}$Tc-sulphur colloid diluted in 15 ml $H_2O$ in a single swallow. Swallows were performed repeatedly for the next 10 minutes at 15 second intervals. Transit after a single swallow was determined by counting the oesophageal activity at 1 second intervals for 15 seconds after maximal activity occurred. The rate was defined by the following:

$$Ct = \frac{Emax. - Et}{Emax} \times 100$$

where Ct = % oesophaeal transit at time t, E max. = maximal count rate in the oesophagus, Et = the oesophageal count rate at time t. They found that patients with motor disorders of the oesophagus such as achalasia, scleroderma and diffuse oesophageal spasm had significantly slower oesophageal clearance.

Russell et al (1981b) assessed oesophageal motor function in 19 patients with symptomatic gastro-oesophageal reflux both before and three months after anti-reflux surgery (Hill repair). As a result of operation the mean lower oesophageal sphincter pressure was raised from 8.6 mmHg to 18.5 mmHg. Although no patient had postoperative reflux, radionuclide transit demonstrated the persistence of oesophageal motor dysfunction in 52% of patients. This disorder may have been of a primary nature producing delayed oesophageal clearance and with time, the reflux symptoms patients experienced. In a separate study by Holloway et al (1983) oesophageal emptying was evaluated in order to quantitate the results of therapy in 29 achalasic patients. Because symptoms have largely been used as criteria for assessment of treatment, the results of radionuclide transit studies were compared with the findings of graded symptoms scores as well as lower oesophageal sphincter pressure. Percentage changes in oesophageal emptying and lower oesophageal sphincter pressure before and after treatment were significantly correlated ($r = 0.76$, $p < 0.01$). Comparison of oesophageal emptying and symptom scores yielded a correlation coefficient of 0.70 ($p < 0.05$). Although significance levels were achieved, it was not possible to establish a level of improvement in emptying rates which would precisely predict eventual success in the individual patient. Thus, the usefulness of this test in follow-up of achalasic patients is not clearly established.

Scintiscanning is the most sensitive non-invasive test for the presence of reflux. In comparison, roentgenographs are not quantitative and require a much greater radiation burden. Cine oesophagraphy has a low sensitivity (it detects only 2/3 patients with reflux), exposes the patient to more radiation and the density of the barium used may influence its passage down the oesophagus. The only test matching scintigraphy with respect to sensitivity is 24 hour pH reflux test, but the latter requires intubation and hence disruption of the normal physiological state. Although not widely utilised as a method of investigation of oesophageal transit, radionuclide techniques have many advantages over other standard tests and therefore have a promising future.

### Gastric

Radionuclide techniques in assessment of gastric emptying in gastro-oesophageal reflux were first reported by Donovan et al in 1977. Since then a number of studies have reported delay of solid or liquid emptying in such patients (Csendes and Henriquez, 1978; Baldi et al, 1981; Velasco et al, 1982; McCallum et al, 1981). The methods used have utilised radionuclide labelled solid, liquid or mixed meals administered to patients in either the supine or upright position. The test requires no intubation or injection which not only creates a more physiological assessment but overcomes the alteration in gastric emptying associated with stressful stimuli (Thompson et al, 1983).

Much debate on the use of these tests has centred on the marker used. 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 by Griffith et al (1966) is not an accurate marker of the solid phase, because of the considerable dissociation of nuclide into the liquid. Conversely $^{51}Cr$ as a liquid marker may be absorbed onto solid food components (Heading et al, 1971). The use of $^{99m}Tc$-sulphur colloid (Meyer et al, 1976) labelled chicken liver overcame the problems of loss of marker to the liquid phase and has become the accepted technique for solid emptying studies. Some other digestible solid markers such as $^{99m}Tc$-egg (Malmud et al, 1982; Velasco et al, 1982) have a high labelling efficiency which is only slightly less than in-vivo labelled chicken liver. The liquid component of a meal may be studied on a separate occasion to the solid meal or by utilising an isotope of markedly different energy (e.g. $^{113m}In$), studies can be performed simultaneously (Heading et al, 1976). To date such a simultaneous study has not been applied to patients with gastro-oesophageal reflux. Although mixed meals have been used (McCallum et al, 1981) no specific solid or liquid marker was used.

The clinical significance of these studies to patients with gastro-oesophageal reflux remain in debate (Heading, 1982; Minami and McCallum, 1984) but they may offer a rational basis for intervention aimed at improving gastric emptying when such a delay is found.

(vi) ENDOSCOPY

Winkelstein (1935) was able to make his observations leading to the paper "Peptic oesophagitis - a new clinical entity" because he was able to view the oesophageal mucosa through an oesophagoscope. The usefulness of endoscopy was not really established until later however. For example, Boros in 1953 examined 50 patients with a flexible oesophagoscope and found only 3 instances of oesophagitis. Siegel and Hendrix (1963) were among the first to try and place the assessment of reflux on a scientific footing. They graded oesophagitis endoscopically as 0 = normal, 1+ = reddening of the mucosa, 2+ = granularity and/or friability of the mucosa. They found that 20 of their 25 reflux patients had endoscopic evidence of oesophagitis but so did 5 of their 10 control patients. Others have since also found that endoscopic inflammation (usually regarded of minor degree) can be diagnosed in patients subsequently thought to be normal (Breen and Whelan, 1978). The opposite also occurs with endoscopy. Palmer (1954) first pointed out that histological changes of oesophagitis could occur in the face of normal endoscopic appearances.

Endoscopic classifications of oesophagitis have been proposed by many authors (Dagradi, 1967; Belsey and Skinner, 1972; Savary and Miller, 1978; Kobayashi and Kasugai 1974; Allison, 1972).

Allison et al (1972) in his classification included elements which related to management (e.g. dilatation) and operation (e.g. the presence or absence of mediastinal involvement). Nevertheless, he introduced into the endoscopic classification the distinction between a wholly squamous lined oesophagus with inflammation in the squamous part and a columnar lined oesophagus with inflammation in the columnar epithelium.

Different endoscopists view similar lesions differently but there does seem to be some general agreement. First, that endoscopy underestimates the histological changes of gastro-oesophageal reflux, and second that erythema alone represents the least degree of endoscopic oesophagitis, that ulceration indicates a more severe degree, and that fibrotic stricture formation represents the worst degree.

(vii) HISTOLOGICAL ASSESSMENT

In an autopsy series of 213 patients Butt and Vinson established that oesophagitis was not a post mortem phenomenon and divided cases into acute and chronic oesophagitis on the presence of absence of acute inflammatory cells (1936). Use of the oesophagoscope offers the opportunity to take biopsies and examine the histology of the mucosa (Behar et al, 1976). Some, however, consider such biopsies to be too small (Ismail-Beigi and Pope, 1974). As a result other techniques have been developed such as the Rubin suction biopsy tube and the Quinton hydraulic tube. The effectiveness of the latter techniques may be impaired by the presence of thick mucus in the oesophagus (Ismail-Beigi and Pope, 1974; Ismail-Beigi et al, 1970). In 1974, Ismail-Beigi and Pope found that in general reflux lesions are randomly distributed over the distal 8 cm of the oesophagus. This fact reduces the need for accurate location of a biopsy site using manometry if multiple biopsies are taken.

Before an appreciation of the histology of oesophageal reflux can be obtained a brief review of normal histology should be undertaken. The stratified non-keratinised epithelium of the human oesophagus has three layers: basal (stratum basale), polygonal or prickle (stratum spinosum and granulosum) and the functional or protective layer (stratum corneum). Beneath the epithelium lies loose connective tissue (lamina propria) and then a thin layer of smooth muscle (muscularis mucosa). Deeper still lie the sub-mucosal and muscle layers.

The histological criteria of reflux oesophagitis came to note when Lodge made the first attempt to infer relationships between the gross and microscopic appearances of oesophagitis in 1955. In the same year Palmer first described hyperplasia of the basal layers and concluded that the presence of sub-epithelial accumulations of lymphocytes, plasma cells and occasional neutrophils indicated oesophagitis. According to these criteria many patients with symptoms of reflux had no histological evidence of inflammation. In addition biopsy specimens from normal controls showed inflammation on occasion. Subsequent study and re-evaluation of the histological criteria by Ismail-Beigi et al (1970) yielded a better correlation between reflux symptoms and histological findings. The new criteria suggested were extension of the papillae more than 2/3 of the way towards the epithelium (> 15% of the thickness of the epithelium). Round cell collections in the lamina propria were considered normal. Neutrophils were not found in specimens from the heartburn group. Using these criteria 85% of subjects with reflux had abnormal histology and 90% of controls had normal biopsy results. Subjects with reflux were separated from control subjects when 2 or more abnormal biopsies were taken.

The established criteria were brought into question to some extent when a study by Weinstein et al (1975) found that 57% of biopsies obtained from the distal 2-5 cm of the oesophagus in asymptomatic subjects exhibited basal cell hyperplasia and elongated papillae. This group went on to conclude that these histological criteria are unlikely to be of significant diagnostic value in a clinical setting. Similar histological features have also been found in another study by Behar et al (1976) in up to 30% of normal subjects.

More recently the presence of a small number of intra-epithelial eosinophils has been found to correlate well with abnormal acid clearance (as established by overnight intra-oesophageal pH probe studies) (Winter et al, 1982). Abnormal acid clearance was found in 17 of 18 patients with intra-epithelial eosinophils indicating a high specificity. Of 35 patients with delayed acid clearance only 17 had intra-epithelial eosinophils and hence this marker has a low sensitivity. Because intra-epithelial eosinophils were present in patients with prolonged acid clearance times in all age groups (including children under 2) it has been suggested that this may be an early lesion. In older patients the presence of eosinophils in greater number implies reflux of greater duration and/or severity.

## 2.4 TREATMENT OF GASTRO-OESOPHAGEAL REFLUX

### (i) MEDICAL

Broadly medical management can be divided into physiological, dietary and pharmacological. All are capable of providing excellent symptomatic and objective improvement in gastro-oesophageal reflux.

### Physiological Treatment

In essence the advice is simple. Regular meals 3 times a day and weight reduction are recommended (Richter and Castell, 1982) although it should be noted that no study has proven the relationship between gastro-oesophageal reflux and obesity (Beauchamp, 1983). The last meal of the day should be taken some hours before going to bed. Elevation of the bed head 6-9 inches has also been shown to be of benefit in reducing reflux events (Johnson and DeMeester, 1981). Common sense also would require avoidance of undue bending or straining if this was associated with symptoms

### Dietary Therapy

Certain food types are well known to aggrevate gastro-oesophageal reflux primarily through reducing the pressure in the lower oesophageal sphincter. Such foods as fats, chocolate, alcohol and carminatives (Nebel and Castell, 1972; Sigmund and McNally, 1969) have been implicated. Foods that have a direct irritative effect on the oesophagus such as citrus juices, tomato products and coffee should be avoided. Their effect may be a pH dependent effect on inflamed mucosa (Price et al, 1978) or it may be due to a high osmolarity (Lloyd and Borda, 1981)

Coffee may also alter sphincter pressure and augment acid secretion (Cohen and Booth, 1975; Thomas et al, 1980; Salmon et al, 1981). Smoking causes a reduction in lower oesophageal sphincter pressure and should be avoided (Dennish and Castell, 1971)

## Pharmacological Treatment

Antacids have gained wide popularity in the management of gastro-oesophageal reflux. They act by increasing the tone of the lower oesophageal sphincter and neutralising the gastric and oesophageal contents. The studies that show improvement, both symptomatic and objective, on antacid therapy have lacked true placebo groups (Graham et al, 1977; Stanciu and Bennett, 1974b). The placebo effect in management of gastro-oesophageal reflux may be more important than currently thought. Alginic acid is also effective in the treatment of reflux disease, but probably no better than antacid therapy (Graham et al, 1977). A cholinergic agent that increases lower oesophageal sphincter tone and improves oesophageal acid clearance is bethanechol. It has been shown to decrease symptoms , decrease antacid use and promote healing of oesophagitis (Farrell et al, 1974; Thanik et al, 1980).

Another agent that acts to increase lower oesophageal sphincter pressure (McCallum et al, 1975) is metoclopramide, a dopamine antagonist. Further it has been shown to increase gastric emptying in gastro-oesophageal reflux patients (Fink et al, 1983b). Its effect in these patients has however only been assessed after acute dosage, no data is available for its long term effect on gastric emptying in such patients. Results of clinical trials have tended to be inconclusive in regard to its value in chronic gastro-oesophageal reflux (McCallum et al, 1977; Wallin et al, 1979; Venables et al, 1973). Further at the dosage of 10 mg four times a day one study (Bright-Asare and El-Bessoussi, 1980) reported one third of patients experienced important side effects of a neurological or psychological nature. Histamine $H_2$-receptor-blocking agents such as cimetidine are able to decrease gastric acid production. Trials using Cimetidine have been successful in controlling the symptoms of reflux (Bright-Asare and El-Bessoussi, 1980) and in some actually leading to significant healing of oesophagitis (Wesdorp et al, 1978). More recently preliminary trials have been conducted with omeprazole, a proton pump poison that produces achlorhydria, (Dent et al, 1984) with encouraging results showing relief of symptoms and complete healing of oesophagitis.

(ii) SURGERY

Although not accurately reported it is thought 5% to 10% of patients with gastro-oesophageal reflux will fail to respond to the best in medical therapy (Richter and Castell, 1982) and progress to anti-reflux surgery. Such surgical treatment has evolved from correction of hiatal hernia alone to the modern techniques of constructing an artificial valve between the stomach and oesophagus (Dillard et al, 1954; Donahue and Bombeck, 1977). The procedures currently utilised to prevent gastro-oesophageal reflux include the Nissen fundoplication (Nissen, 1961) the Hill trans-abdominal gastropexy (Hill, 1967) and the Belsey Mark IV trans-thoracic repair (Skinner and Belsey, 1967). Although the details of these operations vary, common features exist and have been proposed as an explanation for their success. These include securing an abdominal segment of oesophagus for exposure to the positive pressure environment of the abdomen, constructing a valvuloplasty to transmit fundal pressure to the lower oesophageal sphincter and anchoring the distal oesophagus in order to improve the efficiency of peristaltic clearance of refluxed material (Bombeck et al, 1971; DeMeester et al, 1979; 1981). Siewert et al (1973) have shown that the fundoplication responds physiologically in a manner similar to the lower oesophageal sphincter. However, many examples of post-operative relief of symptoms without concomitant increase of lower oesophageal sphincter tone have been reported (Hill, 1972; Moran et al, 1971; Katz et al, 1974; Bahadorzadeh and Jordan, 1975). Further DeMeester et al (1974) also found that an improvement in symptoms did not necessarily mean an absence of abnormal reflux as determined by pH monitoring. They also found that dysphagia was a symptom that while often present immediately post-operatively improved with time. This may be due to adjustment of a stretched oesophagus as suggested by DeMeester et al (1974) or due to an improvement in oesophageal function following cessation of reflux. However Russell et al (1981b) failed to show any improvement in oesophageal function following a Hill repair using a radionuclide technique, suggesting that the dysfunction is a primary one in patients with gastro-oesophageal reflux rather than secondary to the reflux itself.

Complications of anti-reflux surgery are infrequent and include oesophageal perforation, vascular injury, traumatic vagal nerve injury, transient dysphagia and the inability to belch or vomit. The procedures in experienced hands enjoy an operative mortality ranging from 0.2% to 1.6% (Richter and Castell, 1982). Current understanding of the long term outcome for surgical treatment of gastro-oesophageal reflux is still unclear. Brand et al (1979) found that relief of heartburn occurred in most patients 5 to 6 years following surgery. However, comparison of surgical and medical treatments are made difficult by the rapidity of developments in both fields. The last few years has seen the emergence of a silicone prosthesis (Angelchik and Cohen, 1979) for the management of gastro-oesophageal reflux. It does not eliminate hiatal herniation and does not construct a valve mechanism at the gastro-oesophageal junction. Samelson et al (1983) have suggested it acts by interrupting distraction of the lower oesophageal sphincter by gastric wall tension.

The success of such a simple and poorly explained prosthesis exemplifies the problems in defining the etiology of gastro-oesophageal reflux. Surgical correction if it is to be rational requires detailed pre- and post-operative assessment of all factors implicated in its occurrence such as lower oesophageal sphincter pressure, oesophageal emptying and clearance, and gastric emptying. With this knowledge appropriate tailoring of surgery can be undertaken.

## SECTION III

## METHODS OF ASSESSMENT OF UPPER GASTROINTESTINAL MOTILITY

3.1 The Oesophagus

(i) Oesophageal Manometry
a. Technique
b. Validation Studies

(ii) Oesophageal Acid Clearance
a. Technique
b. Validation Studies

(iii) Oesophageal Emptying
a. Technique and Validation
b. Correlation with Barium studies

3.2 The Stomach

(i) Induction of reflux by gastric acid loading
a. Technique
b. Validation

(ii) Radionuclide Gastric Emptying
a. Technique
b. Validation
Reproducibility
Normal controls

(iii) Paracetamol assessed Gastric Emptying
a. Technique and Validation

3.3 The Duodenum

(i) Antropyloroduodenal Manometry
a. Technique
b. Validation

(ii) Duodenogastric Reflux
a. Technique
b. Validation

3.4 Symptoms

(i) Method of Scoring

## 3.1 **THE OESOPHAGUS**

### (i) OESOPHAGEAL MANOMETRY

#### a. Technique

Manometric studies were performed using a continuously perfused 8 channel catheter assembly incorporating a Dent sleeve (Dent, 1976) at the distal end. With the assembly passed pernasally a side hole was located 2 cm distal to the sleeve to measure intra-gastric pressure. The sleeve itself was 6 cm long and positioned in the lower oesophageal sphincter. Five centimetres above its proximal end and then at subsequent 5 cm intervals the remaining 6 side holes were located. The assembly was connected to a low compliance hydraulic-capillary infusion system (Arndorfer Medical Specialties, Wisconsin) which perfused each channel at the rate of 0.5 ml/min (Arndorfer et al, 1977). The perfusate used was distilled water. Statham pressure transducers (Model P23 ID, USA) recorded changes in luminal pressure and were connected to an eight channel Grass Polygraph (Model 7D Polygraph, Grass Instrument Co, Quincy, MASS, USA).

Manometry records were interpreted by one observer and intra-gastric pressure was used as a zero reference in the measurement of sphincter pressures. By utilising the Dent sleeve a continuous record of the lower oesophageal sphincter pressure was obtained. The pressure used for statistical comparison was calculated over a one minute sample at the end of a 5 minute rest period. This was achieved by measuring the lower oesophageal sphincter pressure at 5 second intervals relative to intra-gastric pressure, but without regard to the phase of respiration but excluding swallow waves and from the sum of these measurements calculating a mean.

The contracting pressure of oesophageal contractions was defined as the mean of the maximum heights achieved by the contracting wave.

Co-ordination in the upper sphincter was the percentage of relaxations of the sphincter occurring with pharyngeal contractions. Similarly for the lower oesophageal sphincter a co-ordinate relaxation was one that occurred with initiation of a swallow. Any contraction of the sphincter during contraction proximally was deemed inco-ordinate.

Relaxation was defined as the percentage of swallows that achieved complete relaxation prior to contraction. For upper oesophageal sphincter relaxation it was defined as the return to intra-oesophageal pressure. For the lower oesophageal sphincter it was to the return to intragastric pressure.

No sedation was used during the studies. However local anaesthetic nasal spray (Xylocaine 10%, Astra Pharmaceuticals) and lubricating jelly (Xylocaine 2%, Astra Pharmaceuticals) were routinely used.

b. Validation Studies

The validity of the manometric recording system has been well established (Dent, 1976; Arndorfer et al, 1977). However, no studies have been conducted as to the reproducibility of the oesophageal manometry from day to day. To assess this, 16 normal volunteers were studied (10 males, 6 females, median age 34 years, range 21 - 69) on two separate days seven days apart. On both occasions standard manometric assessment was performed. Table 3.1 shows the results obtained for the group by each variable measured on each day. A paired "t" test revealed no significant difference between the results obtained on either day for the individuals studied. This finding provides a basis for assuming that manometric findings made on the day of oesophageal manometry may be anticipated to be present at the time of subsequent investigations providing they are performed within some days of the initial investigation.

TABLE 3.1

MANOMETRIC ASSESSMENT OF NORMAL CONTROLS ON 2 SEPARATE DAYS. VALUES ARE MEDIAN WITH RANGE IN BRACKETS

| VARIABLE | DAY 1 | DAY 2 | n |
|---|---|---|---|
| Upper oesophageal Sphincter | | | |
| Co-ordination (% normal) | 100 (all 100) | 100 (all 100) | 12 |
| Relaxation (% complete) | 100 (all 100) | 100 (all 100) | 12 |
| Resting pressure (mmHg) | 34.5(13-63) | 33 (18-58) | 12 |
| Contracting pressure(mmHg) | 87 (49-100+) | 100 (75-100+) | 12 |
| Proximal oesophagus | | | |
| Resting pressure (mmHg) | -2 (-5-4) | -2 (-6-1) | 14 |
| Contracting pressure(mmHg) | 55 (34-95) | 43 (24-64) | 14 |
| Type of contractions: | | | |
| primary (%) | 100 (77-100) | 100 (89-100) | 15 |
| secondary (%) | 0 (all 0) | 0 (all 0) | 15 |
| tertiary (%) | 0 (0-23) | 0 (0-11) | 15 |
| Distal oesophagus | | | |
| Resting pressure (mmHg) | -0.5(-6-4) | -1.0(-5-6) | 16 |
| Contracting pressure(mmHg) | 75 (32-131) | 73.5(31-100) | 16 |
| Type of contraction: | | | |
| primary (%) | 95 (75-100) | 97 (56-100) | 16 |
| secondary (%) | 0 (0-4) | 0 (0-14) | 16 |
| tertiary (%) | 3 (0-21) | 0 (0-44) | 16 |
| Lower oesophageal sphincter | | | |
| Co-ordination (% normal) | 100 (86-100) | 100 (96-100) | 16 |
| Complete relaxation (%) | 93 (33-100) | 97.5(15-100) | 16 |
| Resting pressure (mmHg) | 17 (4-25) | 17 (4-40) | 16 |
| Contracting pressure(mmHg) | 49 (21-160) | 63 (24-100) | 16 |
| Intragastric pressure(mmHg) | 2 (-1-6) | 3 (-2-7) | 16 |
| Gradient across LOS (mmHg) | 13.5(2-25) | 13 (2-36) | 16 |

(ii) OESOPHAGEAL ACID CLEARANCE

a. Technique

The test was described by Booth et al in 1968. A stomach pH electrode (Radiometer GK2801C-0) attached to the multi-lumen catheter assembly 5 cm above the proximal end of the Dent sleeve was used. The electrode was connected to a Radiometer pH meter (PHM83, Autocal pH meter, and PHM82) and this in turn connected to the Grass Polygraph for recording pH changes in relation to manometric changes. The assembly was positioned in the supine subject so that the sleeve was positioned in the lower oesophageal sphincter with the pH probe then located in the distal oesophagus. Fifteen ml of acid (pH 1.0) was instilled into the oesophagus (via a manometry channel) and the patient instructed to perform swallows at 15-30 second intervals. The pH was recorded and the number of swallows taken for the oesophageal pH to return to greater than 4 recorded. This procedure was repeated for uninstructed swallows. Also both instructed and uninstructed studies were conducted with the addition of 5 mls of water into the mouth to aid the subject in swallowing and clearing the oesophagus. Studies were terminated if clearance had not occurred by 30 swallows.

b. Validation Studies

The use of this test as a means of assessing oesophageal function by its ability to return oesophageal pH to greater than 4 after instillation of acid has been used for a number of years. However, the test when conducted in normal controls has given a wide range of values by different authors, ranging from less than 10 swallows (Booth et al, 1968) up to a mean of 38 swallows for 20 normal subjects (Krejs et al, 1976). Further the effect of posture on acid clearance was not known, nor was the outcome of altering the volume of instilled acid from 15 ml to 40 ml. Reproducibility of the test from one day to the next was not established. To address these questions a series of studies were performed.

The same 16 normal volunteers used in the oesophageal manometry validation studies (3.1 (i) b.) also had acid clearance studies performed and repeated seven days apart. Table 3.2 shows the results obtained for instructed, uninstructed dry and wet swallows for each of the test days. The instructed dry swallows seemed at least as useful as any of the other four combinations and these were compared with a group of sixteen, age and sex matched, patients with gastro-oesophageal reflux. The median number of dry instructed swallows in this group was 25 (range 11-30). Analysis by a Wilcoxon unpaired test showed no significant difference between the two groups. An additional group of 8 patients (6 males, 2 females) with chest pain for investigation referred to the Department of Surgery at the University of Adelaide also had assessment of

TABLE 3.2

VARIATION IN OESOPHAGEAL ACID CLEARANCE FROM DAY TO DAY.

VALUES SHOWN ARE MEDIAN WITH RANGE IN BRACKETS

| | DAY 1 | | DAY 2 | | n |
|---|---|---|---|---|---|
| Instructed dry | 21 | (8-30+) | 21 | (12-30+) | 16 |
| Instructed wet | 30 | (18-30+) | 27.5 | (13-30+) | 10 |
| Uninstructed dry | 30 | (15-30+) | 30 | (20-30+) | 10 |
| Uninstructed wet | 28.5 | (8-30+) | 30 | (18-30+) | 8 |

acid clearance in the supine and upright position with 15 ml and 40 ml of acid with dry instructed swallows. Table 3.3 shows the results of this study. The test was not significantly altered by posture or volume.

The acid clearance test in this study did not discriminate between normal volunteers and patients with gastro-oesophageal reflux. Posture did not influence the number of swallows required to return the pH to 4. Volume instilled did not alter clearance.

TABLE 3.3

RESULTS OF OESOPHAGEAL CLEARANCE IN PATIENTS FOR INVESTIGATION OF CHEST PAIN PERFORMED IN UPRIGHT AND SUPINE POSITIONS. TWO VOLUMES OF ACID WERE INTRODUCED INTO THE DISTAL OESOPHAGUS, 15 ML AND 40 ML. VALUES SHOWN ARE MEDIAN WITH RANGE IN BRACKETS

| | VOLUME | |
|---|---|---|
| | 15 mls | 40mls |
| Position: | | |
| Upright | 30+ (9-30) | 30+ (22-30+) |
| Supine | 20 (11-30+) | 30+ (16-30+) |

## (iii) OESOPHAGEAL EMPTYING

### a. Technique and Validation

Oesophageal emptying is an essential physiological function for the passage of food to the stomach and as a defense mechanism for the clearance of refluxed gastric contents (Booth et al, 1968; Helm et al, 1983). Although the motility of the normal oesophagus has been extensively investigated by the use of manometric techniques (Duranceau et al, 1983), little has been reported on normal oesophageal emptying. Reports utilising a radionuclide bolus have appeared, but these have been confined mainly to liquid studies (Kazem, 1972; Mayron et al, 1975; Bosch et al, 1977; Tolin et al, 1979; Gross et al, 1979; Blackwell et al, 1983; Richter et al, 1983; Russell et al, 1981a; 1983). There have been considerably fewer reports characterising solid emptying and the agents used have been either a gelatin mixture (Kjellen et al, 1984), capsules (Fisher et al, 1982) or meat cubes (Fisher et al, 1982, Kjellen and Tibbling, 1982; Holloway et al, 1983). Radiological studies utilising barium also have been advocated for assessing solid oesophageal emptying (Donner et al, 1966; Davies et al, 1983). The majority of these studies have been performed in the supine position and the effect of posture has been ignored except to note that rapid liquid emptying occurs in the upright position and slower solid emptying in the supine position (Fisher et al, 1982). Manometric studies performed in the supine and upright position report differences in oesophageal motility for each position (Kaye and Wexler, 1981). It has been advocated also that oesophageal function is more accurately assessed during food ingestion (Mellow, 1983). Studies which reported abnormal radionuclide emptying in gastro-oesophageal reflux patients (Tolin et al, 1979; Blackwell et al, 1983; Russell et al, 1981a) did not first address themselves to the normal behaviour of the oesophagus in an acid environment.

The aims of this study were:

1. to develop a test of oesophageal function using a radionuclide labelled solid bolus and similarly labelled liquid bolus,
2. to determine normal oesophageal emptying for a solid and liquid bolus in the upright position and the supine position,
3. to determine the effect on oesophageal emptying of acidification of the oesophageal lumen.

Subjects

Reproducibility studies were conducted in 25 normal controls (10 males, 15 females, median age 25, range 19-62); solid emptying in 16 subjects and liquid emptying in 9 subjects.

The effect of posture and oesophageal pH was assessed in a different group of 19 normal subjects, 11 using a solid and liquid bolus and a further 8 using a liquid bolus only (11 males, 8 females, median age 29, range 19-69).

All subjects were non smokers and had no gastro-intestinal symptoms nor history of gastro-intestinal disease. No subject was on any medication at the time of investigation and all gave informed consent. No one individual received more than 2 mCi of $^{99m}Tc$ during the course of the study.

Radionuclide assessment

The bolus is prepared by cooking a 100 g mincebeef "hamburger" to which is added 1.6 mCi of $^{99m}Tc$ macro-aggregated albumin. A 10 g disc is then cut from the "hamburger" (Fig. 3.1). The subject has undergone an overnight fast and is seated upright initially with a gamma camera (Searle Pho-Gamma III HP) positioned posteriorly. The subject swallows 5 ml of water following which the meat is chewed into a bolus. The subject is then asked to swallow the bolus and instructed to swallow every 15 seconds on command. Cricoid movement is monitored during the performance of the test to ensure that no additional swallows are taken. The test is continued until the bolus is seen to enter the stomach or until 30 swallows have been carried out (Fig. 3.2). For this study the procedure was then repeated in the supine position. The tests in the

FIGURE 3.1: Typical solid bolus shown along side a 3 cm coin for size comparison.

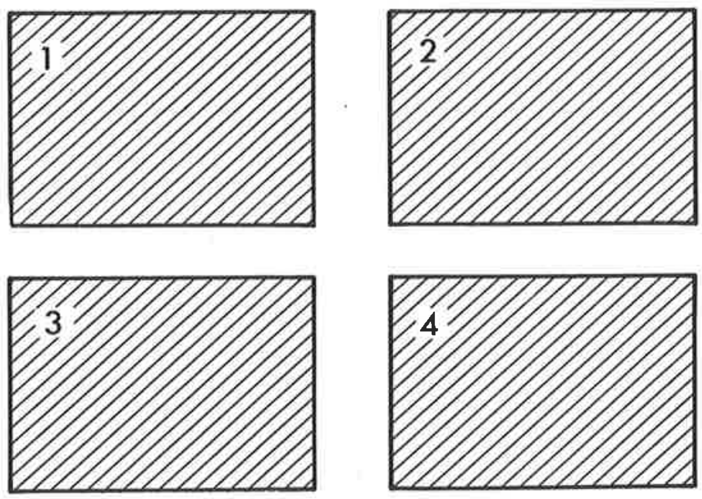
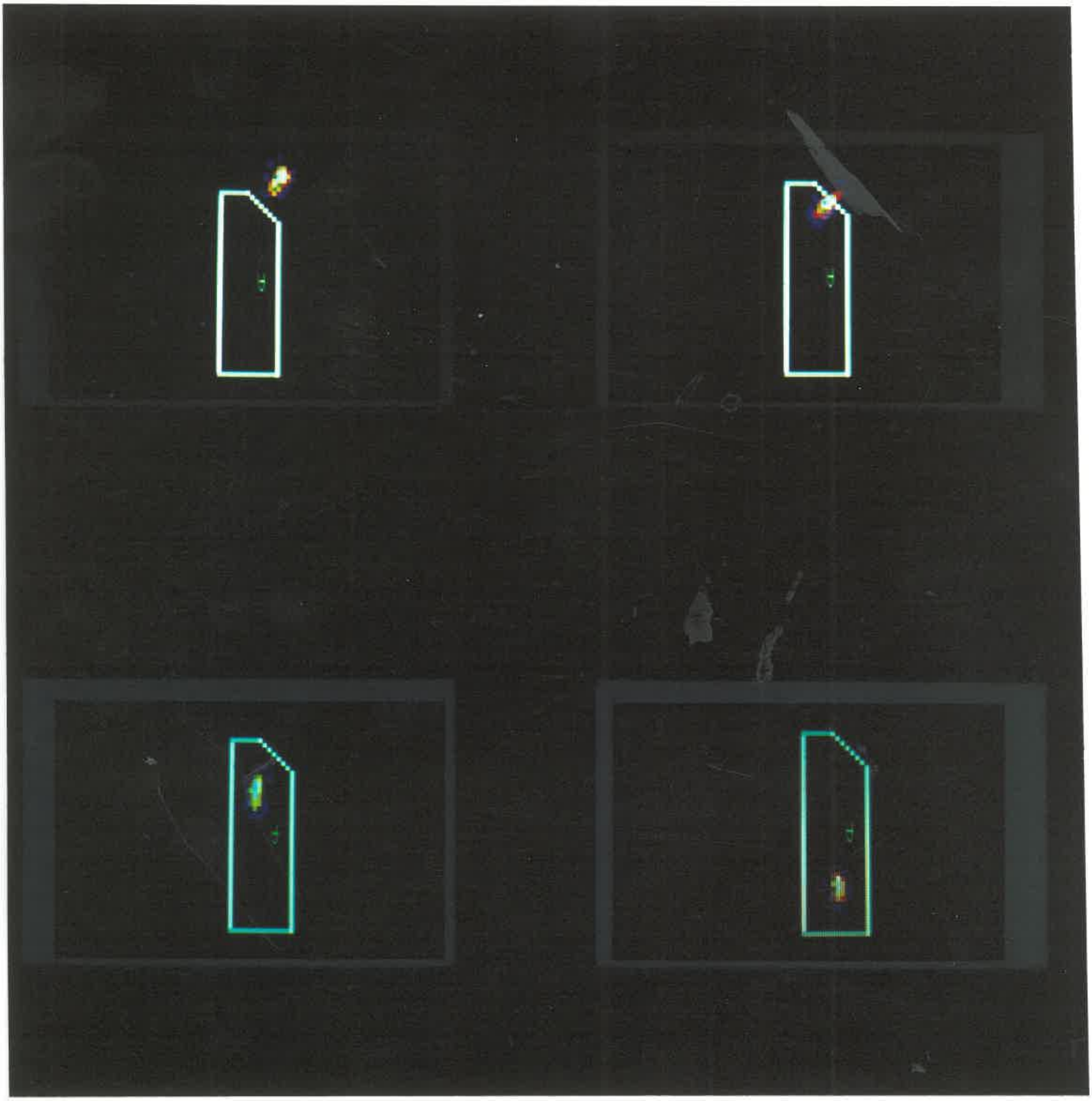


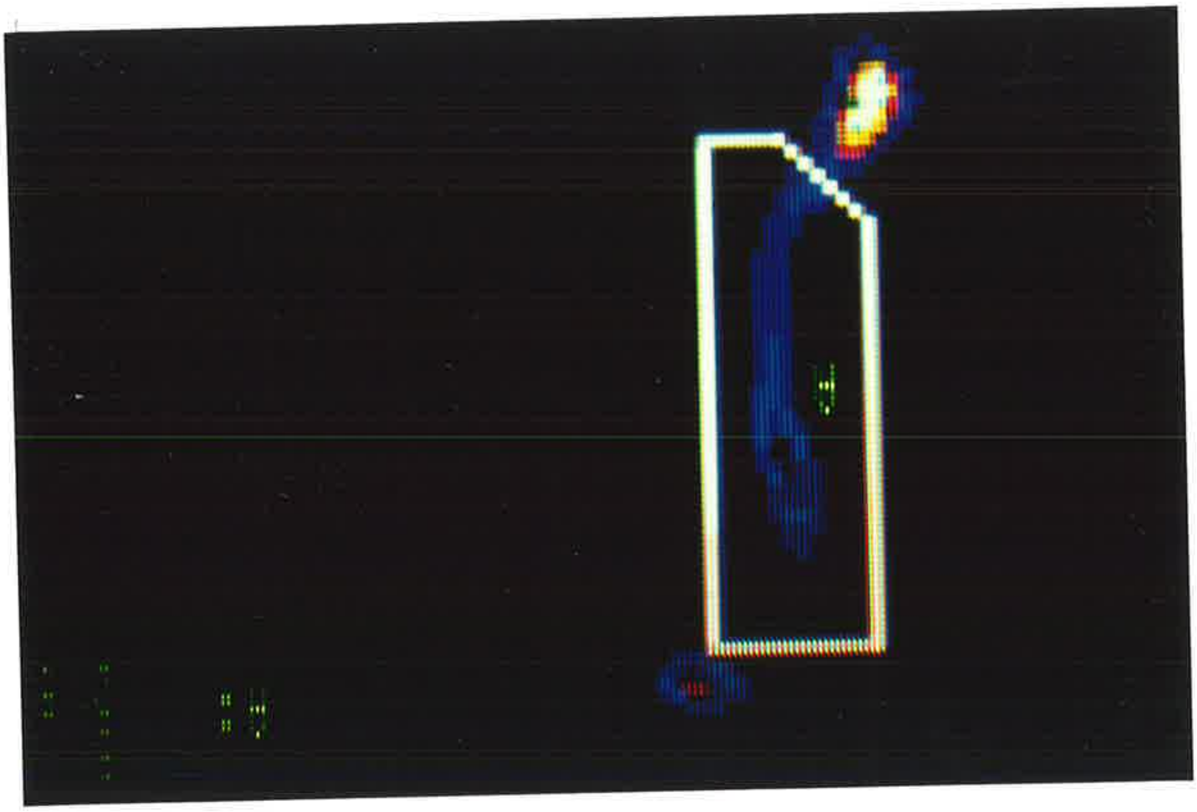

FIGURE 3.2: Upright solid swallow. The white line is computer generated and indicates the oesophageal "region of interest". The colour code has blue for most activity, yellow least. Frame 1 shows bolus descending through upper oesophagus, Frame 2 has the bolus in lower oesophagus. Frame 3 the bolus is squeezed through the lower oesophageal sphincter and 4 shows it in the stomach. The detector is located posteriorly.



upright and supine positions were repeated after the subject swallows 30 ml of 0.1M HCl diluted to pH 1.6. Analysis was performed by computer drawn regions of interest corresponding to oesophagus and stomach. The number of swallows (or time) taken for 95% of the radioactivity to enter the stomach (solid T95) was calculated. Images were collected at 1 second intervals for the first 120 seconds then at 5 second intervals until 450 seconds of recording had elapsed.

The liquid protocol was identical to the above except the bolus comprised 15 ml of water of neutral pH or 0.1N HCl diluted to pH 1.6, each with 300 micro-Ci of $^{99m}Tc$ pertechnetate added (Fig. 3.3). Frames of activity were collected every 0.5 seconds for 60 seconds. The dosimetry calculation for an oesophageal emptying study is shown in Appendix I.

FIGURE 3.3: Liquid swallow showing oesophageal region of interest in white. The frame shown is a summation of 10 seconds of recording and shows activity streaming down the oesophagus into the stomach. The detector is positioned posteriorly for these studies.



Reproducibility Studies

Upright solid and liquid studies were conducted on 16 and 9 subjects respectively, 7 days apart, under identical circumstances in order to determine the reproducibility of the test. A single liquid study was conducted and two solid studies on each test day.

Statistical Analysis

Results were analysed using the Wilcoxon paired signed rank test (Siegel, 1956) and analysis of variance and covariance with repeated measures.

Reproducibility Results

Table 3.4 shows the values obtained for the solid and liquid test on each of the days, seven days apart. Solid swallows showed no significant difference between swallows or between days. Liquid swallows had previously been shown to be reproducible by others (Tolin et al, 1979; Russell et al, 1981a). However, the day effect had not been specifically investigated. Again no significant day effect was found.

Effect of posture

The solid bolus was emptied faster from the oesophagus in the upright position compared with the supine position ($p < .05$; Fig. 3.4). The same relationship between upright and supine emptying of a solid bolus was found when the

TABLE 3.4

REPRODUCIBILITY OF OESOPHAGEAL EMPTYING

| | Day 1 | | Day 7 | |
|---|---|---|---|---|
| | TEST 1 | TEST 2 | TEST 1 | TEST 2 |
| Solid (swallows to clear oesophagus) | 3 (1-14) | 3 (1-9) | 2 (1-9) | 2 (1-9) |
| Liquid (sec to clear oesophagus) | 7 (6-9) | - | 6 (4-9) | - |

*Data are median values with range

oesophageal lumen was acidified ($p < .05$; Fig. 3.4).

Similarly liquid was emptied more rapidly in the upright compared with the supine position in both a neutral ($p < .01$) and an acidified oesophagus ($p < .05$; Fig. 3.5).

<u>Effect of pH</u>

Figure 3.4 illustrates that no significant difference could be detected between the solid bolus emptying in the neutral compared to the acidified oesophagus in either the supine or the upright position. However, figure 3.5 shows that liquid emptying from the oesophagus was delayed in the presence of acid in both the upright ($p < .01$) and supine positions ($p < .05$) when compared to the emptying of water.

The emptying of solid and liquid from the stomach is influenced by a variety of mechanisms (Heading, 1982). For this reason liquid and solid emptying have been studied separately (Collins et al, 1983). It is possible that the oesophagus also handles solid and liquids differently. The problem with assessing solid emptying has been to find an appropriate bolus. Capsules labelled with either isotope (Kjellen et al, 1984) or barium (Hey et al, 1982) have proven unsuitable because of difficulties with patient compliance, failure to clear the oesophagus and many subjects are unable to achieve an adequate initial swallow. In this study (section 3.1 (iii)b) and others

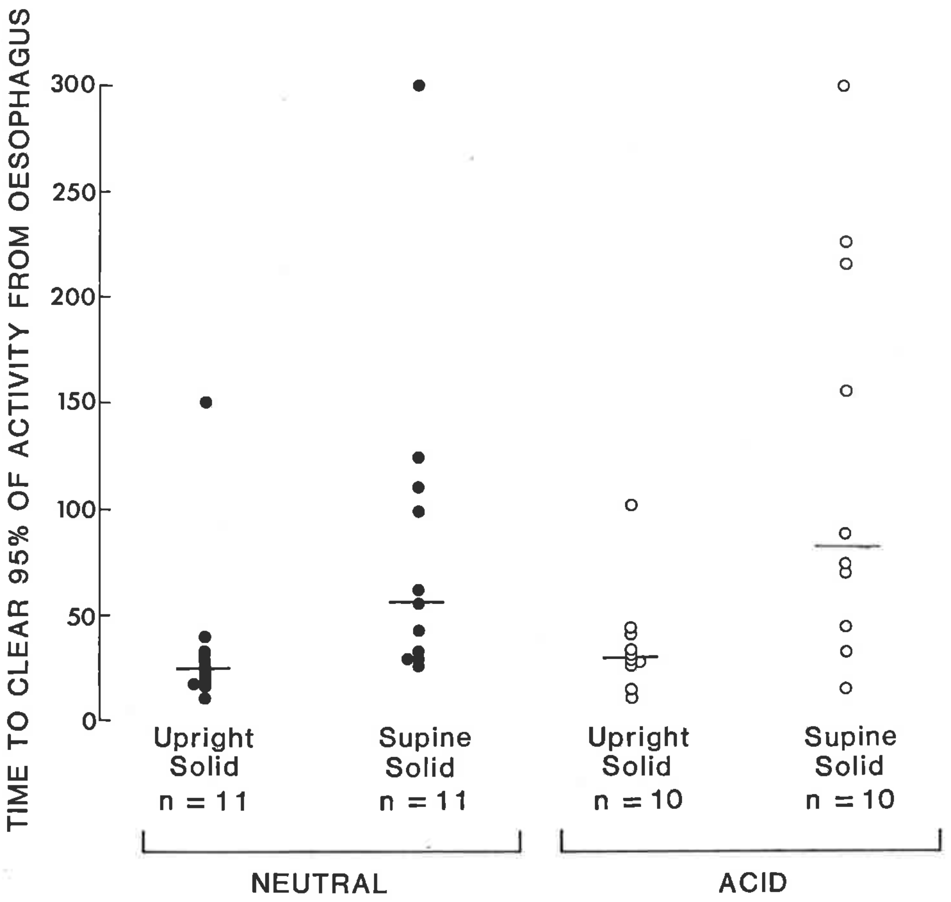



Figure 3.4: Number of swallows required to empty 95% of the activity from the oesophagus of a solid bolus in the upright and supine position with and without oesophageal acidification. Dividing line in each group represents the median value.

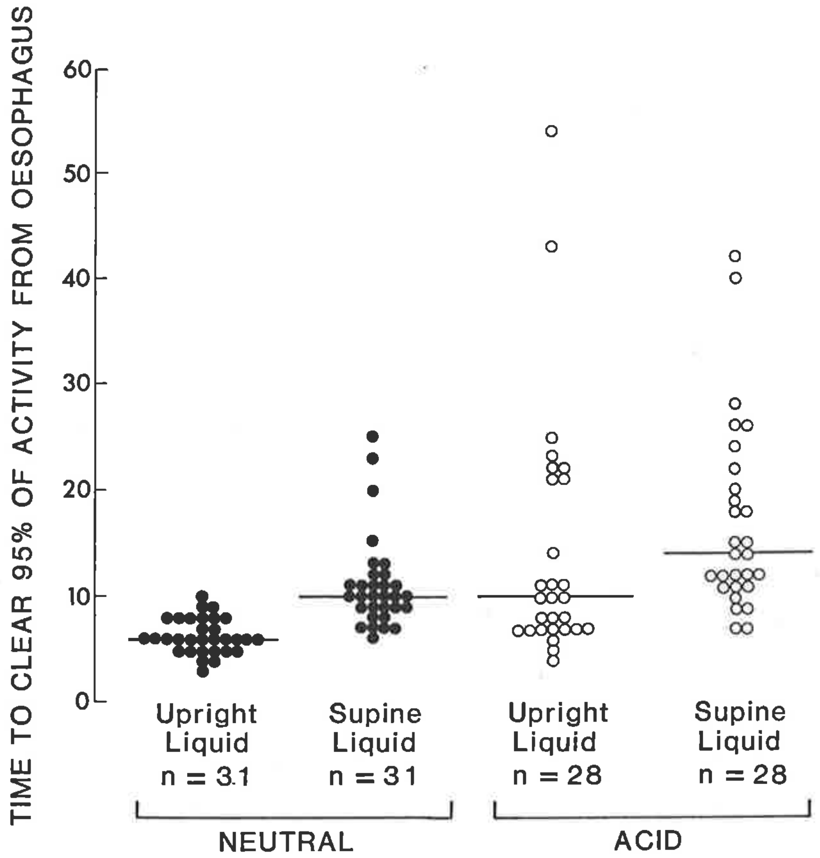



Figure 3.5: Number of swallows required to empty 95% of the activity from the oesophagus of a liquid bolus in the upright and supine position with and without oesophageal acidification. Dividing line in each group represents the median value.

(Kelly, 1961) a marshmallow to assess oesophageal emptying has been used. In this laboratory it was found that only about half of the subjects could swallow the marshmallow and intra subject variation was so great that the test was not reproducible and led to its abandonment. The ideal solid bolus should mimic the physiological setting of a swallow which includes mastication of food, mixing of saliva and subject comfort. The bolus of hamburger appears to satisfy these criteria. All subjects were able to perform the test successfully and the test was reproducible with a low level of radiation exposure. Mellow has recently reported that oesophageal function is different when measured using a solid bolus as opposed to a liquid bolus (Mellow, 1983). Liquid emptying results and methods in this series are similar to that reported by others (Tolin et al, 1979; Russell et al, 1981a). They show that emptying of liquid in the upright position occurs more rapidly than in the supine position. Many previous studies have assessed liquid emptying in the supine position in order to negate the effect of gravity. This ignores the fact that oesophageal emptying usually occurs in the upright position. It is not known whether changes demonstrated in patients in the supine position (Tolin et al, 1979; Blackwell et al, 1983; Russell et al, 1981a, 1983; Benjamin et al, 1983) would also be found in the upright position. Manometric studies indicate a difference for supine swallows when compared with upright swallows (Kaye and Wexler, 1981).

The acid clearance test is based on the ability of the oesophagus to clear itself of acid load (Booth et al, 1968). As discussed earlier (section 3.1 (ii) b.) this is not a reliable indication of oesophageal function. Further, the effect of altering oesophageal pH in normal patients could not be assessed by this technique.

Appreciation of the effect of acid in the normal oesophagus compared with neutral pH was first assessed utilising barium swallows. Donner et al (1966) studied 10 normal controls and were unable to show any abnormality when a barium suspension at pH 1.7 was used. Benz et al (1972) found their control group was delayed in 8 of 16 subjects after acid barium was given. The problem with barium studies is the difficulty in quantifying the qualitative picture. Manometrically, Madsen et al (1983) reported increased secondary peristalsis following instillation of acid in small volumes into the normal oesophagus. However, they found no difference between the acidified and neutral state when more than 5 ml was instilled. Helm et al (1984) showed a 15 ml acid bolus into the oesophagus caused an immediate pressure rise of 10-30 mmHg followed by secondary peristaltic sequences. Further they showed that an increase in amplitude of peristaltic contractions was weakly associated with delay in oesophageal acid clearance. Such may be the mechanism of delay in this series in the presence of an acidic oesophagus with liquid swallows. Helm et al have shown also that oesophageal emptying and clearance are not necessarily the same thing - with only emptying directly relating to the quantity of material within the oesophagus (Helm et al, 1984).

The assessment of oesophageal liquid emptying may have direct relevance to the way the oesophagus handles refluxed material from the stomach. The assessment of solid emptying is a general test of oesophageal function and may prove a useful screening test in various oesophageal disease states.

b. Correlation with Barium Studies

With the validation and assessment of the radionuclide oesophageal emptying test, determined in normal controls, a comparison of the test was undertaken between the radioisotopic technique and conventional barium studies. Isotopes or barium fluroscopy could presumably both be used, but neither have been validated against each other.

Subjects and Methods

10 patients (8 males, 2 females) with chest pain, established not to be cardiac, were referred for evaluation of the oesophagus as a possible cause of their chest pain. As such patients may reasonably be expected to require a barium study it was considered by the Research Review Committee of the Royal Adelaide Hospital to be appropriate to carry out fluroscopic studies of solid and liquid

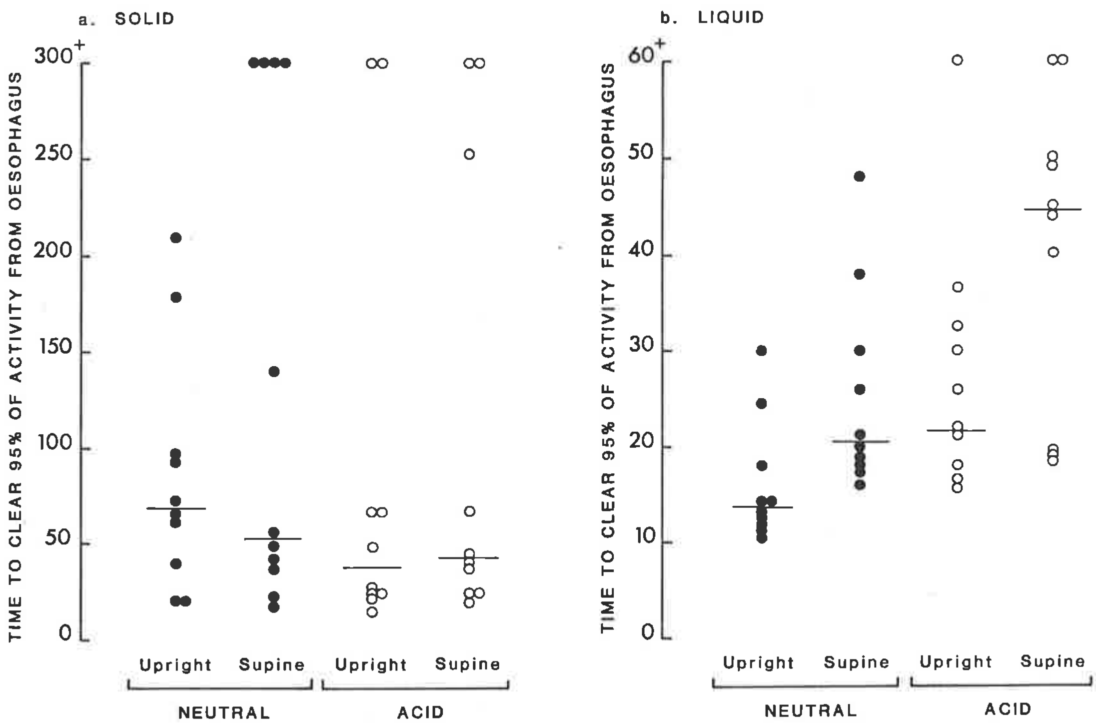
swallows, in the upright and supine position in these patients. Patients underwent the radionuclide and radiological assessment on consecutive days in random order. The isotopic studies were conducted and analysed by the author, the radiological studies by Professor G. Stevenson, without any knowledge of the others results.

The protocol for the radionuclide oesophageal emptying studies was identical to that used in the normal controls. Each subject underwent solid and liquid studies in the upright and supine positions, before and after oesophageal acidification. The only departure from the previous protocol was in the constitution of the bolus used. A standard marshmallow (KRAFT, CANADA) was used, into which was inserted a gelatin capsule (Parke, Davis & Company, No. 4) with 0.2 ml of $^{99m}Tc$ containing 150 micro-Ci. Because of the fragility of the capsule subjects were permitted to lubricate the marshmallow with saliva but not chew.

The radiological assessment was carried out using a fluoroscopic unit within the Department of Radiology of the Royal Adelaide Hospital. The protocol was identical to that used for the radioisotope and recorded on video with time recording so that each swallow could be accurately identified on the tapes. Neutral and acidified barium (pH 1.6) was used as the contrast medium. Again data was analysed by the Wilcoxon matched pair sign rank test.

Results for the radionuclide studies are shown on figure 3.6. The radionuclide results for solid bolus failed to show any significant difference between the upright and supine positions in either the acidified or neutral oesophagus. Similarly no significant difference was found between solid emptying in a neutral or acidic oesophagus when performed in the same position (Fig. 3.6 (a)). On the other hand, liquid results of oesophageal emptying were similar to those obtained in the normal volunteers. Liquid emptying was significantly slower in the supine position for both the neutral ($p < 0.05$) and acidic ($p < 0.05$) oesophagus. The presence of acid in the oesophagus significantly slowed liquid emptying for supine ($p < 0.05$) and upright ($p < 0.01$) studies (Fig. 3.6 (b)). Radiological assessment was not able to show any significant changes in solid bolus emptying when considered in relation to posture or pH (Fig. 3.7 (a)). Liquid studies also failed to show significant changes in the presence of an acidic or neutral oesophagus. The supine acid study was, however, significantly slower ($p < 0.05$) than the upright (Fig. 3.7 (b)).

The findings of the radioisotope oesophageal emptying differed in the patient group from normal controls only in the solid studies. This seemed to be primarily due to the bolus used. Because the subjects were not able to chew the




<u>Figure 3.6</u>:

(a) Time (sec) to clear 95% of activity from the oesophagus in patients with chest pains using a solid bolus (marshmallow) in the upright and supine position with and without oesophageal acidification.

(b) Time (sec) to clear 95% of activity from the oesophagus in patients with chest pain using a liquid bolus in the upright and supine position with and without oesophageal acidification.

Dividing line in each group represents the median value.

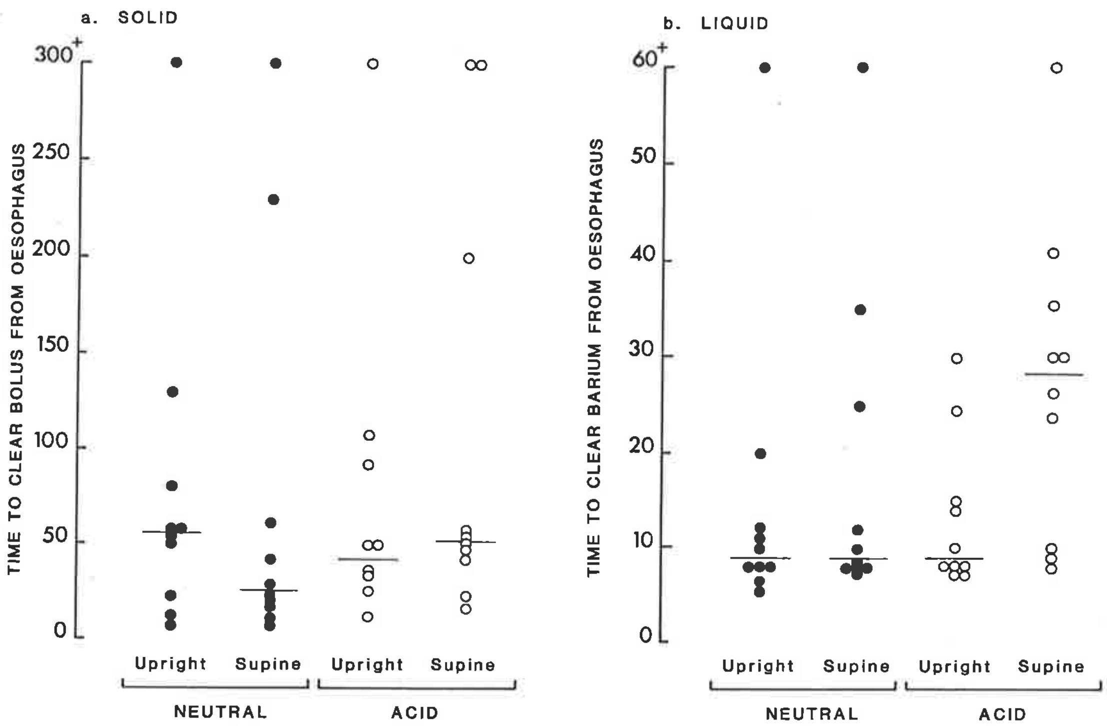



Figure 3.7:

(a) Time (sec) to clear the barium coated marshmallow bolus from the oesophagus in patients with chest pain in the upright and supine position with and without oesophageal acidification.

(b) Time (sec) to clear the liquid barium swallow from the oesophagus in patients with chest pain in the upright and supine position with and without oesophageal acidification.

Dividing line in each group represents the median value.

marshmallow it did not seem to transit the oesophagus well. Also many subjects found the bolus size unduly large and therefore had difficulty swallowing it at all. For this reason subsequent studies have been performed using the 10 g meat bolus which is well tolerated and gave more useful results in normal volunteers. The barium studies failed to provide any useful information in relation to the effect of posture or acidification on barium swallows. This again emphasised the problem in the bolus used. Surprisingly, liquid emptying also failed to show any significant alteration in the presence of acid or even upright and supine in a neutral pH. This may well be because of the lack of quantification possible with barium studies. Barium coated the mucosal surface making it difficult to determine when 95% of the bolus (i.e. most of the swallow) had left the oesophagus. Radioisotope enabled an accurate determination of this parameter. While barium gave useful anatomical detail for functional changes the radioisotopic emptying technique seemed more useful.

## 3.2 **THE STOMACH**

### (i) INDUCTION OF REFLUX BY GASTRIC ACID LOADING

#### a. Technique

The standard acid reflux test was described first by Kantrowitz et al (1969). It is performed usually following the manometric assessment. The subject is required to perform a series of manouevres (Mueller, Valsalva, Cough, deep breathing) which have been found to induce reflux in patients. These are repeated in 4 positions with the patient supine, left lateral decubitus position, right lateral decubitus position and supine with head down 20 degrees. With the pH probe in the distal oesophagus a reflux episode is said to occur when the oesophageal pH drops to less than 4. These manouevres are then repeated after instilling 300 ml of 0.1 normal HCl into the stomach.

#### b. Validation

While the correlation between a positive standard acid reflux test and gastro-oesophageal reflux has been established by others (Benz et al, 1972; Richter and Castel, 1982) its reproducibility is not known. The group of sixteen normal volunteers previously described (section 3.1 (i)b) had the test performed on 2 days seven days apart. Table 3.5 shows the results obtained. There was no significant difference between the two days using an analysis of variance.

TABLE 3.5

REPRODUCIBILITY OF STANDARD ACID REFLUX TESTING

CONDUCTED ON 2 DAYS SEVEN DAYS APART.

VALUES SHOWN ARE MEDIAN WITH RANGE IN BRACKETS

| | DAY 1 | DAY 2 | n |
|---|---|---|---|
| Prior to gastric loading | | | |
| positional episodes | 0 (0-3) | 0 (0-1) | 16 |
| induced episodes | 0 (0-4) | 0 (0-3) | 16 |
| Following gastric loading | | | |
| positional episodes | 1 (0-2) | 0 (0-2) | 9 |
| induced episodes | 0.5 (0-1) | 1 (0-7) | 9 |

## (ii) RADIONUCLIDE GASTRIC EMPTYING

### a. Technique

This method of assessment of gastric emptying has been previously described (Horowitz et al, 1982a; Collins et al, 1983). A solid marker was prepared by injecting 27 mCi of $^{99m}$Tc-SC into a wing vein of a live chicken as described by Meyer et al (1976). After 20 minutes the chicken was killed and the liver removed. The amount of liver containing 1-1.5 mCi of $^{99m}$Tc-Sulphur Colloid was mixed into 100 g ground beef and the resulting "hamburger" cooked on a griller. The total calorie content of the solid meal (25 g protein, 21 g fat) was approximately 270 kcal. The liquid marker was 0.5 - 0.75 mCi of $^{113m}$In-DTPA mixed in 150 ml of 10% dextrose. The whole body radiation dose was calculated to be approximately 40 mrad for each study. The dosimetry calculation for a gastric emptying study is shown in Appendix II.

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

A scintillation camera (400 keV parallel-hole collimator) interfaced to a computer was used for data collection. Data was acquired in list mode into magnetic disc memory via a DEC 11T/55 computer. The energy window alternated regularly between that of $^{113m}In$ (393 keV) and $^{99m}Tc$ (140 keV) using a automatic switching device. During the first 10 post-cibal minutes the energy window alternated every five 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. At the end of data acquisition 100 micro-Ci of $^{99m}Tc$-DTPA in 150 ml of water was given orally and one minute later a left lateral image of the upper abdomen was taken.

The study characteristically comprised 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 subject movement and realigned to a single reference point using the $^{99m}Tc$ marker. This facilitated determination of the region of interest. 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 correction.

Attenuation correction factors were calculated using the lateral image, the distance from the midpoint of the stomach to the collimator surface in centimetres was calculated at all levels from the fundus to pylorus. A line correction factor was generated and applied to the study.

Using the computer display a region of interest was drawn to include the whole stomach, but excluding the small intestine. For each frame of the study the total counts in the region of interest was the sum of the individual line sums, which had been corrected for tissue attenuation. The histograms for the solid and liquid components of the meal (expressed as percentage of the total meal remaining within the stomach vs time), was corrected for radionuclide decay and printed. 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 these histograms. For the solid component these parameters were: the lag period before onset of emptying, the time for 50% emptying (T50), the average rate of linear emptying (expressed as %/min) and the percentage of solid remaining at 100 minutes. For the liquid component, the T50 was obtained. 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.

b. Validation

Considerable work had already been done on validation of the technique (Collins et al, 1983).

Reproducibility

Collins et al (1983) had shown the test to be reproducible over a seven day period. However, whether it was similarly reproducible over longer periods of time in disease states was not known. In order to assess this 9 patients with gastro-oesophageal reflux (3 males, 6 females; median age 48; range 22-60) were studied on two separate occasions. The median time between each test was 6 months (range 3-14). Figure 3.8 shows the individual results obtained for the two tests. No significant difference was found between the two results using a paired "t" test.

Normal Controls

Development of a normal control group was carried out in co-operation with Dr. Michael Horowitz. The control

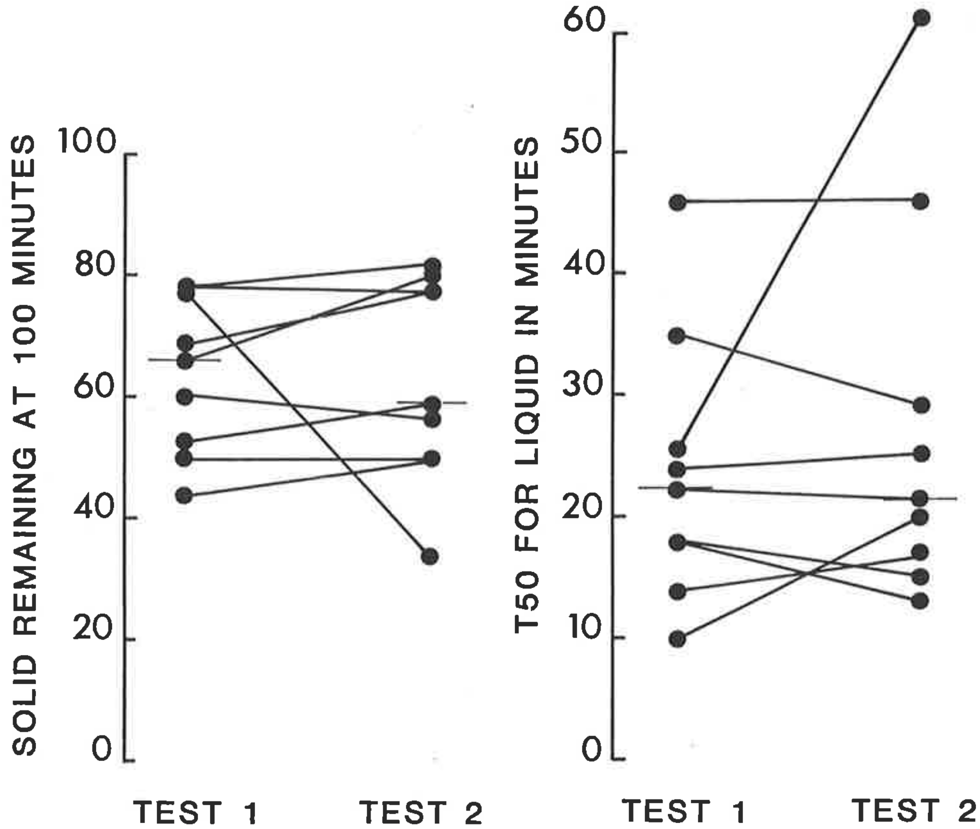



Figure 3.8: Reproducibility of gastric emptying results in patients with gastro-oesophageal reflux.

group comprised 22 normal volunteers (12 males, 10 females, median age 34, range 21 - 62). Their gastric emptying values are displayed in Table 4.4.

### (iii) PARACETAMOL ASSESSED GASTRIC EMPTYING

#### a. Technique and Validation

#### Introduction

A variety of techniques have been developed and refined to assess the emptying of the stomach (Sheiner, 1975; Meyer, 1979a). Radionuclide scanning techniques enable direct quantitative measurements to be made of gastric emptying of the solid and liquid phases of a meal, and these techniques are physiological and non-invasive (Horowitz et al, 1982b). However, they do carry a radiation exposure, are costly, and require the facilities of a nuclear medicine department.

Since gastric emptying is the rate-limiting step in the absorption of paracetamol, plasma paracetamol concentrations have been used as a means of indirect assessment of gastric emptying (Heading et al, 1973; Nimmo et al, 1975; Clements et al, 1978; Goldstraw and Bach, 1981). It has also been reported that salivary concentrations of paracetamol correlate well with concentrations obtained from plasma (Glynn and Bastain, 1973; Adithan and Thangam, 1982; Miners et al, 1984).

The aims of this study were:

1. to confirm that plasma and salivary paracetamol levels could be used interchangeably, and
2. to assess if a significant correlation existed between paracetamol assessed gastric emptying with more frequent sample collection and liquid gastric emptying as determined by the radionuclide technique.

## Subjects

Ten volunteers were studied after informed consent had been obtained (3 males and 7 females, median age 56 years, range 21-67). None had undergone previous gastro-intestinal surgery. All underwent radioisotope assessment of liquid emptying and after the ingestion of paracetamol, plasma and saliva paracetamol concentrations were determined.

## Radionuclide Assessment

The gastric emptying test was performed after an overnight fast. The method was described previously (section 3.2 (ii)). Thirty minutes prior to commencement of the gastric emptying study, a 21-gauge butterfly needle was inserted into an arm vein and flushed with heparinized saline, 5 ml of blood and 1-2 ml of saliva were taken for base line levels. The first ml of blood was always discarded and the line reflushed with heparinized saline at the completion of the 5 ml sampling.

When the subject was seated comfortably in front of the detector 150 ml of water and 10% dextrose containing the liquid marker into which 1 g of paracetamol (PANADOL SOLUBLE, Winthrop) had been dissolved, was given. The subject was instructed to drink the liquid within 30 seconds, and then a series of 6 mouth washes were performed with warm water to remove any residual paracetamol from the oral cavity. Saliva was collected by the patient spitting into a sterile container. Blood and saliva samples were collected over a 3 hour period. During the first hour, collection was at 5 minute intervals, the second hour at 15 minute intervals, and two half hour samples for the remaining hour.

Plasma and salivary paracetamol concentrations were determined by a specific high performance liquid chromatographic procedure (Miners et al, 1984).

Data was analysed by using Spearman Rank correlations ($r_s$) (Siegel, 1956).

Results obtained are shown in Figure 3.9 for all patients with the time taken in minutes for 50% of the liquid marker (T50) to clear the gastric region plotted against the time in minutes to maximum plasma concentration (C max-plasma) (Fig. 3.9a), and the time in minutes to maximum saliva concentration (C max saliva) (Fig. 3.9b).

Figure 3.9c plots time to C max-plasma against time to C max-saliva. There was a significant correlation between time to C max-plasma and time to C max-saliva with T50. A strong correlation was found between time to C max-plasma and time to C max-saliva. When the areas under the 0-3 hour plasma/saliva paracetamol concentration time were compared, there was an $r_s$ value of .742 with a significant correlation ($p < .02$)

The results confirm the finding of saliva paracetamol concentrations correlating well with plasma levels. This offers a convenient and non-invasive method for sample collection which virtually removes the need for any technical assistance. It has been shown that stressful stimuli can greatly alter gastric emptying (Thompson et al, 1983), and saliva collection, therefore, removes the possible variable of stress due to intravenous line insertion. Other reports have established that the rate of absorption of paracetamol in humans is dependent on the rate of liquid gastric emptying (Heading et al, 1973; Holt et al, 1979). However, only one study was performed in the presence of a mixed solid and liquid meal (Holt et al, 1979), and the technique used did not include corrections for attenuation of counts from the gastric region. Previously reported studies also failed to take frequent samples of plasma during the first 30 minutes of the study (Goldstraw and Bach, 1981). As Figure 3.9 demonstrates the

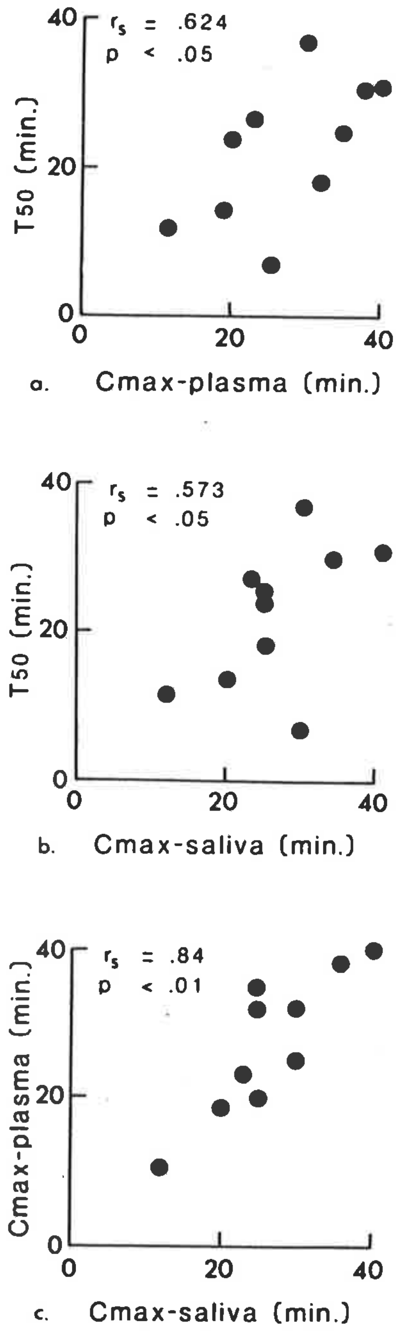



Figure 3.9: Liquid gastric emptying assessed by isotope and paracetamol levels. Individual time in minutes to C max-plasma, C max-saliva and liquid T50 are plotted. Spearman Rank correlations ($r_s$) and significance level are indicated.

majority of the patients had time to C max-plasma and time to C max-saliva within 30-40 minutes. The results obtained in this study verify the significant correlation that exists for the time taken for 50% of the liquid to clear the gastric region and the time taken to reach maximal concentration of paracetamol in both plasma and saliva.

In this study the two patients who had the most rapid gastric emptying determined isotopically had the fifth and seventh fastest rate of gastric emptying respectively as determined by plasma and saliva peak concentrations. The technique of peak saliva paracetamol concentration to assess liquid gastric emptying has an application in studies where repeated assessment of gastric emptying is required. In this situation repeated radionuclide testing would lead to an unacceptable radiation exposure. Salivary paracetamol concentrations could also be used in centres which do not possess the facilities of a nuclear medicine department. Even when a nuclear medicine department is available, the technique may prove useful in other situations. For example, the technique can safely be utilised in patients with post-operative ileus as a means of assessing return of normal liquid gastric emptying within a ward situation. In studying gastric emptying, it is clearly preferable to study both solid and liquid phases at the same time (Heading et al, 1976). If only one isotope can be studied at a time, then simultaneous gastric emptying of both liquid and solid phases could be determined by using a radionuclide labelled solid meal and salivary paracetamol estimations for the liquid phase of emptying. As the use of radionuclides grow, departments of nuclear medicine with the capacity to study dual isotopes may still require the technique. Thus biliary emptying and duodenogastric reflux could be assessed by using one isotope (Mackie et al, 1982) whilst also assessing solid gastric emptying isotopically and liquid emptying using salivary paracetamol concentrations. However, use of paracetamol levels does not offer as reliable a measure of gastric emptying as the presently available radionuclide technique as indicated by the two most rapid emptiers in our study. This may be expected as the plasma/saliva concentration of paracetamol depends not only on absorption, but also on metabolism and distribution (Holt et al, 1979). For this reason further use of this technique in patients groups has not been proceeded with.

## 3.3 **THE DUODENUM**

### (i) ANTROPYLORODUODENAL MANOMETRY

#### a. Technique

Transpyloric flow depends on simultaneous occurrence of favourable conditions for flow in the antrum, pylorus and duodenum. It is therefore necessary to record simultaneously in all three regions. To achieve this a manometric assembly which has 4 side holes in the duodenum, 3 in the antrum and a 5 cm long Dent sleeve sensor positioned in the pylorus was developed.

#### Manometric System

The basic design and infusion system of the manometric assembly was similar to that used for oesophageal manometry (section 3.1 (i)a), except for the use of a normal saline perfused channel just proximal and distal to the sleeve sensor, which permitted assessment of transmucosal potential difference.

#### Transmucosal Potential Difference

The pylorus is a mobile structure which moves relative to the manometric assembly. This mobility makes consistent stationing of a single side hole manometric sensor in the pylorus impossible. Furthermore, human in vitro studies (Schulze-Delrieu and Shirazi, 1983) have demonstrated that the portion of the pylorus which demonstrates tonic activity is only 2-3 mm in length, thus making it difficult to detect by pull-through methods. Close parallels exist between these difficulties at the pylorus and difficulties initially encountered with monitoring lower oesophageal sphincter motility. In this latter instance, the development and application of a sleeve sensor has been associated with an enhancement of our understanding of human lower oesophageal sphincter motility (Dent, 1976). Use of a sleeve sensor in the pylorus overcomes difficulties in monitoring pyloric motor events. In order to ensure that the manometric assembly was correctly positioned, transmucosal potential difference was monitored via the manometric channels at the proximal and distal margins of the sleeve sensor (Turner et al, 1978). There is a transpyloric gradient of transmucosal potential difference of about 25mv.

By perfusing these channels with normal saline from 2 electrically isolated reservoir systems across the transducers a manometric pattern could be obtained. The transducer domes had been modified by inserting a short hollow metal spike over which was passed a one metre length of polyethelene tubing. This tubing was filled with 1% Agar and 1 Molar KCl and its other end connected to a calomel electrode (Flinders Medical Centre, Biomedical Engineering). A reference electrode was also connected via a metre length of similar Agar/KCl tubing which was applied to the skin surface primed with conductive gel. The calomel electrode system was then connected to a low voltage, high impedance differential amplifier with a remote power source (Flinders Medical Centre, Biomedical Engineering) which was then connected to the Grass Polygraph. In this way the potential difference recorded at the two sites was displayed to permit continuous sleeve localisation in the pylorus. The laboratory arrangement is shown in figure 3.10.

b. Validation

In order to validate the method described above, two 12 month old beagle dogs had a gastric and small bowel Thomas cannulae inserted. After recovery from the surgery the dogs were studied in a sling which permitted them to be fully conscious. No sedation was used in any studies. The manometric assembly was passed from the gastric cannula out through the small bowel cannula. With the sleeve in position it was possible to observe antropyloroduodenal activity for periods of up to 6 hours. Figure 3.11 shows the pyloric patterns observed in one dog over a number of different recording periods.

Studies were also conducted under fluoroscopic vision with barium contrast to confirm that the sleeve was localised by the transmucosal potential gradient. Also it enabled fluoroscopic bowel contractions to be seen in associations with manometric wave patterns.

Figure 3.10: A photograph of the laboratory set up used for dog studies. The dog is shown in upper left corner resting in the sling. The various recording instrumentation is arranged in the foreground.

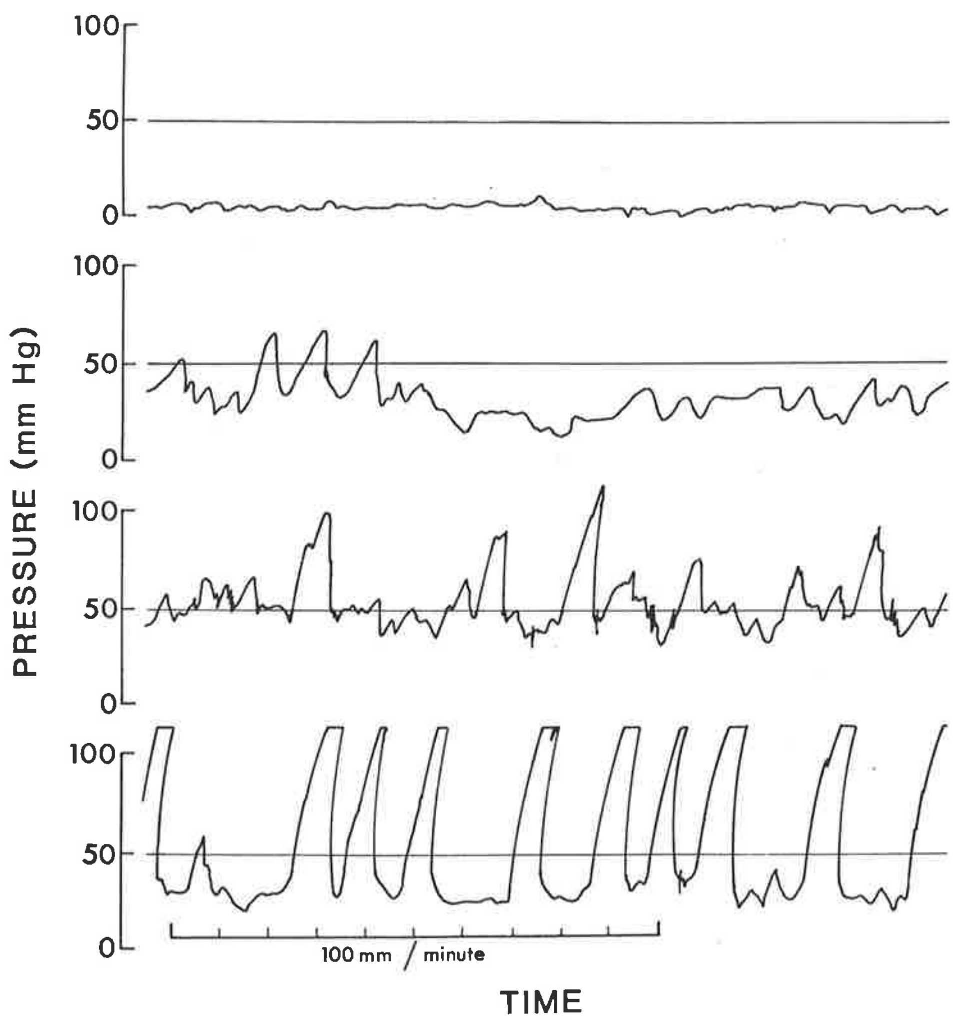
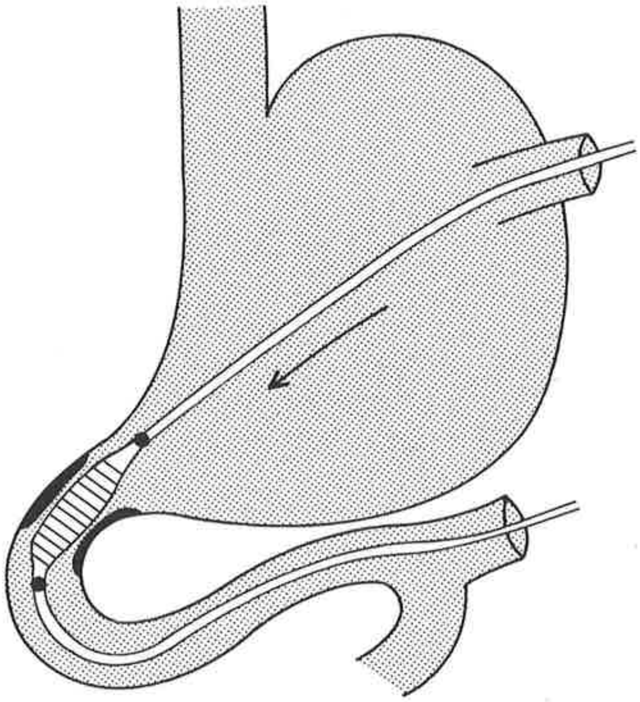



Figure 3.11: Patterns of pyloric activity observed in the same dog during a number of periods.

To assess the usefulness of the transmucosal potential difference movement of the tube was periodically performed as illustrated in Figure 3.12. Abrupt changes in transmucosal potential difference were invariably seen as the channel moved across the dog pylorus.

The sleeve tracings of pyloric pressure have shown that for most of the time there is phasic pyloric contraction with waves sometimes > 70 mmHg, and frequency up to 5/min. Phasic pyloric contractions have been noted to occur in several animals (Biancani et al, 1981). It appears likely that this phasic activity is important for control of transpyloric flow. The sleeve has also signalled intermittent sustained elevation of baseline pyloric pressure either because of partial fusion of vigorous prolonged phasic waves, or because of apparent steady state B~~v~~asal pyloric contraction.

After food, lumen occluding antral peristalsis was associated with propagation of a contractile wave into the duodenum and a transient sharp dip of duodenal pH to as low as 2. There was inhibition of apparently non-propulsive duodenal contractions prior to arrival of these co-ordinated waves. There antral waves occurred at a frequency considerably less than the intrinsic gastric frequency. This supports the currently somewhat unfashionable concept that the antrum empties the stomach intermittently by a



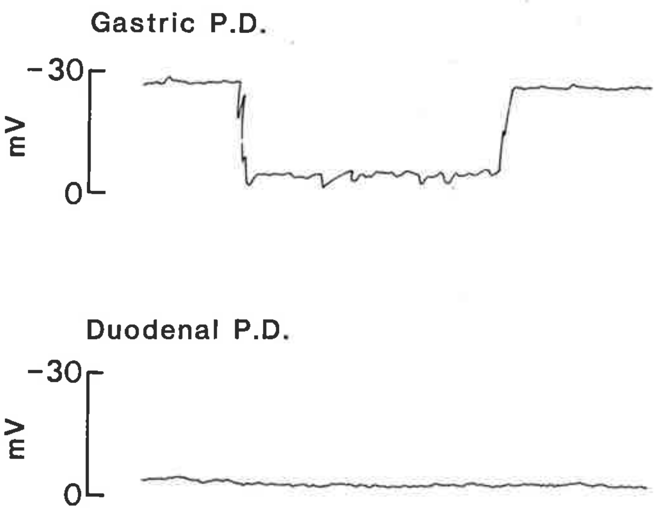


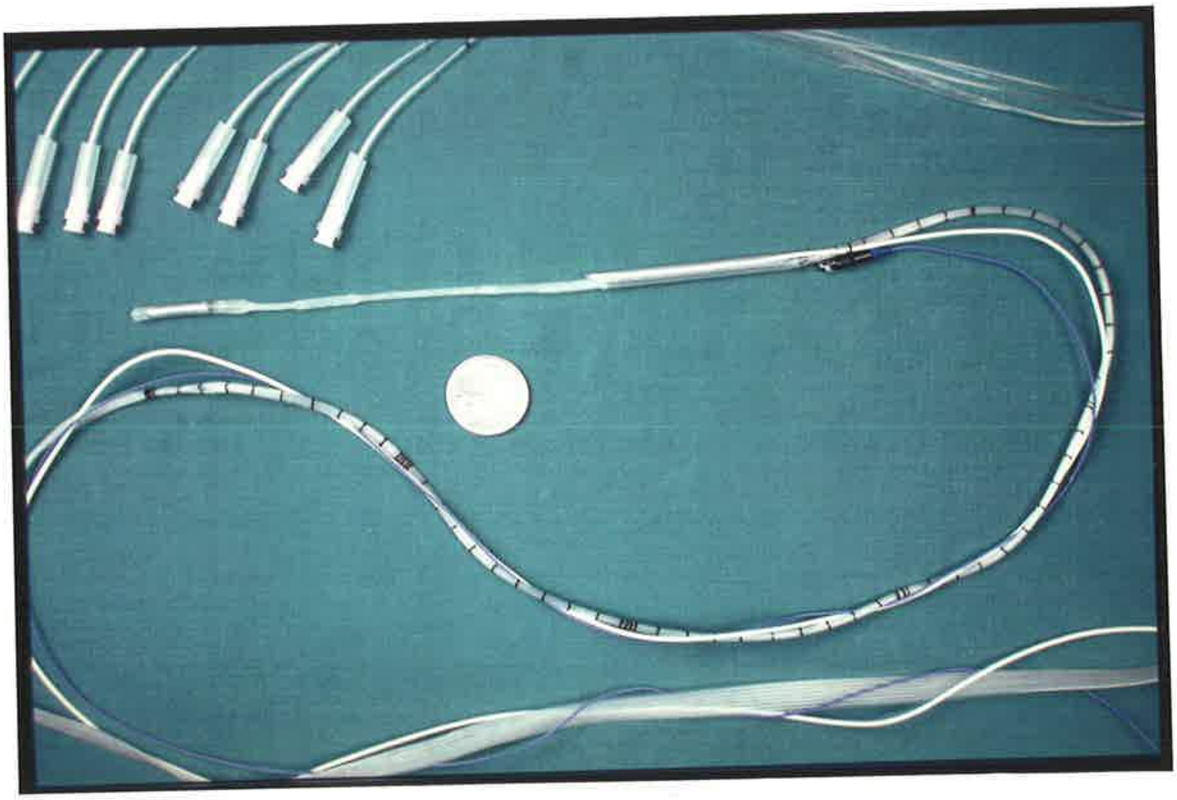

Figure 3.12: Localisation of sleeve sensor was achieved by utilising transmucosal potential difference between the antrum and duodenum. The dots on the tube indicate the location of the detector channels. Abrupt changes observed in antral potential differences with advancing and retreating the tube through the pylorus are illustrated in the trace below.

peristaltic pump action, and that the control of gastric emptying may depend at least in part on the frequency with which this pattern of contraction occurs.

Human studies

The human manometric assembly was essentially identical to that used in the dog studies with the difference being that the distal end of the tube had a 15 cm length of silastic rubber attached to a mercury weight (Fig. 3.13, 3.14). This enabled the tube , which was introduced pernasally, to readily pass into the duodenum with the patient lying on the right side. At the time of writing the human studies have only been conducted to a preliminary level. However, a number of interesting patterns of activity have been observed in the normal control subjects. Figure 3.15 shows a human migrating motor complex, originating in the duodenum, observed using the assembly and figure 3.16 a pattern of human phasic pyloric activity measured by the sleeve sensor, in the absence of antral or duodenal activity. The pyloric activity seen in figure 3.16 occurred for only a 15 minute period in 16 hours of recording in the one subject, illustrating the importance of having the means of continuous pyloric activity assessment.

Figure 3.13: The human duodenal tube shown with a 3 cm coin for size comparison.



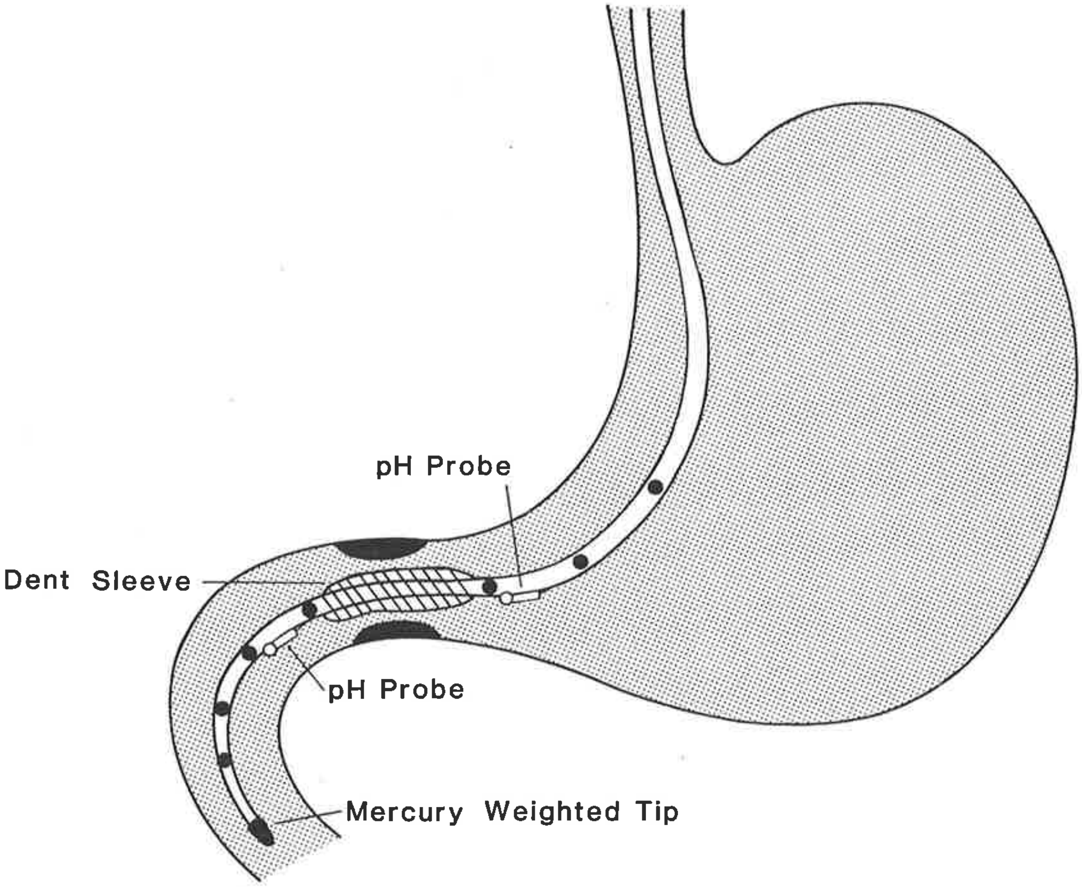



Figure 3.14: A diagramatic representation of the assembly used for human pyloric studies. The dots along the tube length represent manometry channels. The pH probe location is illustrated.

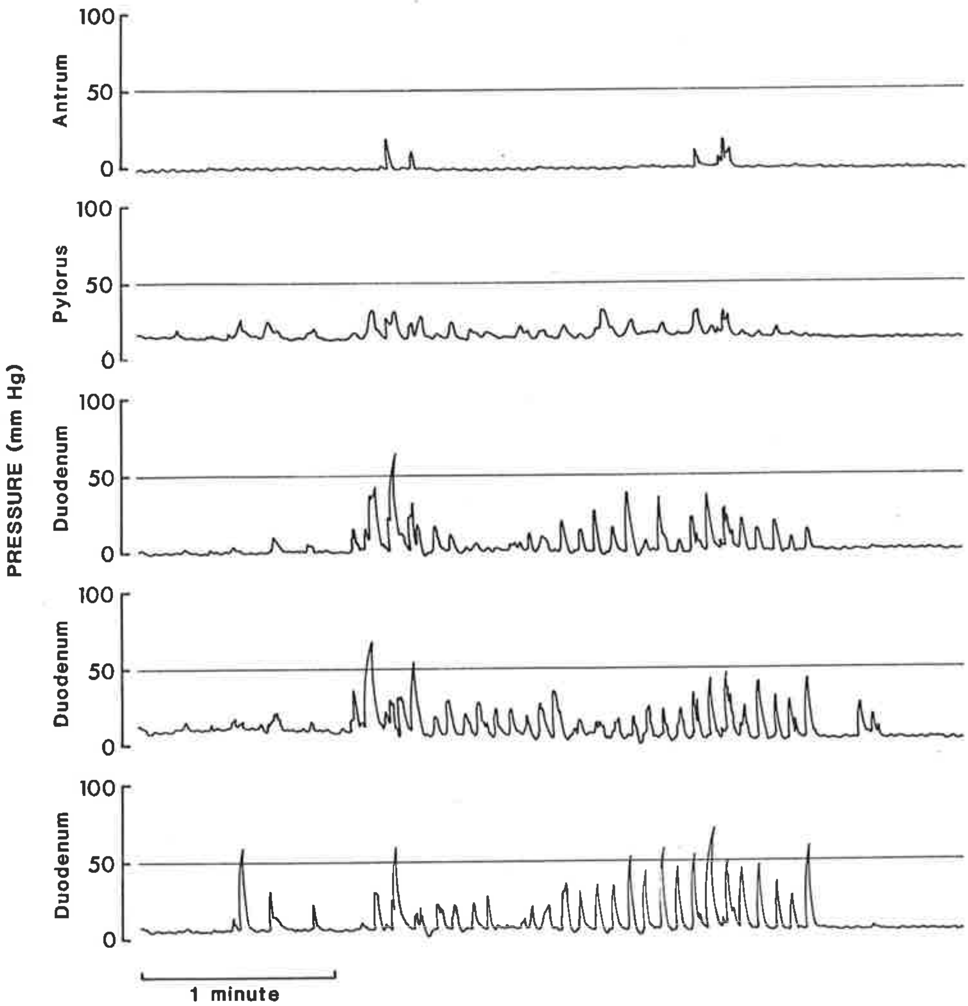



Figure 3.15: A human migrating motor complex arising in the proximal duodenum.

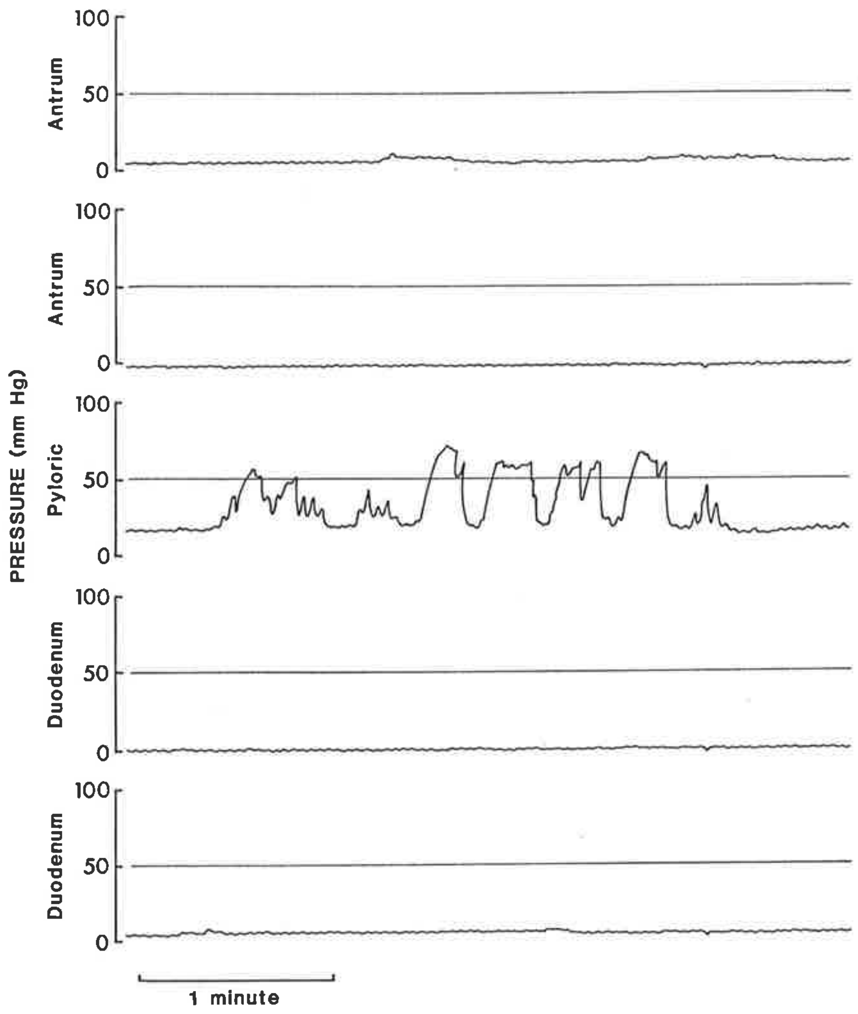



Figure 3.16: Human pyloric pattern observed in the absence of gastric or duodenal activity.

## (ii) DUODENOGASTRIC REFLUX

### a. Technique

In order to recognise motor patterns associated with intermittent transpyloric flow, monitoring of motility was required at the same time as individual instances of flow were recognised. A large pH gradient exists between the stomach and duodenum. Thus a pH electrode (Radiometer stomach electrode) on either side of the pylorus was used to monitor flow of digesta between the stomach and duodenum. The electrodes were attached just distal and proximal to the sleeve in the vicinity of the transmucosal potential difference channel. This enabled accurate localisation of the electrodes in the stomach or duodenum. Figure 3.14 shows a representation of the human assembly when fully equipped.

### b. Validation

Monitoring of pH from within the antrum and duodenum of the dogs has signalled abrupt changes in pH consistent with either passage of acid from the stomach into the duodenum or passage of alkali from the duodenum into the stomach. The episodic changes in pH from the duodenum and stomach have been correlated with canine gastropyloroduodenal motility patterns. Figure 3.17 shows the clearing of an antral alkalinisation by a lumen occluding contraction in the

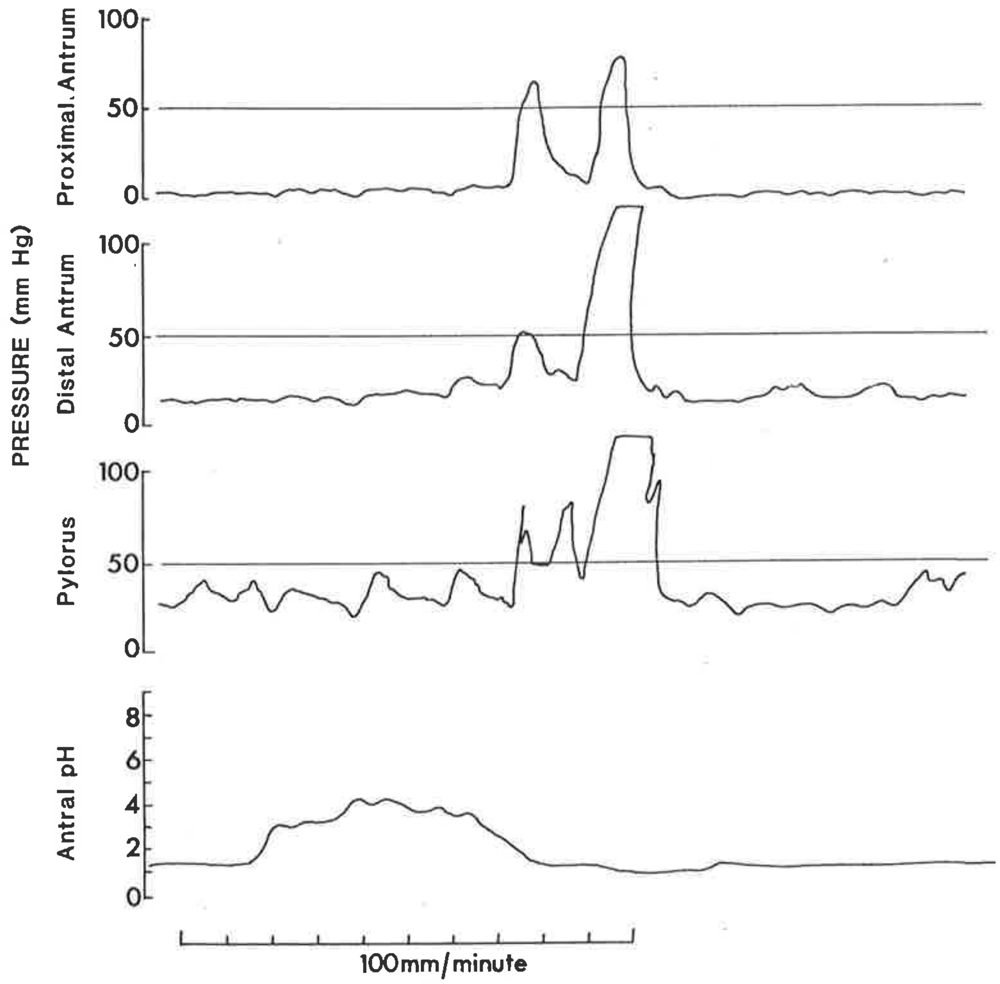



Figure 3.17: Antral alkalinisation in the dog cleared by the lumen occluding contraction.

stomach. With 60 hours of observation in two dogs it was possible to evaluate these antral alkalinisations.

By measuring increases in pH of greater than one pH unit lasting for greater than 5 seconds and timed from initial rise to return to one pH unit greater than previous resting value, the values on Table 3.6 were obtained. Although there were differences in the frequency of duodenogastric reflux events in each dog, the magnitude of the pH rise and duration of each event was similar. The pH changes observed were confirmed to have come from duodenal activity in two ways. Firstly fluoroscopic studies utilising barium showed passage of contrast back into the stomach from the duodenum to be associated with a rise in antral pH. Secondly, by using 0.3 mg of subcutaneous apomorphine, retrograde duodenal waves could be stimulated and a corresponding drop in pH was observed in the stomach (Fig. 3.18). During the canine studies antral alkalinisations were especially frequent during vigorous interdigestive motor activity in keeping with the finding of others that duodenogastic reflux is more common at this time (Keane et al, 1981).

TABLE 3.6

## ANTRAL ALKALINISATION IN THE DOG

| | Frequency episode | pH rise | Duration episode |
|---|---|---|---|
| Dog 1 | 3.1/hr | $\bar{x}$ 2.7, max. 4.7 | $\bar{x}$ 37, max. 160 sec |
| Dog 2 | 0.7/hr | $\bar{x}$ 2.1, max. 3.6 | $\bar{x}$ 40, max. 155 sec |

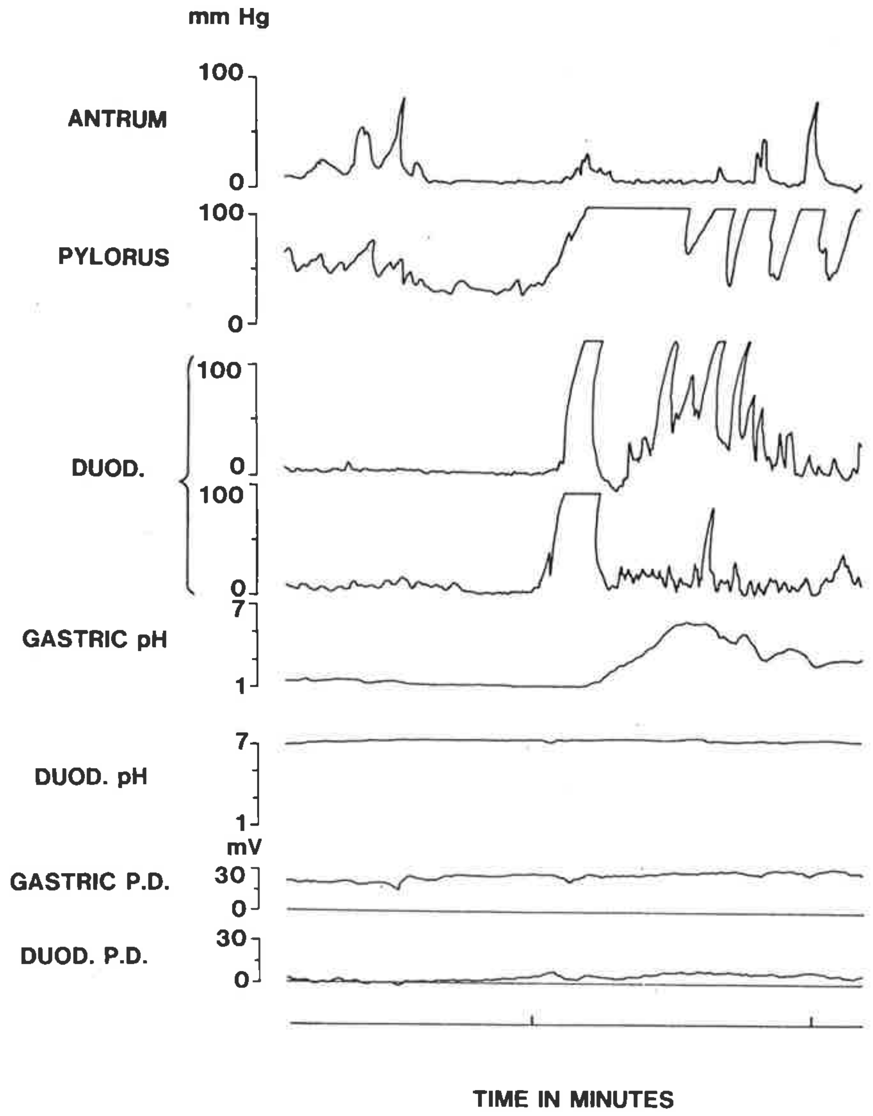



Figure 3.18: A rise in gastric pH following the injection of subcutaneous apomorphine in the dog. This rise is associated with the occurence of retrograde duodenal waves. No tube movement occurred as monitored by the gastric and duodenal transmucosal potential difference.

## 3.4 SYMPTOMS

### (i) METHOD OF SCORING

Evaluation of patients symptoms is at best difficult. The method adopted in most of the patient studies in Section IV is based on that described by de Dombal and Hall (1979). Symptoms were always assessed by one observer during a patient interview prior to investigative procedures.

Symptoms were scored on a scale of 1-3 with mild = 1, moderate = 2, severe = 3, and on a scale of 1-4 for frequency, 2-3 times per month = 1, once a week = 2, 2-3 times per week = 3, and daily = 4. These scores were then multiplied to give a minimum score of zero with a maximum of 12 for each symptom. This assessment was applied to symptoms of nausea, dysphagia, epigastric fullness, constipation, diarrhoea, vomiting, appetite, heartburn and regurgitation. At completion of the interview the observer's assessment of the patients symptoms was read back to the patient for confirmation.

## SECTION IV

## PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX

4.1 Primary Gastro-oesophageal Reflux.

- (i) Oesophageal Emptying
- (ii) Gastric Emptying.

4.2 Effect of Pharmacological Agents.

- (i) Symptoms.
- (ii) Gastric Emptying.
- (iii) Oesophageal Emptying.

4.3 Impact of Nissen Fundoplication

- (i) Pre- and post-operative gastric emptying.
- (ii) Failed Fundoplication.

4.4 Secondary Gastro-oesophageal Reflux.

- (i) Scleroderma.
- (ii) Autonomic Neuropathy.

## 4.1 PRIMARY GASTRO-OESOPHAGEAL REFLUX

### (i) OESOPHAGEAL EMPTYING

#### INTRODUCTION

Tests of oesophageal function have involved the passage of a nasogastric tube assembly which produces a fair degree of patient discomfort, or a barium swallow which is unable to generate quantitative data (section 3.1 (iii)b). A radionuclide test has been developed which has none of these disadvantages but which has the advantage of using food ingestion in a sitting position as the basis of the test (section 3.1 (iii)a). Some patients with gastro-oesophageal reflux are known to have poor acid clearance (Booth et al, 1968) and disordered oesophageal motility (Dodds et al, 1982). However, acid clearance does not necessarily equate with oesophageal emptying (Helm et al, 1984). The aims of this study were to investigate solid oesophageal emptying in both normal controls and patients with objectively demonstrated gastro-oesophageal reflux. In those patients who progressed to anti-reflux surgery oesophageal emptying was measured again 6 months after surgery.

## SUBJECTS AND METHODS

### Subjects

Solid oesophageal emptying studies were performed in 31 normal controls (11 males, 20 females, median age 33, range 19-62). No control subject had any previous history of upper gastro-intestinal symptoms or surgery. All were non-smokers and were not taking any medication at the time of testing.

A group of 73 patients with symptomatic gastro-oesophageal reflux (32 males, 41 females, median age 52.5 years, range 19-72) was studied. All patients had confirmation of their reflux disease with either a positive standard acid reflux test (Kantrowitz et al, 1969) and/or endoscopic evidence of oesophagitis.

The patients studied were also specifically questioned as to the presence or absence of dysphagia as a symptom that occurred at least daily. Dysphagia was defined as an uncomfortable sensation of something sticking in the oesophagus while eating. No patient was diagnosed as having a peptic oesophageal stricture.

Eighteen of these patients (9 males, 9 females, median age 51.5 years, range 19-72) also underwent a fundoplication and were restudied 6 months post-operatively.

## Endoscopy

Endoscopies were performed by a number of observers. The finding was regarded as positive if the endoscopist recorded unequivocal evidence of oesophagitis. It is acknowledged that such a judgement contains a large subjective element (Breen and Whelan, 1978).

## Radionuclide Assessment

The solid bolus test has been described earlier (section 3.1 (iii)).

## Operative Technique

The surgical technique was standardized with the fundus and upper part of the body of the stomach being mobilized and wrapped around the lower 4-5 cm of the oesophagus. The wrap thus used both anterior and posterior walls of the stomach (Jamieson and Duranceau, 1984a). The fundic wrap included the anterior vagus nerve and exluded the posterior vagus nerve and was performed with a No. 52 Maloney bougie in postion in the oesophagus.

## Statistical Analysis

Data were analysed using the Wilcoxon unpaired test and the Wilcoxon paired sign rank test.

RESULTS

The patients with gastro-oesophageal reflux emptied their oesophagus of the bolus more slowly than the control group ($p < .001$, Fig. 4.1). For 26 controls an age matched patient existed and in this group there was still a significant difference between the groups ($p < .01$).

The eighteen patients who underwent surgery did not differ significantly ($p > .05$) from the fifty-three non-operated patients with respect to their oesophageal emptying.

The patient group at the time of initial oesophageal emptying study had 40 patients free of dysphagia and 33 with dysphagia. The group with dysphagia had significantly slower oesophageal emptying ($p < .001$, Fig. 4.2).

Endoscopy results were available for 59 patients, 27 with oesophagitis and 32 without. There was no significant difference ($p > .05$) between the two groups with respect to their oesophageal emptying (Fig. 4.3).

The operative group at the time of post-operative study was free of symptoms of heartburn, regurgitation or dysphagia. Figure 4.4 shows the pre-operative oesophageal emptying values and the post-operative values six months after surgery. No difference between the two groups was

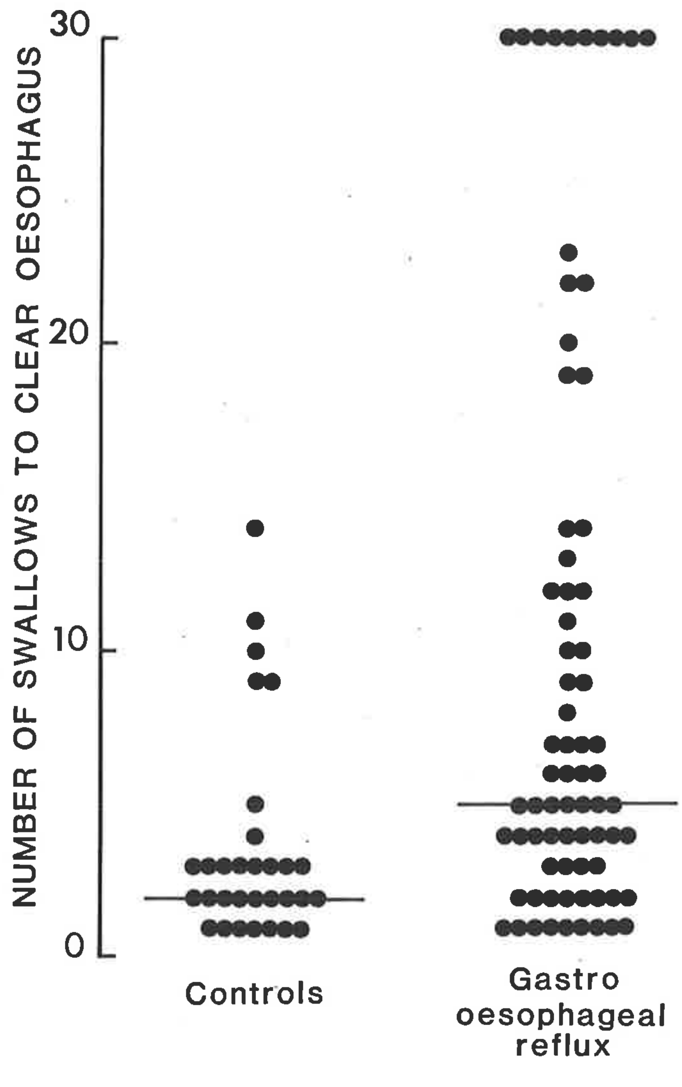



Figure 4.1: Number of Swallows to clear the oesophagus of 95% of activity for normal controls and patients with gastro-oesophageal reflux. The test was ceased if 30 swallows failed to clear the oesophagus. The median value for each group is shown by the bars.

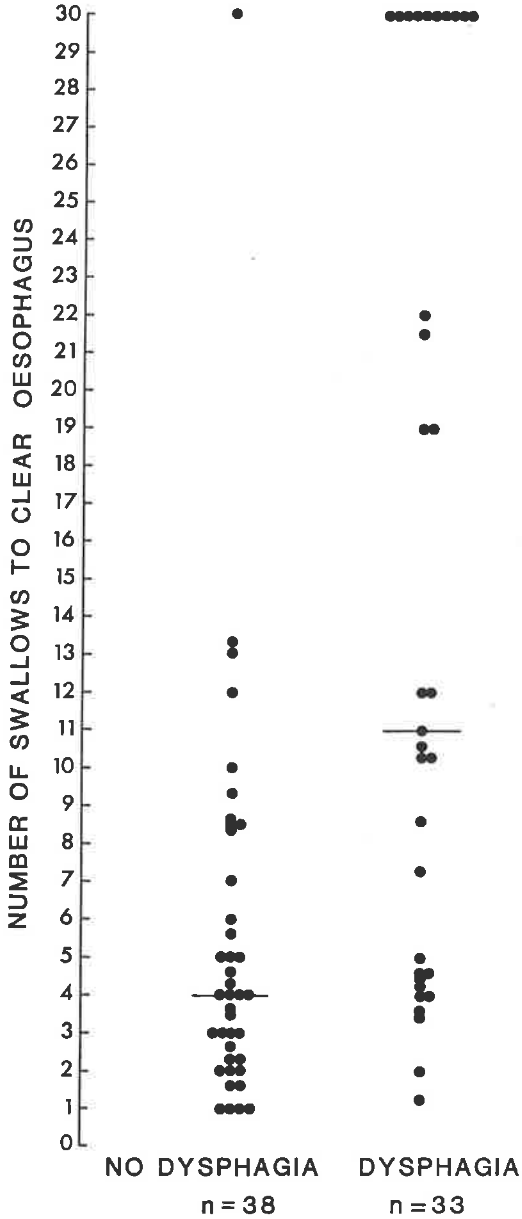



Figure 4.2: Oesophageal emptying values obtained for patients with and without dysphagia. The median values are shown by the bars.

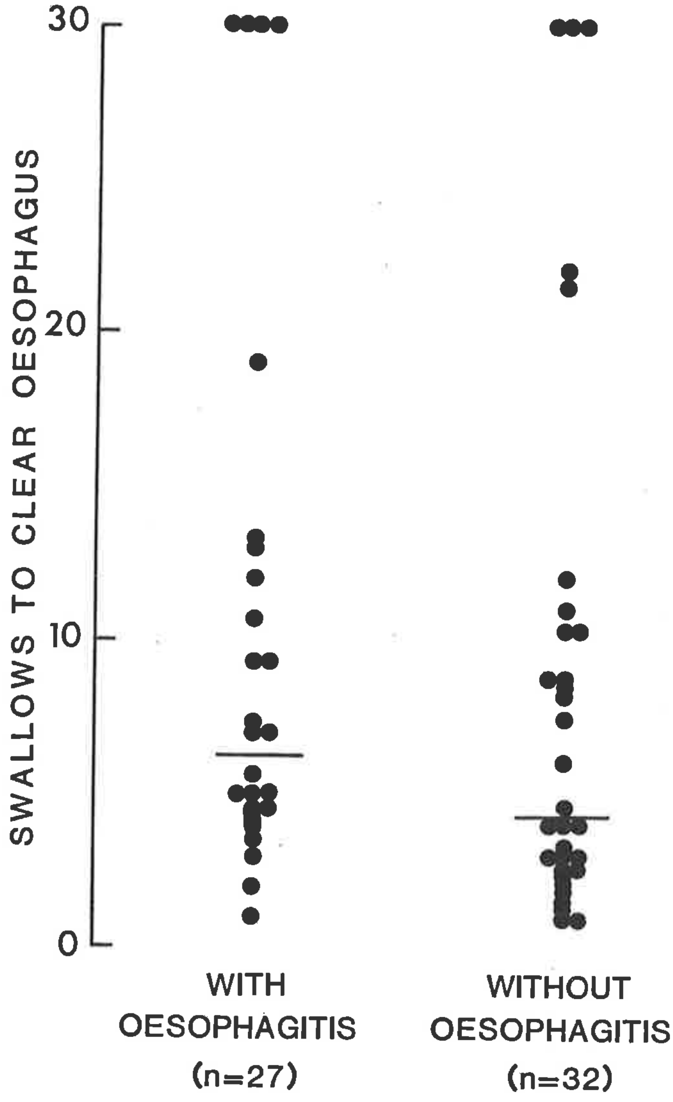



Figure 4.3: Oesophageal emptying values obtained for patients with and without oesophagitis. The median values are shown by the bars.

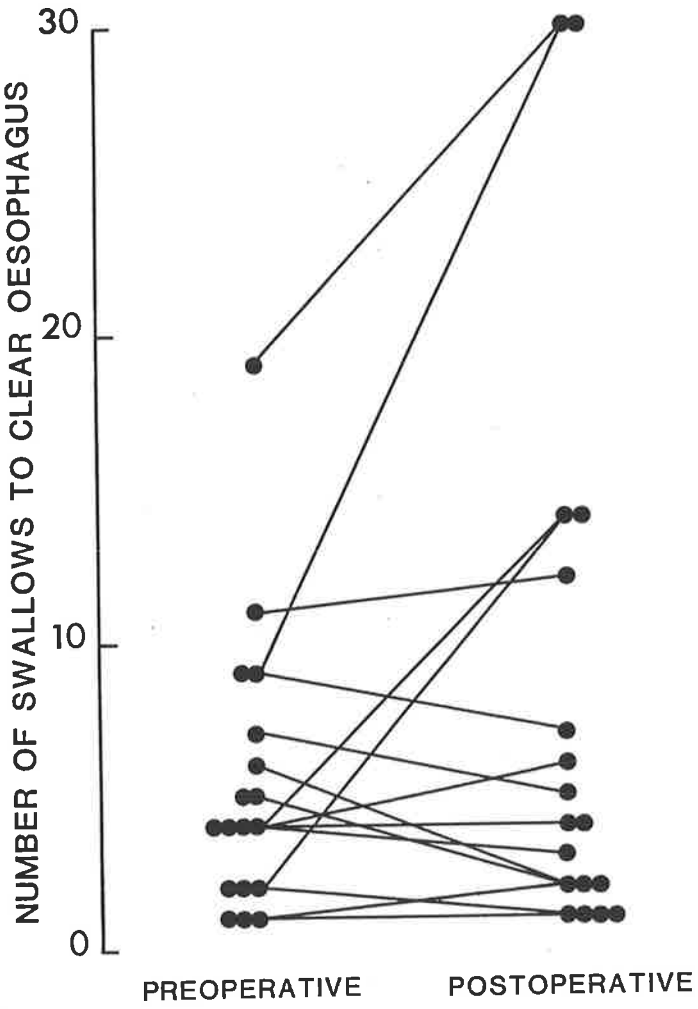



Figure 4.4: Preoperative and postoperative oesophageal emptying studies for patients with gastro-oesophageal reflux who underwent fundoplication. Median values shown by the bars.

found ($p > .05$). Two patients did not clear their oesophagus in 30 swallows at post-operative study, but neither complained of any dysphagia.

## DISCUSSION

Poor oesophageal clearance of refluxed material is thought to be an important pathogenetic mechanism in patients with symptomatic gastro-oesophageal reflux (Krejs et al, 1976; Stanciu and Bennett, 1974a). This impaired clearance has been measured usually by use of the acid clearance test (Booth et al, 1968). This involves the insertion of a pH probe into the distal oesophagus followed by instillation of a standard amount of acid. More recently radionuclide labelled liquid swallows have been used (Tolin et al, 1979; Blackwell et al, 1983; Russell et al, 1983) to assess oesophageal function in patients with gastro-oesophageal reflux. Such investigation has the advantage of being non-invasive and more physiological than the acid clearance test. These studies, however, have been performed in the supine position which does not simulate what normally occurs in the post prandial period when reflux is known to occur most frequently (De Meester et al, 1976).

This study used a solid bolus which was swallowed in the upright position. It provided a quantitative measure of oesophageal dysfunction. A significant difference in oesophageal emptying was found between our normal controls and the 73 gastro-oesophageal reflux patients. The presence of pre-existing oesophagitis was not associated with slower oesophageal emptying, giving support to the view that oesophageal dysfunction in gastro-oesophageal reflux patients is a primary disorder and not mediated by muscosal injury (Russell et al, 1981b). The group of 33 patients in whom dysphagia was present had significantly slower oesophageal emptying, than the non-dysphagia group of patients. However, considerable overlap existed between the two groups (Fig. 4.2). This highlights the difficulty in the objective assessment of symptoms.

Although the median age of the controls and the patients was significantly different and there was a significant correlation between delay in emptying and increasing age ($r_s = .423$ $p < .001$) in the patient group, however this age related slowing in emptying did not explain fully the difference between our control and patient group. When 26 patients were age matched with 26 controls, a significant difference in oesophageal emptying persisted between the groups.

The 18 patients who underwent fundoplication were not significantly different in their age, sex or oesophageal emptying from the gastro-oesophageal reflux group who did not proceed to surgery.

Fundoplication did not improve the ability of the oesophagus to empty itself, despite excellent symptomatic improvement. Two patients whose oesophageal emptying worsened considerably post-operatively were both symptom free at the time of testing. Russell et al (1981b), studied transit of a radionuclide liquid in the supine position to assess oesophageal function before and after anti-reflux surgery in twenty patients. They also found that there was no improvement in oesophageal function after successful surgery. These findings suggest that oesophageal dysfunction in reflux patients is a primary abnormality.

The use of a radionuclide labelled solid food bolus appears to be a simple and non-invasive method of assessing one aspect of oesophageal function in patients with gastro-oesophageal reflux disease.

### (ii) GASTRIC EMPTYING

#### INTRODUCTION

Delayed gastric emptying of solids and liquids has been reported in a significant percentage of patients with gastro-oesophageal reflux (McCallum et al, 1981; Little et al, 1980; Baldi et al, 1981; Velasco et al, 1982). These reports have assessed gastric emptying for a liquid meal (Baldi et al, 1981; Velasco et al, 1982) a solid meal (Little et al, 1980) and a combined solid and liquid meal

(McCallum et al, 1981). However they did not assess solid and liquid emptying simultaneously in such patients. Correlations between delayed gastric emptying and manometric (McCallum et al, 1981) and endoscopic findings have been noted (Litte et al, 1980).

A gastric emptying technique which simultaneously assesses solid and liquid emptying has been utilised, in order to better characterise the gastric emptying abnormalities in gastro-oesophageal reflux patients. Correlations have also been sought between endoscopic findings, lower oesophageal sphincter pressure and symptoms of regurgitation and epigastric fullness with the rate of gastric emptying.

## SUBJECTS AND METHODS

### Subjects

Gastric emptying tests were performed in 22 normal volunteers, 12 males and 10 females (median age 34, range 21-62). All were non-smokers and had no evidence of gastrointestinal disease. Tests were also performed in 72 patients with gastro-oesophageal reflux. The patient group comprised 33 males and 39 females, (Median age 49, range 19-72). Sixty-nine patients had undergone standard acid reflux testing (Kantrowitz et al, 1969) and oesophageal manometry incorporating a Dent Sleeve (Dent, 1976). Resting lower oesophageal sphincter pressure was measured by taking the median value of thirty pressure readings unassociated with swallowing, during a five minute rest period. Sixty-four of the patients had an endoscopy performed. All 72 patients had a positive standard acid reflux test and/or oesophagitis on endoscopy to substantiate the clinical diagnosis of gastro-oesophageal reflux disease.

Symptomatic Assessment

Prior to the performance of gastric emptying the last 43 patients entered in this study had a history taken and each was questioned about regurgitation and epigastric fullness. Symptoms were scored by the method outline in section 3.4 (de Dombal and Hall, 1979).

Endoscopy

Endoscopies were performed by a number of observers. In all patients the gastric emptying study was performed between 7 days and 28 days after the endoscopy. The endoscopic finding was regarded as positive if the endoscopist recorded unequivocal evidence of oesophagitis. It is acknowledged that such a judgement contains a large subjective element (Breen and Whelan, 1978).

Radionuclide assessment

This has been previously described (section 3.2 (ii)a).

The normal range in this study for both solid and liquid was defined as the value within which 95% of the observations fell.

## Statistical Analysis

Data was analysed using the Wilcoxon unpaired test and Spearman rank correlation coefficient ($r_s$).

## RESULTS

### Manometry

The resting lower oesophageal spincter pressure and the solid remaining at 100 minutes and liquid T50 are shown in figure 4.5 and 4.6. There was no significant correlation between sphincter pressure and solid ($r_s$ = -0.085, $p > .05$) or liquid ($r_s$ = -0.189, $p > .05$) gastric emptying.

### Endoscopy

All but 8 patients had an endoscopy prior to their gastric emptying study. On endoscopy 28 had no definite evidence of oesophagitis, the remaining 36 had unequivocal evidence of oesophagitis. There was no significant difference between the oesophagitis and non oesophagitis group for their liquid T50. However the percentage of solid remaining at 100 minutes was greater ($p < .05$) in the oesophagitis group (Fig. 4.7)

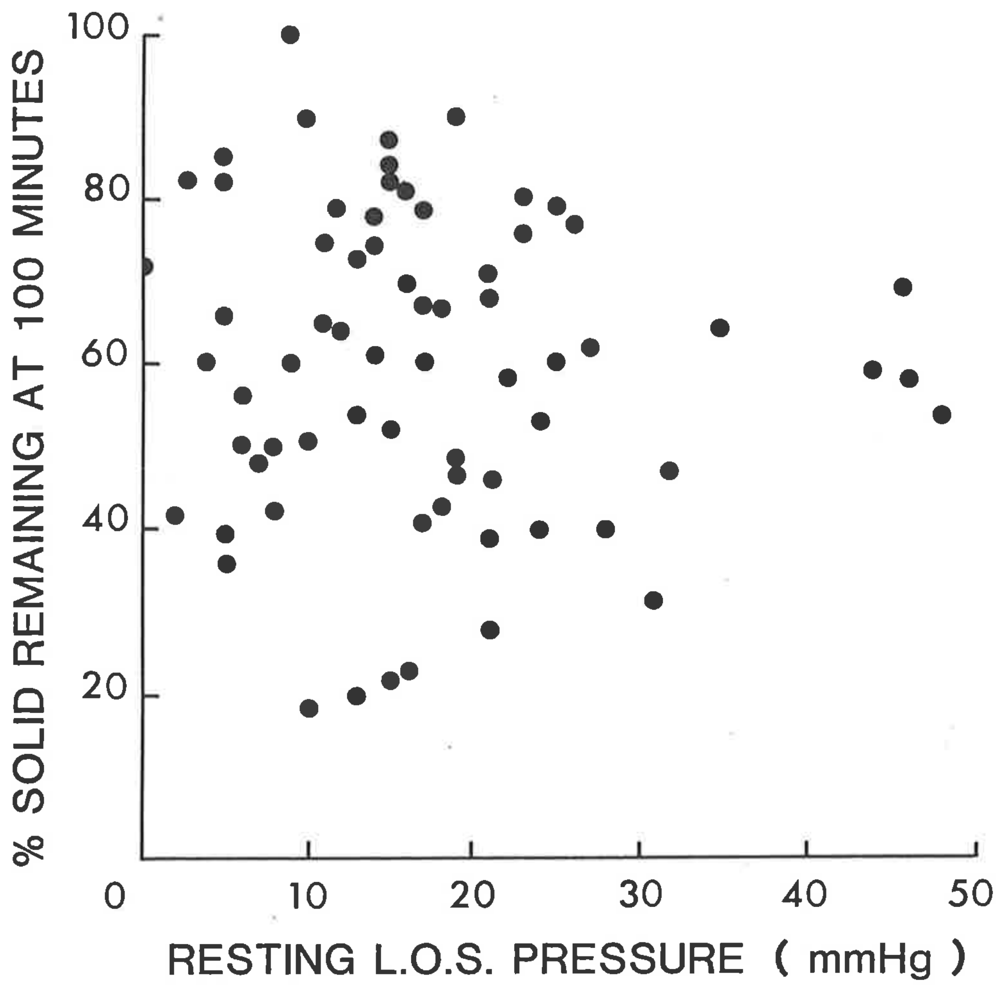



Figure 4.5: Resting lower oesophageal sphincter pressures plotted against percentage of solid remaining in the stomach at 100 minutes.

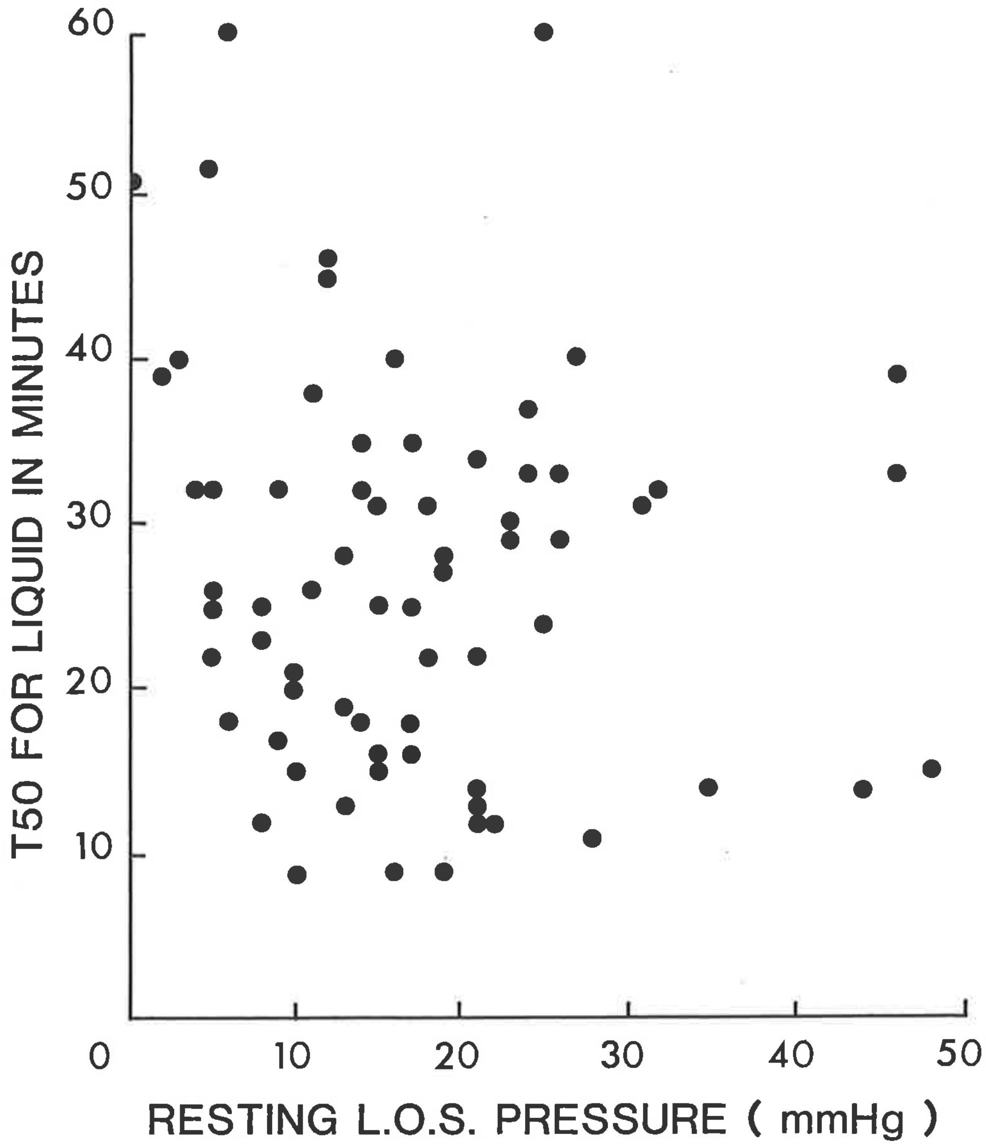



Figure 4.6: Resting lower oesophageal sphincter pressures plotted against time for 50% of liquid marker to empty from the stomach.

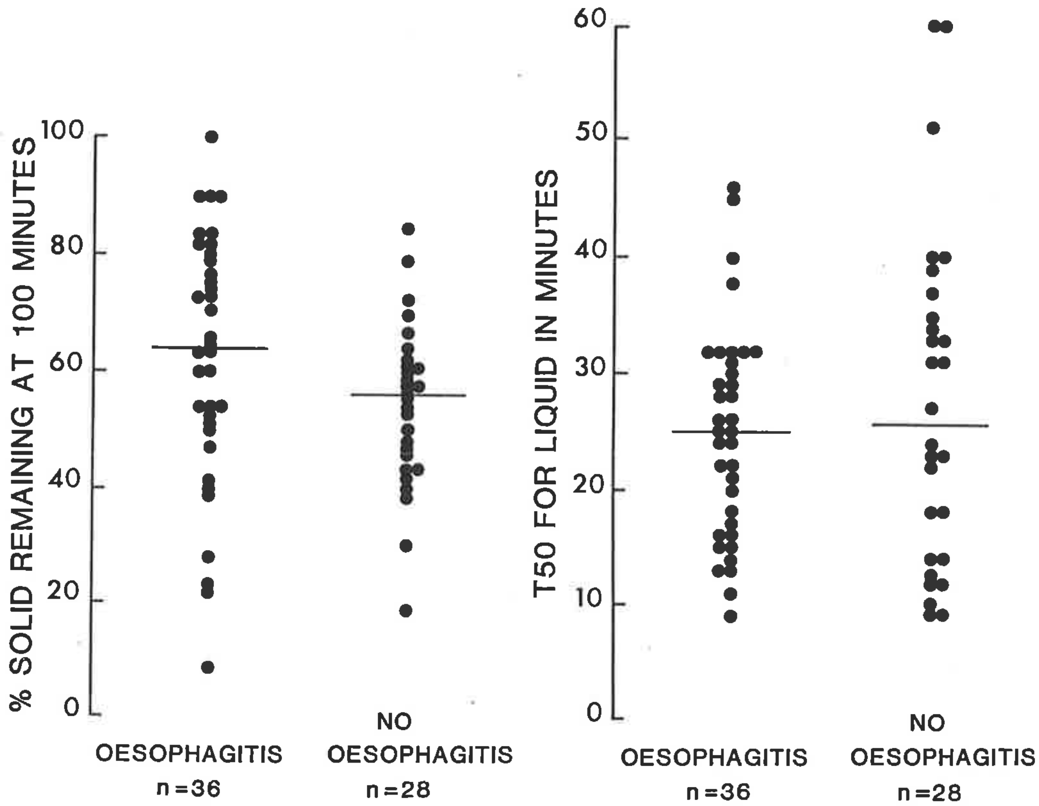



Figure 4.7: Patients with and without oesophagitis and their solid and liquid gastric emptying values. Line dividing each group represents the median value.

## Symptoms

In the last 43 patients a prospective review of their symptoms of epigastric fullness and regurgitation was undertaken. Epigastric fullness after meals was described in 36 patients with a median score of 9 (range 1-12) and regurgitation in 30 patients, median score 8 (range 3-12). No correlation existed between scored epigastric fullness and solid ($r_s = 0.206$, $p > .05$) or liquid ($r_s = 0.138$, $p > .05$) emptying. Similarly no correlation was found between regurgitation and solid ($r_s = .006$, $p > .05$) or liquid ($r_s = 0.209$, $p > .05$) emptying.

## Gastric emptying

Table 4.1 shows that as a group, patients with gastro-oesophageal reflux commenced solid emptying (lag period) from the stomach later than controls. This group also emptied at a slower rate. Significantly more of the solid marker remained at 100 minutes in the patients than controls (Fig. 4.8). Liquid T50 was also slower in these patients (Fig. 4.8). A significant correlation ($r_s = 0.337$, $p < .01$) existed between the emptying T50 and the percentage of solid remaining at 100 minutes.

Neither solid nor liquid gastric emptying values were normally distributed (Fig. 4.8).

TABLE 4.1

RESULTS OF GASTRIC EMPTYING IN CONTROLS
AND PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX (G.O.R.).
VALUES ARE MEDIANS WITH RANGE IN BRACKETS

| | CONTROLS | G.O.R. | SIGNIFICANCE LEVEL |
|---|---|---|---|
| No. of Subjects | 22 | 72 | - |
| Solid lag period (min) | 35 (9-69) | 45 (14-104) | $p < .01$ |
| Solid emptying rate (%/min) | 1.25 (0.7-2.3) | 0.76 (0.2-2.0) | $p < .0001$ |
| Solid remaining at 100 min (%) | 30 (12-65) | 60 (9-100) | $p < .0001$ |
| T50 liquid | 18 (11-35) | 25.5 (9-78) | $p < .005$ |

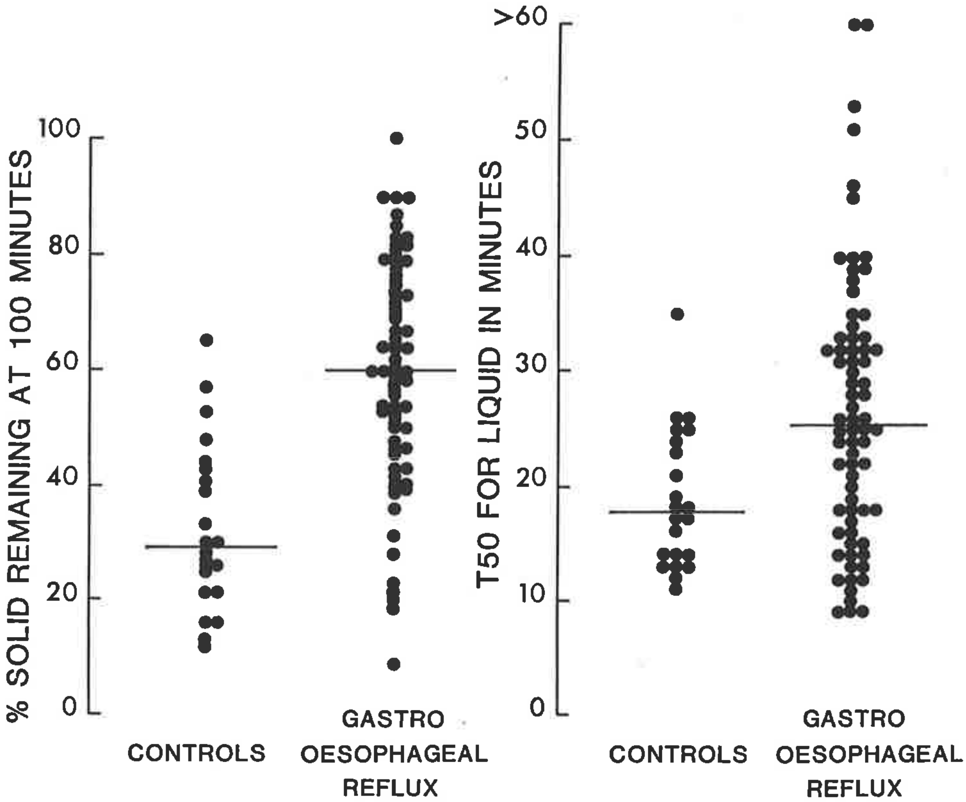



Figure 4.8: Gastric emptying values for controls and patients with gastro-oesophageal reflux. Line dividing each group represents the median value.

## DISCUSSION

The recent application of techniques which accurately quantify gastric emptying in patients with gastro-oesophageal reflux has raised a number of questions concerning the etiology and management of the disease. In these patients both solid and liquid emptying was assessed simultaneously with 32 patients (44%) showing a solid emptying delay and 27 patients (38%) a liquid delay. Sixteen of these patients had delay in both solid and liquid emptying. Furthermore there was a significant correlation between the rates of solid and liquid emptying indicating that both types of meal are affected in such patients. The results confirm the observation that delayed gastric emptying is present in a significant proportion of patients with gastro-oesophagel reflux. It is apparent that delayed emptying of solids, delayed emptying of liquids and delayed emptying of both solids and liquid can occur in individual patients.

The significantly prolonged period for the solid component of the meal to commence emptying from the stomach in gastro-oesophageal reflux patients has not been observed previously and probably reflects a delayed redistribution of solid food from fundus to antrum. A reduction in proximal stomach tone could explain both the prolonged lag period and the delay in liquid emptying in these patients. However, the delayed linear emptying rate of solid suggests antral dysmotility, which has been described previously in gastro-oesophageal reflux patients (Behar and Ramsby, 1978). Fink et al (1983a), has also reported a significant delay in gastric emptying in patients with gastro-oesophageal reflux and severe gastritis, compared to those without gastritis. This may be a condition which either predisposes to, or results from antral dysmotility.

Factors such as medications and cigarette smoking (Grimes and Goddard, 1978) which may have influenced gastric emptying were not permitted prior to study. The age difference between controls and patients has been found in our laboratory (Horowitz et al, 1984) and by others (Moore et al, 1983) not to be a significant factor over such a relatively narrow range.

These results have been supported by other studies which have used both radionuclide and intubation techniques. Donovan et al (1977), measured solid and liquid emptying in 10 patients, with 5 showing delayed liquid and 3 delayed solid emptying. Csendes and Henriquez (1978) used a phenol red inert marker technique in 19 patients with oesophagitis and showed that liquid emptying was delayed in 6 of their patients. These findings in regard to delayed liquid emptying were similar to those of Clark et al (1981) and Baldi et al (1981), who used radionuclide techniques. However, Velasco et al (1982) using a sequential radionuclide technique reported delayed solid emptying, but normal liquid emptying in patients with gastro-oesophageal reflux. McCallum et al (1981) used a mixed liquid and solid meal technique and found that 41% of patients fell outside their normal range. However they were not able to determine whether it was the solid phase, liquid phase, or both which was responsible for the delay in their studies.

The variable liquid emptying findings reported may be due to the differing caloric (or osmotic) contents of the liquids used (Collins et al, 1983). The observation of the prolonged solid lag period was not reported by these workers.

How the observed gastric emptying abnormalities relate to gastro-oesophageal reflux remains unclear. Little et al (1980) suggested that patients with endoscopic oesophagitis were more likely as a group, to have delayed solid emptying than patients without oesophagitis. This study found also that those patients with pre-existing oesophagitis tended to empty a solid meal slower than those without oesophagitis. Figure 4.7 shows there is considerable overlap, between the two groups and with the normal range. However it may indicate that patients with delayed gastric emptying have a more severe form of gastro-oesophageal reflux disease.

McCallum et al (1981) found no correlation between resting lower oesophageal sphincter pressure and the gastric emptying of a mixed meal. Similarly no correlation was found between lower oesophageal sphincter pressure and solid or liquid emptying.

This study indicates that the clinician cannot be confident of diagnosing delayed gastric emptying from symptoms alone. Thus those symptoms which might be expected to be associated with delayed gastric emptying (ie regurgitation and epigastric fullness after eating) failed to correlate significantly with the gastric emptying values. A similar lack of correlation between symptoms and delayed gastric emptying in reflux patients was reported by Velasco et al in 1982.

If delayed emptying plays a role in the pathogenesis of the disease it may relate to gastric distension. Pettersson et al (1980) argued that gastric distension causes a change in gastric wall tension in the region of the lower oesophageal sphincter. Samelson et al (1983) used a sphincter model to show that the distal end of the sphincter is stretched open before the remainder of the sphincter is affected. Delayed emptying of food may act to distend the stomach and thus the lower oesophageal sphincter and permit more frequent episodes of reflux to occur. A further factor may be prolongation of the post prandial state. It has been observed that gastro-oesophageal reflux episodes occur more frequently after meals (De Meester et al, 1976). In as much as delay in gastric emptying prolongs the post prandial state, it may also prolong this tendency to increased reflux events.

A further area where the delayed emptying may have relevance is that of treatment. Drugs aimed at increasing gastric emptying have been shown to alter oesophageal motility (Behar and Ramsby, 1978) and gastric emptying (Fink et al, 1983b) in the short term. However long-term studies have not shown gastric prokinetics to be significantly better than placebo in the treatment of gastro-oesophageal reflux (McCallum et al, 1977; Goethals, 1979).

Whether surgery to aid gastric emptying has a place in patients with reflux disease is also uncertain. Burford and Lischer (1956) concluded on theoretical grounds that a gastric drainage procedure should allow more rapid emptying of the stomach. They carried out a Finney pyloroplasty alone in patients with severe reflux disease with good results in 15 of 16 patients. Herrington (1960) advocated the use of vagotomy and drainage in hiatal hernia repair. In general such an approach to gastro-oesophageal reflux has not gained favour. However, Stanghellini and Malagelada (1983a) have reported 3 patients who developed severe dyspeptic symptoms after anti-reflux surgery and who then benefited from antrectomy. Anti-reflux surgery has been reported as both increasing (section 4.3 (i)) and not altering (Velasco et al, 1982) gastric emptying. These differences may relate to the different surgical techniques used.

At present there are many unanswered questions in this field. As answers become apparent it may be that more rational medical and surgical therapy can be applied to the treatment of patients with gastro-oesophageal reflux disease.

## 4.2 EFFECT OF PHARMACOLOGICAL AGENTS

INTRODUCTION

A number of studies have been reported showing the value of pharmacological agents in the treatment of gastro-oesophageal reflux (Farrell et al, 1973; 1974; McCallum et al, 1977; Valenzuela, 1981; Goethels, 1979; Corinaldesi et al, 1983; Fink et al, 1983b). In general they have regarded patients with gastro-oesophageal reflux as an homogeneous group and subjected them to double blind and blinded crossover trials of both oral and IV metoclopramide and domperidone for periods ranging from two weeks to several months (Johnson, 1973). The results have tended to be inconclusive in regard to the value of these therapeutic agents in chronic gastro-oesophageal reflux (McCallum et al, 1977; Goethels, 1979, Corinaldesi et al, 1983; Wallin et al, 1979; Dilawari and Misiewicz, 1973). One explanation for this lack of conclusiveness may stem from the finding that only 40% of patients with gastro-oesophageal reflux have delayed gastric emptying (McCallum et al, 1981; Velasco et al, 1982). Metoclopramide and domperidone both enhance lower oesophageal sphincter tone and gastric emptying (Valenzuela, 1981; Wallin et al, 1979, Dilawari and Misiewicz, 1973; Cohen et al, 1976; Schulze-Delrieu, 1979; McCallum et al, 1983, Stanciu and Bennett, 1973; Perkel et al, 1979, Bron and Massih, 1980) and would be expected to be of particular use in patients with disordered gastric emptying and gastro-oesophageal reflux. Fink et al (1983b) found that gastro-oesophageal reflux patients with normal and delayed gastric emptying benefited from metoclopramide in an acute situation. It is not known if a similar result would occur with long-term treatment. It is also not known if stratifying patients into normal or delayed emptiers would alter the outcome. The aim of this study was to try and answer these questions by comparing the symptomatic response to oral metoclopramide and domperidone over a four week period in patients with gastro-oesophageal reflux. Patients were stratified according to whether they had delayed or normal gastric emptying.

(i) SYMPTOMS

## SUBJECTS AND METHODS

### Subjects

Patients were selected from those attending the Department of Surgery at the Royal Adelaide Hospital, for standard acid reflux testing (Kantrowitz et al, 1969) and oesophageal manometry. Only patients with symptomatic gastro-oesophageal reflux and positive standard acid reflux testing took part in the trial. There were 23 patients, 8 males and 15 females, median age 50 years (range 22-69). No patient had a history of upper abdominal surgery and no patient was receiving any medication known to alter gastric emptying.

Radionuclide assessment

This was as previously described (section 3.2 (ii)a). Previously determined laboratory values for 22 controls were used to determine the normal range for the solid and liquid emptying.

Drug treatment

After the gastric emptying test the patients were commenced on a double blind trial of domperidone, metoclopramide or placebo. Metoclopramide was given 10 mg four times a day before meals, domperidone 20 mg four times a day before meals and placebo four times a day before meals. At the end of four weeks treatment, patients were re-assessed and commenced on the next treatment. This continued until all three treatments had been administered. Possible side effects were discussed with patients prior to commencement of therapy and a 24 hour contact telephone number provided. The inclusion of a placebo was also made clear to all patients. Before commencement of therapy and at the four week review the patients had their symptoms assessed as outlined in section 3.4. The symptoms assessed were dysphagia, regurgitation, epigastric fullness, heartburn, nausea, vomiting, constipation, diarrhoea and anorexia (de Dombal and Hall, 1979).

To aid recollection of the month's symptoms, patients were supplied with a diary on which they were asked to record symptoms daily. If previously using antacid (Mylanta, Parke-Davis) they were also supplied with bottles of antacid which could be freely taken but were brought in to be measured at the end of each four weeks.

If side effects were considered by the patient or doctor to be significant then the treatment was ceased and the next blinded treatment given.

The code was broken at the end of the study.

## Statistical methods

Results were analysed using the Hotelling $T^2$ test for differences between 2 mean vectors (Morrison, 1967) and regression analysis.

## RESULTS

All but one patient commenced the three treatments. That patient completed 2 of the 3 treatments but withdrew from further participation in the trial. Side effects encountered during each treatment regimen are shown in Table 4.2. Four patients withdrew from a treatment course due to side effects, 3 from the metoclopramide treatment and one from the domperidone. Providing a patient completed more than 2 weeks treatment then their symptoms assessment at

TABLE 4.2

## SIDE EFFECTS DURING TREATMENT

| | NO. PATIENTS | SIDE EFFECTS |
|---|---|---|
| Metoclopramide | | |
| | 1 | Menstrual disturbance |
| | 3 | Dizziness |
| | 2 | Depression (1 withdrew) |
| | 4 | Lethargy (2 withdrew) |
| | 1 | Dry mouth |
| Domperidone | | |
| | 1 | Excessive salivation |
| | 1 | Galactorrhoea (withdrew) |
| Placebo | | |
| | 1 | Muscle spasms |
| | 1 | Depression |
| | 1 | Dizziness |

time of withdrawal was included. Where treatment was ceased before two weeks no symptom scoring was performed. The patient who failed to complete all 3 courses withdrew from the last treatment which was metoclopramide. One patient withdrew from metoclopramide treatment because of lethargy and one patient from the domperidone group because of galactorrhoea. Therefore data was obtained on 23 patients for placebo, 22 for domperidone and 21 for metoclopramide. Gastric emptying status prior to treatment is shown in Figure 4.9. Eleven patients fell outside the normal range for solid gastric emptying and 5 for liquid gastric emptying. In all, 13 patients had a delay of solid and or liquid emptying, leaving 10 patients with gastric emptying within the normal range for solid and liquid. Regression analysis with components for metoclopramide, domperidone and placebo effects and also a component for prior treatment effects (for example when domperidone was preceded by metoclopramide and placebo etc.), showed no significant difference in symptom scores between the 3 treatments. However all treatments showed a significant ($p < .0001$) improvement when compared with the pre-treatment scores (Fig. 4.10). When patients were subdivided into those with normal solid and liquid gastric emptying and those with delay of solid and/or liquid emptying no significant difference was found between these two groups in response to treatments received (Fig. 4.10). When antacid consumption during each month was considered, again no significant

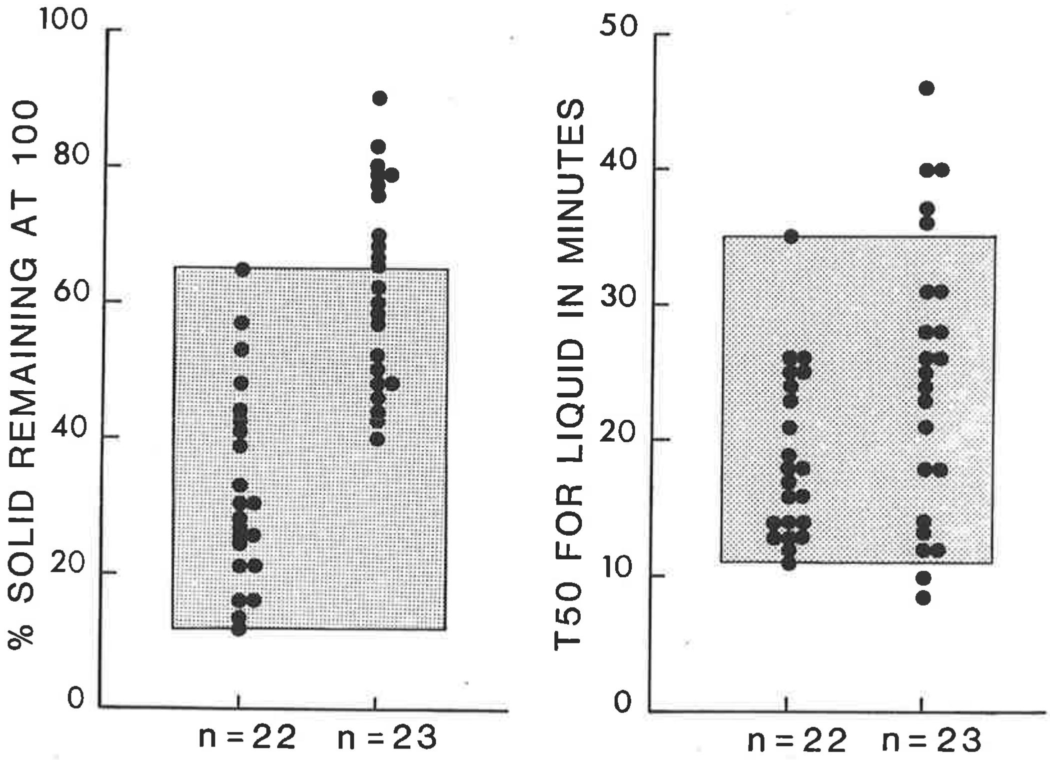



Figure 4.9: Results of gastric emptying studies in controls and patients prior to commencement of treatment. The shaded area represents the normal range.

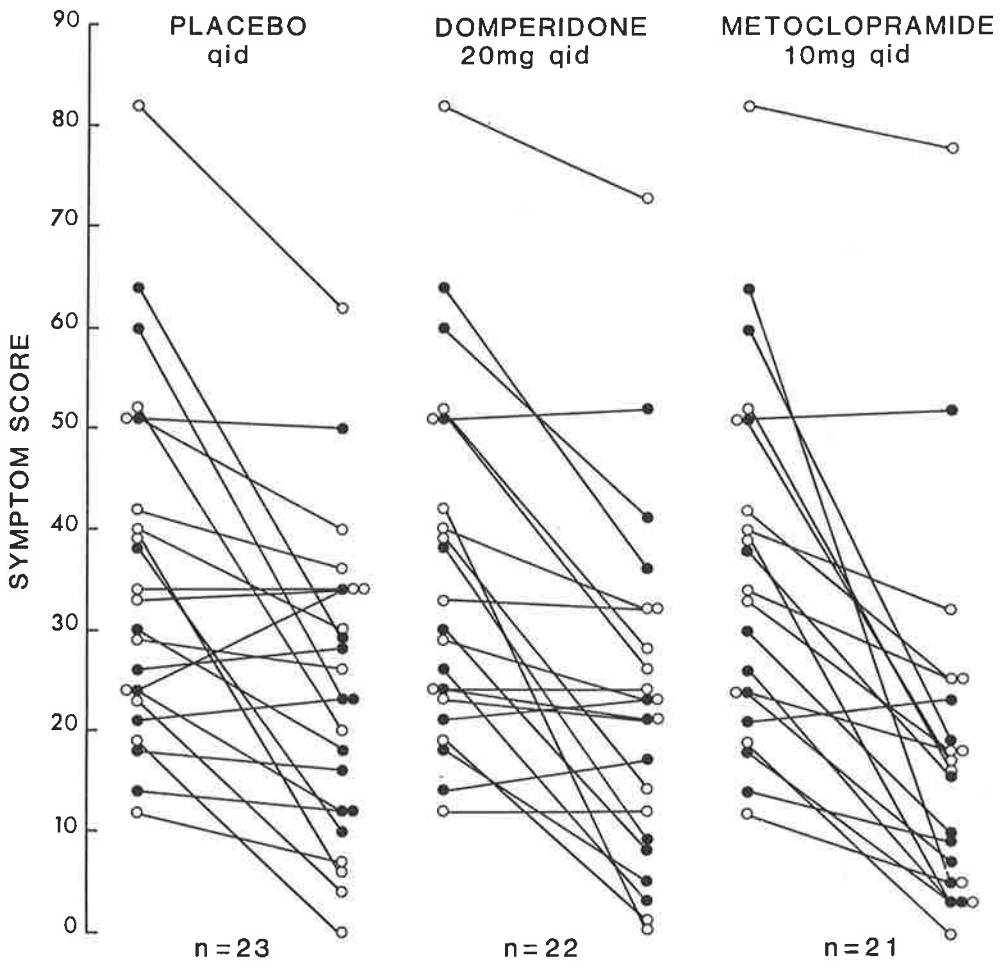



Figure 4.10: Symptom score at pre-treatment assessment and the corresponding patient score at conclusion of each treatment period. The solid dots are those of patients with normal solid and liquid emptying, the open dots represent patients with delay of solid and/or liquid emptying.

difference was found for the placebo or active treatment periods.

## DISCUSSION

The significance of the delay in gastric emptying found in patients with gastro-oesophageal reflux is not clear (McCallum et al, 1981; Velasco et al, 1982).

Metoclopramide and domperidone have been shown to accelerate gastric emptying in patients with gastro-oesophageal reflux (Corinaldesi et al, 1983; McCallum et al, 1983). It is not surprising that the use of such agents has been of equivocal benefit (McCallum et al, 1977; Goethels, 1979; Corinaldesi et al, 1983; Wallin et al, 1979, Dilawari and Misiewicz, 1973) as more than half of the patients with gastro-oesophageal reflux have normal gastric emptying to begin with. It has been demonstrated that acute improvement in gastric emptying occurs following pharmacological intervention (Fink et al, 1983b), but it is not known if these changes are sustained over weeks or months of treatment. The relatively inconclusive benefit of such treatment over a long period of time perhaps suggests that the action is not sustained (McCallum et al, 1977; Goethels, 1979; Corinaldesi et al, 1983; Wallin et al, 1979; Dilawari and Misiewicz, 1973).

This study has shown a significant symptomatic improvement in patients with gastro-oesophageal reflux who receive medication. However there was no significant difference in the response between the active treatments of domperidone and metoclopramide and the inactive treatment, the placebo. Nor did the consumption of antacid vary significantly between the 3 groups. No advice was given on diet or anti-reflux measures to any patient. Nor was antacid given to the patients if not already in use. It appears that the reassurance and security perceived by the patient in participating in the trial was of significant beneficial effect. No difference in outcome was observed for patients who had pre-existing gastric emptying delay. If more rapid gastric emptying is of benefit to such patients previous work would suggest that both normal and delayed patients receive the benefit equally (Fink et al, 1983b). This is supported by the findings of this study. Of concern however are the reported side effects. The dose of metoclopramide used is within the recommended therapeutic range for such patients, yet 11 side effects were reported with 3 of the 22 patients who received it unable to complete the course of treatment. The placebo treatment group also reported 3 significant side effects, an aspect that should not be forgotten when considering the overall incidences of side effects in such patients. The domperidone treatment period was associated with excessive salivation but more importantly Galactorrhoea in a 22 year old female 36 hours after commencing treatment (Maddern, 1983). This is an important side effect to be aware of when prescribing this agent.

This study does not provide an explanation why the active agents were no more effective than the placebo. It could have been because the acceleration of gastric emptying was not sustained or because gastric emptying per se is not an important factor in the pathogenesis of symptoms of reflux. This latter seems unlikely and it is believed that more study is required of these gastric prokinetics before one can be confident of their usefulness in the treatment of gastro-oesophageal reflux disease.

## (ii) GASTRIC EMPTYING

### INTRODUCTION

In order to answer the questions posed by the previous study as to the effect of chronic administration of domperidone on gastric emptying a pre- and post-treatment gastric emptying study was conducted.

### Methods

A subset of 10 patients (4 males, 6 females, median age 49.5, range 34-69) had a follow-up gastric emptying study conducted at the conclusion of one months treatment with Domperidone 20 mg qid. The study was conducted one hour after taking domperidone following an overnight fast. Data were analysed using a Wilcoxon paired sign rank test.

## Results

Pre and post gastric emptying studies for solid and liquid are shown in figure 4.11. No significant difference was found between the two studies.

## Discussion

The effect of long-term administration of gastric prokinetics on gastric emptying has not been studied. The acute effects have been well documented (Corinaldesi et al, 1983; McCallum et al, 1983), but whether they are sustained is not known. These results would indicate that from an objective measurement of gastric emptying no long-term improvement in gastric emptying of solid or liquid gastric emptying was observed.

## (iii) OESOPHAGEAL EMPTYING

## INTRODUCTION

The success of agents such as metoclopramide and domperidone in treating gastro-oesophageal reflux may be primarily due to their effect on oesophageal function. Both agents have been shown to increase lower oesophageal sphincter tone and improve oesophageal motility (Bron and Massih, 1980; Schulze-Delrieu, 1979). The effect of chronic

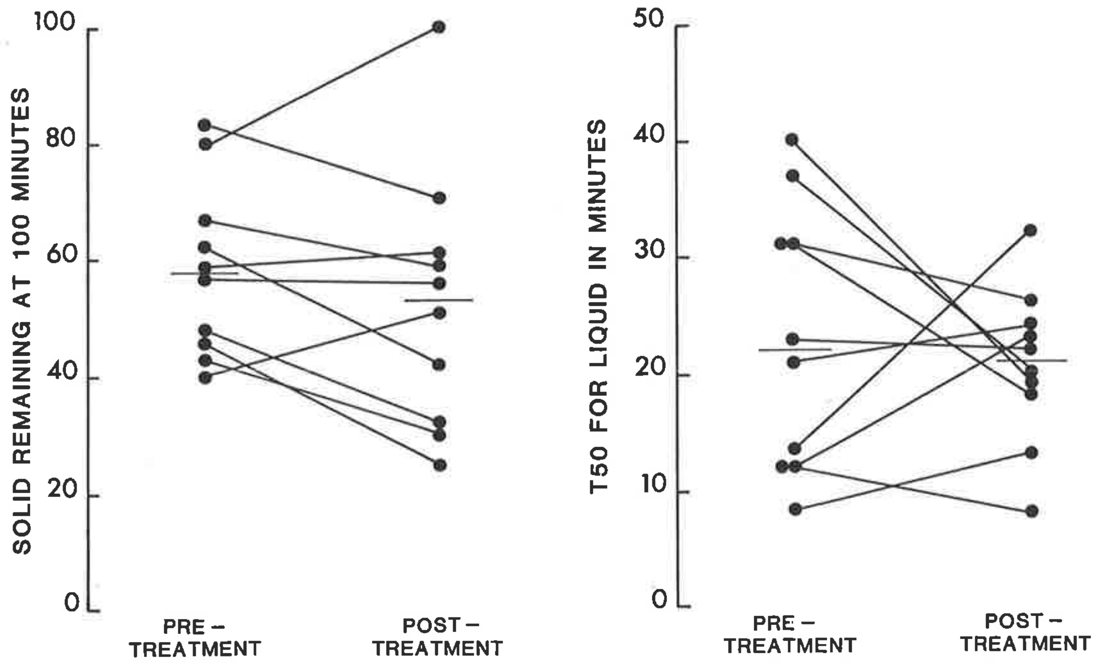



Figure 4.11: Solid and liquid gastric emptying results before and after one months treatment with domperidone (20 mg four times a day). The median values are shown by the bar.

administration of domperidone on the ability of oesophagus to clear a solid bolus has not been studied.

## Methods

A subset of 11 patients (6 females, 5 males, median age 45, range 24-69) received solid oesophageal emptying studies before and after one months treatment with domperidone 20 mg qid. Data were analysed using a Wilcoxon paired sign rank test.

## Results

Figure 4.12 shows the oesophageal emptying results before and after treatment. No significant difference existed in the solid oesophageal emptying following treatment compared with the pre-treatment value, although there was a trend towards more rapid emptying following treatment in 8 of the 11 patients.

## Discussion

Chronic administration of domperidone in patients with gastro-oesophageal reflux does not seem to be statistically significant in improving the ability of the oesophagus to clear itself of a solid bolus. The observed manometric effects of acute administration of domperidone (Bron and Massih, 1980) may indeed persist in chronic administration but they are not demonstrated by significant improvement of oesophageal function, although with larger numbers of

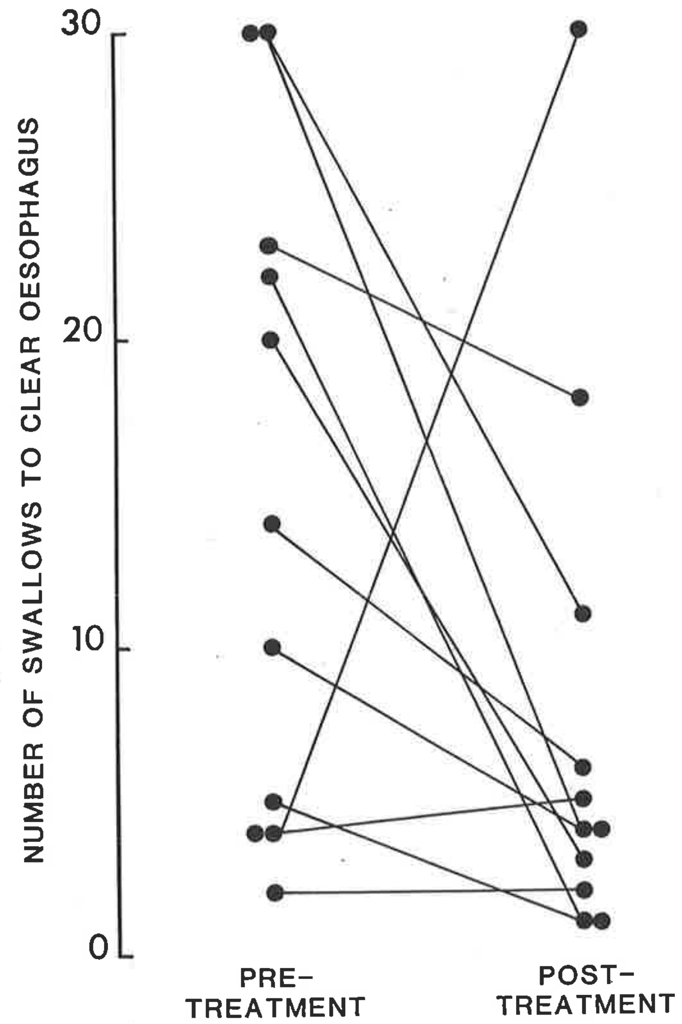



Figure 4.12: Number of swallows to clear the oesophagus in patients before and after one months treatment with domperidone (20 mg four times a day).

patients the trend observed may become significant. Both the gastric emptying results and the oesophageal emptying results following one months treatment with domperidone would indicate that care should be taken in using such treatment for prolonged periods. As demonstrated in Section 4.2 (i) the symptomatic improvement with domperidone was not significantly better than placebo.

## 4.3 IMPACT OF NISSEN FUNDOPLICATION

### (i) PRE- AND POST-OPERATIVE GASTRIC EMPTYING

### INTRODUCTION

Nissen first described his anti-reflux procedure in 1956 (Nissen, 1956). Since then there have been numerous reports of fundoplication of the stomach in the treatment of gastro-oesophageal reflux although techniques have varied widely (Jamieson and Duranceau, 1984). The great majority of patients experience complete relief of heartburn and regurgitation following such operations (Ellis et al, 1976; Papp, 1979; Goodall and Temple, 1980; Ellis et al, 1973). Despite its success in treatment of gastro-oesophageal reflux its precise mechanism of action is not understood completely (Fisher et al, 1978). Patients studied before and after fundoplication have shown an increase in lower oesophageal sphincter pressure (Ellis et al, 1976; Papp, 1979; Goodall and Temple, 1980). However, not all patients who undergo fundoplication have an increase in lower oesophageal sphincter pressure post-operatively (Fisher et al, 1978; Bjerkeset et al, 1980). It has been shown that an operation impairs the ability of the lower oesophageal sphincter to completely relax. This creates a residual lower oesophageal sphincter pressure at all times which acts as a barrier to gastric contents refluxing (Kiroff et al, 1984; Dent et al, 1982).

Reports over the last few years have implicated delayed gastric emptying as a factor associated with patients suffering from gastro-oesophageal reflux (McCallum et al, 1981; Little et al, 1980). It has been noted that patients with recurrent reflux symptoms after fundoplication had abnormally delayed gastric emptying (section 4.3 (ii)). However, these studies did not show what effect, if any, the operation itself may have had on gastric emptying. Therefore, this study was designed to assess the effect of fundoplication on solid and liquid emptying from the stomach in patients with gastro-oesophageal reflux disease.

## MATERIALS AND METHODS:

### Subjects

Twenty one patients (11 males, 10 females, median age 47, range 19-72) were studied after giving informed consent for the study. All patients were referred for surgical treatment following unsuccessful medical management of gastro-oesophageal reflux and described symptoms of heartburn and regurgitation. All had been symptomatic for more than two years and had objective evidence of gastro-oesophageal reflux on standard acid pH testing. Unequivocal oesophagitis on endoscopy was observed in eleven patients.

The surgical technique employed was a standard one with the fundus and upper part of the body of the stomach being mobilized and wrapped around the lower 4-5 cm of the oesophagus. The wrap thus used both anterior and posterior walls of the stomach (Jamieson and Duranceau, 1984). The fundic wrap included the anterior vagus nerve and excluded the posterior vagus nerve and was performed with a No. 52 French Maloney bougie in position in the oesophagus.

Radionuclide assessment

Prior to surgery and again six months post-operatively patients underwent an assessment of solid and liquid gastric emptying using the radionuclide technique which has been described previously (section 3.2 (ii)a).

Statistical Analysis

Data was analysed using the Wilcoxon matched pairs signed ranks test.

RESULTS

All patients were available for follow-up at 6 months, and the early results of their operation assessed as being good to excellent. Symptoms of heartburn and regurgitation were absent. In all patients solid emptying was slower than liquid emptying and was characterised by a lag period followed by linear emptying. There was a significant decrease in the percentage of solid remaining at 100 minutes in the post-operative group compared with the pre-operative group (Fig. 4.13). The lag period was not significantly altered, but the rate of emptying was more rapid in the post-operative group (Table 4.3).

The liquid emptying was non-linear and followed a mono-exponential pattern. Liquid T50 was significantly faster also (Fig. 4.14) in the post-operative group compared to the pre-operative group (Table 4.3).

## DISCUSSION

The success of a fundoplication in controlling the symptoms of heartburn and regurgitation has been well established in short-term follow-up studies (Ellis et al, 1976; Papp, 1979; Goodall and Temple, 1980; DeMeester et al, 1974; Bushkin et al, 1977). Its success has been attributed primarily to its effect on the lower oesophageal sphincter by simply increasing the mean resting pressure (Papp, 1979; Goodall and Temple, 1980; Ellis et al, 1973). It has also been shown to create an effective one way valve mechanism, at least against sudden pressure increases. It may also produce a residual lower oesophageal sphincter pressure that prevents transient lower oesophageal sphincter relaxations (Kiroff et al, 1984; Dent et al, 1982) and therefore gastro-oesophageal reflux.

Some patients with gastro-oesophageal reflux, both with and without oesophagitis have been found to have a delay in gastric emptying (McCallum et al, 1981; Little et al, 1980).

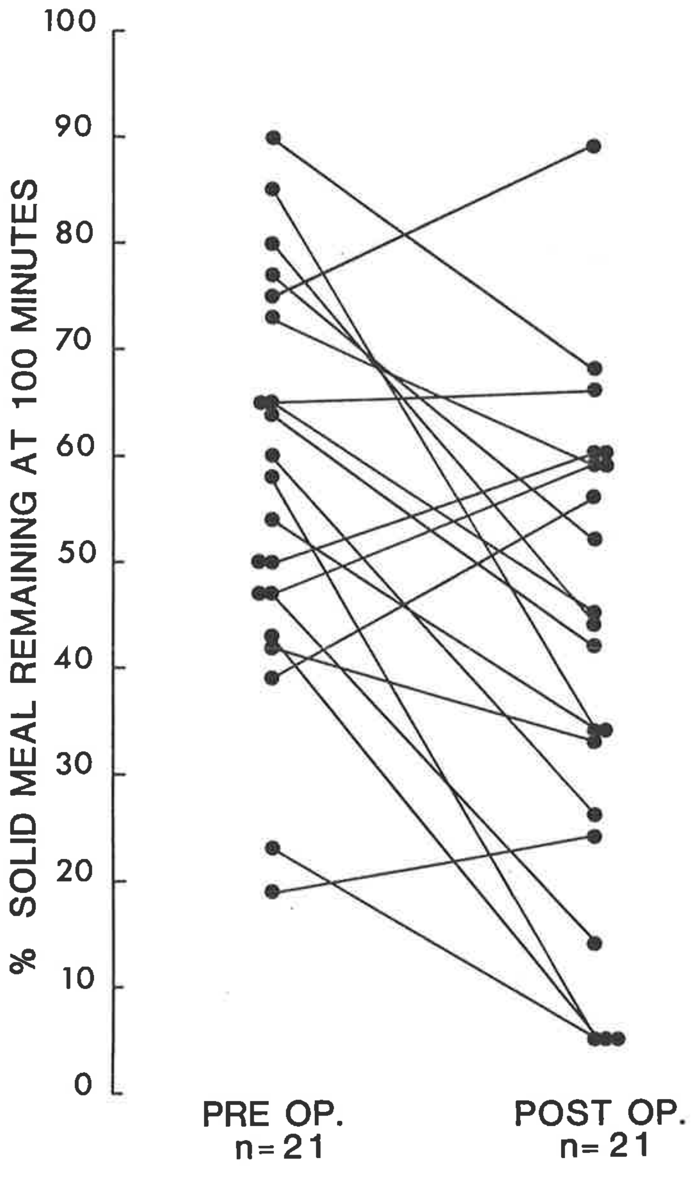



Figure 4.13: Solid gastric emptying pre- and post-fundoplication.

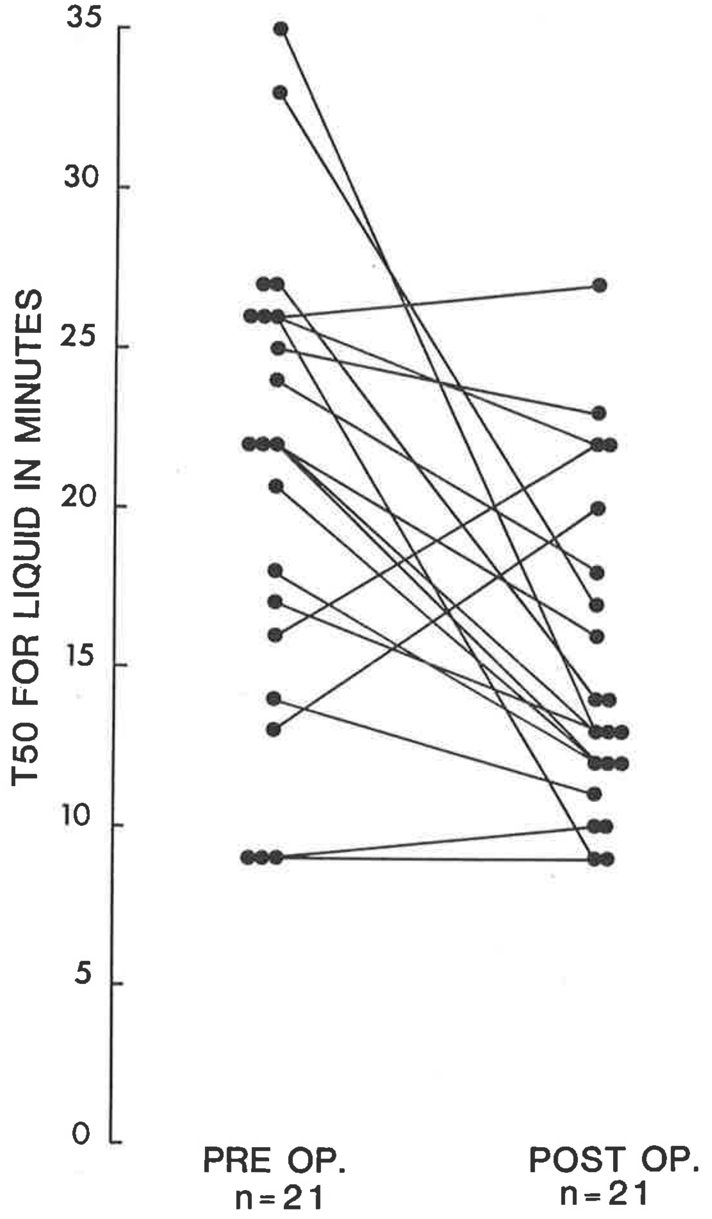



Figure 4.14: Liquid gastric emptying pre- and post-fundoplication.

TABLE 4.3

RESULTS OF GASTRIC EMPTYING IN PATIENTS BEFORE AND AFTER NISSEN FUNDOPLICATION.
VALUES ARE MEDIAN WITH RANGE IN BRACKETS

| | PREOPERATIVE | POSTOPERATIVE | SIGNIFICANCE LEVEL |
|---|---|---|---|
| Number of subjects | 21 | 21 | - |
| Solid lag period (min) | 51 (17-79) | 49 (12-68) | n.s. |
| Solid linear rate (%/min) | 0.8 (0.2-1.5) | 1.0 (0.4-1.7) | $p < .01$ |
| Solid retention at 100 min (%) | 50 (19-90) | 44 (5-89) | $p < .01$ |
| Liquid T50 (min) | 22 (9-35) | 13 9-27) | $p < .01$ |

The significance of this in the pathogenesis of gastro-oesophageal reflux is uncertain, but may relate to prolongation of the post prandial state or gastric distension and its effect on the lower oesophageal sphincter (Jamieson and Duranceau, 1983). However, the delayed emptying does not appear to correlate with basal lower oesophageal sphincter pressure (Fig. 4.5, Fig. 4.6).

This study shows that both solid and liquid gastric emptying are enhanced following fundoplication. Liquid gastric emptying was more rapid in all but 5 patients following operation. Solid emptying was also more rapid post-operatively in 14 patients. The lag period for solid emptying did not alter significantly from pre-operative assessment, with the increase in emptying being achieved by a more rapid rate of emptying rather than a shorter period prior to emptying commencing. Stress can delay gastric emptying (Stanghellini et al, 1983b) and a possible explanation of these findings might be that the second test (i.e. post-operatively) was performed with a patient less fearful of the investigation. However, reproducibility studies found no significant difference from the first test administration when compared with the second in the same subject (Collins et al, 1983). The reason for the increased gastric emptying may relate to increased fundal tone which in turn is a result of decreased fundal capacity following the fundoplication. Fundal tone is the principal determinant of gastric emptying of liquids (Behar and Ramsby, 1978; Hinder and Kelly, 1977) while antral activity is responsible for controlling the emptying of solids (Hinder, 1983; Rees et al, 1979; Holt et al, 1982).

Decreased fundal capacity would thus be an explanation for the observed liquid emptying acceleration. Present understanding of solid emptying makes the explanation for the observed increase in solid emptying more difficult to explain. Velasco et al (1982) found no alteration in solid gastric emptying of 10 patients or liquid gastric emptying in 6 patients studied before and after anti-reflux surgery. However, their patients had a posterior gastropexy operation and therefore probably had no alteration in their fundal capacity.

Although gastric drainage operations have been used in the treatment of gastro-oesophageal reflux (Burford and Lischer, 1956; Herrington, 1960), they generally have fallen from favour (Vansant and Baker, 1976). It is worth noting that in this study six patients had delayed gastric emptying for solid pre-operatively (i.e. outside our laboratory normal range, and five of these six patients had normal solid emptying post-operatively. This means that one could not use a test such as in this study pre-operatively, to select patients who should have gastric drainage procedure added to their anti-reflux operation. If delayed gastric emptying per se is found to be an important pathogenetic mechanism in the development of symptomatic gastro-oesophageal reflux then enhancement of emptying by fundoplication may be a further mechanism by which this procedure achieves its excellent results.

## (ii) FAILED FUNDOPLICATION

### INTRODUCTION

Long-term follow-up results of anti-reflux surgery have been reported infrequently. However, it appears that an increasing number of patients develop recurrence of their symptoms as time passes (Ellis et al, 1976; Jamieson and Duranceau, 1984). Even short term follow-up studies reveal a significant number of patients with recurrent symptoms of reflux (Papp, 1979; Goodhall and Temple, 1980; DeMeester et al, 1974; Bushkin et al, 1977). Little is known of the pathogenesis of these surgical failures. However, delayed gastric emptying is implicated in the pathogenesis of reflux disease (McCallum et al, 1981; Little et al, 1980). As described in section 4.3 (i) anti-reflux surgery enhances gastric emptying, therefore a study into the gastric emptying of patients who have failed anti-reflux surgery was conducted. The aim of the study was to investigate the solid and liquid gastric emptying in patients who presented with recurrence of gastro-oesophageal reflux symptoms following anti-reflux surgery.

## METHODS

### Subjects

Sixteen patients (6 males, 10 females, median age 59 years, range 33-75) who presented to the Department of Surgery of the University of Adelaide with recurrent reflux symptoms of heartburn or regurgitation, following anti-reflux surgery were investigated. Objective evidence of reflux was said to be present if as well as symptoms, patients demonstrated unequivocal evidence of oesophagitis on endoscopy or evidence of acid reflux on standard acid reflux testing. The median time between operation and investigation was 39 months (range 13-89). Most of the patients had undergone a total fundoplication, with the operations having been performed by eight different surgeons. Three patients had undergone a Belsey type operation. Associated procedures carried out at the time of anti-reflux surgery were a biliary drainage operation in one patient and highly selective vagotomy in another.

A control group of the 21 patients who had undergone a standardised fundoplication approximately 6 months previously was used (Section 4.1 (i)). For further comparison the 22 normal volunteers (12 males, 10 females, median age 36, range 21-62) were also considered. So too was a group of 83 patients with documented gastro-oesophageal reflux (39 males, 44 females, median age 51, range 19-75). A final sub-group of 32 of this latter group of patients (17 males, 15 females, median age 52.5, range 19-75) who progressed to anti-reflux surgery were also used for comparison.

Radionuclide assessment

The previously described technique was used (Section 3.2 (ii) a).

Statistical anlaysis

Data were analysed using the Wilcoxon unpaired test.

RESULTS

The gastric emptying results for normal volunteers, patients with gastro-oesophageal reflux, the sub-group that progressed to anti-reflux surgery, those re-studied at six months following a standardised fundoplication and the group with a failed anti-reflux procedure are shown in figure 4.15 and 4.16. Solid emptying was characterised by a pre-emptying period (lag period) followed by a linear emptying pattern. The percentage of solid remaining at 100 minutes (Figure 4.15) was significantly greater, median 66%, (range 27-100) in the failed operative group compared with the post-fundoplication patients, median 43% (range 5-89) ($p < 0.0001$), normal volunteers (median, 30%, range 12-65) ($p < 0.0001$), patients with gastro-oesophageal reflux, median

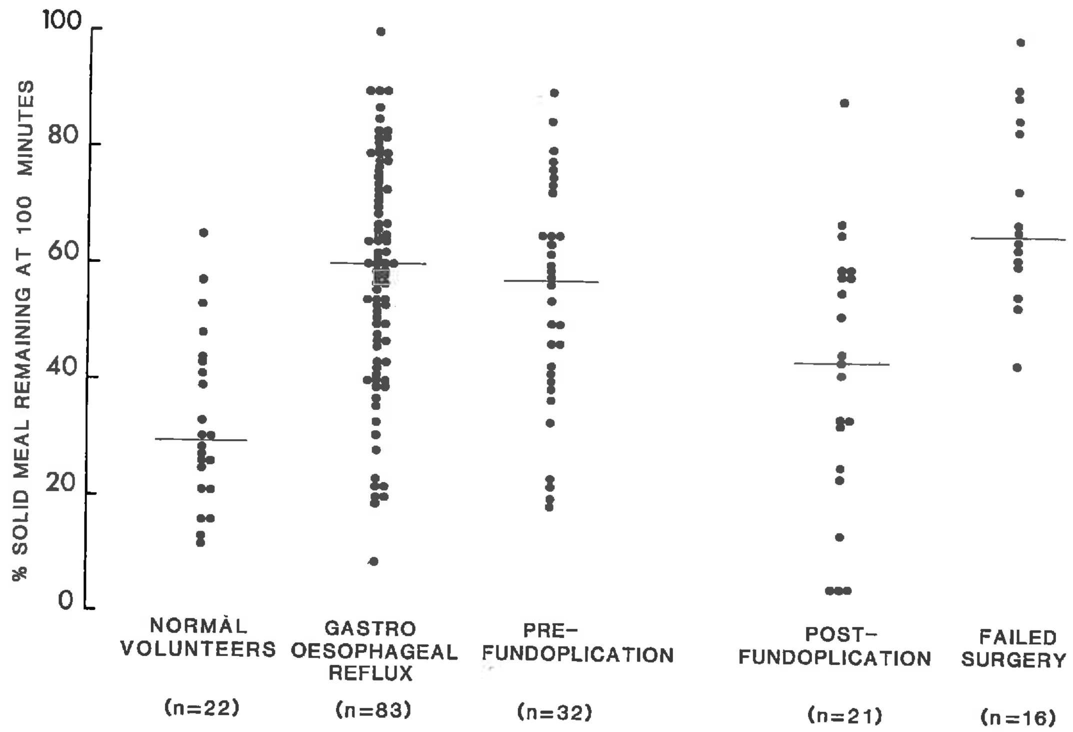



Figure 4.15: Solid gastric emptying values for normal volunteers, gastro-oesophageal reflux patients, pre-operative patients, post-fundoplication patients and the failed operative group. The line dividing groups represents the median value.

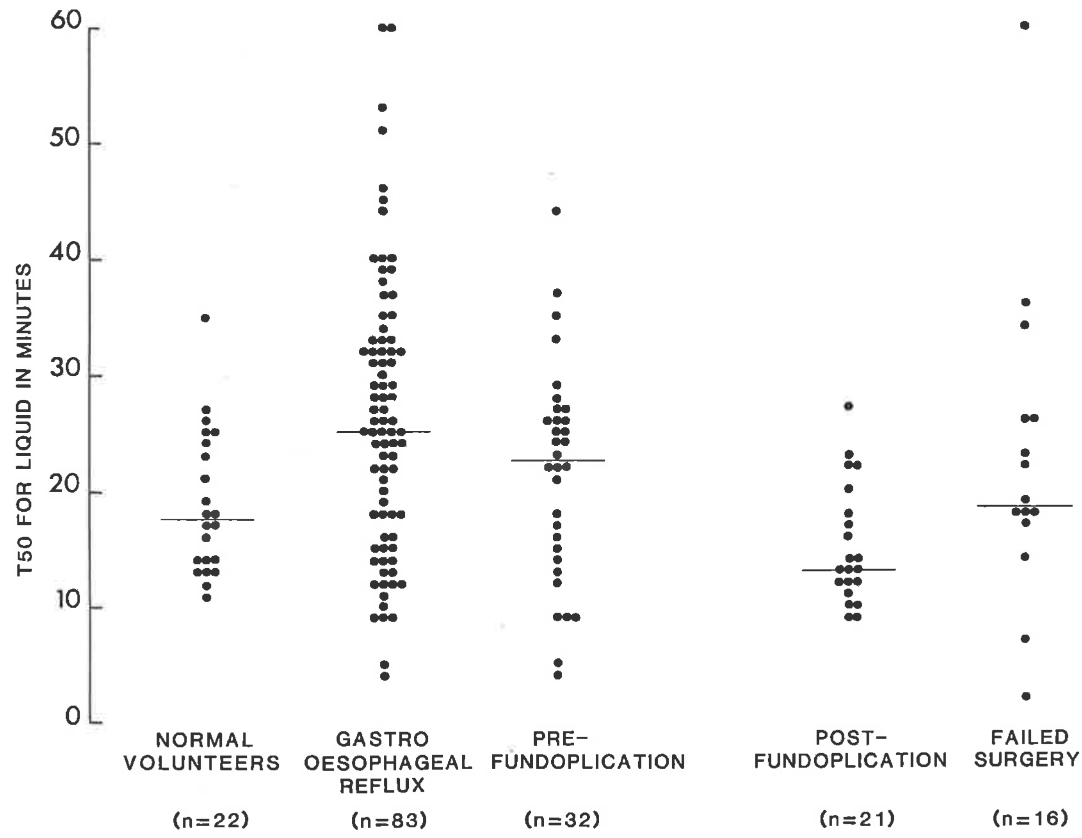



Figure 4.16: Liquid gastric emptying values for normal volunteers, gastro-oesophageal reflux patients, pre-operative patients, postfundoplication patients and the failed operative group. The line dividing groups represents the median value.

60%, (range 9-100) (p < 0.05) and pre-operative patients, median 57.5%, (range 19-90) (p < 0.05). There was no significant difference between the lag period for the failed operative group and the other patient groups and in particular to the post-fundoplication patients (p < 0.0001) (Table 4.4).

Liquid gastric emptying followed a mono-exponential pattern of emptying. The time taken for 50% of the liquid marker to clear the gastric region of interest (Figure 4.16) was significantly slower (p <0.01) in the failed operative group, median 18.5 min, (range 2-60) compared with post-fundoplication patients, median 13 min, (range 8-27) (Table 4.4). This was, however, not the case when the failed operative group was compared with the group of gastro-oesophageal reflux patients who were significantly slower (p <0.05) (median 25 min, range 4-78).

## DISCUSSION

The success of anti-reflux surgery and in particular fundoplication has been well demonstrated by others (Ellis et al, 1976; Kiroff et al, 1984; Papp, 1979; Goodhall and Temple, 1980; DeMeester et al, 1980, Bushkin et al, 1977). The low failure rate associated with the procedure makes it difficult for one surgeon to provide enough data for analysis of possible factors which might have contributed to the failure of the surgery. This study is based on patients

TABLE 4.4

RESULTS OF GASTRIC EMPTYING IN NORMAL VOLUNTEERS, CONTROL PATIENTS 6 MONTHS FOLLOWING FUNDOPLICATION, AND PATIENTS WITH RECURRENCE OF GASTRO-OESOPHAGEAL REFLUX FOLLOWING ANTI-REFLUX SURGERY. VALUES ARE MEDIANS WITH RANGE IN BRACKETS

| | NORMAL VOLUNTEERS | CONTROL PATIENTS | FAILED OPERATION | SIGNIFICANCE LEVEL BETWEEN CONTROLS AND FAILED GROUP |
|---|---|---|---|---|
| No of subjects | 22 | 21 | 16 | |
| Solid lag period (min) | 35 (9-69) | 48 (12-84) | 51.5 (24-100) | n.s. |
| Solid emptying rate (%/min) | 1.25 (0.7-2.3) | 1.0 (0.4-1.7) | 0.71 (0.43-1.67) | p<.0001 |
| Solid remaining (at 100 min(%) | 30 (12-65) | 43 (5-89) | 66 (27-100) | p<.0001 |
| T50 liquid | 18 (11-35) | 13 (8-27) | 18.5 (2-60) | p<.01 |

referred to one centre for assessment of recurrent reflux symptoms of heartburn and regurgitation following anti-reflux surgery, performed by eight different surgeons.

Failure of anti-reflux surgery has not been well studied. Dehiscence of the suture line following a repair has been reported (Leonardi et al, 1981; Hill et al, 1979; Henderson, 1978). Nissen fundoplications have also been known to "slip" (Leonardi et al, 1981; Hill et al, 1979; Henderson, 1978). Such events could presumably be due to extreme pressure being exerted on the repair in association with vomiting or "gas bloat" (Leonardi et al, 1981). However, in the study group no attempted vomiting event had occurred and "gas bloat" was not recorded as a major problem in any patient. Further, in the early years post-operatively many of these patients had been symptom free. The recurrence of symptoms in this group did not appear to be associated with one precipitating event but rather occurred over an extended period of time. A number of studies have shown that many patients with gastro-oesophageal reflux have delayed gastric emptying (McCallum et al, 1981; Little et al, 1980). It has been suggested that this delay plays a role in the etiology of the disease. Failure to correct this delay may permit gastro-oesophageal reflux to recur. It was earlier shown (section 4.4 (i)) that patients who underwent fundoplication improved their gastric emptying at 6 months post-operatively when compared with their pre-operative values. A group of such patients who had had successful anti-reflux surgery was as close to a control group as was possible for the study. In comparison with such a group, the failed surgical group have significantly slower solid and liquid emptying. If a comparison is made with patients who have a gastric emptying study prior to anti-reflux surgery the failed operative group is significantly slower than the pre-operative group for solid but not liquid emptying. This result is repeated when the failed operative group is compared for solid emptying with the group of 83 patients with gastro-oesophageal reflux which were studied, althouth interesting the failed group is more rapid than the total reflux group for liquid emptying, perhaps due to some acceleration in liquid emptying induced by the anti-reflux surgery. The cause of the delayed emptying in the failed operative group may reflect that the patient had extreme delay from the outset and that the fundoplication has not improved the rate of emptying sufficiently or it may indicate that vagal damage had occurred at the time of surgery (Bushkin et al, 1977; Herrington et al, 1982). Such damage may aggrevate already delayed emptying or create a significant delay in a previously normal patient.

Another way to study that delayed gastric emptying is associated with recurrent reflux would be to study a larger group of patients prospectively with gastric emptying studies both before and after their surgery and then after a prolonged follow-up. However, as already mentioned, the number of patients who develop recurrent reflux is relatively small. In section 4.3 (i) only one patient had delayed emptying outside our normal range, after surgery. Therefore, the number of patients studied would have to be very large indeed, and in view of the time and cost involved in such a project it is unlikely that such a study would be carried out.

Neither the pre-operative patients not the post-operative patients are an ideal control group. The pre-operative group have not undergone an operation whereas the post-operative groups have been followed for only 6 months which is not a comparable time to the failed operative group who have a median time of follow-up of 39 months. In spite of the deficiencies in the study it does raise the possibility that delay of gastric emptying of particularly solid, may be a factor in leading to recurrence of symptoms. One possible mechanism would be the continual gastric distention occuring with the delayed emptying. This might place continuing stress on the anti-reflux construction leading to its gradual weakening with time. If this is the case, then it may be of some relevance to the surgical management of these patients. For example the addition of highly selective vagotomy (Carlberger, 1975) at the time of initial surgery or re-operation may improve the gastric emptying. In established failures with delayed gastric emptying re-operation probably should include some form of drainage procedure or it may even be more rational to carry out an antrectomy with Roux-en-Y diversion (Washer et al, 1984). Therefore, whilst the place of gastric emptying procedures in patients with gastro-oesophageal reflux remains uncertain, it is an area which deserves continuing study.

## 4.4 SECONDARY GASTRO-OESOPHAGEAL REFLUX

### (i) SCLERODERMA

INTRODUCTION

Although it is well documented that progressive systemic sclerosis is associated with abnormalities in oesophageal motor function (Creamer et al, 1976; Saladin et al, 1966; Turner et al, 1973; Clements et al, 1979; Weihrauch and Korting, 1982), little is known about gastric motor function and gastric emptying in patients with this disease (Barker et al, 1979; Rees et al, 1982). Oesophageal emptying of refluxed material is regarded as an important defence mechanism of the oesophagus in the prevention of symptoms of heartburn and dysphagia (Booth et al, 1968; Skinner and Booth, 1970; Stanciu and Bennett, 1974a). Gastric emptying may be an important factor in the development of gastro-oesophageal reflux (McCallum et al, 1981; Little et al, 1980). Progressive systemic sclerosis is frequently complicated by gastro-oesophageal reflux with resultant oesophagitis and stricture formation. These complications are often progressive and difficult to treat (Orringer et al, 1976; Henderson and Pearson, 1973). In this study the radionuclide technique for oesophageal and gastric function studies has been used to document changes in upper gastrointestinal motility in a group of randomly selected patients with progressive systemic sclerosis.

## METHODS

Oesophageal and gastric emptying tests were performed in 22 normal volunteers (12 males, 10 females) who were non-smokers and had no evidence of gastrointestinal disease (median age 34, range 21-62), and 12 patients with progressive systemic sclerosis all of whom had been symptomatic for at least 12 months prior to this study. There were 10 females and 2 males in the patient group, median age 45 (range 27-69). The diagnosis of progressive systemic sclerosis was established according to several clinical and laboratory tests. All patients had Raynaud's phenomenon, digital or palmar telangiectasia, sclerodactyly and nailfold capillary abnormalities. Many also had one or more of digital ulcers, calcinosis and evidence of visceral involvement (pulmonary, gastro-intestinal and cardiac). All patients had antinuclear antibody. No account of gastrointestinal symptoms was taken in choosing patients for the study. Any medication known to influence gastric emptying was ceased for at least 24 hours prior to the study.

Informed consent was obtained in all cases and the study was approved by the Research Review Committee of the Royal Adelaide Hospital.

### Symptomatic Assessment

Prior to performance of gastric and oesophageal emptying, patients were asked if they suffered from any difficulty in swallowing or from heartburn. Symptoms were scored by the usual method (deDombal and Hall, 1979).

### Statistical Analysis

Results were analysed using the Wilcoxon unpaired test.

## RESULTS

### Symptoms

It was found that 9 of the 12 patients suffered heartburn with a median symptom score of 7 (range 2-12). Of these 9 patients, 7 had delay in gastric emptying of solid or liquid and the remaining 2 patients had normal emptying studies.

It was found that 7 of the 12 patients suffered dysphagia, with a median symptom score of 4 (range 3-12). All patients with dysphagia had delayed oesophageal emptying.

### Oesophageal emptying

The group of patients with progressive systemic sclerosis had significantly delayed oesophageal emptying (Table 4.5). In 7 of the 12 patients oesophageal emptying rates were outside the control range (Fig. 4.17). All 7 of

TABLE 4.5

RESULTS OF GASTRIC AND OESOPHAGEAL EMPTYING IN CONTROLS AND PATIENTS WITH PROGRESSIVE SYSTEMIC SCLEROSIS (P.S.S.) VALUES ARE MEDIANS WITH RANGE IN BRACKETS

| | CONTROL | P.S.S. | SIGNIFICANCE LEVEL |
|---|---|---|---|
| Number of Subjects | 22 | 12 | - |
| Solid lag period (min) | 35 (9-69) | 46 (20-80) | $p < .02$ |
| Solid linear rate (%/min) | 1.25 (0.7-2.3) | 0.44 (0.15-0.95) | $p < .0001$ |
| Solid retention at 100 min (%) | 30 (12-65) | 77.5 (49-92) | $p <.0001$ |
| Liquid T50 (min) | 18 (11-35) | 33 (11-57) | $p < .001$ |
| Swallows to empty oesophagus (T95) | 2 (1-9) | 30 (2-30+) | $p < .0001$ |

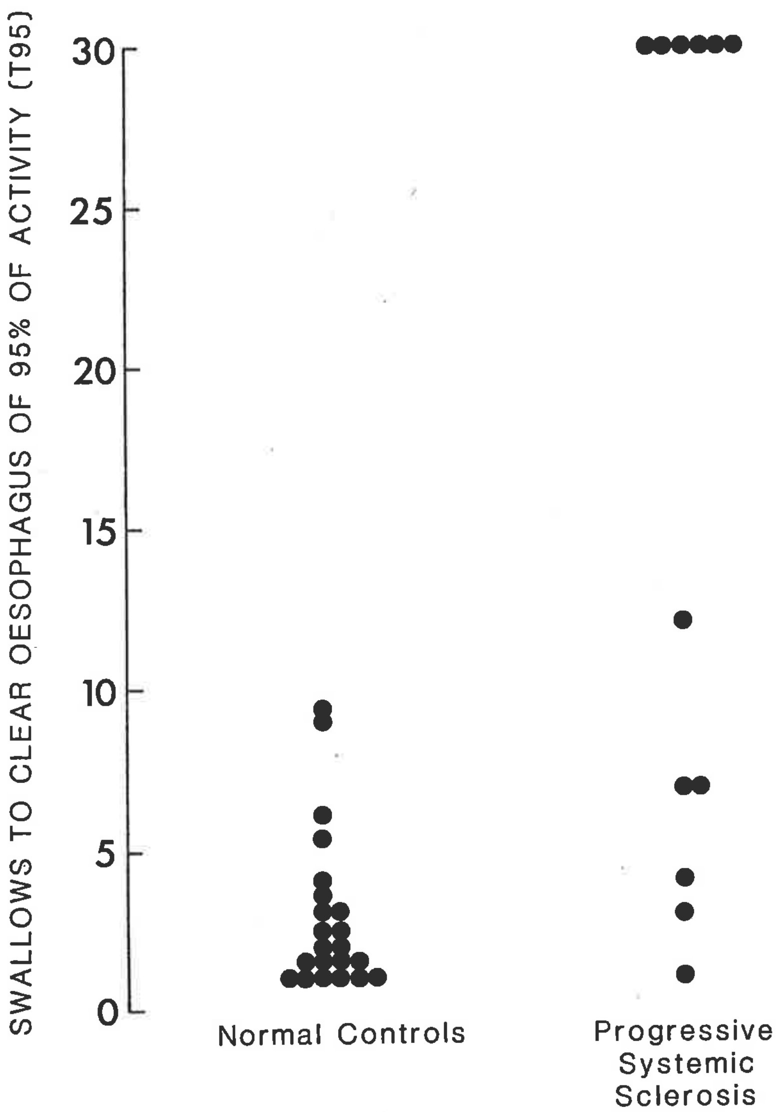



Figure 4.17: The number of swallows required to clear the oesophagus of 95% of activity of a standard bolus (T95) in controls and patients with progressive systemic sclerosis. The test was ceased if 30 swallows failed to clear the oesophagus.

these patients also had emptying rates outside control range for either solid (6 patients) or liquid (4 patients) gastric emptying.

## Gastric emptying

Solid emptying: In all subjects solid emptying was slower than liquid emptying and was characterised by a lag period followed by linear emptying. There was a significant delay of solid food emptying in the progressive systemic sclerosis group, with a prolonged lag period, increased percentage of activity remaining in the stomach at 100 minutes and reduction in the rate of linear emptying (Table 4.5) (Fig. 4.18). Nine of the 12 patients had solid emptying times outside the control range (Fig. 4.19).

Liquid emptying: The liquid emptying was non-linear and followed a mono-exponential pattern. Liquid emptying was delayed in the progressive systemic sclerosis group with an increased T50 (Table 4.5) (Fig. 4.18). In 7 of the 12 patients liquid emptying was outside the control range (Fig. 4.20).

## DISCUSSION

Upper gastrointestinal symptoms occur frequently in progressive systemic sclerosis with the symptoms of oesophagitis and sometimes stricture formation being encountered most often. Assessment of such patients in the

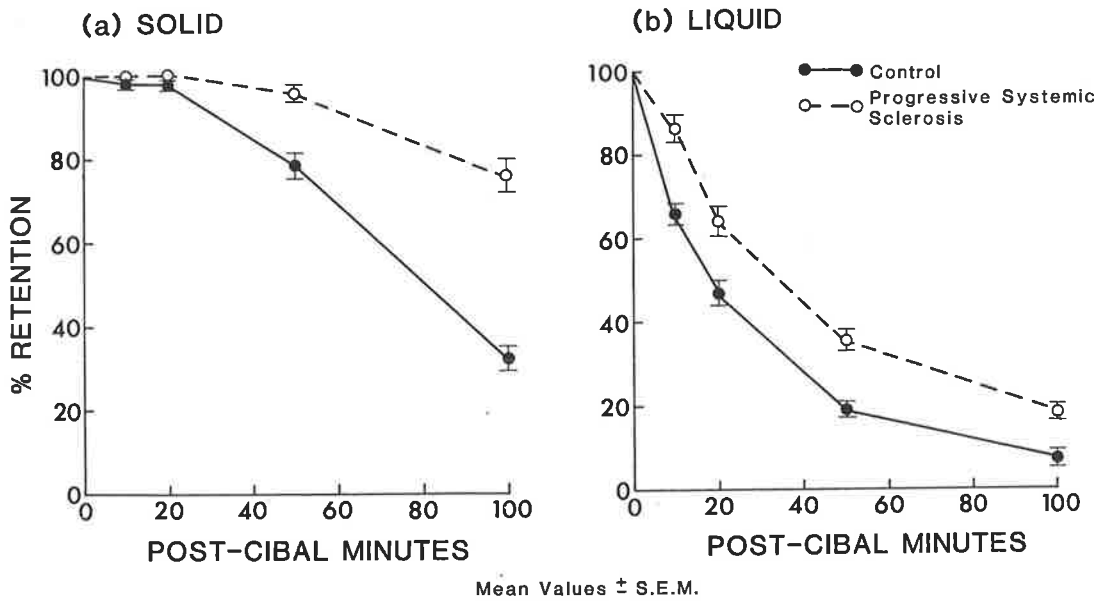



Figure 4.18: Composite solid and liquid gastric emptying curves for normal controls and patients with progressive systemic sclerosis.

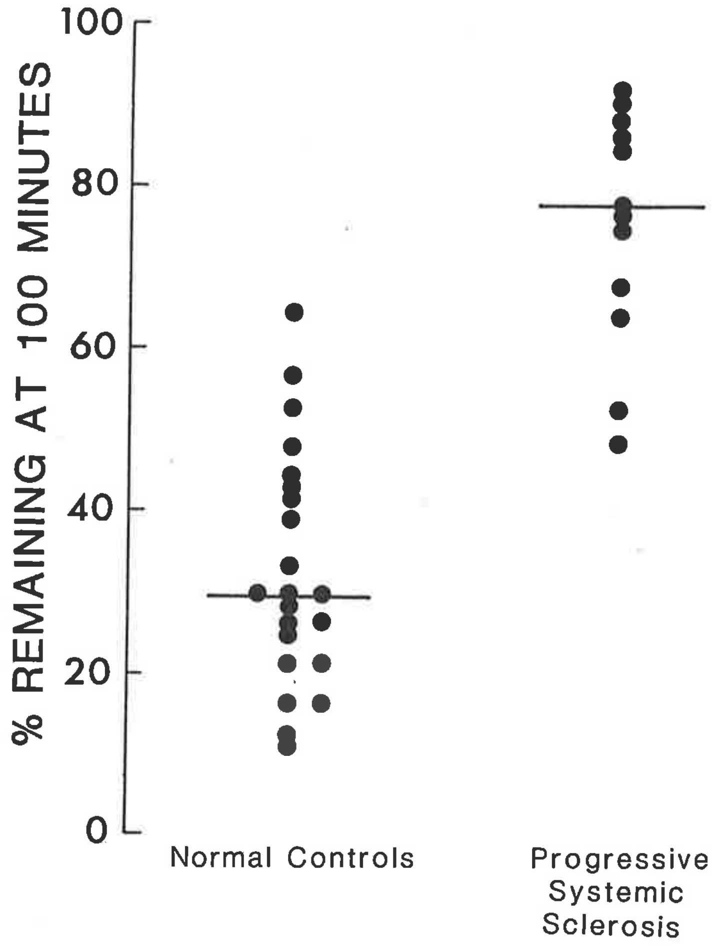



Figure 4.19: Individual solid gastric emptying results, expressed as percentage of solid meal remaining at 100 minutes, for controls and patients with progressive systemic sclerosis. The line dividing each group represents the median value.

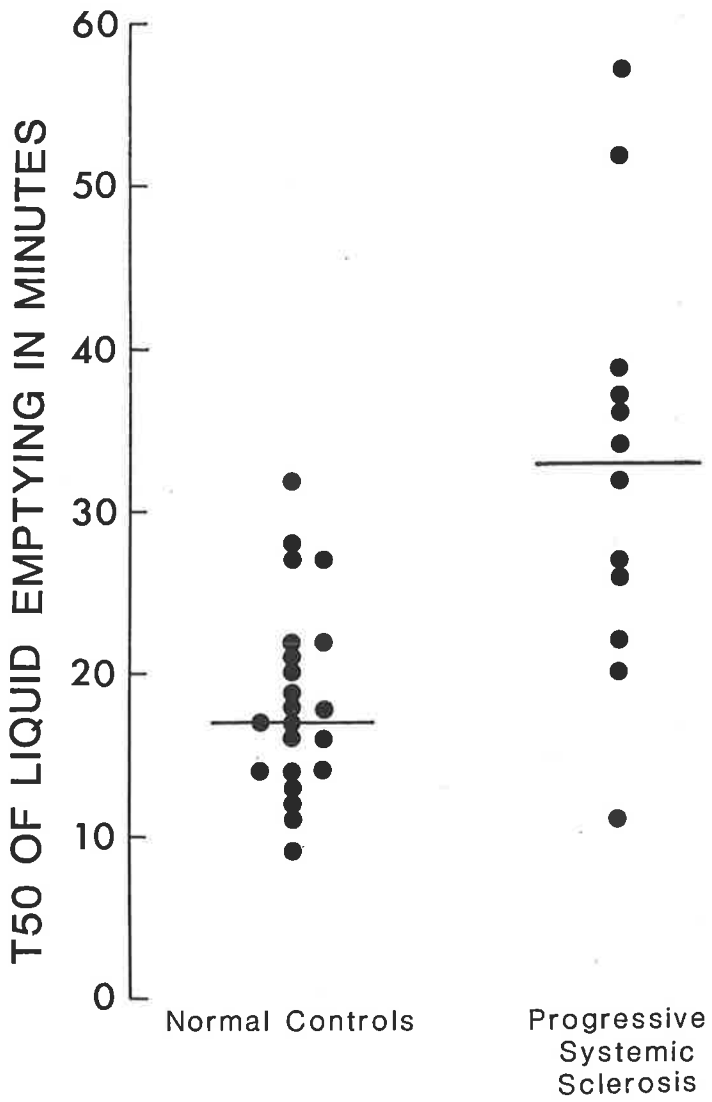



Figure 4.20: Individual liquid gastric emptying results expressed as the time taken for 50% of the liquid meal to clear the gastric region (T50) for controls and patients with progressive systemic sclerosis. The line dividing each group represents the median value.

past has been by manometric techniques (Creamer et al, 1976; Saladin et al, 1966; Turner et al, 1973; Clements et al, 1979) which are not always well tolerated by patients or readily available. Assessment of gastric function in these patients has been much less studied. Barker et al (1979) using a liquid meal reported that two patients with systemic sclerosis displayed mass retropulsion of the contents of the antrum into the fundus. Rees et al (1982) found that fasting motor activity in the antrum, duodenum and proximal jejunum was abnormal in scleroderma patients who had clinical and radiological evidence of small bowel involvement.

The radionuclide techniques used are well tolerated and can be used routinely to assess patients with progressive systemic sclerosis. Poor oesophageal emptying was present in 7 of 12 patients. Those 7 patients were also found to have delayed gastric emptying confirming the observation that progressive systemic sclerosis frequently extends beyond the oesophagus in its gastrointestinal involvement (D'Angelo et al, 1969). Oesophageal motor abnormalities are probably responsible for the delayed oesophageal emptying we have observed, and the motor abnormalities no doubt play a role in the development of dysphagia in these patients. Should oesophagitis and stricture formation occur, then this will lead to a worsening of the dysphagia.

The solid gastric emptying delay in 9 of the 12 patients and the liquid delay in 7 of the 12 was found in randomly selected patients suffering from progressive systemic sclerosis (i.e. the patients were not selected because they had gastrointestinal symptoms). This high percentage displaying delay in gastric emptying has not been recorded previously in progressive systemic sclerosis.

Treatment of the oesophageal symptoms of these patients is difficult. Medical management has usually attempted to increase the pH of any refluxed material. The results of this study indicates that drugs which promote gastric emptying may be of value in these patients. Agents such as metoclopramide have been used with varying success in patients with gastro-oesophageal reflux although no studies have been published with stratified patients according to their gastric emptying status prior to chronic treatment (Stanciu and Bennett, 1973; McCallum et al, 1977; 1983). Further, no systematic studies of such agents appears to have been made in patients with progressive systemic sclerosis and symptoms of reflux.

Anti-reflux surgery is designed to prevent reflux occurring, but because of poor motor function in the oesophageal body there is a tendency for the passage of a bolus into the stomach to be impeded and for this reason dysphagia may be aggravated. To try and prevent this problem, it has been suggested that a "floppy" valvuloplasty should be constructed (Donahue and Bombeck, 1977). However, it is known that recurrence of symptoms after anti-reflux surgery occurs more commonly in patients with progressive systemic sclerosis than in patients operated on for primary gastro-oesophageal reflux (Orringer et al, 1981). This study at least raise the possibility that systemic sclerosis patients being operated on for severe gastro-oesophageal reflux problems should also have gastric emptying problems treated at the same time. As the problem is possibly antro-duodenal (Barker et al, 1979) this may mean antrectomy either with a gastroduodenal anastomosis or gastro-jejunostomy with a Roux-en-Y loop.

Prior to management decisions being taken with these patients, it may be important, therefore, to adequately document their gastric emptying status. These studies indicate that the majority of patients with progressive systemic sclerosis and gastro-oesophageal reflux symptoms have a gastric emptying problem. However, in terms of the individual patient, this cannot be assumed. This is illustrated by our two patients with heartburn, who had normal gastric and oesophageal emptying studies.

## (ii) AUTONOMIC NEUROPATHY

### INTRODUCTION

Oesophageal motor dysfunction, characterised by a reduction in the primary peristaltic wave with frequent spontaneous contractions has been demonstrated in patients with diabetes mellitus by manometric and radiological Techniques (Vix, 1969; Silber, 1969; Madelstam et al, 1969; Vela and Balart, 1970; Horgan and Doyle, 1971; Stewart et al, 1976; Hollis et al, 1977). Oesophageal dysfunction is relatively common in diabetes mellitus, may be asymptomatic and is often associated with peripheral neuropathy (Hollis et al, 1977). The treatment of oesophageal disorders in diabetics is often unsatisfactory.

The radionuclide technique to measure oesophageal emptying in diabetic patients with autonomic neuropathy has been used and the effect of acute and chronic administration of oral domperidone on oesophageal emptying (Bron and Massih, 1980; Pozzessere et al, 1982) and symptoms of dysphagia and heartburn has been assessed in these patients.

### SUBJECTS AND METHODS

A control group of 31 subjects (median age 33, range 19-62) 11 males, 20 females was used. No subject had a history of upper gastrointestinal symptoms or surgery. All were non-smokers and no medication was being taken.

The diabetic group comprised 12 patients (6 male, 6 female), mean age 43 years (range 21-61), who were ambulant outpatients, had insulin dependent diabetes for at least 10 years and were subsequently demonstrated to have autonomic neuropathy. All had other complications of diabetes mellitus including nephropathy, retinopathy and peripheral neuropathy. All were non-smokers and were not taking medications known to affect gastrointestinal motility. Informed consent was obtained in all cases and the study was approved by the Research Review Committee of the Royal Adelaide Hospital.

All diabetic patients underwent: (a) a subjective assessment of symptoms of dysphagia and heartburn, (b) an objective assessment of autonomic nerve function by standard non-invasive physiological methods, (c) assessment of the acute and chronic effect of domperidone on oesophageal emptying.

Assessment of symptoms of dysphagia and heartburn

Patients were evaluated by a standard questionnaire for symptoms of dysphagia and heartburn. They were 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 (symptoms influenced daily activities). Delayed oesophageal emptying due to organic obstruction was excluded by upper gastrointestinal endoscopy.

Objective assessment of autonomic nerve function

Parasympathetic function was evaluated by the hear 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 abnormal results on tests of parasympathetic function, according to criteria outline by Ewing and Clarke (1982).

Measurement of oesophageal emptying

The solid bolus test (section 3.1 (iii)a)was used in each subject three oesophageal emptying tests were performed. Two initial oesophageal emptying tests were separated by a maximum period of 7 days. One hour before each test, patients were given 40 mg of domperidone orally or placebo in double blind fashion. All patients then received domperidone (20 mg three times a day, 30-60 minutes prior to meals). The third oesophageal emptying test was performed 60 minutes after the administration of 40 mg domperidone orally, when each patient had taken domperidone for 35-51 days (median 38). Symptoms of dysphagia and heartburn were recorded again at this time. Drug compliance was assessed by tablet counts at each visit.

## Statistical Methods

Data were evaluated using the Wilcoxon matched pair signed rank test and the Spearman rank correlation coefficient ($r_s$).

## RESULTS

The symptom of dysphagia was present in 5 of 12 patients prior to treatment (median score 2, range 2-3). After treatment with domperidone for 37-51 days it was present in 4 patients (median score 1.5, range 1-2). Heartburn was initially present in 6 patients (median score 1.5, range 1-5) and following treatment only 2 patients complained of heartburn, one severe, the other mild. Neither of these changes were statistically significant. Only 2 of the 5 diabetic patients with oesophageal emptying outside the normal range complained of dysphagia, the same two also describing heartburn. Oesophageal emptying was significantly slower ($p < 0.001$) in the placebo treated diabetic group compared to the control (Fig. 4.21). Oesophageal emptying did not significantly alter after administraion of domperidone either after acute or after chronic administration (Fig. 4.22).

## DISCUSSION

Tests measuring oesophageal radionuclide transit using liquid or solid food boluses are non-invasive and relatively

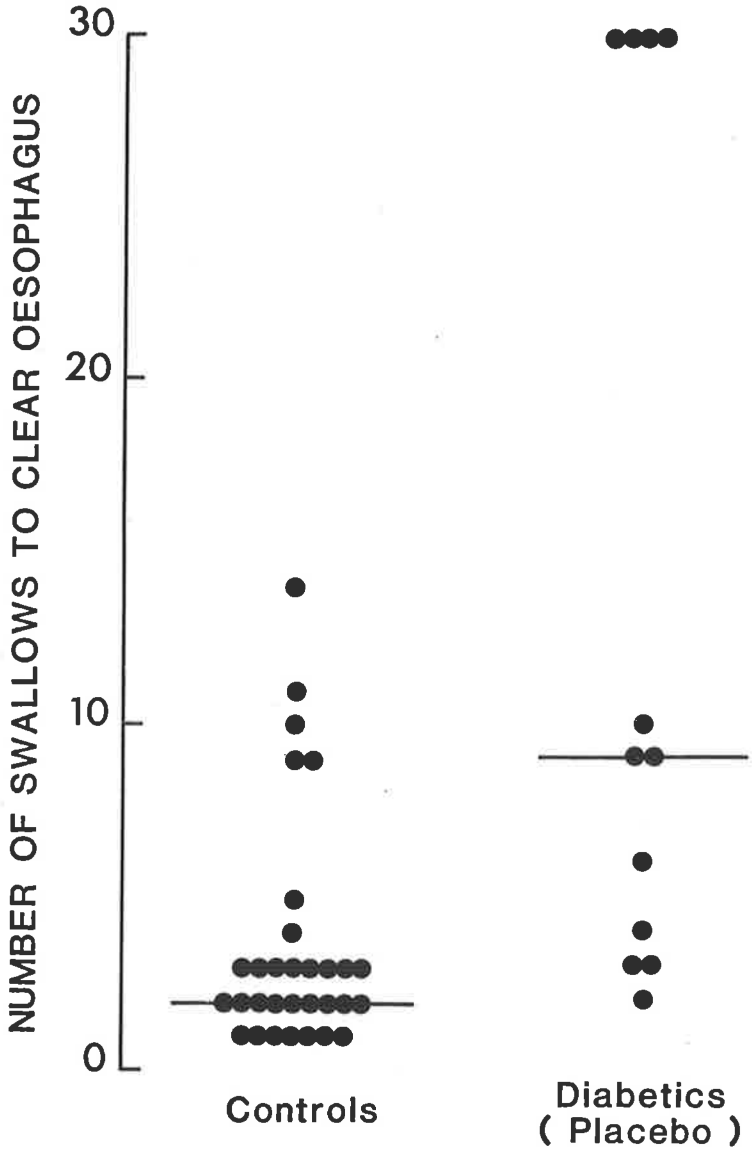



Figure 4.21: Oesophageal emptying values obtained for controls and diabetic patients. The line dividing each group represents the median value.

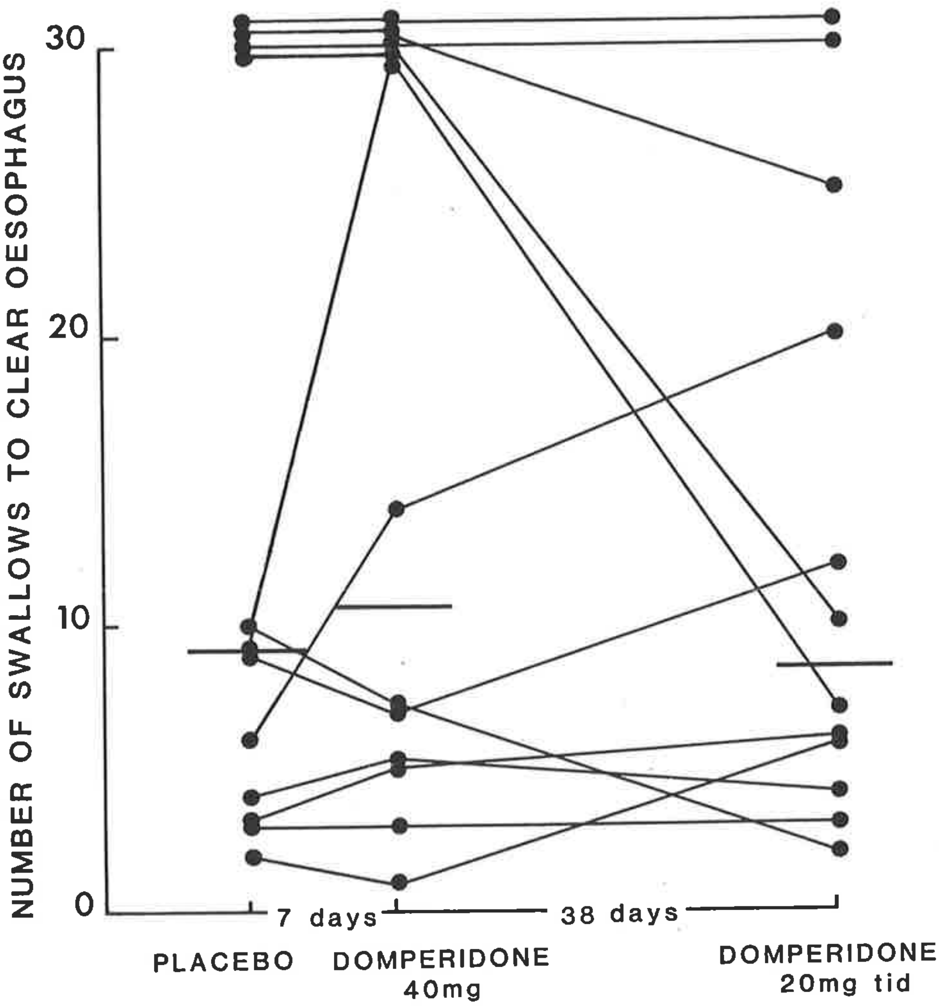



Figure 4.22: Oesophageal emptying values for diabetic patients after placebo, oral domperidone 40 mg and 37-51 days of chronic domperidone (20 mg three times a day). The line dividing each group represents the median value.

simple to perform. Recent evidence suggests that they are as sensitive as manometric techniques in detecting oesophageal dysfunction in diabetes (Russell et al, 1983) and other oesophageal motility disorders (Tolin et al, 1979; Blackwell et al, 1983). The finding of a marked delay of oesophageal emptying in 4 of the 12 diabetics studied (of which 3 were asymptomatic) is consistent with this. The use of a solid food bolus may be more appropriate than liquid in the detection of clinically significant abnormalities of oesophageal emptying, as patients usually complain of solid food dysphagia.

The etiology of the oesophageal dysfunction in diabetes mellitus may be due to vagal neuropathy (Hollis et al, 1977). The use of prokinetic drugs such as metoclopramide and bethanechol in the treatment of disordered oesophageal motility (and the resulting delayed emptying) has been suggested and supported by objective evidence of increased contractile activity in the oesophagus after administration (Hollis et al, 1977). However although manometric studies may demonstrate objectively that increased motor activity occurs after such pharmacological intervention, this may not correlate with increased emptying.

Domperidone is a new gastrokinetic drug which is a potent peripheral dopamine antagonist like metoclopramide but lacks cholinergic activity and does not cross the bloodbrain barrier, consequently neurological side effects are rare. Reports (Bron and Massih, 1980; Pozzessere et al, 1982; Brogden et al, 1982; Horowitz et al, 1985) have indicated that domperidone is effective in a variety of gastrointestinal disorders.

This study demonstrates that domperidone does not improve oesophageal emptying of a solid bolus in patients with diabetic autonomic neuropathy. The results show a trend toward improving the symptoms of heartburn after treatment, however, the numbers of patients are small and the change is not statistically significant. Further, a placebo was not included in the prolonged treatment course. The same dose of oral domperidone has previously been demonstrated to increase both solid and liquid gastric emptying in these patients (Horowitz et al, 1985). It therefore appears likely that the oesophageal emptying disorder in diabetics is more resistant to treatment with prokinetic drugs than delayed gastric emptying.

## SECTION V

## SUMMARY AND CONCLUSIONS

### METHODS USED IN THE ASSESSMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE

The array of options available for the investigations of gastro-oesophageal reflux disease have been outlined in section II. A number of them are now mainly of historic interest in understanding the evolution of concepts of gastro-oesophageal reflux. The measurement of lower oesophageal spincter pressure by a low compliance infusion system is particularly useful in documenting patients who have no recordable pressure in the lower oesophageal sphincter and it can also be used to monitor changes following active interventions such as fundoplication. However, such pressure measurement does not predict the presence or absence of reflux disease. Further, to record accurately a continuous trace from the lower oesophageal sphincter region it is necessary to use some form of sleeve sensor. Such a sleeve is capable of recording the maximal pressure despite movements of the sphincteric region.

In patients with gastro-oesophageal reflux the recording of oesophageal motility is helpful in diagnosing causes for symptoms of reflux; e.g. progresssive systemic sclerosis, diabetes. It may also reveal conditions such as oesophageal spasm which can mimic reflux symptoms. Such an assessment assumes even more importance if a patient's symptoms are considered serious enough to warrant surgery.

This study has shown that oesophageal manometry is a reproducible technique which is able to measure the motility variables in a reproducible fashion from one day to the next. Debate still centres on the methods used and the interpretation of the measurements obtained and a universally accepted code remains to be developed.

Tests of oesophageal function that are able to translate the motility appearances into a more physiological assessment continue to be sought. Oesophageal acid clearance has not been found useful in this study and was not used further. However, the principle of clearance has been developed in the form of radioisotopic techniques for measurement of the oesophageal emptying of an ingested bolus. The solid bolus method described uses a physiological environment in which to measure oesophageal function. Its main advantages are that it is reproducible, non-invasive, easy to perform providing the appropriate equipment is available and it is well tolerated by patients. It offers a useful screening method for impaired oesophagal emptying, and is capable of showing differences between the upright and supine position. It is however not as sensitive as a liquid bolus in detecting the subtle changes that occur in an acidified oesophagus and may not be as useful as liquid in measuring the results of pharmacological manipulations of oesophageal function. However, dysphagia for solids is an important symptom of reflux and there has been no satisfactory way of assessing this prior to this study. Radioisotopic swallows allow a quantitative assessment of oesophageal function in a way not possible with barium studies. At present the test complements rather than supplants oesophageal manometry.

Objective evidence of pathological gastro-oesophageal reflux is not always easily obtained. Symptoms can be misleading or absent, endoscopy often fails to detect abnormality, and histology is not always conclusive. Although 24 hour pH monitoring, particularly with the ambulant solid state devices currently available, offers the best technique in demonstrating abnormal reflux, its use has limitations in patient compliance and logistics. Short term pH testing by loading the stomach with acid seems to be a useful reproducible measure of demonstrating reflux, and probably will continue to be a first line investigation for reflux. The elaborate 24 hour pH studies will be restricted to less clear-cut cases of gastro-oesophageal reflux, or where secondary complications such as oesophageal spasm or pulmonary involvement occur.

Determination of gastric emptying by radionuclide techniques have become more sophisticated over the last decade. In that time a number of studies have tried to unravel the connection (if any) between delayed gastric emptying and gastro-oesophageal reflux. The isotopic technique used in this study has been demonstrated to be reproducible over short intervals (7 days) in normal subjects. Changes are also reproducible some months later in gastro-oesophageal reflux patients. The technique is complex and not readily applied from one institution to the next. It was for this reason and the concern about multiple testing and consequent radiation doses that led to a study into the usefulness of paracetamol assessed gastric emptying. This technique was fundamentally simple, and safe for patients. However, it was found to be unsatisfactory in individual patients, probably due to individual variation in gastro-intestinal absorbtion and metabolism. Perhaps it will have a place in institutions without nuclear medicine facilities and also in situations where groups are to be assessed rather than individuals. A useful finding from the study was the demonstration of the strong correlation between blood and saliva levels of paracetamol. This may have useful applications for both research and clinical situations.

The importance of gastroduodenal motility in gastro-oesophageal reflux has been inadequately studied in the past. This has been mainly due to difficulties in the methodology. A method has been developed utilizing many of the principles learnt from oesophageal motility and adapted for the antropyloroduodenal region.

The incorporation of the sleeve sensor for pyloric measurements is novel, and the use of transmucosal potential difference to localize the sleeve was successful. This technique not only permits continuous recording of pyloric function but also allows prolonged studies to be performed without resort to radiological investigations and the inevitable radiation exposures.

Measurement of duodenogastric reflux by use of an antral pH probe was carried out in a dog model and offered a simple measure of duodenogastric reflux. Its principle limitation is that it fails to provide any information as to the nature of the refluxed material except that it is alkaline relative to gastric contents. It does, however, offer a method of detecting when reflux events have occurred to aid in description of the recorded motility events, and may act as an indicator in timing gastric content sampling. The technical problems of such a methodology proved much more challenging than originally anticipated. For this reason the technique is offered as a method for investigating patients with gastro-oesophageal reflux in order to better explain the abnormalities responsible for their condition as no actual studies were conducted on such patients. For example, the delay in gastric emptying noted in section IV in patients with gastro-oesophageal reflux disease requires a description of the motor abnormalities responsible for the delay. Is the delay due to pyloric spasm, poor antral contractions, duodenogastric reflux or some other mechanism? These questions can now be addressed in humans.

PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX

The patient group studied was a selected group, in that all had been referred to the Department of Surgery of the University of Adeladie for assessment of their suspected gastro-oesophageal reflux. Not all were intended to be candidates for operation, although almost half proceeded to surgical intervention. The patients studied therefore represented the severe end of the reflux spectrum, but it is this end of the spectrum that is likely to be most rewarding in detecting departure from normal.

Indeed a number of abnormal findings were found that represented new observations or more complete descriptions of previous findings. The solid oesophageal emptying studies were useful in quantifying the degree of oesophageal dysmotility present. This impairment was extremely variable within the group but significant hold up was not an uncommon feature. This method of assessment was also useful in localising the site of hold-up which frequently could not be accurately assessed from the patients description. The localisation enabled attention to be directed toward the upper or lower oesophagus during manometry investigation and obviated unnecessary investigations. It also offered a means of objectively measuring the degree of dysphagia present. Whilst dysphagia is a symptom and therefore a subjective phenomenon the ability to describe the degree of hold-up associated with the reported symptom may be useful in patient classification and in monitoring the progress of medical and surgical procedures. The delay in oesophageal emptying in gastro-oesophageal reflux disease was not correlated significantly with the presence or absence of oesophagitis. This indicated that the oesophageal dysmotility may precede the symptoms of reflux and not be a result of it. A correlation would be expected if the motility disturbance was secondary to the oesophageal injury. However it was shown that even successful anti-reflux surgery did little to alter the oesophageal motility as assessed by the solid bolus study.

Measurement of gastric emptying in this group of patients also proved useful. A wide range of values was found with 44% of patients having a delay of solid emptying and 38% a liquid delay. Only 40% of gastro-oesophageal reflux patients had normal solid and liquid emptying.

The delay in gastric emptying seems to be poorly correlated with the other measurements made in these patients. Both patients' symptoms and lower oesophageal sphincter pressures were poorly correlated with the gastric emptying results obtained. Oesophagitis was correlated at a statistically significant level with delayed solid emptying but its clinical significance was not conclusive. The fact that there is no clear relationship between the gastric emptying and other measures made in gastro-oesophageal reflux underlies its importance in the complete assessment of the disease complex, and the outcome of subsequent interventions.

Many patients with progressive systemic sclerosis suffer from a severe form of gastro-oesophageal reflux disease. A study of oesophageal and gastric emptying abnormalities in such patients was undertaken and this demonstrated poor oesophageal emptying as has been previously demonstrated. However the delayed gastric emptying seen in many of these patients has not previously been described.

## OUTCOME OF TREATMENT IN GASTRO-OESOPHAGEAL REFLUX

This thesis has considered the response to pharmacological and surgical intervention in the management of patients with gastro-oesophageal reflux. Patients who were treated on metoclopramide and domperidone for one month periods, responded well at the end of the treatment period. However this response was not significantly different from that obtained with the placebo treatment. The management of such patients with agents designed to increase gastric emptying therefore failed to show significant benefits over the placebo. This result must be considered not only in terms of cost but also the significant number of side effects associated with the active treatments.

The possibility that response to such medications was dependent on a pre-existing delay in gastric emptying was also investigated and it was found that the symptomatic response occurred equally in the delayed and normal gastric emptying groups. These results were consistent with the gastric emptying response of one months treatment with domperidone which showed no significant change. This was similar to the result found for oesophageal emptying although many had improved oesophageal emptying after one months treatment with domperidone. In general it would be reasonable to suggest that chronic management of gastro-oesophageal reflux patients with metoclopramide or domperidone is unable to give superior results to placebo and on the grounds of possible side effects and cost should not be employed.

Surgical response on the other hand was demonstrated both symptomatically and objectively to have a good result. Naturally in a clinical study of this kind no placebo operation was possible, although the results of such a procedure may be important. A standardised fundoplication conducted on a representative subset of all gastro-oesophageal reflux patients studied was shown to signficiantly increase the rate of solid and liquid gastric emptying at 6 months following operation. All patients studied also reported good symptomatic outcome. This increased rate of gastric emptying may be explained by an increased fundal tone facilitating more rapid gastric emptying, although it would be anticipated to only have improved the liquid emptying. The fact that solid was also improved may indicate that the relationship between fundal tone and solid emptying is indeed more complex than currently thought. Whether or not the findings of increased gastric emptying in such patients is related to the good symptomatic outcome following fundoplication reported in most series, is not established. However, it would be interesting to assess prospectively failures of the surgery and determine the post-operative change in gastric emptying at 6 months. For example, if no improvement in emptying occurred, are these patients more likely to develop a recurrence?

An attempt to address this issue was made in this study by measuring gastric emptying in proven surgical failures. The operative technique was not standardised and a number of different surgeons were involved. The selection of an appropriate control group was also difficult. Not withstanding these problems the results of this study may have important implications in the management of such patients. It was found that as a group such patients had a significant delay of solid emptying compared with any available control group. Liquid delay was not so clearly delayed, although if post-fundoplication patients only were considered then the delay was significant. Whether the delay was primary or secondary cannot be stated, but it does suggest that surgical procedures might be undertaken in some patients designed to minimise the delay present. To only improve liquid emptying while ignoring the solid emptying delay may do little to prevent a further recurrence.

## CONCLUSION

Factors contributing to the presence of gastro-oesophageal reflux are numerous. This thesis helps to clarify some of the mechanisms important in gastro-oesophageal reflux disease.

The stomach acts as a reservoir for ingested food and liquid and gastric secretions. It also receives contents, such as bile and trypsin refluxed from the duodenum. Agents such as acid, pepsin, bile and trypsin are all potentially injurious agents to oesophageal mucosa if reflux occurs into the oesophagus. Some gastro-oesophageal reflux is a normal event. This is particularly true in the post prandial period. Ingested food is held in the gastric fundus which in turn increases the degree of gastric fundal distention. This increased distention predisposes to relaxation at the lower oesophageal spincter and such transient lower oesophageal spincter relaxation permits reflux to occur into the oesophagus. This refluxed material in the normal oesophagus is rapidly cleared by primary or secondary peristaltic waves. As a result the symptoms of reflux fail to develop.

The mechanisms that lead to development of reflux disease are poorly understood but may include a number of abnormalities. Duodenogastric reflux may be increased in such patients allowing the gastric contents to contain an increased content of noxious substances for a prolonged period of time. These are then refluxed back into the oesophagus causing increased oesophageal damage and an impairment of lower oesophageal sphincter function which permits more reflux and so a cycle develops.

Another mechanism may in fact involve normal refluxing of gastric contents but in association with poor oesophageal motility. This impaired motility leads to poor oesophageal clearance of the refluxed material and consequently prolonged exposure of the oesophageal mucosa which leads to further damage again precipitating a cycle.

Delayed gastric emptying was present in 60% of the patients studied. The delay was for solid alone, liquid alone or a combination of the two. This delay of gastric emptying may be responsible for a change in gastric wall tension in the region of the lower oesophageal sphincter which may act to distend the stomach and thus the lower oesophageal sphincter and permit more frequent episodes of reflux to occur. In addition to this mechanism the prolongation of the post prandial state increases the frequency of gastro-oesophageal reflux. Either mechanism increases the volume of material refluxed and again the potential for a vicious cycle occurs.

Methods of reporting the delay in gastric emptying by radioisotopic techniques are frequently debated. Although the use of the liquid T50 and the percentage of solid remaining at one hundred minutes are useful measures of gastric emptying they are not the only ones possible. The solid pre-emptying period (lag period) is a relatively reliable measure and may give valuable information as to the site of the delay being either fundal or antral. The rate of emptying is not always reliably measured in gross delay of solid emptying. However when found to be slow it may well suggest localisation of the delay to the antral region by inferring impaired ability of the "antral mill" to grind the ingested food to a suitable particle size. These observations reflect the conventional wisdom of the dual roles of the stomach. With further work it may well emerge that the complex interplay between the fundal "hopper" and the "antral mill" do not permit the roles of solid and liquid emptying to be so easily divided. The relationship between effective antral contractions, pyloric co-ordination and duodenal motility must also play an important role. It seems unlikely that the complete regulation of gastric outflow can be explained simply by a dual compartment model.

It is important that future studies of delayed gastric emptying in patients with gastro-oesophageal reflux should examine both the solid and liquid component. A delay in solid emptying may require a different management both surgical and medical from a delay in liquid emptying. Delay in both may represent a more advanced state of the disease spectrum or a separate entity. These are questions which remain unresolved. They do however illustrate the importance of assessing both solid and liquid emptying in such patients.

While delay of gastric emptying creates a favourable environment in which gastro-oesophageal reflux can occur, failure to clear the refluxed material is also an important factor. Impaired solid oesophageal emptying was found to be present in some patients with gastro-oesophageal reflux. This delay reflects poor oesophageal function, permitting prolonged exposure of refluxed material to the oesophageal mucosa. The delay appears to be a primary one, as cessation of reflux following surgical intervention does not reverse the changes nor does the presence of oesophagitis correlate with increased delay. Symptomatic assessment offers only a poor correlation between the gastric emptying results and heartburn and epigastric fullness. Dysphagia on the other-hand correlates well with delayed oesophageal emptying.

Management of reflux disease by use of agents that enhance gastric emptying has a sound theoretic basis. However, work is still required to resolve the value of chronic administration of currently available agents such as metoclopramide and domperidone. It may be that the primary cause of the delay is unresponsive to such medication, and alternative therapies are required. Further, studies of the efficacy of agents that promote gastric emptying in management of reflux disease, must be assessed after prolonged administration and not acute dosage. The placebo effect in patients with gastro-oesophageal reflux disease is also an important factor in their medical management, and should not be ignored. Indeed it possibly should be exploited to aid in the treatment of such patients.

Surgical intervention by fundoplication has been shown to be successful both symptomatically and from the point of view of increased gastric emptying. Surgical failures are difficult clinical problems. Current management frequently involves repeating or modifying the existing procedure. The significant solid and liquid delay found in these patients may well offer a basis for rational reoperation. To only improve liquid emptying while ignoring the solid emptying delay may do little to prevent a further recurrence. What operative procedure best achieves this end has not yet been adequately demonstrated, but offers an important area of further enquiry. At the present time an antrectomy with Roux-en-Y reconstruction is probably a reasonable approach.

Some of the factors important in the development of gastro-oesophageal reflux disease have been addressed in this thesis and other factors to study have opened up as a result. The challenge, however, remains of understanding the factors which are most important in the development of gastro-oesophageal reflux disease.

APPENDIX I

## RADIATION DOSIMETRY FOR OESOPHAGEAL EMPTYING STUDIES USING SOLID AND LIQUID TRACERS

1. Solid Tracer: Technetium-99m sulphur colloid

The average activity in the transit = 200 microcurie

The average 50% gastric emptying time = 80 minutes

The critical absorbed dose factors S:*

(a) Stomach to Stomach Wall = $1.3 \times 10^{-4}$ Rad/micro-Ci-hr

(b) Stomach to Whole Body = $1.9 \times 10^{-6}$ Rad/micro-Ci-hr

Dose = A x t x S**

Dose from Stomach to Stomach Wall $= 200 \times \frac{80}{60} \times 1.44 \times 1.3 \times 10^{-4}$
= 50 mR

Dose from Stomach to Whole Body $= 200 \times \frac{80}{60} \times 1.44 \times 1.9 \times 10^{-6}$
= 0.7 mR

**Dose to any other organ is at least an order less than that to the stomach wall.**

*** MIRD Pamplet No. 11. "S" Absorbed Dose per Unit cumulated activity for selected radionuclides and organs.**

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

2. Fluid Tracer: Technetium-99m in water

The average activity in the drink = 200 microcurie

The average 50% gastric emptying time = 20 minutes

The critical absorbed dose factors S:

(a) Stomach to Stomach Wall = $1.3 \times 10^{-4}$ Rad/micro-Ci-hr

(b) Stomach to Whole Body = $1.9 \times 10^{-6}$ Rad/micro-Ci-hr

Dose = A x t x S

Dose from Stomach to Stomach Wall $= 200 \times \frac{20}{60} \times 1.44 \times 1.3 \times 10^{-4}$
= 12 mR

Dose from Stomach to Whole Body $= 200 \times \frac{20}{60} \times 1.44 \times 1.9 \times 10^{-6}$
= 0.2 mR

**Dose to all other organs is at least an order less than that to the stomach wall.**

APPENDIX II

## RADIATION DOSIMETRY FOR GASTRIC EMPTYING STUDIES USING SOLID AND LIQUID TRACERS

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 | = $1.3 \times 10^{-4}$ Rad/micro-Ci-hr |
| (b) Stomach to Whole Body | = $1.9 \times 10^{-6}$ Rad/micro-Ci-hr |
| Dose | = A x t x S** |
| Dose from Stomach to Stomach Wall | = $1 \times 10^{3} \times \frac{80}{60} \times 1.44 \times 1.3 \times 10^{-4}$ <br> = 250 mR |
| Dose from Stomach to Whole Body | = $1 \times 10^{3} \times \frac{80}{60} \times 1.44 \times 1.9 \times 10^{-6}$ <br> = 3.7 mR |

*** MIRD Pamplet No. 11. "S" Absorbed Dose per Unit cumulated activity for selected radionuclides and organs.**
**** A = activity of radionuclide; t = effective half-life of radionuclide.**

2. Fluid Tracer: Indium 113m DPTA

| | |
|---|---|
| The average activity in the drink | = 1 millicurie |
| The average 50% emptying time | = 20 minutes |
| The absorbed dose factors S: | |
| (a) Stomach to Stomach Wall | = $7.1 \times 10^{-4}$ Rad/micro-Ci-hr |
| (b) Stomach to Whole Body | = $4.7 \times 10^{-6}$ Rad/micro-Ci-hr |
| Dose | = A x t x S |
| Dose from Stomach to Stomach Wall | = $1 \times 10^{-3} \times \frac{20}{60} \times 7.1 \times 10^{-4}$ <br> = 340 mR |
| Dose from Stomach to Whole Body | = $1 \times 10^{-3} \times \frac{20}{60} \times 4.7 \times 10^{-6}$ <br> = 2.2 mR |

## BIBLIOGRAPHY


Adithan, C., Thangam, J. (1982) A comparative study of saliva and serum paracetamol levels using a simple spectrophotometric method. Br. J. Clin. Pharmacol. 14:107-9.

Adler, R.H., Firme, C.N., Lanigan, J.M. (1958) A valve mechanism to prevent gastroesophageal reflux and esophagitis. Surgery 44:63-76.

Ahtaridis, G., Snape, W.J., Cohen, S. (1981) Lower esophageal sphincter pressure as an index of gastroesophageal acid reflux. Dig. Dis. Sci. 26:993-8.

Allison, P.R. (1948) Peptic ulcer of oesophagus. Thorax 3:20-42.

Allison, P.R. (1951) Reflux esophagitis, sliding hiatal hernia, and the anatomy of repair. Surg. Gynecol. Obstet. 92:419-31.

Allison, P.R. (1972) Reflux oesophagitis its pathology and treatment. Scand. J. Thorac. Cardiovasc. Surg. 6:318-22.

Anders, H.E., Bahrmann, E. (1932) Uber die sogenannten Hiatushernien des Zwerchfels im hoheren alter und ihre Genese. Ztschnr. F. Klin. Med. 122:736-96.

Andersson, S., Grossman, M.I. (1965) Profile of pH, pressure, and potential difference at gastroduodenal junction in man. Gastroenterology 49:364-71.

Angelchik, J-P., Cohen, R. (1979) A new surgical procedure for the treatment of gastroesophageal reflux and hiatal hernia. Surg. Gynecol. Obstet. 148:246-8.

Arndorfer, R.C., Stef, J.J., Dodds, W.J., Linehan, J.H., Hogan, W.J. (1977) Improved infusion system for intraluminal esophageal manometry. Gastroenterology 73:23-7.

Atkinson, M., Edwards, D.A.W., Honour, A.J. Rowlands, E.N. (1957a) The oesophagogastric sphincter in hiatus hernia. Lancet 2:1138-42.

Atkinson, M., Edwards, D.A.W., Honour, A.J., Rowlands, E.N. (1957b) Comparison of cardiac and pyloric sphincters: A manometric study. Lancet 2:918-22.

Atkinson, M., Sumerling, M.D. (1959) The competence of the cardia after cardiomyotomy. Gastroenterologia (Basel) 92:123-34.

Aylwin, J.A. (1953) The physiological basis of reflux oesophagitis in sliding hiatal diaphragmatic hernia. Thorax 8:38-45.

Bahadorzadeh, K., Jordan, P.H. (1975) Evaluation of the Nissen Fundoplication for treatment of hiatal hernia: Use of Parietal Cell Vagotomy without Drainage as an Adjunctive Procedure. Ann. Surg. 181:402-8.

Baldi, F., Corinaldesi, R., Ferrarini, F., Stanghellini, V., Miglioli, M., Barbara, L. (1981) Gastric secretion and emptying of liquids in reflux esophagitis. Dig. Dis. Sci. 26:886-9.

Barker, M.C.J., Cobden, I., Axon, A.T.R. (1979) Proximal stomach and antrum in stomach emptying. Gut 20:309-11.

Barrett, N.R. (1952) Hiatus hernia. Proc. Roy. Soc. Med. 45:279-86.

Barrett, N.R. (1954) Hiatus hernia - a review of some controversial points. Br. J. Surg. 42:231-43.

Beauchamp, G. (1983) Gastroesophageal reflux and obesity. Surg. Clin. North Am. 63:869-76.

Behar, J.,Biancani, P., Sheahan, D.G. (1976) Evaluation of esophageal tests in the diagnosis of reflux esophagitis. Gastroenterology 71:9-15.

Behar, J., Ramsby, G. (1978) Gastric emptying and antral motility in reflux esophagitis. Effect of oral metoclopramide. Gastroenterology 74:253-6.

Behar, J., Sheahan, D.G., Biancani, P., Spiro, H.M., Storer, E.H. (1975) Medical and surgical management of reflux esophagitis. A 38-month report on a prospective clinical trial. N. Engl. J. Med. 293:263-8.

Belsey, R.H.R., Skinner, D.B. (1972). Management of esophageal strictures. In: Skinner, D.B., Belsey, R.H.R., Hendrix, T.R., Zuidema, G.D. (eds). Gastroesophageal reflux and Hiatal Hernia. Boston, Little, Brown. Ch. 14 pp 173-96.

Benjamin, S.B., O'Donnell, J.K., Hancock, J., Nielsen, P., Castell, D.O. (1983) Prolonged radionuclide transit in "Nutcracker Esophagus". Dig. Dis. Sci. 28:775-9.

Benz, L.J., Hootkin, L.A., Margulies, S., Donner, M.W., Cauthorne, R.T., Hendrix, T.R. (1972) A comparison of clinical measurements of gastroesophageal reflux. Gastroenterology 62:1-5.

Bernstein, L.M., Baker, LA. (1958) A clinical test for Esophagitis. Gastroenterology 34:760-81

Bertalanffy, F.D. (1960) Mitotic rates and renewal times of the digestive tract epithelia in the rat. Acta Anat. (Basel) 40:130-48.

Biancani, P., CiCalzi, L.K., McCallum, R.W. (1981) Mechanism of histamine-induced excitation of the cat pylorus. J. Clin. Invest. 68:582-8.

Bjerkeset, T., Nordgard, K., Schjonsby, H. (1980) Effect of Nissen Fundoplication Operation on the Competence of the Lower Esophageal Sphincter. Scand. J. Gastroenterol. 15:213-7.

Blackwell, J.N., Hannan, W.J., Adam, R.D., Heading, R.C. (1983) Radionuclide Transit studies in the detection of Oesophageal Dysmotility. Gut 24:421-6.

Bombeck, C.T., Coelho, R.G.P., Castro, V.A. et al. (1971) An experimental comparison of procedures for the operative correction of gastroesophageal reflux. Bull. Soc. Int. Chir. 30:435-43.

Bombeck, C.T., Dillard, D.H., Nyhus, L.M. (1966) Muscular anatomy of the gastroesophageal junction and role of phrenoesophageal ligament: autopsy study of sphincter mechanism. Ann. Surg. 164:643-54.

Booth, D.J., Kemmerer, W.T., Skinner, D.B. (1968) Acid clearing from the distal esophagus. Arch. Surg. 96:731-4.

Boros, E. (1953). Relationship of the esophagus to heartburn. Rev. Gastroenterol. 20:132-7.

Bosch, A., Dietrich, R., Lanaro, A.E., Frias, Z. (1977) Modified Scintigraphic Technique for the Dynamic Study of the Esophagus. Int. J. Nucl. Med. Biol. 4:195-9.

Botha, G.S.M., Astley, R., Carre I.J. (1957) A combined cineradiographic and manometric study of the gastro-oesophageal junction. Lancet 1:659-62.

Brand, D.L., Eastwood, I.R., Martin, D., Carter, W.B., Pope, C.E. (1979) Esophageal symptoms, manometry, and histology before and after antireflux surgery: a long-term follow-up study. Gastroenterology 76:1393-401.

Breedijk, M., Akkermans, L.M.A. (1984) Twenty-four hour ambulatory pH recording with computerised analysis. Med. Biol. Eng. Comput. 22:609-12.

Breen, K.J., Whelan, G. (1978) The diagnosis of reflux oesophagitis: An evaluation of five investigative procedures. Aust. N.Z. J. Surg. 48:156-61.

Bremner, C.G., Schlegel, J.F., Ellis, F.H. (1970) Studies of the "gastroesophageal sphincter mechanism": the role of the phrenoesophageal membrane. Surgery 67:735-40.

Bright-Asare, P., El-Bessoussi, M. (1980 ) Cimetidine, metoclopramide, or placebo in the treatment of symptomatic gastroesophageal reflux. J. Clin. Gastroenterol. 2:149-56.

Brink, B.M., Schlegel, J.F., Code, C.F. (1965) The pressure profile of the gastroduodenal junctional zone in dogs. Gut 6:163-71.

Brogden, R.N., Carmine, A.A., Heel, R.C., Speight, T.M., Avery, G.S. (1982) Domperidone. A review of its pharmacological activity, pharmacokinetics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as an antimetic. Drugs 24:360-400.

Bron, B., Massih, L. (1980) Domperidone: a drug with powerful action on the lower esophageal sphincter pressure. Digestion 20:375-8.

Burford, T.H., Lischer, C.E. (1956) Treatment of short esophageal hernia with esophagitis by Finney pyloroplasty. Ann. Surg. 144:647-52.

Bushkin, F.L., Neustein, C.L., Parker, T.H., Woodward, E.R. (1977) Nissen fundoplication for reflux peptic esophagitis. Ann. Surg. 185:672-7.

Butin, J.W., Olsen, A.M., Moersch, H.J., Code, C.F. (1953) Study of esophageal pressures in normal persons and patients with cardiospasm. Gastroenterology 23:278-93.

Butt, H.R., Vinson, P.P. (1936). Esophagitis: pathologic and clinical study. Arch. Otolaryngol. 23:550-72.

Byrnes, C.K., Pisko-Dubienski, Z.A. (1963) An anatomical sphincter of the oesophago-gastric junction. Bull. Soc. Int. Chir. 22:62-8.

Carlberger, G. (1975) Gastric emptying of a fluid test meal in healthy volunteers and patients with duodenal ulcer before and after selective proximal vagotomy. Scand. J. Gastroenterol. 10 (Suppl. 35):45-7.

Carlson, H.C., Code, C.F., Nelson, R.A. (1966) Motor action of the canine gastroduodenal junction: a cineradiographic, pressure and electric study. Am. J. Dig. Dis. 11:155-72

Castel, D.O. (1982) Clinical applications of esophageal manometry. Dig. Dis. Sci. 27:769-71.

Chung, R.S.K., Johnson, G.M., Denbesten, L. (1977) Effect of sodium taurocholate and ethanol on hydrogen ion absorption in rabbit esophagus. Am. J. Dig. Dis. 22:582-8.

Clark, J., Wisbey, M., Cushieri, A. (1981) Gastric emptying and Gastro-oesophageal Reflux. Br. J. Surg. 68:356.

Clements, J.A., Heading, R.C., Nimmo, W.S., Prescott, L.F. (1978) Kinetics of acetaminophen absorption and gastric emptying in man. Clin. Pharmacol. Ther. 24:420-31.

Clements, P.J., Kadell, B., Ippoliti, A., Ross, M. (1979) Esophageal Motility in Progressive Systemic Sclerosis (PSS). Comparison of Cine-Radiographic and Manometric Evaluation. Dig. Dis. Sci. 24:639-44.

Code, C.F., Carlson, H.C. (1968) Motor activity of the stomach. In: Code, C.F., Heidel, H. eds. Handbook of Physiology, Section 6: The alimentary canal. Vol 4. Baltimore:Williams and Wilkins. pp 1903-16.

Code, C.F., Marlett, J.A. (1975) The interdigestive myo-electric complex of the stomach and small bowel of dogs. J. Physiol. (Lond.) 246:289-309.

Cohen, S., Harris, L.D. (1970) Lower esophageal sphincter pressure as an index of lower esophageal sphincter strength. Gastroenterology 58:157-62.

Cohen, S., Booth, G.H. (1975) Gastric acid secretion and lower-esophageal-sphincter pressure in response to coffee and caffeine. N. Engl. J. Med. 293:879-9.

Cohen, S., Morris, D.W., Schoen, H.J., Di Marino, A.J. (1976) The effect of oral and intravenous metoclopramide on human lower esophageal sphincter pressure. Gastroenterology 70:484-7.

Collins, P.J., Horowitz, M., Cook, D.J., Harding, P.E., Shearman, D.J.C. (1983) Gastric emptying in normal subjects - a reproducible technique using a single scintillation camera and computer system. Gut 24:1117-25.

Corinaldesi, R., Stanghellini, V., Zarabini, G.E., Calamelli, R., Raiti, C., Paternico, A., Barbara, L. (1983) The effect of Domperidone on the gastric emptying of solid and liquid phases of a mixed meal in patients with dyspepsia. Curr. Ther. Res. 34:982-6.

Creamer, B. (1955). Oesophageal reflux. Lancet 1:279-81.

Creamer, B., Andersen, H.A., Code, C.F. (1976) Esophageal motility in patients with scleroderma and related diseases. Gastroenterologia 86:763-75.

Crispin, J.S., McIver, D.K., Lind, J.F. (1967) Manometric study of the effect of vagotomy on the gastro-esophageal sphincter. Can. J. Surg. 10:299-303.

Crummy, A.B. (1966). The water test in the evaluation of gastroesophageal reflux - its correlation with pyrosis. Radiology 87:501-4.

Csendes, A., Henriquez, A. (1978) Gastric emptying in patients with reflux esophagitis or benign strictures of the esophagus secondary to reflux compared to controls. Scand. J. Gasterol. 13:205-7.

Csendes, A., Oster, M., Brandsborg, O., Moller, J.T., Overgaard, H., Brandsborg, M., Funch-Jensen, P., Amdrup, E. (1979) The effect of vagotomy on human gastroesophageal sphincter pressure in the resting state and following increases in intra-abdominal pressure. Surgery 85:419-24.

Dagradi, A.E. (1967). Esophagitis. Gastroint. Endosc. 14:113-6.

D'Angelo, W.A., Fries, J.F., Masi, A.T., Shulman, L.E. (1969) Pathologic observations in systemic sclerosis (scleroderma). Am. J. Med. 46:428-40.

Davies, H.A., Evans, K.T., Butler, F., McKirdy, H., Williams, G.T., Rhodes, J. (1983) Diagnostic Value of "Bread-Barium" Swallow in Patients with Esophageal Symptoms. Dig. Dis. Sci. 28:1094-100.

Debas, H.T., Farooq, O., Grossman, M.I. (1975) Inhibition of gastric emptying as a physiological action of cholecystokinin. Gastroenterology 68:1211-7.

DeDombal, F.T., Hall, R. (1979). The evaluation of medical care from the clinician's point of view: What should we measure, and can we trust our measurements? In: Evaluation of the efficacy of medical action. Amsterdam:Elsevier - North Holland Pub. Co. pp:13-29.

DeMeester, T.R., Johnson, L.F., Joseph, G.J., Toscano, M.S., Hall, A.W., Skinner, D.B. (1976) Patterns of gastroesophageal reflux in health and disease. Ann. Surg. 184:459-70.

DeMeester, T.R., Johnson, L.F., Kent, A.H. (1974) Evaluation of current operations for the prevention of gastroesophageal reflux. Ann. Surg. 180:511-25.

DeMeester, T.R., Lafontaine, E., Joelsson, B.E., Skinner, D.B., Ryan, J.W., O'Sullivan, G.C., Brunsden, B.S., Johnson, L.F. (1981) Relationship of a hiatal hernia to the function of the body of the esophagus and the gastroesophageal junction. J. Thorac. Cardiovasc. Surg. 82:547-58.

DeMeester, T.R., Wernly, J.A., Bryant, G.H., Little, A.G., Skinner, D.B. (1979) Clinical and in vitro analysis of determinants of gastroesophageal competence: a study of the principles of antireflux surgery. Am. J. Surg. 137:39-46.

DeMeester, T.R., Wang, C.I., Wernly, J.A., Pellegrini, C.A., Little, A.G., Klementschitsch, P., Bermudez, G., Johnson, L.F., Skinner, D.B. (1980) Technique, indications, and clinical use of 24 hour esophageal pH monitoring. J. Thorac. Cardiovasc. Surg. 79:656-70.

Dennish, G.W., Castell, D.O. (1971) Inhibitory effect of smoking on the lower esophageal sphincter. N. Engl. J. Med. 284:1136-7.

Dent, J., (1976) A new technique for continuous sphincter pressure measurement. Gastroenterology 71:263-7.

Dent, J., Heddle, R., Downton, J., MacKinnon, M., Toouli, J., Lewis, I. (1984) Omeprazole heals ulcerative peptic esophagitis. Gastroenterology 86:1062.

Dent, J., Dodds, W.J., Friedman, R.H., Sekiguchi, T., Hogan, W.J., Arndorfer, R.C., Petrie, D.J. (1980) Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J. Clin. Invest. 65:256-67.

Dent, J., Toouli, J., Sidey, P., Barnes, B. (1982) Incomplete relaxation of the lower esophageal high pressure zone - a possible mechanism of action of fundoplication. Gastroenterology 82:1042.

Dick, R.C.S., Hurst, A. (1942) Chronic peptic ulcer of oesophagus and its association with congenitally short oesophagus and diaphragmatic hernia. Q. J. Med. 11:105-20.

Dilawari, J.B., Misiewicz, J.J. (1973) Action of oral metoclopramide on the gastrooesophageal junction in man. Gut 14:380-2.

Dillard, D.H., Griffith, C.A., Merendino, K.A. (1954) Surgical construction of esophageal valve to replace "cardiac sphincter"; experimental study. Surg. Forum 5:306-14.

Dodds, W.J. (1976a) Instrumentation and methods for intraluminal esophageal manometry. Arch. Int. Med. 136:515-23.

Dodds, W.J., Dent, J., Hogan, W.J., Helm, J.F., Hauser, R., Patel, G.K., Egide, M.S. (1982) Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N. Engl. J. Med. 307:1547-52.

Dodds, W.J., Hogan, W.J., Helm, J.F., Dent, J. (1981) Pathogenesis of reflux esophagitis. Gastroenterology 81:376-94.

Dodds, W.J., Hogan, W.J., Miller, W.N. (1976b) Reflux esophagitis. Am. J. Dig. Dis. 21:49-67.

Dodds, W.J., Hogan, W.J., Miller, W.N., Stef, J.J., Arndofer, R.C., Lyndon, S.B. (1975) Effect of increased intraabdominal pressure on lower esophageal sphincter pressure. Am. J. Dig. Dis. 20:298-308.

Donahue, P.E., Bombeck, C.T. (1977) The modified Nissen fundoplication - reflux prevention without gas bloat. Chir. Gastroent. (Surg. Gastroent) 11:15-27.

Donnelly, B. (1953) Gastro-oesophageal regurgitation and oesophageal hiatus hernia - with special reference to the differential diagnosis of angina pectoris. Br. J. Radiol. 26:441-54.

Donner, M.W., Silbiger, M.L., Hookman, P., Hendrix, T.R. (1966) Acid-Barium Swallows in the Radiographic Evaluation of Clinical Esophagitis. Radiology 87:220-5.

Donovan, I.A., Harding, L.K., Keighley, M.R.B., Griffin, D.W., Collis, J.L. (1977) Abnormalities of gastric emptying and pyloric reflux in uncomplicated hiatus hernia. Br. J. Surg. 64:847-8.

Dornhorst, A.C., Harrison, K., Pierce, J.W. (1954) Observations on the normal oesophagus and cardia. Lancet 1:695-8.

Duranceau, A.C., Devroede, G., La Fontaine, E., Jamieson, G.G. (1983) Esophageal motility in asymptomatic volunteers. Surg. Clin. North. Am. 63:777-86.

Edwards, D.A.W. (1982) The Anti-reflux Mechanism, its Disorders and their Consequences. Clin. Gastroenterol. 11:479-96.

Ehrlein, H.J. (1981) Gastric and duodenal motility in relation to duodenogastric reflux in healthy dogs. Scand. J. Gastroenterol. 16, Suppl. 67:23-7.

Eliska, O. (1973) Phreno-oesophageal membrane and its role in the development of hiatal hernia. Acta. Anat. (Basel) 86:137-50.

Ellis, F.H., El-Kurd, M.F.A., Gibb, S.P. (1976) The effect of fundoplication on the lower esophageal sphincter. Surg. Gynecol. Obstet. 143:1-5.

Ellis, F.H., Garabedian, M., Gibb, S.P. (1973) Fundoplication for gastroesophageal reflux - indications, surgical technique, and manometric results. Arch. Surg. 107:186-92.

Ewing, D.J., Clarke, B.F. (1982) Diagnosis and management of diabetic autonomic neuropathy. Br. Med. J. 285:916-8.

Farrell, R.L., Roling, G.T., Castell, D.O. (1973) Stimulation of the incompetent lower esophageal sphincter - A possible advance in therapy of heartburn. Am. J. Dig. Dis. 18:646-50.

Farrell, R.L., Roling, G.T., Castell, D.O. (1974) Cholinergic therapy of chronic heartburn. Ann. Int. Med. 8:573-6.

Fink, S.M., Barwick, K.W., DeLuca, V., Sanders, F.J., McCallum, R.W. (1983a) Incidence and significance of histologic gastritis in patients with gastroesophageal reflux. Gastroenterology 84:1153.

Fink, S.M., Lange, R.C., McCallum, R.W. (1983b) Effect of Metoclopramide on normal and delayed gastric emptying in Gastroesophageal reflux patients. Dig. Dis. Sci. 28:1057-61.

Fischer, H. (1909) Ueber funktionelle Anpassung am Fledermausmagen. Arch. f.d. ges. Physiol., Bonn. 129:113-37.

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

Fisher, R.S., Malmud, L.S., Applegate, G., Rock, E., Lorber, S.H. (1982) Effect of bolus composition on esophageal transit: concise communication. J. Nucl. Med. 23:878-82.

Fisher, R.S., Malmud, L.S., Lobis, I.F., Maier, W.P. (1978) Antireflux surgery for symptomatic gastroesophageal reflux: mechanism of action. Am. J. Dig. Dis. 23:152-60.

Fisher, R.S., Malmud, L.S., Roberts, G.S., Lobis, I.F. (1976) Gastroesophageal (GE) scintiscanning to detect and quantitate GE reflux. Gastroenterology 70:301-8.

Flood, C.A., Hennig, G.C. (1958) Results of medical treatment in hiatus hernia. Gastroenterology 35:62-72.

Friedland, G.W., Melcher, D.H., Berridge, F.R., Gresham, G.A. (1966) Debatable points in the anatomy of the lower oesophagus. Thorax 21:487-98.

Fyke, F.E. Jr., Code, C.F., Schlegel, J.F. (1956) The gastroesophageal sphincter in healthy human beings. Gastroenterologia 86:135-50.

Geboes, K., Desmet, V. (1978) Histology of the esophagus. Front. Gastrointest. Res. 3:1-17.

Glynn, J.P., Bastain, W. (1973) Salivary excretion of paracetamol in man. J. Pharm. Pharmacol. 25:420-1.

Goethals, C. (1979) Domperidone in the treatment of post-prandial symptoms suggestive of gastroesophageal reflux. Curr. Ther. Res. 26:874-80.

Goldstraw, P., Bach, P. (1981) Gastric emptying after oesophagectomy as assessed by plasma paracetamol concentrations. Thorax 36:493-6.

Goodall, R.J.R., Temple, J.G. (1980) Effect of Nissen fundoplication on competence of the gastro-oesophageal junction. Gut 21:607-13.

Goyal, R.K., Cobb, B.W. (1981) Motility of the pharynx, esophagus and the esophageal sphincters. In: Johnson, L.R. (ed): Physiology of the Gastrointestinal Tract. Vol. 1. New York, Raven Press, pp. 359-92.

Graham, D.Y., Lanza, F., Dorsch, E.R. (1977) Symptomatic reflux esophagitis: a double-blind controlled comparison of antacids and alginate. Curr. Ther. Res. 22:653-8.

Griffith, G.H., Owen, G.M., Kirkman, S., Shields, R. (1966) Measurement of rate of gastric emptying using chromium-51. Lancet 1:1244-5.

Grimes, D.S., Goddard, J. (1978) Effect of cigarette smoking on gastric emptying. Br. Med. J. 2:460-1.

Gross, R., Johnson, L.F., Kaminski, R.J. (1979) Esophageal emptying in achalasia quantitated by a radioisotope technique. Dig. Dis. Sci. 24:945-9.

Gubaroff, A. von (1886) Ueber den Verschluss des menschlichen Magens an der Cardia. Arch. f. Anat. u. Entwcklngsgesch, Leipz. pp. 395-402.

Ham, A.W. (1974). Histology of the esophagus. Eds. Ham, A.W., Cormack, D.H. Histology, 7th Edition. Philadelphia, J.B. Lippincott, pp. 652-4.

Harmon, J.W., Johnson, L.F., Maydonovitch, C.L. (1981) Effects of acid and bile salts on the rabbit esophageal mucosa. Dig. Dis. Sci. 26:65-72.

Harrington, S.W. (1940) Diagnosis and treatment of various types of diaphragmatic hernia. Am. J. Surg. 50:381-446.

Hay, D.J., Goodall, R.J.R., Temple, J.G. (1979) The reproducibility of the station pullthrough technique for measuring lower oesophageal sphincter pressure. Br. J. Surg. 66:93-7.

Heading, R.C. (1982) Gastric emptying: A clinical perspective. Clin. Sci. 63:231-5.

Heading, R.C., Nimmo, J., Prescott, L.F., Tothill, P. (1973) The dependence of paracetamol absorption on the rate of gastric emptying. Br. J. Pharmacol. 47:415-21.

Heading, R.C., Tothill, P., Laidlaw, A.J., Shearman, D.J.C. (1971) An evaluation of $^{113m}$Indium DTPA chelate in the measurement of gastric emptying by scintiscanning. Gut 12:611-5.

Heading, R.C., Tothill, P., McLoughlin, G.P., Shearman, D.J.C. (1976) Gastric emptying rate measurement in man. A double isotope scanning technique for simultaneous study of liquid and solid components of a meal. Gastroenterology 71:45-50.

Heil, T.H., Mattes, P., Peros, G. (1981) Reflux and emptying rate in resected stomach. Scand. J. Gastroenterol. 16 (Suppl. 67):9-11.

Helm, J.F., Dodds, W.J., Hogan, W.J., Soergel, K.H., Egide, M.S., Wood, C.M. (1982) Acid neutralizing capacity of human saliva. Gastroenterology 83:69-74.

Helm, J.F., Dodds, W.J., Pelc, L.R., Palmer, D.W., Hogan, W.J., Teeter, B.C. (1984) Effect of esophageal emptying and saliva on clearance of acid from the esophagus. N. Engl. J. Med. 310:284-8.

Helm, J.F., Dodds, W.J., Riedel, D.R., Teeter, B.C., Hogan, W.J., Arndorfer, R.C. (1983) Determinants of esophageal acid clearance in normal subjects. Gastroenterology 85:607-12.

Helvetius (1719) cited by Lerche (1950). Lerche, W. (1950) The esophagus and pharynx in action: A study of structure in relation to function. Thomas; Blackwell; Ryerson.

Henderson, R.D. (1976) Motor disorders of the esophagus. Baltimore, Williams and Wilkins

Henderson, R.D. (1980). The Esophagus: Reflux and Primary Motor Disorders. Williams and Wilkins. Baltimore, London.

Henderson, R.D. (1978) Nissen hiatal hernia repair: Problems of recurrence and continued symptoms. Ann. Thorac. Surg. 28:587-93.

Henderson, R.D., Pearson, F.G. (1973) Surgical management of esophageal scleroderma. J. Thorac. Cardiovasc. Surg. 66:686-92.

Herrington, J.L. Jr. (1960) Hiatal hernia with esophagitis: treatment by hernia repair, vagotomy and pyloroplasty or antrectomy. Ann. Surg. 151:812-26.

Herrington, J.L., Meacham, P.W., Hunter, R.M. (1982) Gastric ulceration after fundic wrapping: vagal nerve entrapment, a possible causative factor. Ann. Surg. 195:574-81.

Hey, H., Jorgensen, F., Soresen, K., Hasselbalch, H., Wamberg, T. (1982) Oesophageal transit of six commonly used tablets and capsules. Br. Med. J. 285:1717-9.

Higgs, B., Shorter, R.G., Ellis, F.H. (1965) A study of the anatomy of the human esophagus with special reference to the gastroesophageal sphincter. J. Surg. Res. 5:503-7.

Hill, L.D. (1967) An effective operation for hiatal hernia: An eight year appraisal. Ann. Surg. 166:681-92.

Hill, L.D. (1972) Surgery and gastroesophageal reflux. Gastroenterology 63:183-5.

Hill, L.D., Ilves, R., Stevenson, J.K., Pearson, J.M. (1979) Reoperation for disruption and recurrence after Nissen fundoplication. Arch. Surg. 114:542-8.

Hinder, R.A. (1983) Individual and combined roles of the pylorus and the antrum in the canine gastric emptying of a liquid and a digestible solid. Gastroenterology 84:281-6.

Hinder, R.A., Kelly, K.A. (1977) Canine gastric emptying of solids and liquids. Am. J. Physiol. 233E:E335-40.

His, W. (1903) Studien an geharteten Leichen uber Form und Lagerung des menschlichen Magens. Arch. Anat. Entw. Gesch. pp. 345-67.

Hoffman, G.C., Vansant, J.H. (1979) The gastroesophageal scintiscan: comparison of methods to demonstrate gastroesophageal reflux. Arch. Surg. 114:727-8.

Hollis, J.B., Castell, D.O., Braddom, R.L. (1977) Esophageal function in diabetes mellitus and its relation to peripheral neuropathy. Gastroenterology 73:1098-102.

Holloway, R.H., Krosin, G., Lange, R.C., Baue, A.E., McCallum, R.W. (1983) Radionuclide esophageal emptying of a solid meal to quantitate results of therapy in achalasia. Gastroenterology 84:771-6.

Holt, S., Heading, R.C., Carter, D.C., Prescott, L.F., Tothill, P. (1979) Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol. Lancet 1:636-9.

Holt, S., Reid, J., Taylor, T.V., Tothill, P., Heading, R.C. (1982) Gastric emptying of solids in man. Gut 23:292-6.

Hopwood, D., Logan, K.R., Coghill, G., Bouchier, I.A.D. (1977) Histochemical studies of mucosubstances and lipids in normal human oesophageal epithelium. Histochem. J. 9:153-61.

Horgan, J.H., Doyle, J.S. (1971) A comparative study of esophageal motility in diabetes with neuropathy. Chest 60:170-4.

Horowitz, M., Cook, D.J., Collins, P.J., Harding, P.E., Hooper, M.J., Walsh, J.F., Shearman, D.J.C. (1982a) Measurement of gastric emptying after gastric bypass surgery using radionuclides. Br. J. Surg. 69:655-7.

Horowitz, M., Cook, D.J., Collins, P.J., Harding, P.E., Shearman, D.J.C. (1982b) The application of techniques using radionuclides to the study of gastric emptying. Surg. Gynecol. Obstet. 155:737-44.

Horowitz, M., Harding, P.E., Chatterton, B.E., Collins, P.J., Shearman, D.J.C. (1985) Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. Dig. Dis. Sci. (in press).

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. Clin. Sci. 67:213-8.

Ismail-Beigi, F., Horton, P.F., Pope, C.E. (1970) Histological consequences of gastroesophageal reflux in man. Gastroenterology 58:163-74.

Ismail-Beigi, F., Pope, C.E. (1974) Distribution of the histological changes of gastroesophageal reflux in the distal esophagus of man. Gastroenterology 66:1109-13.

Jackson, C. (1922) The diaphragmatic pinchcock in so called "cardio spasm". Laryngoscope 32:139-42.

Jahnberg, T. (1977) Gastric adaptive relaxation. Effects of vagal activation and vagotomy. An experimental study in dogs and in man. Scand. J. Gastroenterol. 12(suppl):1-32.

Jamieson, G.G., Duranceau, A. (1984) What is a Nissen fundoplication? Surg. Gynecol. Obstet. 159:12-4.

Jamieson, G.G., Duranceau, A.C. (1983) The defence mechanisms of the esophagus. Surg. Clin. North. Am. 63:787-99.

Johnson, A.G. (1973) Flatulent dyspepsia. Postgrad. Med. J. 49:104-7.

Johnson, L.F., DeMeester, T.R. (1974) Twenty-four hour pH monitoring of the distal esophagus: a quantitative measure of gastroesophageal reflux. Am. J. Gastroenterol. 62:325-32.

Johnson, L.F., DeMeester, T.R. (1981) Evaluation of elevation of the head of the bed, bethanechol, and antacid foam tablets on gastroesophageal reflux. Dig. Dis. Sci. 26:673-80.

Kantrowitz, P.A., Corson, J.G., Fleischli, D.J., Skinner, D.B. (1969) Measurement of gastroesophageal reflux. Gastroenterology 56:666-74.

Katz, L.A., Maas, L.C., Vastola, D.L., Kaunitz, V.H. (1974) Physiological effects of surgical repositioning of the lower esophageal sphincter. Gastroenterology 66:720A.

Kaye, M.D., Mehta, S.J., Showalter, J.P. (1976a) Manometric studies of the human pylorus. Gastroenterology 70:477-80.

Kaye, M.D., Rein, R., Johnson, W.P., Showalter, J.P. (1976b) Responses of the competent and incompetent lower oesophageal sphincter to pentagastrin and abdominal compression. Gut 17:933-9.

Kaye, M.D., Showalter, J.P. (1971) Manometric configuration on the lower esophageal sphincter in normal human subjects. Gastroenterology 61:213-23.

Kaye, M.D., Wexler, R.M. (1981) Alteration of esophageal peristalsis by body position. Dig. Dis. Sci. 26:897-901.

Kazem, I. (1972) A new scintigraphic technique for the study of the esophagus. A.J.R. 115:681-8.

Keane, F.B., DiMagno, E.P., Malagelada, J-R. (1981) Duodenogastric reflux in humans: its relationship to fasting antroduodenal motility and gastric, pancreatic, and biliary secretion. Gastroenterology 81:726-31.

Kelly, J.E., Jr. (1961) The marshmallow as an aid to radiologic examination of the esophagus. N. Engl. J. Med. 265:1306-7.

Kelly, K.A., Code, C.F., Elveback, L.R. (1969) Patterns of canine gastric electrical activity. Am. J. Physiol. 217:461-70.

Kelly, K.A., Code, C.F. (1971) Canine gastric pacemaker. Am. J. Physiol. 220:112-8.

Kelly, K.A. (1981) Motility of the stomach and gastroduodenal junction. In: Johnson, L.R. (ed): Physiology of the Gastrointestinal Tract. Vol.1. New York, Raven Press, pp. 393-410.

Kiroff, G.K., Maddern, G.J., Jamieson, G.G. (1984) A study of factors responsible for the efficacy of fundoplication in the treatment of gastro-oesophageal reflux. Aust. N.Z. J. Surg. 54:109-12.

Kissin, B., Kaley, M.M. (1974) Alcohol and cancer. In: Kissin, B. and Begleiter, H. (eds.): The biology of alcoholism. New York, Plenum Publishing, pp. 481-511.

Kjellen, G., Svedberg, J.B., Tibbling, L. (1984) Solid bolus transit by esophageal scintigraphy in patients with dysphagia and normal manometry and radiography. Dig. Dis. Sci. 29:1-5.

Kjellen, G.,Tibbling, L. (1978) Influence of body position, dry and water swallows, smoking, and alcohol on esophageal acid clearing. Scand. J. Gastroenterol. 13:283-8.

Kjellen, G., Tibbling, L. (1982) Esophageal transit of a radionuclide, solid bolus in normals. Gastroenterology 82:1101.

Kobayashi, S., Kasugai, T. (1974). Endoscopic and biopsy criteria for the diagnosis of esophagitis with a fiberoptic esophagoscope. Am. J. Dig. Dis. 19:345-52.

Krejs, G.J., Seefeld, U., Brandli, H.H., Bron, B.A., Caro, G., Schmid, P., Blum, A.L. (1976) Gastro-oesophageal reflux disease: correlation of subjective symptoms with 7 objective oesophageal function tests. Acta. Hepato-Gastroenterol. (Stuttg.) 23:130-40.

Kronecker, H., Meltzer, S.J. (1883). Der schluckmechanismus, seine Erregung und seine Hemmung. Arch. f. Physiol., Leipz (Suppl) pp. 338-62.

Laitinen, S.T., Larmi, T.K.I. (1981) Lower esophageal sphincter and the gastroesophageal antireflux mechanism. World J. Surg. 5:845-53.

Lawler, N.A., McCreath, N.D. (1951) Gastro-oesophageal regurgitation. Lancet 2:369-74.

Lear, C.S., Flanagan, J.B. Jr., Moorrees, C.F. (1965) The frequency of deglutition in man. Arch. Oral Biol. 10:83-100.

Leigh Collis, J. (1966). Peptic stricture of the oesophagus. Acta. Chir. Belg. Suppl. 2:41-8.

Leigh Collis, J., Kelly, T.D., Wiley, A.M. (1954) Anatomoy of the crura of the diaphragm and the surgery of hiatus hernia. Thorax 9:175-89.

Lendrum, F.C. (1937) Anatomic features of the cardiac orifice of the stomach, with special reference to cardiospasm. Arch. Intern. Med. 59:474-511.

Leonardi, H.K., Crozier, R.E., Ellis, F.H. (1981) Reoperation for complications of the Nissen fundoplication. J. Thorac. Cardiovasc. Surg. 81:50-6.

Liebermann-Meffert, D., Allgower, M. (1983) The muscular counterpart of the lower esophageal sphincter (LES). 2nd International Conference on Diseases of the Esophagus: Chicago, 1983.

Liebermann-Meffert, D., Allgower, M., Schmid. P., Blum, A.L. (1979) Muscular equivalent of the lower esophageal sphincter. Gastroenterology 76:31-8.

Lind, J.F., Crispin, J.S., McIver, D.K. (1968) The effect of atropine on the gastroesophageal sphincter. Can. J. Physiol. Pharmacol. 46:233-8.

Lind, J.F., Warrian, W.G., Wankling, W.J. (1966) Responses of the gastroesophageal junctional zone to increases in abdominal pressure. Can. J. Surg. 9:32-8.

Linsman, J.F. (1965) Gastroesophageal reflux elicited while drinking water (water siphonage test): its clinical correlation with pyrosis. Am. J. Roentgenol. Radium Ther. Nuc. Med. 94:325-32.

Little, A.G., DeMeester, T.R., Kirchner, P.T., O'Sullivan, G.C., Skinner, D.B. (1980) Pathogenesis of esophagitis in patients with gastroesophageal reflux. Surgery 88:101-7.

Livstone, E.M., Sheahan, D.G., Behar, J. (1977) Studies of esophageal epithelial cell proliferation in patients with reflux esophagitis. Gastroenterology 73:1315-9.

Lloyd, D.A., Borda, I.T. (1981) Food-induced heartburn: effect of osmolality. Gastroenterology 80:740-1.

Lodge, K.V. (1955) Pathology of non-specific oesophagitis. J. Path. and Bact. 69:17-24.

McCallum, R.W., Berkowitz, D.M., Lerner, E. (1981) Gastric emptying in patients with gastroesophageal reflux. Gastroenterology 80:285-91.

McCallum, R.W., Fink, S.M., Lerner, E., Berkowitz, D.M. (1983) Effects of Metoclopramide and Bethanechol on delayed gastric emptying present in gastroesophageal reflux patients. Gastroenterology 84:1573-7.

McCallum, R.W., Ippoliti, A.F., Cooney, C., Sturdevant, R.A.L. (1977) A controlled trial of Metoclopramide in symptomatic gastroesophageal reflux. N. Engl. J. Med. 296:354-7.

McCallum, R.W., Kline, M.M., Curry, N., Sturdevant, R.A.L. (1975) Comparative effects of metoclopramide and bethanechol on lower esophageal sphincter pressure in reflux patients. Gastroenterology 68:1114-8.

McShane, A.J., O'Morain, C., Lennon, J.R., Coakley, J.B., Alton, B.G. (1980) Atraumatic non-distorting pyloric sphincter pressure studies. Gut 21:826-8.

Mackie, C.R., Wisbey, M.L., Cuschieri, A. (1982) Milk $^{99m}Tc-^{m}$-EHIDA test for enterogastric bile reflux. Br. J. Surg. 69:101-4.

Maddern, G.J. (1983) Galactorrhoea due to Domperidone. Med. J. Aust. 2:539-40.

Madsen, T., Wallin, L., Boesby, S., Larsen, V.H. (1983) Oesophageal peristalsis in normal subjects: Influence of pH and volume during imitated gastro-esophageal reflux. Scand. J. Gastroenterol. 18:513-8.

Magendie, F. (1822) A summary of physiology. Baltimore, Coale.

Malmud, L.S., Fisher, R.S., Knight, L.C., Rock, E. (1982) Scintigraphic evaluation of gastric emptying. Seminars in Nuclear Medicine 12:116-25.

Malmud, L.S., Fisher, R.S. (1981). Scintigraphic evaluation of disorders of the oesophagus, stomach, and duodenum. Medical Clin. North Am. 65:1291-310.

Mandelstam, P., Siegel, C.I., Lieber, A., Siegel, M. (1969) The swallowing disorder in patients with diabetic neuropathy-gastroenteropathy. Gastroenterology 56:1-12.

Marchand, P. (1957). A study of the forces productive of gastroesophageal regurgitation and herniation through the diaphragmatic hiatus. Thorax 12:189-202.

Martin, S., Pangborn, R.M. (1971) Human parotid secretion in response to ethyl alcohol. J. Dent. Res. 50:485-90.

Mayron, L.W., Kaplan, E., Friedman, A.M., Gindler, J.E. (1975) The use of $^{81m}Kr$ in deglutition kinetic studies. Int. J. Nucl. Med. Biol. 2:42-3.

Mellow, M.H. (1983) Esophageal motility during food ingestion: a physiologic test of esophageal motor function. Gastroenterology 85:570-7.

Meltzer, S.J. (1897) A future experimental contribution to the knowledge of the mechanism of deglutition. J. Exp. Med. 2:453-64.

Menin, R.A., Malmud, L.S., Petersen, R.P., Maier, W.P., Fisher, R.S. (1980) Gastroesophageal scintigraphy to assess the severity of gastroesophageal reflux disease. Ann. Surg. 191:66-71.

Meshkinpour, H., Glick, M.E., Sanchez, P., Tarvin, J. (1982) Esophageal manometry: A benefit and cost analysis. Dig. Dis. Sci. 27:772-5.

Meyer, J.H. (1979a) New dimensions in digestive physiology. Dig. Dis. Sci. 24:97-100.

Meyer, J.H., Thomson, J.B., Cohen, M.B., Shadchehr, A., Mandiola, S.A. (1979b) Sieving of solid food by the canine stomach and sieving after gastric surgery. Gastroenterology 76:804-13.

Meyer, G.W., Castell, D.O. (1981) In support of the clinical usefulness of lower esophageal sphincter pressure determination. Dig. Dis. Sci. 26:1028-31.

Meyer, J.H., MacGregor, I.L., Gueller, R., Martin, P., Cavalieri, R. (1976) $^{99m}$Tc-tagged chicken liver as a marker of solid food in the human stomach. Am. J. Dig. Dis. 21:296-304.

Milstein, B.B. (1961) The mechanism at the cardia - anatomical and surgical aspects. Br. J. Radiol. 34:471-4.

Minami, H., McCallum, R.W. (1984). The physiology and pathophysiology of gastric emptying in humans. Gastroenterology 86:1592-610.

Miners, J.O., Attwood, J., Birkett, D.J. (1984) Influence of sex and oral contraceptive steroids on paracetamol metabolism. Br. J. Clin. Pharmacol. 16:503-9.

Moore, J.G., Tweedy, C., Christian, P.E., Datz, F.L. (1983) Effect of age on gastric emptying of liquid-solid meals in man. Dig. Dis. Sci. 28:340-4.

Moran, J.M., Pihl, C.O., Norton, R.A., Rheinlander, H.F. (1971) The hiatal hernia-reflux complex. Current approaches to correction and evaluation of results. Am. J. Surg. 121:403-11.

Morgan, E.H. (1962). Studies of intraluminal pressure and pH at the gastroesophageal junction. Q. Bull. N.W. Unive. Med. Sch. 36:258-67.

Morgan, K.G., Schmalz, P.F., Go, V.L.W., Szurszewski, J.H. (1978) Effects of pentagastrin, G17, and G34 on the electrical and mechanical activities of canine antral smooth muscle. Gastroenterology 75:405-12.

Morrison, D.F. (1967) Multivariate statistical methods. New York: McGraw-Hill.

Mosher, H.P. (1923) Anatomical and clinical observations on the lower end of the esophagus and the diaphragm. Trans. Amer. Laryng. Ass. 45:58-100.

Mosher, H.P. (1930) Lower end of oesophagus at birth and in adult; semon lecture for 1929. J. Laryng. and Otol 45:161-80

Nebel, O.T., Castell, D.O. (1972) Lower esophageal sphincter pressure changes after food ingestion. Gastroenterology 63:778-83.

Nimmo, W.S., Heading, R.C., Wilson, J., Tothill, P., Prescott, L.F. (1975) Inhibition of gastric emptying and drug absorption by narcotic analgesics. Br. J. Clin. Pharmacol. 2:509-13.

Nissen, R. (1956) Eine einfache operation zur beeinflussung der refluxoesophagitis. Schw. Med. Wochenschr. 86:590-2.

Nissen, R. (1961) Gastropexy and "fundoplication" in surgical treatment of hiatal hernia. Am. J. Dig. Dis. 6:954-61.

Orringer, M.B., Dabich, L., Zarafonetis, C.J.D., Sloan, H. (1976) Gastroesophageal reflux in esophageal scleroderma: diagnosis and implications. Ann. Thorac. Surg. 22:120-30.

Orringer, M.B., Orringer, J.S., Dabich, L., Zarafonetis, C.J.D. (1981) Combined Collis gastroplasty-fundoplication operations for scleroderma reflux esophagitis. Surgery 90:624-30.

Palmer, E.D. (1954). Subacute erosive ("peptic") esophagitis: Clinical study of one hundred cases. Arch. Int. Med. 94:364-74.

Palmer, E.D. (1955) Subacute erosive ("peptic") esophagitis; histolopathologic study. Arch. Path. 59:51-7.

Palmer, E.D. (1968) The hiatus hernia - esophagitis - esophageal stricture complex. Twenty year prospective study. Am. J. Med. 44:566-79.

Pantoja, J.L., Defilippi, C., Valenzuela, J.E., Csendes, A. (1979) Nonsteroidal antiinflammatory drugs: effect on pyloric sphincter and duodenogastric reflux. Dig. Dis. Sci. 24:217-20.

Papp, J.P. (1979) Determination of the lower esophageal sphincter pressure in patients having a Nissen or Belsey fundoplication. Am. J. Gastroenterol. 71:154-7.

Perkel, M.S., Moore, C., Hersh, T., Davidson, E.D. (1979) Metoclopramide therapy in patients with delayed gastric emptying: A randomized double-blind study. Dig. Dis. Sci. 24:662-6.

Peters, P.M. (1955) Closure mechanisms at the cardia with special reference to the diaphragmatico-oesophageal elastic ligament. Thorax 10:27-36.

Pettersson, G.B., Bombeck, C.T., Nyhus, L.M. (1980) The lower esophageal sphincter: Mechanisms of opening and closure. Surgery 88:307-14.

Pope, C.E. (1967) A dynamic test of sphincter strength: Its application to the lower esophageal sphincter. Gastroenterology 52:779-86.

Pope, C.E., Meyer, G.W., Castell, D.O. (1981) Is measurement of lower esophageal sphincter pressure clinically useful? Dig. Dis. Sci. 26:1025-7.

Pozzessere, C., Materia, E., Corazziari, E., Anzini, F. (1982) Effects of domperidone on oesophageal motor activity and gastro-oeophageal reflux. Ital. J. Gastroenterol. 14:159-61.

Price, S.F., Smithson, K.W., Castell, D.O. (1978) Food sensitivity in reflux esophagitis. Gastroenterology 75:240-3.

Ramond, Borrien, Jacquelin, C. (1921) Sur l'abouchement de l'oesophage dans l'estomac. Bull. et. mem. Soc. Anat. de Par. xci:204.

Rees, W.D.W., Go, V.L.W., Malagelada, J.-R. (1979) Antroduodenal motor response to solid-liquid and homogenized meals. Gastroenterology 76:1438-42.

Rees, W.D.W., Leigh, R.J., Christofides, N.D., Bloom, S.R., Turnberg, L.A. (1982) Interdigestive motor activity in patients with systemic sclerosis. Gastroenterology 83:575-80.

Rex, J.C., Andersen, H.A., Batholomew, L.G., Cain, J.C. (1961) Esophageal hiatal hernia: a 10-year study of medically treated cases. J.A.M.A. 178:271-4.

Richter, J.E., Blackwell, J.N., Wu, W.C., Cowan, R.J., Johns, D.N., Castell, D.O. (1983) Assessment of liquid bolus transit (LBT) by simultaneous Radionuclide transit and Esophageal manometry. Gastroenterology 84:1285.

Richter, J.E., Castell, D.O. (1982) Gastroesophageal reflux: pathogenesis, diagnosis and therapy. Ann. Int. Med. 97:93-103.

Roux, J. (1939) Le segment cardio-oesophagien. Bronchoscop; Oesophagoscop. et. Gastroscop. pp. 81-113.

Rudd, T.G., Christie, D.L. (1979) Demonstration of gastroesophageal reflux in children by radionuclide gastroesophagography. Radiology 131:483-6.

Russell, C.O.H., Gannan, R., Coatsworth, J., Neilsen, R., Allen, F., Hill, L.D., Pope, C.E. (1983) Relationship among esophageal dysfunction, diabetic gastroenteropathy, and peripheral neuropathy. Dig. Dis. Sci. 28:289-93.

Russell, C.O.H., Hill, L.D., Holmes, E.R., Hull, D.A., Gannon, R., Pope, C.E. (1981a) Radionuclide transit: a sensitive screening test for esophageal dysfunction. Gastroenterology 80:887-92.

Russell, C.O.H., Pope, C.E., Gannan, R.M., Allen, F.D., Velasco, N., Hill, L.D. (1981b) Does surgery correct esophageal motor dysfunction in gastroesophageal reflux? Ann. Surg. 194:290-6.

Safaie-Shirazi, S., Zike, W.L., Mason, E.E. (1975) Esophageal stricture secondary to reflux esophagitis. Arch. Surg. 110:629-31.

Saladin, T.A., French, A.B., Zarafonetis, C.J.D., Pollard, H.M. (1966) Esophageal motor abnormalities in scleroderma and related diseases. Am. J. Dig. Dis. 11:522-35.

Salmon, P.R., Fedail, S.S., Wurzner, H.P., Harvey, R.F., Read, A.E. (1981) Effect of coffee on human lower oesophageal function. Digestion 21:69-73.

Samelson, S.L., Weiser, H.F., Bombeck, C.T., Siewert, J.R., Ludtke, F.E., Hoelscher, A.H., Abuabara, S.F., Nyhus, L.M. (1983) A new concept in the surgical treatment of gastroesophageal reflux. Ann. surg. 197:254-9.

Sanchez, G.C., Kramer, P., Ingelfinger, F.J. (1953) Motor mechanisms of the esophagus, particularly of its distal portion. Gastroenterology 25:321-32.

Savary, M., Miller, C. (1978). The Esophagus. In: Gassman, A.G. (ed.) Handbook and Atlas of Endoscopy. Selothurn, Switzerland.

Schneyer, L.H., Pigman, W., Hanahan, L., Gilmore, R.W. (1956) Rate of flow of human parotid, sublingual and submaxillary secretions during sleep. J. Dent. Res. 35:109-14.

Schulze-Delrieu, K. (1979) Metoclopramide. Gastroenterology 77:768-79.

Schulze-Delrieu, K., Mitros, F., Shirazi, S. (1978) Morphological evolution of experimental esophagitis. Gastroenterology 74:1091.

Schulze-Delrieu, K., Shirazi, S.S. (1983) Neuromuscular differentiation of the human pylorus. Gastroenterology 84:287-92.

Sheiner, H.J. (1975) Progress report: gastric emptying tests in man. Gut 16:235-47.

Siegel, S. (1956) Nonparametric statistics for the behavioural sciences. New York: McGraw-Hill.

Siegel, C.I., Hendrix, T.R (1963). Esophageal motor abnormalities induced by acid perfusion in patients with heartburn. J. Clin. Invest. 42:686-95.

Siewert, R., Jennewein, H.M., Waldeck, F., et al. (1973) Experimentelle und klinische Untersuchungen zum Wirkungsmechanismus der Fundoplicatio. Langenbecks. Arch. Chir. 333:5-22.

Sigmund, C.J., McNally, E.F. (1969) The action of a carminative on the lower esophageal sphincter. Gastroenterology 56:13-8.

Silber, W. (1969) Diabetes and oesophageal dysfunction. Br. Med. J. 3:688-90.

Skinner, D.B. (1966). Symptomatic esophageal reflux. Am. J. Dig. Dis. 11:771-9.

Skinner, D.B., Belsey, R.H.R. (1967) Surgical management of esophageal reflux and hiatus hernia. Long-term results with 1,030 patients. J. Thorac. Cardiovasc. Surg. 53:33-54.

Skinner, D.B., Booth, D.J. (1970) Assessment of distal esophageal function in patients with hiatal hernia and/or gastroesophagaeal reflux. Ann. Surg. 172:627-37.

Skinner, D.B., Camp, T.F. (1968) Relation of esophageal reflux to lower esophageal sphincter pressures decreased by atropine. Gastroenterology 54:543-51.

Skinner, D.B., Hendrix, T.R. (1972) Diagnostic Tests. In: Gastroesophageal reflux and hiatus hernia. Churchill Livingstone, Chapter 7:87-106.

Sonnenberg, A., Steinkamp, U., Weise, A., Berges, W., Weinbeck, M., Rohner, H.G., Peter, P. (1982) Salivary secretion in reflux esophagitis. Gastroenterology 83:889-95.

Stanciu, C., Bennett, J.R. (1973) Metoclopramide in gastrooesophageal reflux. Gut 14:275-9.

Stanciu, C., Bennett, J.R. (1974a) Oesophageal acid clearing: one factor in the production of reflux oesophagitis. Gut 15:852-7.

Stanciu, C., Bennett, J.R. (1974b) Alginate/antacid in the reduction of gastro-oesophageal reflux. Lancet 26:109-11.

Stanghellini, V., Malagelada, J-R. (1983a) Gastric manometric abnormalities in patients with dyspeptic symptoms after fundoplication. Gut 24:790-7.

Stanghellini, V., Malagelada, J-R., Zinsmeister, A.R., Go, V.L.W., Kao, P.C. (1983b) Stress-induced gastroduodenal motor disturbances in humans: possible humoral mechanisms. Gastroenterology 85:83-91.

Stewart, E.T. (1981). Radiographic evaluation of the esophagus and its motor disorders. Med. Clin. North Am. 65: 1173-94.

Stewart, I.M., Hosking, D.J., Preston, B.J., Atkinson, M. (1976) Oesophageal motor changes in diabetes mellitus. Thorax 31:278-83.

Strunz, U. (1979) Hormonal control of gastric emptying. Acta. Hepato-Gastroenterol. 26:334-41.

Strunz, U.T., Grossman, M.I. (1978) Effect of intragastric pressure on gastric emptying and secretion. Am. J. Physiol. 234:E552-5.

Strunz, U.T., Code, C.F., Grossman, M.I. (1979) Effect of gastrin on electrical activity of antrum and duodenum of dogs. Proc. Soc. Exp. Biol. Med. 161:25-7.

Thanik, K.D., Chey, W.Y., Shah, A.N., Gutierrez, J.G. (1980) Reflux esophagitis: effect of oral bethanechol on symptoms and endoscopic findings. Ann. Int. Med. 93:805-8.

Thomas, F.B., Steinbaugh, J.T., Fromkes, J.J., Mekhjian, H.S., Caldwell, J.H. (1980) Inhibitory effect of coffee on lower esophageal sphincter pressure. Gastroenterology 79:1262-6.

Thompson, D.G., Richelson, E., Malagelada, J-R. (1983) Perturbation of upper gastrointestinal function by cold stress. Gut 24:277-83.

Thurer, R.L., DeMeester, T.R., Johnson, L.F. (1974) The distal esophageal sphincter and its relationship to gastroesophageal reflux. J. Surg. Res. 16:418-23.

Tileston, W. (1906) Peptic ulcer of the oesophagus. Am. J. Med. Sci. 132:240-65.

Tocornal, J.A., Snow, H.D., Fonkalsrud, E.W. (1968) A mucosal flap valve mechanism to prevent gastroesophageal reflux and esophagitis. Surgery 64:519-23.

Tolin, R.D., Malmud, L.S., Reilley, J., Fisher, R.S. (1979) Esophageal scintigraphy to quantitate esophageal transit (Quantitation of esophageal transit). Gastroenterology 76:1402-8.

Turner, K.S., Powell, D.W., Carney, C.N., Orlando, R.C., Bozymski, E.M. (1978) Transmural electrical potential difference in the mammalian esophagus in vivo. Gastroenterology 75:286-91.

Turner, R., Lipshutz, W., Miller, W., Rittenberg, G., Schumacher, H.R., Cohen S. (1973) Esophageal dysfunction in collagen disease. Am. J. Med. Sci. 265:191-9.

Tuttle, S.G., Grossman, M.I. (1958) Detection of gastro-esophageal reflux by simulataneous measurement of intraluminal pressure and pH. Proc. Soc. Exp. Biol. 98:225-7.

Valenzuela, J.E. (1981) Effects of domperidone on the symptoms of reflux oesophagitis. The Royal Society of Medicine International Congress and Symposium Series 36:67-75.

Vineberg, A.M., Komarov, S.A. (1933) The influence of the vagus nerve on esophageal secretion. Am. J. Physiol. 104:73-80.

Vix, V.A. (1969) Esophageal motility in diabetes mellitus. Radiology 92:363-4.

Wald, H., Polk, H.C. (1983) Anatomical variations in hiatal and upper gastric areas and their relationship to difficulties experienced in operations for reflux esophagitis. Ann. Surg. 197:389-92.

Wallin, L., Boesby, S., Madsen, T. (1979) Effect of Metoclopramide on oesophageal peristalsis and gastro-oesophageal sphincter pressure. Scand. J. Gastroenterol 14:923-7.

Washer, G.F., Gear, M.W.L., Dowling, B.L., Gillison, E.W., Royston, C.M.S., Spencer, J. (1984) Randomized prospective trial of Roux-en-Y duodenal diversion versus fundoplication for severe reflux oesophagitis. Br. J. Surg. 17:181-4.

Weihrauch, T.R., Korting, G.W. (1982) Manometric assessment of oesophageal involvement in progressive systemic sclerosis, morphoea and Raynaud's disease. Br. J. Dermatol. 107:325-32.

Weinstein, W.M., Bogoch, E.R., Bowes, K.L. (1975) The normal human esophageal mucosa: a histological reappraisal. Gastroenterology 68:40-4.

Weiser, H.F., Siewert, J.R. (1982) Investigations with the 24-hour solid-state pH metry: Correlation between gastroesophageal reflux extent and reflux sequelae. Surg. Gastroenterol. 1:327-34.

Welch, R.W., Drake, S.T. (1980) Normal lower esophageal sphincter pressure: A comparison of rapid vs slow pull-through techniques. Gastroenterology 78:1446-51.

Wernly, J.A., DeMeester, T.R., Bryant, G.H., Wang, C.I., Smith, R.B., Skinner, D.B. (1980) Intra-abdominal pressure and manometric data of the distal esophageal sphincter. Their relationship to gastroesophageal reflux. Arch. Surg. 115:534-9.

Wesdorp, E., Bartelsman, J., Pape, K., Dekker, W., Tytgat, G.N. (1978) Oral cimetidine in reflux esophagitis: A double blind controlled trial. Gastroenterology 74:821-4.

White, C.M., Poxon, V., Alexander-Williams, J. (1981) A study of motility of normal human gastroduodenal region. Dig. Dis. Sci. 26:609-17.

Wilbur, B.G., Kelly, K.A. (1973) Effect of proximal gastric, complete gastric, and truncal vagotomy on canine gastric electric activity, motility, and emptying. Ann. Surg. 178:295-303.

Willis, T. (1679) Pharmaceutice rationale. Oxford (English Edition).

Winans, C.S. (1976) The fickle pylorus. Gastroenterology 70:622-3.

Winans, C.S., Harris, L.D. (1967) Quantitation of lower esophageal sphincter competence. Gastroenterology 52:773-8.

Winkelstein, A. (1935). Peptic esophagitis - a new clinical entity. JAMA 104:906-9.

Winter, H.S., Madara, J.L., Stafford, R.J., Grand, R.J., Quinlan, J-E.,Goldman, H. (1982) Intraepithelial eosinophils: A new diagnostic criterion for reflux esophagitis. Gastroenterology 83:818-23.

Wolf, B.S., Khilnani, M.T. (1966). Progress in gastroenterological radiology. Gastroenterology 51:542-59.

Wolf, B.S. (1973) Sliding hiatal hernia: the need for redefinition. Am. J. Roentgenol. Radium. Ther. Nuc. Med. 117:231-47.

Woodward, D.A. (1970). Response of the gullet to gastric reflux in patients with hiatus hernia and oesophagitis. Thorax 25:459-64.

Wooler, G.H. (1952) Mechanism of the cardia. Proc. Roy. Soc. Med. 45:290.