THERAPY FOR PERSISTENT CLINICALLY SIGNIFICANT GASTRO-OESOPHAGEAL REFLUX: The Design of a Randomized Clinical Trial of Surgical versus Medical Management

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Master of Science

McMaster University

June 1979

A CLINICAL TRIAL OF THERAPY FOR GASTRO-OESOPHAGEAL REFLUX

MASTER OF SCIENCE
(Medicine)

McMASTER UNIVERSITY
Hamilton, Ontario

TITLE: Therapy for Persistent Clinically Significant Gastro-oesophageal Reflux: The Design of a Randomized Clinical Trial of Surgical versus Medical Management

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NUMBER OF PAGES: viii, 142

ABSTRACT

Every day a physician treating patients carries out a series of experiments - whether he is aware of it or not. Many of the decisions he makes need to be made against a background of inadequate information concerning the effectiveness of the therapies he prescribes.

This manuscript begins with a review of the currently available scientific literature concerning gastro-oesophageal reflux - its pathogenesis, diagnosis and therapy. Then, the design of a prospective randomized control trial of therapy for persistent clinically significant gastro-oesophageal reflux is described. The design is for an intervention study to determine the effectiveness of therapy in patients randomized to either surgical or medical treatment for this disorder.

Subjects for the study will be drawn from among patients referred from primary care physicians to gastroenterology clinics for treatment. These patients to be eligible will have to have failed to respond to standard medical therapy.

Data for analysis will be collected utilizing a self administered questionnaire to record symptoms and the degree of incapacity caused by them.

It is hoped that results obtained from the performance of the trial described in this document will be of assistance in guiding the decision making process of physicians caring for patients with symptomatic gastro-oesophageal reflux.

ACKNOWLEDGEMENTS

To the Faculty, Staff and Student Class of Clinical Epidemiology and Biostatistics (1978-79), I express my gratitude for making my year at MAC a superb educational experience and a great deal of fun.

I must particularly mention Peter Tugwell, Dave Sackett and Charlie Goldsmith for reading my prose, correcting its imperfections, prodding with pertinent questions and always being there when I needed help. Without them, this document would never have met its deadlines. I wish to thank Linda Teiml who patiently constructed the layout and typed the manuscript. Without her efficient help, this document may have had to be completed on another continent.

Finally, I dedicate the thesis to my wife Lynette, who patiently endured its evolution.

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Chapter 1

Introduction

Gastro-oesophageal (GE) reflux is a very common phenomenon. Indeed 36% of "normal" hospital staff in one survey were found to have at least a monthly episode of heartburn (Nebel, et al. 1976). The boundary between "*physiological*" reflux which occurs in asymptomatic individuals predominantly in relationship to meals (Johnson, et al. 1974) or when aroused from sleep, but rarely while asleep (Dodds, 1979) and "*pathological*" reflux which is usually associated with worrying symptoms and often with evidence of damage to the oesophageal mucosa in the form of oesophagitis (Behar, et al. 1976 , Ismail-Beigi, et al. 1970) has bedeviled the interpretation of many studies of this condition. This study concerns the management of patients with *persistent clinically significant* gastro-oesophageal reflux.

The research question may be stated as follows:-

Among patients with symptomatic gastro-oesophageal reflux, is surgery superior to medical therapy in minimizing symptoms and maximizing function?

The major objective of this study is to determine whether anti-reflux surgery is at least *twice* as successful as optimal medical management in achieving the pain free state or (if heartburn persists) will result in a 50% or greater improvement in the severity of this

symptom compared to the improvement attained on medical therapy.

The rationale of the study is the need to put into perspective, based on scientific evidence, the use of a technically feasible and relatively commonly performed operative procedure for a symptom complex which is currently either predominately ignored by many patients or oevertreated by clinicians.

The significance of the work is as follows:-

1) Early operations aimed at preventing reflux by correcting hiatus herniae (Allison, 1951, 1973) had a high failure rate in the management of patients with gastro-oesophageal reflux - symptoms either persisted or soon recurred. More recently operations aimed at providing a barrier to the reflux of gastric contents in a cephalad direction ("*the anti-reflux operations*") have been shown in many patients to prevent reflux (Fisher, et al. 1978). In some this is associated with an improvement in the functional competence of the lower oesophageal sphincter zone (LES) while giving relief of the symptoms of reflux (DeMeester, et al. 1974).

2) Antacids have for years been used by the sufferers of symptomatic reflux and usually these patients report prompt relief of that episode. Based on the demonstrated influence of antacids on gastric acidity and on lower oesophageal sphincter function (Castell, et al. 1971), this medication has a logical place in the treatment of heartburn - the major symptom of this disorder. However, a recent report (Meyer, et al. 1979) indicates that a preparation containing the usual ingredients of most antacid mixtures - aluminum and magnesium -

hydroxide - was no more effective than placebo in alleviating heartburn.

3) Cimetidine, a histamine antagonist (H2-blocker) has recently been shown, in a multi-centre double blind trial to be more effective than placebo for the relief of heartburn (Behar, et al. 1978). Most studies on drug therapy have tended to be short term involving patients with symptoms of widely varying severity.

4) The few controlled studies published involving anti-reflux surgery have been on small numbers of patients with severe disease (DeMeester, et al. 1974[1], Behar, et al. 1975[2]).

Thus there is a need to define the role of surgery in the treatment of this disorder. A multi-centre study will make it possible to include, in the study, large numbers of patients covering a spectrum of the severity range. A properly designed and executed trial will allow anti-reflux surgery to be evaluated in accordance with scientifically designed and executed principles.

Chapter II

Review of Literature on Gastro-oesophageal Reflux

2.1 Historical Aspects

To a large extent advances in our understanding of gastro-oesophageal reflux have paralleled the use of new investigative techniques. In 1879, a description of oesophageal ulceration first appeared in the literature (Quincke: quoted in Earlam, 1976). Fifty-five years later the term oesophagitis was introduced. This description appeared in the German (Hamperl: quoted in Earlam, 1976) and the North American (Winkelstein, 1935) literature about the same time. The year 1958 produced two articles related to (a) the ability to measure acid reflux (Tuttle, et al. 1958) and (b) the possibility of differentiating its symptoms more easily from those of ischaemic heart disease (Bernstein, et al. 1958, 1962). Perhaps the major contribution to current beliefs as to the pathogenesis of reflux came from the use of the technique of oesophageal manometry developed by Code, Ingelfinger and their colleagues in the 1950's using oesophageal balloons (Ingelfinger, 1958) and refined during the 1960's with the advent of the use of a perfused catheter system (Cohen, et al. 1970). The 1970's produced the technique of scintiscanning to demonstrate reflux directly (Fisher, et al. 1976).

Despite these advances, a good understanding of this problem has been impaired for many years by the way in which the *anatomical* defect of hiatus hernia has been confused, in the literature, with the

pathophysiological disorder of gastro-oesophageal reflux (Rex, 1961). Certainly severe reflux and large herniae occur together but there is ample evidence in the literature to demonstrate that herniae may occur without reflux (Dyer, et al. 1968, Vandervelde, et al. 1964) and reflux may occur without a hiatus hernia (Skinner, et al. 1970). I will not attempt to review the long history of hiatus hernia and its associated surgical procedures, but will merely mention surgery for hiatus hernia in the context of surgery for relief of gastro-oesophageal reflux.

2.2 Pathogenesis of Gastro-oesophageal Reflux

Gastro-oesophageal reflux may be considered, according to the circumstance, as physiologic or pathologic. Using sensitive procedures such as scintiscanning, and pH monitoring, gastro-oesophageal reflux has been demonstrated in asymptomatic individuals (Fisher, et al. 1976, Dodds, et al. 1979, Haddad, 1970, Kantrowitz, et al. 1969, Kaye, 1977, Venkatachalan, et al. 1972). In fact when one considers the stress placed on the integrity of the gastro-oesophageal sphincter mechanism by some of the acitivities of daily living, such as large meals and alcohol followed by cigarettes or cigars, it is amazing that it does so well.

Patients with reflux who develop symptoms may be considered to have:

1) a responsive oesophageal mucosa - if heartburn is to occur and 2) cricopharyngeal dysfunction (in addition to lower oesophageal sphincter dysfunction) - if regurgitation is to be experienced.

Although the standardized test to quantitate the sensitivity of the oesophageal mucosal surface utilizes response to acid perfusion, the gastric refluxate may include not only gastric secretions, but also duodenal juice which may have backwashed across an incompetent pyloric sphincter mechanism. When gastric content refluxes into the oesophagus the oesophageal mucosa is exposed to the influence of a variable mixtures of hydrochloric acid (HCL), pepsin, bile salts and pancreatic enzymes - some of these substances (HCL, bile salts, pepsin ...) have been shown either singly or in combination to be damaging to oesophageal mucosa (Goldberg, et al. 1969, Gillison, et al. 1972).

Against this formidable array of aggressive factors, the defense of the mucosa appears to rely predominately on gravity (Pattrick, 1970), oesophageal peristalsis (these include both primary peristaltic waves as well as secondary peristaltic contractions in response to refluxed material (Stanciu, et al. 1974[2], Dodds, et al. 1979) and on the integrity of the lower oesophageal sphincter (Cohen, et al. 1970)).

Indeed, it is believed (based on animal studies) that gastro-oesophageal reflux may create a vicious cycle whereby the resulting inflammation in the oesophageal mucosa penetrating to the muscularis produces a motor disorder of the distal oesophagus. This may impede oesophageal clearance. The resulting prolonged contact time between the oesophageal mucosa and the destructive elements of the refluxate may increase the severity of the oesophageal inflammation, further impairing the integrity of the gastro-oesophageal anti-reflux mechanism and allowing greater quantities of gastric material to enter the oesophagus (Fisher, et al. 1978).

2.2.1 What Normally Prevents Reflux?

Normally, a positive pressure gradient exists across the gastro-oesophageal junction from the positive pressure abdominal cavity to the negative pressure thoracic cavity - thus an anti-reflux mechanism must be present to prevent gastric material from entering the oesophagus.

A variety of *mechanical* factors including the cardio-oesophageal angle, diaphragmatic pinchcock mechanism, phreno-oesophageal ligament, mucosal rosette formed by gastric folds and the distal para-oesophageal pressure, have been postulated as being important in preventing reflux. The last of this array is most widely accepted as the important mechanical anti-reflux factor (Inglefinger, 1958, 1971). It is postulated that in normal subjects the distal oesophageal segment is buttressed by intra-abdominal pressure.

The major determinant of gastro-oesophageal competence is probably the physiologic lower oesophageal sphincter pressure zone which is tonically contracted in the basal state and relaxes with swallowing or oesophageal distension (Christensen, et al. 1973). It is a zone 2-5 cms. long which when measured using infused, open-tipped recording catheters is 12-30 mmHg above intra-abdominal pressure levels. The factors regulating its strength are still incompletely understood but probably include hormonal, neural and mechanical mechanisms. The basal LES pressure is able to respond in an adaptive fashion to (i) stimuli such as food ingestion (presumably via the ability of food in the stomach to cause hormonal release for the upper gastro intestinal (GI) tract) and (ii) alterations in intra-abdominal pressure probably

via neural arc mechanisms.

There is a variety of evidence to suggest that LES pressure is not the sole determinant of gastro-oesophageal competence. Edwards believes that the high pressure zone measured by manometry at the lower end of the oesophagus contains *extrinsic* factors of a mechanical nature in addition to the *intrinsic* component supplied by the lower oesophageal sphincter. Indeed he postulates that the *physiologic sphincter* is designed to resist reflux due to forces within the gut (eg. gastric distension producing a rise in intra-gastric pressure). The *mechanical* part of the anti-reflux mechanism is aimed at opposing extramural forces such as those operating when intra-abdominal pressure is elevated by bending or lying down (Edwards, 1976, 1978). Perhaps the low pressure found in many with this disorder may, at least in some patients, be secondary to the effect of reflux on the lower oesophagus. The controversy continues (Pope, 1976, Ahtaridis, et al. 1979) and is currently unresolved.

In the rest of this chapter, I will discuss the methods used to assess the effects of reflux on the oesophagus and the investigative techniques available to detect and at times to quantify reflux. Lastly an overview of therapeutic options will be attempted.

The following section will cover: Tests of Oesophageal Function: *Techniques to Detect Reflux*: Measurement of pH profile across the oesophagogastric junction, Radiological demonstration of reflux and Gastro-oesophageal scintiscanning. *Methods of Assessing the Effects of Reflux*: Upper gastrointestinal tract endoscopy with visualisation of

the oesophageal mucosa, Histological examination of biopsy samples taken from the oesophageal mucosa and The acid perfusion test. A description of those techniques which will be used in this study, will be found in the Appendix, Section A.

2.3 Techniques to Detect Reflux

2.3.1 pH Profile Across the Gastro-oesophageal Junction

The clinical use of a small glass pH electrode placed in the lumen to detect acid reflux into the oesophagus was reported first in the late 1950's (Tuttle, et al. 1958, 1960). Measurement of the pH profile across the gasro-oesophageal junction is currently considered the most accurate indicator of gastro-oesophageal reflux and the bench-mark against which other procedures are usually compared (Fisher, et al. 1978). It relies on the fact that normal intragastric pH is less than 3 (Earlam, 1974) and normal intra-oesophageal pH is above 5 (Bombeck, et al. 1973). The competence of the gastro-oesophageal sphincter zone can be gauged by the distance over which the pH changes from the gastric to the lowest oesophageal pH. Values for oesophageal pH < 4 are considered as evidence of reflux. (Tuttle, et al. 1960)

In an effort to ensure that the pH electrode was in liquid contents (rather than up against mucosa), and in addition, to place the lower oesophageal sphincter under stress in those patients who have symptoms but a normal basal pH profile, the test has been modified to measure lower oesophageal luminal pH after instillation of 200-300 ml 0.1N. HCL into the stomach with or without provocative manoeuvres such as

the Valsalva manoeuvre and straight leg raising. Some patients find the test uncomfortable and fail to perform the manoeuvres properly.

More serious, however, are some technical problems that can occur with the use of this fragile instrument. Withdrawal of the glass electrode from stomach into the oesophagus does not always result in consistent, reproducible pH changes at the junction. (Payne, et al. 1974)

While the use of acid loading and provocative manoeuvres certainly increases the number of patients with positive tests, one wonders what this additional step is doing to gastro-oesophageal functional integrity. Instillation of this volume of acid into the stomach certainly inhibits release from the gastric antrum of hormones such as gastrin and enhances release of others, e.g. gastric inhibitory peptide. These and perhaps other as yet unnamed hormones, may have profound effects on lower oesophageal sphincter function.

This procedure has been accused of being too sensitive, in that using this technique, the oesophageal pH in healthy persons was found to be below the accepted "normal" values in a variety of circumstances. The proponents of the test would describe these persons as asymptomatic refluxers. Recently, Cohen and coworkers, produced data which suggests that all symptomatic refluxers have a positive test in the basal state or after instillation of low volumes of acid (120 ± 29.1 mls.), while asymptomatic individuals with low LES pressures refluxed after higher volumes of acid (333.3 ± 40.8 mls.) and asymptomatic individuals with normal LES pressures did not reflux even after 500 ml. of acid had been

added to their gastric reservoir (Ahtaridis, 1979).

The use of prolonged pH monitoring indicates that "physiologic" reflux, i.e. pH reflux occurring predominantly after meals, (Atkinson, et al. 1977) is brief being rapidly cleared by either primary or secondary oesophageal peristalsis (Johnson, et al. 1974, Dodds, et al. 1979).

A display of 4 studies using this test is found below:

Author	Tuttle (1960)			Benz (1972)			Behar (1976)			Stanciu (1977)		
Test Result	+	-	T	+	-	T	+	-	T	+	-	T
Symptoms	79	2	81	29	0	29	70	7	77	96	12	108
No Symptoms	3	40	43	3	18	21	2	18	20	7	16	23
	82	42	124	32	18	50	72	25	97	103	28	131
A →	79/81 = 98%			29/29 = 100%			70/77 = 91%			96/108 = 89%		
B →	40/43 = 93%			18/21 = 86%			18/20 = 90%			16/ 23 = 70%		
C →	3/82 = 4%			3/32 = 9%			2/72 = 3%			7/103 = 7%		
D →	2/42 = 5%			0/18 = 0%			7/25 = 28%			12/ 28 = 43%		

A = Positivity in symptomatic patients
B = Negativity in asymptomatic patients
C = False positive rate
D = False negative rate
T = Total

It is difficult to talk of sensitivity, specificity and predictive value of this test since we don't know what is "health" or disease in this setting (Galen & Gambino, 1975). If we consider the presence of symptoms "free of disease" the sensitivity of this test varied from 89-100%

Likewise in these terms the specificity of the test varied from 70-93%. The test was accompanied by a low "false positive" rate (3 - 9%) in these studies. However there was a wide variation in the values obtained in asymptomatic patients. The "false negative" rate was quite variable.

All these studies have been done by investigators with good reputations in this field. Considering the potential technical problems with the instrument these values are perhaps not surprising. Can we combine these results from the 4 studies to produce a summary statement to indicate the value of this test? Using the Mantel-Haenszel approach to pooling data (Fleiss, 1973) we can calculate a mean odds ratio of 74, an overall χ^2 of 232.34 on 4 df (<0.001), a χ^2 homogeniety of 29.61 on 3 df, and a χ^2 for association of 202.73 on 1 df. These results indicate a between centre variation (on inspection of the data it appears to be coming mainly from the work of Stanciu, et al. 1977). Thus it seems unwise to attempt to combine the data. Nevertheless, the trend is the same for all studies - symptomatic individuals have a positive test, asymptomatic individuals on a whole have a negatjve test.

Since this test has been used as the benchmark for reflux in many studies it is not known whether the asymptomatic individuals with positive tests are asymptomatic refluxers or whether the false positive rate for this test is up to 10%. The failure to produce a positive test in 0-43% of symptomatic patients may be due to the fact that reflux is intermittent. This explanation is supported by studies using prolonged pH monitoring (Johnson, et al. 1974, Atkinson, et al. 1977).

If smaller volumes of acid were added to the stomach, the number of "false positive" tests ought to diminish but likewise the number of

"False Negatives" ought to increase.

Summary

This test gives satisfactory service in the hands of several recognized gastroenterological units. However, the fragility of this expensive instrument, technical problems with reproducibility and its lack of ready availability limits the usefulness of this test in clinical practice. It will not be used as a measure of reflux in the proposed intervention study.

2.3.2 Radiological Demonstration of Reflux

(i) *The Barium Oesophagram* (Swallow) has traditionally been one of the first methods used to demonstrate gastro-oesophageal reflux. A readily available technique, its main value is in demonstrating anatomical phenomena such as hiatus herniae (if one is interested in such things) and oesophageal lesions such as strictures and carcinomas. Many radiologists have developed their own different methods to demonstrate reflux (Dyer, et al. 1968). These include variations in viscosity of barium used and in the enthusiasm with which provocative manoeuvres are undertaken. It is a relatively insensitive and poorly standardized procedure for demonstrating reflux producing a diagnosis in 10-15% of patients with clinical symptoms of reflux (Pope, 1972). This paper gives no data on which to base this statement. However in fairness to the author this article is a review for a general audience. Thus this test does not play a major role in demonstrating gastro-oesophageal reflux.

(ii) *Cine-oesophagography* has the attraction of producing a record of the entire examination which is then available for review at any time. However the equipment is not universally available and the amount of radiation exposure to the patient is in the order of > 2000 millirads, an amount of concern if other procedures with exposure to lower radiation doses can be of value. This procedure detects reflux in only a small number of symptomatic patients (Battle, et al. 1973). The data from this article may be displayed as follows:

	Cineradiography		
	Reflux Detected	Reflux Not Detected	Total
Patients with Heartburn	12	114	128
Asymptomatic Controls	0	24	24
	12	138	152

Thus in accord with the way I have been using the terms in this manuscript (see section on pH profile)

Sensitivity = 12/128 = 9%

Specificity = 24/ 24 = 100%

Even among the group with endoscopic evidence of oesophagitis the sensitivity of the test was still low being T2/89 = 14%. Clearly this is not a valuable test for detecting gastro-oesophageal reflux.

2.3.3 Gastro-Oesophageal Scintiscanning

Scintiscanning is the newest procedure in the field and looks a very promising diagnostic technique to be added to the armamentarium, aimed at detecting gastro-oesophageal reflux (Fisher, et al. 1976). The test can be used qualitatively to detect reflux if the oesophagus is visualized in any of the serial scintiscans. It is a sensitive and direct method of detecting reflux. It is claimed to also be a method of *quantitating* the degree of reflux. In fact, it measures not only reflux but a combination of reflux and oesophageal clearance. Another advantage to the patient is the low exposure to irradiation (about 20 millirads.) In the original paper describing this test a *positive* reflux index (described as the level of reflux at which visualization of the oesophagus occurs) was found when (oesophageal counts - oesophageal background/maximal gastric counts) exceeded 4%.

While several units are currently evaluating this test, only one has published figures on its use (Fisher, et al. 1976). In that study 30 patients with heartburn and a *positive acid reflux test* were compared with 20 asymptomatic normals. The test showed a high positivity rate (sensitivity) in patients with symptoms - 90% (27/30) - a high negativity (specificity) in asymptomatic subjects - 90% (28/30) and a low false positive rate - 7% (2/29). This test is technically easy and the equipment needed for its performance is available in the 5 institutions participating in the study. Its reproducibility and interpreter variability will be extensively tested during the pilot study preceding the trial. Currently it is proposed to use it as the direct measure of the presence of reflux.

2.4 Methods of Assessing the Effects of Reflux on the Oesophageal Mucosa

2.4.1 Upper Gastro-intestinal Endoscopic Examination of the Oesophagus

Since the advent of flexible fiberoptic endoscopy, the endoscopic diagnosis of oesophagitis has become increasingly popular. The endoscopic criteria for oesophagitis (Battle, 1973; Kobayashi, 1974) can be found in the details of investigations - section A of the appendix. Difficulties in using this investigation as an outcome event arise since patients with symptomatic reflux may have a normal appearing mucosa (Ismail-Beigi, et al. 1970). Likewise the "early" changes (Grade 1) of endoscopic oesophagitis (see Appendix A) have also been found in normal people (Brunnen, 1969).

That this technique identifies mucosal changes not specific to reflux is emphasised by descriptions of the more severe changes (Grades 2 and 3, see Appendix A) in the oesophageal mucosa of patients with duodenal ulcer (Winkelstein, 1957), vomiting and stress ulcer syndrome (Skillman, et al. 1972), and after naso-gastric intubation (Moersch, et al. 1959). Many of these patients did not have symptoms consistent with gastro-oesophageal reflux. The literature abounds with the controversy of the value or lack of such endoscopic evaluation of the oesophageal mucosa seeking the results of reflux.

The main use of endoscopy in this study will be to seek evidence of gastric or duodenal ulcers - the finding of these will exclude the patient from the study - and to obtain biopsy samples for histological examination.

2.4.2 Study of Histological Changes in Oesophageal Biopsy Specimens

There is no obvious disagreement over the diagnosis of "oesophagitis" - evidence of inflammation in the oesophageal mucosa - in patients who have oesophageal erosions, superficial or deep ulceration. However, there is controversy over the histological counterpart of vascular dilatation (the generalized pink flush to the mucosa described by some endoscopists as mild endoscopic oesophagitis and believed by others to be a variant of normal).

Pope and his associates (Ismail-Beigi, et al. 1970) introduced the concept that histological examination of *suction biopsy* samples of oesophageal mucosa could be used to identify changes, namely (a) basal cell hyperplasia of the squamous epithelium and (b) location of the papillae close to the epithelial surface, which were the histological consequences of gastro-oesophgeal reflux. A display of their findings and that of another recent study by Behar (1975[1] and 1976) are shown on the next page. These appear to be carefully performed studies. Ismail-Beigi, et al. used three "blinded" pathologists to read the biopsies with 80% initial agreement and 100% after review and discussion. This latter manoeuvre was carried out prior to breaking the code on the biopsies. All symptomatic patients had reflux demonstrated by pH profile test. None of the asymptomatic controls had a positive pH reflux test.

The 77 symptomatic patients studied by Behar, et al. were males with heartburn of at least 2 years duration. Only one pathologist read the biopsies, we don't know if the samples were coded. The 20 asymptomatic controls were age matched normal subjects without any

Author	Ismail-Beigi (1970)			Behar (1975[1] and 1976)		
Test	Histological Examination of Oesophagus					
Result	+	-	Total	+	-	Total
Symptoms	28	5	33	73	4	77
No Symptoms	2	19	21	2	18	20
	30	24	54	75	21	97
Sensitivity	28/33 = 85%			73/77 = 95%		
Specificity	19/21 = 91%			18/20 = 90%		
Pos. Predictive Value	28/30 = 93%			73/75 = 97%		
Neg. Predictive Value	19/24 = 79%			18/21 = 86%		

gastrointestinal symptoms.

Because of the differences in selection of subjects, it does not seem right to combine the data from these two studies. However, the trend is the same in each study and despite the differences in prevalence of symptoms (40% versus 20%) the predictive value of a positive test is similar in each.

However, a recent publication (Seefeld, et al. 1977) was unable to confirm these results in that these histological changes were not found in patients with demonstrable reflux. In a further publication Weinstein, et al. (1975) have demonstrated these findings in biopsy samples taken from this same site (2 cms above the lower oesophageal sphincter) in 57% of the biopsies from 19 "normal" controls.

Weinstein included controls who had experienced heartburn previously and who had also positive acid perfusion tests. Unfortunately none of the patients in Weinstein's group had an objective assess-

ment of oesophageal reflux performed and thus cannot be exactly compared with the "normal" controls in Ismail-Beigi's or Behar's study. In the 14 normals who had a negative acid perfusion test, 27 of 70 biopsies, (41%), had these histological changes observed.

Finally, in a study of 100 patients with established reflux - quantitated by 24-hour pH monitoring (Johnson, et al. 1978) - the authors found a significant correlation between papillary length and percent of time that the oesophageal pH was less than 4. However, the correlation was not high (r = 0.33) and the procedure used for taking biopsies in this study was not the suction technique (used in the 3 other studies). Thus these results cannot be directly compared with the previous studies of Ismail-Beigi and of Behar.

Where therefore does the situation stand with regard to the histological assessment of reflux? The short answer is still in confusion. The differences in results in these studies may well be explained by other factors not analysed such as alcohol and tobacco (Johnson, et al. 1975) consumption both of which may influence the histological appearance of the oesophageal mucosa. The site from which the biopsies were taken may also be important. The changes at 3-8 cms. above the sphincter zone may have better discriminating power to separate refluxers and normals than those closer to the lower oesophageal sphincter. Also the criteria for the technique of morphometric analysis is likely to have varied greatly from study to study

2.4.3 Acid Perfusion Test

Bernstein and Baker's (1958) description of the ability to

reproduce retrosternal heartburn in patients with endoscopic evidence of oesophagitis by perfusion of the oesophagus with acid afforded a technique to improve the understanding of oesophageal pain. That the oesophageal mucosa was sensitive to a variety of stimuli had been described at least 25 years previously by balloon distension of the lower oesophagus (Pollard, et al. 1931).

This test has been applied in many studies and has been recognized as of value by some (Benz, 1972) and is downgraded as non-specific by others (de Moraes-Filho, 1974). A comparative display of some of the results is seen below.

Author	Tuttle 1960			Benz 1972			Behar 1976		
Test	Acid Perfusion Test								
Result	+	-		+	-		+	-	
Symptoms +	66	15	81	29	0	29	68	9	77
Symptoms -	0	43	43	3	18	21	3	17	20
	66	58	124	32	18	50	71	26	97
Sensitivity	66/81 = 82%			29/29 = 100%			68/77 = 88%		
Specificity	43/43 = 100%			18/21 = 86%			17/20 = 85%		
Pos. Predictive Value	66/66 = 100%			29/32 = 91%			68/71 = 96%		
Neg. Predictive Value	43/58 = 74%			18/18 = 100%			17/26 = 65%		

Thus in all these studies the sensitivity and specificity are reasonably high but variable. However, again the worry about "false" positive and "false" negative tests arises. All groups appeared to have performed the tests the same way; none did observer variation

studies to estimate what effect this might have on the values obtained.

I have combined these results using the Mantel-Haenszel technique (Fleiss, 1973). This analysis reveals an overall chi-square of 154.76 on 3 degrees of freedom ($p < 0.001$) with a chi-square for homogeneity of 0.422 on 2 degrees of freedom ($p > 0.1$). As the chi-square for homogeneity is non significant, the differences in the proportions of positive tests between symptomatic and asymptomatic individuals appears to be consistent across the three studies. The value for the chi-square for testing this association is 154.34 on 1 degree of freedom ($p < 0.001$). From this, I conclude that symptomatic individuals respond markedly and significantly differently from asymptomatic individuals on this test. The summary estimate of the odds ratio is 158. Some of the "false" negative tests may be due to recent intensive antacid therapy (Tuttle, 1960). The "false" positives illustrate that this is a test for the reproduction of oesophageal pain, not of reflux. De Moraes-Filho argued that the pain comes from acid contact with the gastric mucosa since he was able to obtain a positive test in 15 of 36 patients with duodenal ulcer - 13 of these were from among 22 patients with histological or endoscopic evidence of oesophagitis. Irrespective of the exact mechanism of the pain and the prevalence of oesophageal reflux in patients with duodenal ulcer, confusion concerning potentially "false" positive responders due to ulcer disease can usually be resolved. Such patients can be excluded from this group by the performance of an upper gastro-intestinal tract endoscopy.

2.4.4 Discussion of Investigative Tests

How then does one utilize these investigations to aid in the delineation of this disorder?

Since the diagnostic significance of a single abnormal result is not clear, it seems logical to use several investigations to attempt to clarify the situation. Only one investigator (Behar, et al. 1976) appears to have looked at this situation. The same 77 patients and 20 age matched asymptomatic controls had, among other tests, a pH profile, an acid perfusion study and morphological examination of oesophageal biopsies. The sequence in which the tests were done was not mentioned but he interpreted them in parallel (Galen & Gambino, 1975).

If, as stated in the discussion on the section on pH profile, we consider all the patients with chronic symptoms as representing the disease state and those asymptomatic controls as representing health, we can assess the value of a combination of tests used in the study. From the previous sections we have observed in the paper of Behar, et al. 1976, the following results:-

pH profile across the gastro-oesophageal junction

Sensitivity = 70/77 = 91%

Specificity = 18/20 = 90%

Positive predictive value = 70/72 = 97%

Negative predictive value = 18/25 = 72%

Acid perfusion test

Sensitivity = 68/77 = 88%

Specificity = 17/20 = 85%

Positive predictive value = 68/71 - 96%

Negative predictive value = 17/26 = 65%

Histological "Abnormalities" in oesophageal mucosa

Sensitivity = 73/77 = 95%

Specificity = 18/20 = 90%

Positive predictive value = 73/75 = 97%

Negative predictive value = 18/22 = 86%

If we now look at any two tests in parallel but accepting an outcome as positive only if *both* tests are positive - not if either is positive (Galen & Gambino, 1975) - we find that for: -

i) The combination of pH reflux and acid perfusion we observe that the

Sensitivity = 67/77 = 87%

Specificity = 19/20 = 95%

Positive predictive value = 67/68 = 99%

Negative predictive value = 19/29 = 66%

ii) The combination of pH reflux and oesophageal histology we observe the following:-

Sensitivity = 69/77 = 90%

Specificity = 20/20 = 100%

Positive predictive value = 69/69 = 100%

Negative predictive value = 20/28 = 71%

Thus for a loss of sensitivity we have gained in specificity and positive predictive value. Note: had we accepted either test as positive in the combination testing to mean a positive result, we would have lost both in specificity and positive predictive value as

compared to single testing.

It can be seen, therefore, that at least in this study where the prevalence of symptoms was 77% the use of a combination of tests analyzed in parallel is of more value in separating symptomatic refluxers from asymptomatic individuals. In the examples given in this section the prevalence of symptomatic patients was usually around 50% or greater. Lower prevalence rates would obviously reduce the positive predictive values of individual tests. However in the study proposed the prevalence of patients with symptomatic reflux should be very high. Those tests will not be used to diagnose reflux but to confirm its presence and quantitate its effects.

Likewise, Behar also examined these tests in several other groups likely to be seen in a gastroenterology clinic namely chest pain of indeterminant cause associated with minor abnormalities of oesophageal mobility function (11 patients) as well as 14 with duodenal ulcer. None of these patients had the symptoms of reflux. The results are summarized in the following table.

	pH Profile +	Acid Perfusion +	Histology +
Chronic Chest Pain (11)	2 (18%)	11 (100%)	3 (27%)
Duodenal Ulcer (14)	5 (36%)	5 (36%)	6 (43%)

These data indicate: (a) that it is foolish to rely on one positive test to confirm a diagnosis of symptomatic gastro-oesophageal reflux, (b) if more than one of these tests is used, the results should be

interpreted in parallel requiring more than one positive test to be present to enhance specificity and (c) to use other procedures such as an oesophageal manometry study and upper gastrointestinal endoscopy to rule out disorders that may have similar symptoms to patients with symptomatic gastro-oesophageal reflux.

2.5 What Does the Patient Who Develops Symptomatic Reflux Experience and What is Available For His Treatment?

2.5.1 Clinical Manifestations

The major clinical manifestiations of reflux are heartburn and regurgitation (these and other terms are defined in the next chapter). Dysphagia may occur *intermittantly* associated with these symptoms or persistently associated with distal oesophageal stricture formation. Less common important problems include odynophagia, iron-deficiency anemia due to occult blood loss from the damaged oesophageal mucosa, and massive haemorrhage secondary to oesophagitis. The intensity of the symptoms may not correlate with the volume of reflux, the size of any associated hiatal hernia or the severity of endoscopic or histological changes in the mucosa. The more severe symptoms tend to be associated with longer contact time between the destructive elements of the refluxed material and the sensitive mucosa (Booth, et al. 1968, Johnson, et al. 1974). This may be reflected by more frequent reflux episodes and prolonged acid clearance times.

2.5.2 Medical Therapy

The principles of therapy might be discussed under a variety of

headings:

2.5.2.1 Decrease gastro-oesophageal pressure gradient. (Rationale is to use gravity or hydrostatic pressure to diminish this gradient). Clinical experience suggests that weight reduction in the obese is often successful in decreasing symptoms (Nebel, et al. 1972). It is noted that the weight loss in obese non-refluxers is associated with a fall in intragastric pressure and a rise in lower oesophageal sphincter pressure (Orlando, et al. 1979). Likewise in symptomatic patients nocturnal reflux as assessed by pH monitoring, has been shown to be reduced by elevating the head of the bed on blocks in patients with reflux (Johnson, et al. 1974). In addition most patients are advised to avoid wearing tight clothing, to minimize bending at the waist and straining to lift heavy objects. Although patients have reported symptomatic improvement with these manoeuvres, I am unable to find in the literature any experimental studies to support the merit of these procedures.

2.5.2.2 Neutralize acid or decrease acid secretion.

Dietary advice is often given to reduce spicy foods and ingest small, regular bland feedings. I am unable to find any documented evidence to support the concept that this has an effect on acid secretion.

Antacids are used predominantly for symptom relief. In fact they have a documented dual mode of action in that they buffer acid and in addition increase LES pressure (Castell, et al. 1971). Thus resist-

ance to gastro-oesophageal reflux is increased and the quantity of reflux should diminish.

Despite this evidence of an effect on the lower oesophageal sphincter, a recent study suggests that antacids are no better than placebo in achieving relief of heartburn (Meyer, et al. 1979). This study is currently in abstract form only. There are insufficient details so far published to allow an adequate methodological critique to be performed.

Recently *Cimetidine*, a Histamine antagonist, which has been shown to markedly reduce acid secretion, has been documented in a multi-centre trial to effectively reduce heartburn, the major symptom of gastro-oesophageal reflux. It was more effective than placebo and associated with less antacid use (Behar, et al. 1978).

This study involved 5 centres and 94 patients. Each patient received over an 8 week period 1200 mg daily of cimetidine (49 patients) or an equivalent number of placebo tablets (45 patients). Seventy percent of the patients had experienced heartburn for over 1 year. Compliance described as at least 75% of medication being consumed (as judged by pill count of returned containers) was excellent. Only 1 patient failed to reach this standard.

Heartburn severity (as judged by asking the patient to place a mark across a line anchored at one end by the words *none* and by *excruciating* at the other) was significantly reduced in both groups at the 8 week period as compared to the pretreatment levels ($p < 0.05$). However the improvement in the cimetidine group was greater than that in the placebo treated patients ($p < 0.05$).. No actual numbers are

quoted in the text but inspection of the graph indicates that, on average, the placebo treated patients' heartburn severity fell *to 65%* of their baseline levels. The cimetidine treated group had a fall in their mean heartburn severity *to 50%* of their baseline values. The frequency of episodes was also decreased in both groups with the cimetidine effect being greater than that of the placebo. The percentage of patients achieving the pain free state during the day was around 20-30% but was not different between the 2 groups. The placebo had a similar effect to this on night time heartburn episodes. However cimetidine therapy achieved a 70% pain free rate in this category ($p < 0.05$).

This seems to be, on a whole, a well designed and executed study. The randomization procedure appears to have delivered comparable groups of patients into each of the 2 treatment regimens with regard to age, sex, duration of symptoms and source of referral. The assessors and patients alike were "blinded" as to the medication used. Data from the 10 patients who were withdrawn from the study (6 on placebo, 4 on cimetidine) were analysed for the period of the study that they completed. The 1 non-compliant subject (on placebo) was dropped and his results were not analyzed. Although one might not agree with such action the exclusion of this patient is unlikely to have influenced the conclusions reached.

However, there are some other criticisms of the study. The method of assessing symptoms while standardized, may have been difficult for people unused to a mathematical approach to making judgements. We are not given any data concerning the variation between patients in

their use of this scale (only mean values can be estimated by eyeballing the figures in the publication). The use of the word "excruciating" may have caused many patients to avoid the severe end of the scale: - the plotted pretreatment mean is around the 48/100 mark. Since pre-therapy antacid use was estimated only and consumption during the trial measured the marked fall in antacid use initially may be an overestimation of the truth. However during the trial the placebo treated group consistently consumed significantly more antacid ($p < 0.05$) than the patients on cimetidine implying a greater need for symptom relief. Histological changes in the oesophageal mucosa were not assessed because inadequate number of samples arrived. This was left to the discretion of each investigator. Lack of uniformity in the biopsy technique occurred. Thus the samples which were received by the pathologist were too variable in composition to allow an adequate assessment of this measurement of the effects of reflux. We are not given any details of any non-pharmaceutical therapy that might have been used in either group.

Only one other report is available concerning the use of this drug in the treatment of reflux. Wesdorf and associates (1978) randomized 26 patients to cimetidine or placebo. The 24 patients who completed the 8 week trial showed improvement in 6 of 12 on cimetidine and 2 of 12 on placebo. The authors comment that these differences are not statistically significant but quote no levels. The Fisher exact test, I computed, gives a value of $p = 0.21$. With this small sample size they would have had trouble detecting any significant difference apart from universal success on the cimetidine. Certainly the trend is

similar to that observed by Behar, et al. 1978.

2.5.2.3 *Avoidance of agents which aggravate symptoms and reduce LES pressure* (Nebel, et al. 1972). These include:

Fatty meals (Nebel, et al. 1973), Chocolate (Babka, et al. 1973), Tobacco (Dennish, et al. 1971), Alcohol in very high doses (Hogan, et al. 1972), Anticholinergic drugs (Fisher, et al. 1977).

2.5.2.4 *Use agents which increase resistance to gastro-oesophageal reflux* or speed up transit through the stomach. These include:

Bethanecol (Farrel, et al. 1974), Antacids (Castel, et al. 1971), Alginic acid (Stanciu, et al. 1974[1]), Metoclopramide (Hollander, et al. 1978).

2.5.3 Surgical Therapy

Anti-reflux procedures are designed to increase gastro-oesophageal junction resistance to reflux. Whether the success of such operations is due to improved lower oesophageal sphincter pressure alone or to altered mechanical factors or to a combination of both is controversial (Fisher, et al. 1977, 1978, Edwards, 1978). Allison (1951) described an operation to correct hiatus herniae, believed then to be the cause of reflux. He surmized that heartburn was due to reflux of gastric contents into the oesophagus and that oesophagitis was a consequence of reflux. Although his operation was believed to prevent reflux, it had a relatively high failure rate with a return of symptoms in about 20% of patients (Allison, 1973). This was a popular operation throughout the 1950's and early 1960's (Woodward, 1978). Following Allison's pioneering efforts, the currently utilized operations (the Nissen fundoplication, the Hill gastropexy and the Belsey Mark IV),

which are described and illustrated in the Appendix, were introduced to the surgical scene. Reported operative mortality is low (0-1%) and the usually reported recurrence rates after these procedures vary from 0-12% in the published literature (Woodward, 1978). Nevertheless, there are a variety of symptoms which have been described to follow these operations. Perhaps the most troublesome of these has been named "the gas bloat syndrome". It consists of an inability to vomit or eructate air, often in the face of abdominal distension. This is believed to occur in about 50% of patients post operatively and may still be present in about 20% by the end of 1 year. (Woodward, 1978).

Very few comparative studies have been applied to these procedures. Most surgeons are unable to emulate the superb results of the operations originators and their proteges.

DeMeester and associates (1974) compared the 3 anti-reflux procedures in a prospective randomized fashion. They operated on 15 patients in each group whose symptoms were unresponsive to medical therapy. All had a positive acid reflux rest. The results are tabulated on the following page. These assessments were done by the surgical unit which performed the surgery (there is no mention of independent assessment). They appear to be carefully done but are difficult to compare with retrospectively collected figures which make up the overwhelming number of reports in the published literature. In this article the Nissen procedure gave the best results for symptom relief. It will be used as the operation of choice in the intervention trial details of which appear in Chapter 3.

The only published control trial of surgical versus medical

Procedure	Nissen	Belsey	Hill
Number of Patients	15	15	15
Heartburn Relief	100%	60%	80%
* Complications:			
unable to vomit	55%	50%	30%
unable to belch	15%	15%	7%
abdominal distension	15%	20%	27%
excessive flatus	100%	100%	100%
diarrhoea	38%	13%	50%
Average Hospital Stay (Days)	12	20	12

therapy was performed by Behar and his colleagues (1975)[2]. In this study 31 patients in a Veterans Administration hospital were randomized to surgical (15) or medical (16) therapy. Surgery was either the Belsey (10) or the Hill (5) procedure. Medical therapy consisted of antacids, elevation of the head of the bed, bland diet and weight reduction. In addition they all had a positive pH profile, a positive acid perfusion test, positive histological changes on oesophageal mucosal biopsies and a dimished lower oesophageal sphincter pressure. Eighty-four percent had an abnormal oesophagoscopy. Thus they were all at the *severe* end of the oesophagitis spectrum.

Eleven of the surgical patients obtained symptom relief. Four

* Note percentages are used since not every patient was checked for each complication. Wound complications were not recorded. Other problems included some dysphagia with each procedure, pneumonia and pleurisy (Belsey) perforation of the oesophagus (Nissen) decreased gastric motility with bezoar formation (Hill), arterial injury to the coeliac axis (Hill).

of these traded that symptom for *dysphagia* or *abdominal distension* and *pain*. *Only* 3 of the medically treated patients experienced symptom relief with 4 more showing improvement. There are many difficulties in evaluating this study from the published account. The patient sample description remains incomplete. We know that they are all U.S. male veterans with a 13% alcoholism rate whose heartburn was of at least 2 years duration. We don't know if their alcoholism was successfully treated or not. Likewise, we do not know about their smoking habits, nor about frequency of symptoms. We are told that heartburn was severe but are given no description of its severity. We do not know how many patients were overweight and who lost weight. We know nothing about compliance with therapy. The symptomatic evaluation was done by 1 interviewer who was aware of the patient's treatment group. We do not know how the sample size was calculated, the end points selected or the criteria for success determined. The study was performed prior to cimetidine became available.

2.5.3.1 Summary

This study may have been influenced by bias in the application of the measurement technique. If this is not so, we can state that surgery is superior to standard medical therapy in terms of effectiveness in U.S. veterans with severe oesophagitis. It leaves unanswered whether less severe forms of oesophagitis in non-veteran males or females would respond similarly.

Chapter III

The Intervention Study

3.1 Criteria and Definitions

Criteria and definitions are required in order to (i) achieve consistency among the investigators involved in the trial and (ii) ensure satisfactory communication with clinicians who may wish to apply in their practices knowledge gained during this study. The definitions of clinical states and criteria must at times be arbitrarily selected for the purpose of this study.

3.1.1 Terms Used to Describe Reflux

Gastro-oesophageal reflux - the retrograde flow of gastric contents into the oesophagus. As mentioned in Chapters 1 and 2, this phenomenon may be asymptomatic.

Objective evidence of gastro-oesophageal reflux - for the purpose of this study this will be taken as demonstration of retograde flow of gastric contents labelled with a radio-isotope into the oesophagus as detected by the *scintiscan*. In some of the articles mentioned in the literature review (Chapter 2) the pH profile across the lower oesophagus, barium reflux on cine-radiography of the oesophagus or of an oesophagram have been used to define this state.

Clinically significant gastro-oesophageal reflux - for the purposes of this study this is defined as the symptom of *heartburn*

(which may or may not be accompanied by other associated symptoms) in a patient who is demonstrated to have *objective evidence of gastro-oesophageal reflux* as defined in section 3.1.1.

"Physiological reflux - gastro-oesophageal reflux in an asymptomatic individual. Studies using pH probe prolonged monitoring indicate that this occurs after the act of swallowing associated with inappropriate relaxation of the lower oesophageal sphincter. It is infrequent and transient occurring in relationship to meals or arousal from sleep. It has not been recorded during EEG monitored sleeping.

" Pathological" reflux - gastro-oesophageal reflux which is associated with the symptoms of heartburn and/or regurgitation.

3.1.2 Terms Used in Relationship to Investigations and Operations

"Known to have the disease" - it is often difficult to know what this term implies. In this manuscript, this term will be used to identify patients with the symptoms of reflux. In this study, it will imply heartburn of at least 1 years duration.

Sensitivity of an investigation (Positivity in disease) - the percentage of true positive results obtained when the test is applied to patients known to have the disease.

Specificity of an investigation (Negativity in health) - the percentage of true negative results obtained when the test is applied to subjects known to be free of the disease in question.

False positive result - a positive result occurring in a subject who is known to be free of the disease in question.

False negative result - a test result that is negative in a

patient who is known to have the disease

Predictive value of a positive test - the percentage of positive results that are true positives when the test is applied to a population containing both healthy and diseased subjects.

Anti-reflux surgery - surgical procedures aimed at preventing gastro-oesophageal reflux by reinforcement and restoration of the lower oesophageal sphincter function. In this study the "fundoplication" of Nissen will be used as the anti-reflux procedure of choice. The major thrust of this procedure appears to be the production of a reinforced intra-abdominal segment of the lower oesophagus which is more effectively compressed when intra-gastric pressure rises. If consensus cannot be reached on using the Nissen procedure, either the dissenting surgeon will not be included in the study or if the majority of surgeons have difficulty in accepting that this procedure must be used in *all* cases, an escape clause will be inserted allowing the Hill procedure in circumstances where the Nissen is considered technically inappropriate.

Gastric surgery - the occurence of *abdominal surgery* at which part or all of the patient's stomach was resected and/or an incision made through the pylorus and/or a perforation of the stomach or duodenum oversewn.

Vagotomy - an operative procedure at which the path of the vagus nerve from the proximal end of the oesophagus to the distal enf of the pylorus was interrupted by surgical resection of a segment of its length. The area resected may involve the major trunks and/or minor branches of the nerve.

Criteria for "peptic" ulceration (gastric or duodenal) - the

presence of a defect (break) in the epithelial lining of the stomach (gastric ulcer) or of the duodenum (duodenal ulcer) observed at upper gastrointestinal endoscopy. These lesions are considered "superficial" (often called erosions) if the epithelial defect does not penetrate the muscularis mucosae or "chronic" if the defect penetrates the muscularis mucosae into the submucosa.

Scleroderma (Systemic sclerosis) - a disorder of connective tissue characterised by sclerosis of collagen. Its clinical manifestations include thickening of the skin such that it becomes immobile upon the underlying tissues. Of importance to this study, many such patients display reduced peristalsis of the oesophagus, demonstrated by oesophageal manometry, and/or the symptoms of gastro-oesophageal reflux.

Biliary Tract Disease - the finding of an abnormality either on a plain x-ray film of the abdomen interpreted as gall stones and/or on a cholecystographic series of films interpreted as a poorly functioning or non-functioning gall bladder with or without the presence of gall stones in the gall bladder or the duct system.

3.1.3 Criteria for "High Anaesthetic Risk"

Congestive cardiac failure - a cardio-thorac ratio on a PA chest X-ray that equals or exceeds 0.5.

Severe pulmonary disease - a pO2 value on a blood gas analysis $\leq$ 60 mmHg. The sample must be taken while the patient is breathing room air.

Severe renal disease - a blood urea nitrogen value $\geq$ 50 mg %.

Severe hepatic disease - a prothrombin time prolonged 4 seconds

over controlled values in a patient with decompensated liver disease.

Decompensated liver disease - the presence of ascites and/or oedema and/or impaired mental function (inability to construct a 5 pointed star or perform a serial 7's estimation).

3.1.4 Criteria for Description of Clinical States

Heartburn (pyrosis) - a continuous, warm, burning sensation situated behind the lower end of the sternum or deep to the anterior abdominal wall of the epigastrium. It will usually, but need not, last less than 1 hour at an episode. During this time it may, but need not, vary in intensity. It may, but need not, radiate upwards behind the sternum to the neck, jaws or arms. It may, but need not, occur within 1 hour of eating a meal, upon lying recumbent or bending over. It may, but need not, awake the sufferer from sleep. The ingestion of a liquid bolus (often antacid) in a volume of 15 mls. or more may (but need not) produce relief of this sensation within 5 minutes. It may, but need not, be accompanied by eructation of gas and/or the regurgitation of fluid into the mouth.

This sensation needs usually to be differentiated from two other disorders with high prevalence. These are:

a) *"Biliary tract pain"* - which may be defined as a continuous discomfort sufficiently severe to interfere with usual activities, located deep to the body wall in the right upper quadrant or epigastrium and lasting ≥ 2 hours. It may (but need not) radiate to the back, neck or the interscapular area. It may (but need not) be accompanied by nausea, vomiting and anorexia.

If the clinician suspects that the patient has biliary tract disease, a cholecystogram will be performed prior to the patient entering any reflux investigative work-up

"Symptomatic ischaemic heart disease" of the typical angina type - which may be described as continuous pain, discomfort, tightness, heaviness, or pressure situated deep to the anterior chest wall at the level of the lower sternum, and lasting less than 15 minutes. It typically is (but need not be) precipitated by exercise and relieved within 5 minutes by rest. It may, but need not be, radiate upwards behind the sternum to the neck jaws and arms. The key features which should alert the physician to suspect cardiac pain rather than heartburn are the quality of the pain and its relationship to exercise and rest. It should be noted that unstable angina and myocaridal infarction may occur in a patient who has experienced typical angina. In these situations the pain is longer than 15 minutes and may (but need not) be accompanied by sweating and/or nausea and/or vomiting and/or weakness and/or faintness and/or shortness of breath. Clinically features suggesting ischaemic heart disease will lead to an ECG and a cardiac consultation prior to commencing on any reflux investigative work up.

Odynophagia - painful swallowing.

Regurgitation - the retrograde appearance of bitter or sour fluid appearing in the mouth without preceding nausea (a distinguishing feature to differentiate it from vomiting). It may be bile stained.

Dysphagia - difficulty in or inability to swallow a food or fluid bolus.

Oesophagitis - for the purpose of this study this term will be

used to indicate a change in the oesophageal mucosa, in a patient with significant reflux, which fulfills the *histological* or *endoscopic* criteria as shown in the Appendix, Section A. Thus it will be used with the qualifying adjectives histologic or endoscopic. It will not be used synonymously with heartburn.

Distal oesophageal stricture - for the purposes of this study this is defined as a narrowing of the distal oesophagus such that it prevents the passage of a standard GIF-K OLYMPUS endoscope into the stomach.

3.1.5 Miscellaneous

The use of gender - in this manuscript, for the sake of simplicity:

the gender of the following individuals will be referred to as *male*: patients, clinicians, surgeons, data manager;

the gender of the following individuals will be referred to as *female*: nurses, dieticians, research associates and assistants. This is not meant to imply that individuals not of the designated gender will be excluded from participation in the study.

"Unable to find literature support for a concept" - means that a search involving standard gastrointestinal texts, index medicus and a Medline search from 1960 to 1979 was unable to locate any articles which shed enough light on the problem to adequately support the concept.

3.2 The Study Design

Among patients with symptomatic GE reflux, is anti-reflux surgery superior to optimal medical therapy in minimizing symptoms and maximizing function?

In light of this question, this chapter contains information relating to the patient involvement in this trial. The Summary Study Design Flow Diagram (see Section 3.12) summarizes a patient's progress through the steps of presentation, assessment, investigations, randomization, therapy and follow-up.

It is proposed to conduct this multi-centre trial in 5 major university teaching hospitals in the city of Melbourne (popuation: 2.7 million). The subjects to be studied will be those attending the gastroenterological clinics of these institutions, presenting with heartburn. These patients are drawn from referrals from primary care physicians in an area enclosing the whole of metropolitan Melbourne. A minority of patients will come from internists. All successive patients will be assessed for eligibility.

3.2.1 Entry Procedure

The gastroenterology registrar (of equivalent seniority to a fellow in North American medicine) will screen all referral letters to these clinics to select those who are potentially eligible. He will keep a written record in the clinic, which meets weekly, of the numbers of patients entered into the assessment and those excluded on clinical grounds. The research nurse, a member of the nursing staff specifically attached to the clinic as a research assistant for the purpose of this

study, will check weekly to see that it is updated. All patients eligible for consideration will be asked to complete the self-assessment questionnaire having had its function and method of completion explained to them by the registrar or research nurse. This form will be checked by the research nurse for completeness and then, if complete, it will be filed separately from the patient's clinic record before the patient visits one of the clinic gastroenterologists. The questionnaire, a copy of which is included in the Appendix, Section C, contains information concerning the patient's symptoms.

Next the patient is seen by a clinician involved in the study, at that centre. He takes a history and performs a physical examination. At this stage, if the clinician has any reason to doubt the diagnosis of symptomatic reflux, he will use the usual investigative procedures to rule out other disorders. For example, he may seek a cardiac consultation, may organize an ECG and/or exercise ECG if ischaemic heart disease is suspected. He may procede with an oral cholecystogram if biliary tract disease appears likely.

If at the completion of the clinical assessment, the patient is still considered eligible, the nature of the study is explained to him and the physician completes the status assessment form. The clinician ensures that all the pertinent clinical details are included on this document (see Appendix: D - Initial Clinical Assessment Form) prior to the patient leaving the clinic. While the investigative procedures are being organized, the clinic research assistant completes the demographic items on the initial clinic assessment form. At the end of each clinic, the study's chief investigator from that institution, will check the

assessment forms for completeness. The research assistant then insures that all completed documents are forwarded to the methods centre.

At this initial visit, each patient is given a diary notebook into which he will be asked to record symptoms, circumstances associated with episodes and details of medication used, including antacid consumption. The patient will be requested to fill it in daily for 2 weeks prior to each visit to the clinic. This diary will serve several functions. For the patient, it is hoped that it can be used as an aid to memory for events which will be included in the questionnaire. A randomization schedule will be set up whereby 10% of the study patients will be phoned monthly by the methods section research associate to remind them of its use and to determine if there are any problems with its completion. Later in the analysis stage, a comparison will be made between the quality of these diaries, which in any month, belonged to an owner who received a telephone reminder and those who did not.

The patient then enters the investigative work-up phase which includes a scintiscan, oesophageal manometry and acid perfusion test, and gastrointestinal endoscopy and oesophageal biopsy as detailed in Section A of the Appendix.

After each test, patients may be excluded from the study as detailed in the exclusion criteria (section 3.4). Those remaining are now eligible to be approached for informed consent (section 3.5) in order to enter the treatment phase of the study.

3.3 Entry Criteria

A patient to enter consideration for the study needs to have

suffered from heartburn for at least 1 year. These patients then have to have *objective evidence of reflux* as demonstrated by a positive scintiscan examination. In addition, they require to have an *acid sensitive oesophageal mucosal lining* as demonstrated by a positive acid perfusion test reproducing their hearburn.

3.4 Exclusions

A patient will be excluded from entry into the study if one or more of the following exists:

1. Unable or unwilling to give informed consent.
2. Not legally adults.
3. Patients confined to bed for more than 12 hours daily (i.e., in a continuous 24 hour period).
4. Other conditions causing or likely to cause problems in the interpretation of symptoms:
   - oesophageal motility disorders (as defined by manometry studies)
   - previous gastric surgery including vagotomy (as defined in section 3.1)
   - previous oesophageal surgery for reflux
   - gastric or duodenal ulcer (as defined by the findings at upper gastrointestinal endoscopy).
5. Currently requiring therapy with drugs likely to aggravate the symptoms of reflux:
   - anti-metabolite drugs, phenylbutazone, salicylates, indomethacin.

6. Comorbid conditions likely to be associated with a high "anaesthetic" risk:

- severe pulmonary, hepatic or renal disease (as defined in section 3.1)
- congestive heart failure (as defined in section 3.1).
- cancer other than skin cancer.

7. Pregnancy.

8. No objective evidence of gastro-oesophageal reflux, as determined by a negative scintiscan.

9. No evidence of an acid sensitive oesophageal mucosa, as determined by a negative acid perfusion test.

3.5 Informed Consent

Patients who are eligible for entry into the study will be approached once the inclusion and exclusion criteria are satisfied, for informed consent (a copy of the document is found in Appendix, section I). The study will be fully explained: - the uncertainty whether medical or surgical therapy is superior in the treatment of this disorder; the nature of the surgery (its non-experimental nature, its possible risks); the necessary investigations; the randomization procedure; and the follow-up process. The patient will be assured that his participation will be free of worry about the standard of care, should he choose to withdraw. Likewise any information which is obtained in the process of the study, will be held in strict confidence.

3.6 Allocation of Subjects to Treatment Groups

Patients will be stratified and allocated by randomization to groups in order to maximize the probability that the comparison between surgical and medical therapies can be made on comparable groups of patients free of selection bias.

3.6.1 Stratification Procedure

Three patient strata will be used as follows:

Stratum 1 by Centre (1-5)

Stratum 2 by age (i) less than 50 years

(ii) greater than or equal to 50 years.

Stratum 3 by Clinical Features.

i) Severe Disease. Patients will be allotted to this category if *any* of the following apply:

From the questionnaire responses (section C in Appendix)

A) Physical Incapacity - any difficulty with dressing (items 19-20)

and/or

B) Occupational or Social Incapacity

- any difficulty with doing housework (items (21-23)
- any loss of time from work (item 17)
- Heartburn that interferes *a great deal* with occupational or social function (items 12-16)

and/or

C) Severe Symptoms

- Heartburn graded as *very severe* (item 10)
- the presence of *dysphagia* and/or regurgitation (items 24,27)

From the endoscopy findings (section A in the Appendix)

D) Grade 3 or 4 Endoscopic Oesophagitis

ii) Less Severe Disease. The absence of any of the criteria which would classify the patient as having severe disease.

When the completed questionnaires are received at the Methods Centre, the Research Associate will place the patient into a Stratum as determined by: (i) the Centre where he is to receive therapy, (ii) his age and (iii) the response to the items 10, 12-16, 17, 19-20, 21-23, 24 and 27. This allocation will be checked by the Principal Clinical Investigator and then entered in the Allocation Book. The final allocation must await information from the endoscopic investigation.

3.6.2 Randomization Procedure

This will be performed by a phone call to the central methods office. The principal methods investigator or his deputy receiving the call will determine the patient's final strata allocation from the information received concerning the endoscopic findings. He will then consult the randomization schedule previously drawn up and listed in a book, and allot the therapy. This schedule will be balanced within strata every 2 or 4 patients. This sequence will be likewise determined by random allocation, i.e., whether balanced every 2 or every 4 will be organised according to a randomization schedule.

3.7 Therapy

From the inclusion criteria, it can be seen that all patients entering the trial as well as having had symptoms at least for 1 year would have had and failed to respond to conventional medical therapy. The augmented medical therapy programme will consist of continuation of this recommended conventional therapy (with attempts to determine degree of compliance) and to add an agent (Cimetidine) to reduce the acidity of the refluxate.

3.7.1 Medical Regimen

A patient randomized to the medical therapy group will receive:

A) Instructions on sleeping with *the head of his bed elevated* on 4 inch high blocks.

B) Assessment by a dietitian who will assign the patient to a dietary regimen total caloric composition of which is such that he should achieve ideal body weight (as defined by the Australian National Health and Medical Research Council standards). If the patient is already at that level his dietary allowance will be aimed at maintaining this weight. If under ideal body weight, the apparent reason will be determined (e.g. oesophageal stricture) and where possible corrected. Advice will be given not to eat for 3 hours prior to retiring to sleep.

C) Each patient will be instructed to record details of therapy used for symptom relief, during the 2 weeks prior to each visit, on the diary used for symptom enumeration.

D) *Cimetidine* will be prescribed in a dose of 1200 mgs. daily in 4 divided doses of 300 mgs. each.

E) A liquid *antacid* (Aluminum hydroxide-magnesium hydroxide) mixture will be given with instructions to take 15 mls. for relief of a specific heartburn episode. The amount consumed between visits will be quantitated by direct inspection of the previously dispensed bottles.

F) Patients will be advised to avoid anti-cholinergic agents and salicylates, but if the physicians responsible for their care so desire, other agents, such as metoclopramide and bethanecol, can be prescribed, provided that these drugs and their dosages are documented.

G) Patients will be advised not to smoke cigarettes.

3.7.2 Surgical Therapy

Patients randomized to this regimen will receive:

A) *An anti-reflux procedure* to be performed as soon as possible after the selection process. The Nissen procedure has been chosen as the operation of choice. Each surgeon is likely to want to do his favourite procedure, based either on experience related to his specialty (thoracic surgeons tend to do the Belsey procedure) or to clinical impressions based on personal recurrence rates or side effects. Thus, if consensus cannot be negotiated, it may be necessary to allow performance of the Hill procedure via an escape clause.

B) Cimetidine 1200 mg. daily in divided doses.

C) A liquid antacid mixture for symptom relief with similar instructions concerning dosage as given to the medical group patients. (see 3.7.1).

D) A diary in which to record symptoms and antacid use (see 3.7.1).

E) Should they wish to continue to sleep with the bed head elevated this will not be considered a protocol violation.

3.8 Follow Up Procedures

3.8.1 Clinic Visits

Once therapy has been commenced *all* patients will be seen every 2 weeks for the first 8 weeks. They will be instructed to bring their diaries and all unconsumed medication at each visit. The clinic research nurse will weigh each patient. Then she will measure and record the volume of antacid left and the number of cimetidine tablets remaining in the patient's medicine containers. She will then complete the necessary items on the follow-up clinical assessment form and will attempt to ensure that the patient has understood all instructions given on the questionnaire. She will check the filled in questionnaire for completeness and seal it in an envelope prior to the patient seeing his clinician. The dietitian at each follow up visit will review the patient's weight and diary contents. With this information and that obtained at interview will adjust the patient's dietary management to achieve the programme therapy goals.

A similar clinical assessment will be performed at the 3 month visit. The patient will be requested to complete a questionnaire similar to that completed at previous visits. In addition the scintiscan, endoscopy and acid perfusion tests will be repeated. The patients are seen again at 6, 9 and 12 months after initiation of therapy. The data gathered at the 12 month visit will be the same as that at the 3 month visit.

3.8.2 Compliance

Since it is important to determine whether the success or failure of a regimen is related to the use of the prescribed therapy, the following manoeuvres will be used to determine the level of compliance:

i) Pill counts at each clinic visit will be used to estimate the amount of medication consumed between visits.

ii) Patient's weight at each visit to determine the success of the weight reduction programme.

iii) Asking the patient at each visit about problems with compliance with instructions.

iv) A random check at home to perform a pill count and determine if the bed head is elevated or not.

3.9 Endpoints

This is an intervention study in which the primary and only hard endpoint, which can be measured as an event, will be the production of the *pain free state*. This is also the major clinical endpoint compatable with the research question. The sample size is calculated predominately on the estimated occurrence of this event.

Lesser degrees of improvement are considered worthwhile and also meet the study objectives. However even if heartburn is relieved, other symptoms may persist and new symptoms may occur. Thus in the analysis changes in these and in the patient's occupational, social and emotional function from pretreatment values to those determined at follow-up will be measured as clinical endpoints.

Other non-clinical endpoints include:

i) change in the volume of antacid used.

ii) change in degree of positivity of the acid perfusion test - as recorded by a prolongation of or reduction in the time of acid perfusion to produce heartburn.

iii) change in endoscopic findings.

iv) change in the amount of reflux on scintiscan.

v) change for better or worse in oesophageal biopsy findings.

The non-clinical endpoints will be assessed to determine whether symptomatic change is associated with, or unrelated to, these other measures of assessing the degree of reflux and its effects on the oesophageal mucosa. In this regard they are secondary endpoints, i.e., changes which may be able to provide explanations for alterations in the symptoms under study.

Many of the endpoints are subjective. The nature of the study is such that the clinician cannot be "blinded" as to the patient's therapy. Thus major design efforts must be made to minimize observer bias. These include the following:-

i) The symptom severity change will be judged from the patient's questionnaire responses which will not be available to the clinician. The patient will not have access to his previous replies when completing each assessment.

ii) The antacid volume consumed will be computed at the analysis stage from the data supplied on the clinical assessment form completed by the research nurse.

iii) The results of the scintiscan and the oesophageal biopsies

will be assessed under code.

iv) As outlined in Chapter 4, once a *utility value* for a particular condition is established this will be applied to each patient's data in a retrospective manner by two assessors. These people will be "blinded" as to the patients identity, his treatment group and whether the particular state being assessed is a pretherapy or post treatment situation.

3.10 Drop Outs and Withdrawals

As this is an *intervention* study where the main question relates to *effectiveness* of therapy the following guidelines for the treatment of drop outs, withdrawals and the counting of events are to be used.

A patient will be considered a drop out if lost to follow up by:

1. His disappearance with inability to be traced.
2. Refusal to continue in the study.
3. Refusal for the clinician responsible for his care to continue the patient in the study.
4. Death or serious injury preventing follow up.
5. Protocol violations such as surgery in a medically randomized patient.

A withdrawal form will be completed for all patients who drop out of the study. This withdrawal form, a copy of which is found in the Appendix, section G, will contain information concerning the date of withdrawal, the reason for withdrawal and patient's status at the time of withdrawal. Attempts will be made to keep check of all withdrawn

patients via their family doctors. Vigorous attempts will be made to get at least the self administered questionnaire completed by the patient at the time of exit from the study as well as at 3 months and 12 months, even if this requires home visits to procure such information.

On a whole, the *conservative approach* to the treatment of withdrawals will be utilized. The patient's status as determined by the questionnaire will be analyzed *in the group to which the patient was originally allotted* irrespective of whether the patient was on therapy at all or had violated the protocol and switched to the opposite group at the time of the assessment.

The data on any withdrawn patient will be scrutinized by an independent (not involved in the study) assessor to determine whether, in an individual case, there are other factors present which would suggest that the above guidelines are inappropriate for that particular case.

3.11 Discussion on Study Design

(including justification for inclusions, exclusions, investigations, etc.)

3.11.1 Inclusions

The selection of a 12 month period of symptoms is to an extent an arbitrary decision. However, it is designed to separate those with mild transient symptoms of brief duration from those with persistent problems. Indeed most patients tend to ignore initial mild symptoms for at least a year prior to diagnosis by a physician (Brunnen, et al. 1969). *Heartburn* was selected as the significant symptom of gastro-oesophageal

reflux as it is usually the earliest, most common symptom of reflux and the one which best correlates with evidence of reflux (Johnson, et al. 1974). Regurgitation and dysphagia are important but far less frequently complained of by patients with reflux. A commentary on the two investigative inclusion criteria (section 3.3) is found in sections 3.11.2 and 3.11.3.

3.11.2 Investigations

The scintiscan has been chosen as the method of choice for the *demonstration of reflux* because of its sensitivity and ease of performance. The equipment required to perform this test is available in all 5 Nuclear Medicine departments. Cineradiography is too insensitive by comparison (see section 2.3.2) and in addition has the disadvantage of exposing the patient to a higher dosage of radiation than the scintiscan. The pH profile is a time honoured method of demonstrating reflux across the gastro-oesophageal junction. However this test is technically more difficult to perform. Likewise the equipment is not available in all centres handling patients for this study. The acid perfusion test has been chosen to produce a semi-objective easily performed and standardized method of assessing the sensitivity of the oesophageal mucosa to refluxed material by *reproducing the heartburn of such patients*. Upper gastrointestinal endoscopy is required *to exclude a disorder* in the stomach or duodenum which can give *a similar symptom complex* and a positive acid perfusion test. These include gastric or duodenal ulcers. In addition, the state of the oesophageal mucosa will be assessed visually and suction biopsies will be taken. An improvement

in the histological features of oesophagitis in a mucosal biopsy from the oesophagus may well be the most sensitive indication of a response to therapy. This possibility is intuitively appealing but as yet such evidence is not unequivocally available.

3.11.3 Study Design and Sequence of Investigative Events

Following the clinical assessment, the *scintiscan* examination will be the first investigation performed. This is the least invasive procedure. *Oesophageal manometry* and the *acid perfusion study* require intubation and thus have a lower patient acceptance level but nevertheless are usually well tolerated. Motility disorders are likely to be rare in this group but should readily be determined by the manometry technique. The acid perfusion test may result in the exclusion of some individuals who have reflux symptoms. However, inclusion of only patients with a positive test should serve to make the group remaining more uniform and more clinically credible. The results can be analysed to determine whether changes in this test will correlate with changes in heartburn severity.

The *endoscopy* performed last has high patient acceptance when performed by an experienced endoscopist with the patient adequately sedated. The features found upon histological examination of the biopsy samples obtained may serve as an important objective outcome measurement to determine whether therapy influences this effect of reflux. The endoscopy is performed last because of all the procedures it carries the highest (but still small) risk of morbidity to the patient from instrumentation and biopsy. It is the most efficient way

to exclude other upper gastrointestinal tract pathology (such as ulcers and cancer) and obtain biopsies of the oesophagus at the same time.

The appeal of this sequence is that, in general, it moves from the least invasive procedure to finish with the most expensive investigation - which, although it has high patient acceptability carries the highest risk of morbidity.

Since the investigative protocol is equivalent to testing in series (Galen & Gambino, 1975) the use of 2 tests (the scintiscan and the acid perfusion test) which both need to be positive for the patient to procede, will result in a tendency to lose sensitivity at the expense of increasing specificity. All patients who make it through the sequence of clinical assessment, scintiscan, acid perfusion and motility followed by endoscopy and biopsy should be "diseased".

It should be emphasized that the major reasons for performing an investigative work up and attempting to quantitate the results of these procedures is to ensure, as best as one can, that the population of patients gathered to enter the trial has sufficient documentation of the presence of reflux and its effects that:

i) *any conclusions* drawn from the results of the study will have clinical credibility,

ii) *any physician* wishing to generalize the results of the study will be aware of the type of population to which the results refer,

iii) *any investigator* wishing to refute the study will have adequate details concerning the patient population and procedures to reproduce the research, and lastly

iv) to exclude patients who have other disorders likely to cause similar symptoms.

3.11.4 Exclusions

The rationale behind most of the exclusions relates to the importance of (i) the patient being truly able to give informed consent, (ii) avoiding additional pathology that may cause confusion in the clinical assessment at follow up, (iii) avoiding conditions that may aggravate the disorder and cause a differential response to therapy from that occurring in patients without the aggravating conditions, and (iv) avoiding conditions that posed high anaesthetic risks. Pregnancy is included because reflux is common during that state and usually remits promptly with delivery of the foetus. In addition, I believe it is unwise to expose a pregnant woman to any form of irradiation that can possibly be avoided.

3.11.5 Stratification

It is desired to stratify the patient sample prior to randomization in order to reduce the likelihood that patients with either good or bad prognostic features will fall predominately into one group or the other. If this occurred, a potential source of bias would be created which may give rise to serious problems in interpreting the results. There is very little information available in the literature to aid in this exercise.

The *centre strata* are required since patients referred to and treated at any one centre have a high likelihood of representing a

different part of the disease spectrum than those treated at any other centre.

The Age Strata are included since the more severe grades of endoscopic oesophagitis and higher complication rates appear to occur in the older age group.

The Clinical Strata. Since this trial includes patients with differing degrees of disease severity, it is desirable to stratify on clinical criteria. There are no *objective* criteria, to my knowledge, on which to make this judgement. I have elected to select symptoms which traditionally represent more severe disease - regurgitation and dysphagia - and to use the patient's responses relating to his degree of physical, occupational and social incapability to form two clinical strata. Since oesophageal stricture, Grades 3 and 4 oesophagitis seem to require more clinical attention, I have included them in the severe stratum.

3.11.6 Medical Therapy

There is a wide variety of possible items from which to make up a medical regimen. Within the standard therapy items advice to sleep with the head of the bed elevated is to be utilized since this manoeuvre, as well as being logical and supported by clinical impressions, has also been found objectively to reduce the presence of reflux at night (see section 2.5.2). The patients will be issued with a list of food items to be avoided. They have all been shown to reduce LES pressure (section 2.5.2) but none have been tested formally in a controlled study.

Advice not to eat late at night is given to lessen the impact (in terms of severity) of postural reflux which appears to be worse with a full stomach than with an empty one. Cimetidine, a histamine (H2) antagonist , has been shown in a multi-centre double blind clinical trial to be effective in the treatment of symptomatic gastro-oesophageal reflux (see section 2.5.2.). This drug is thought to be effective in this disorder because of its ability to markedly reduce acid secretion by the stomach. Cimetidine will be the cornerstone of the medical regimen. The use of antacid therapy poses a problem. Since cimetidine is being given in doses sufficiently large to reduce gastric acid secretion by approximately 85% it does not seem logical to attempt to give antacids in sufficiently high doses to produce the same effect. Since antacids will also be used by the surgical group *for symptom relief*, I propose to give both groups of patients measured amounts of antacid in liquid form with instructions to use a standard amount of it (15 ml.) for each episode of heartburn. They will be asked to record at each visit the amount used.

3.11.7 Surgical Therapy

The Nissen procedure has been selected as the operation of choice as it is currently considered the most effective anti-reflux operation (see section 2.5.3). Since all surgeons involved in this trial will be general (i.e., predominantly abdominal) surgeons, it is unlikely that they would wish to perform the Belsey procedure on any patient. Thus the Belsey operation will not be among those offered. Attempts will be made at the initial preliminary study to obtain

consensus on the operation to be used.

For a comment on the drug therapy in this group of patients, see section 3.11.8.

3.11.8 Why Select the Medical and Surgical Regimens This Way?

The use of the eligibility criterion that patients must have had symptoms for at least one year and be resistant to conventional therapy should ensure that patients with mild diseases will not be included in this study. If one then asked all patients to undergo augmented medical therapy and to fail on it prior to randomization to surgery or further augmented medical therapy, I believe that the number of subjects (a) available for randomization would be small (patients are unlikely to wish to wait the extra time), (b) who would continue in the augmented medical therapy would be extremely small. One would have asked patients who failed on augmented therapy to take a 50% chance (by randomization) of staying on the same therapy which failed.

Had the surgical group received only anti-reflux surgery and the medical group "augmented" medical therapy, the results would have reflected a "pure" comparison between the two regimens. However, in the event that anti-reflux surgery is not 100% successful in relieving heartburn, there is a high risk of protocol violation by this group of patients in an attempt to gain symptom relief. Thus the surgical group are being given both antacids and cimetidine as a pragmatic manoeuvre to avoid having to worry about this possibility. Thus we are testing the effectiveness of surgical therapy plus medical therapy over and above that of medical therapy alone.

Other drugs could have been added to the "augmented" medical regimen. However, the addition of bethanecol (an anti-cholinergic agent) and/or an alginic acid - antacid compound would, I believe, have resulted in a lower compliance rate because of the use of multiple drug therapy. In addition, alginic acid is disliked by some patients because of the need to (i) chew it thoroughly prior to swallowing, (ii) remove small particles from the teeth (or dentures) afterwards.

The regimens selected have, I believe (i) clinical credibility, (ii) a high likelihood of patient and investigator acceptance, (iii) a better chance of a good compliance rate than if multiple drug therapy were used and (iv) less risk of protocol violation than if any other regimen currently available was implemented.

3.12 Summary of Intervention Study Design

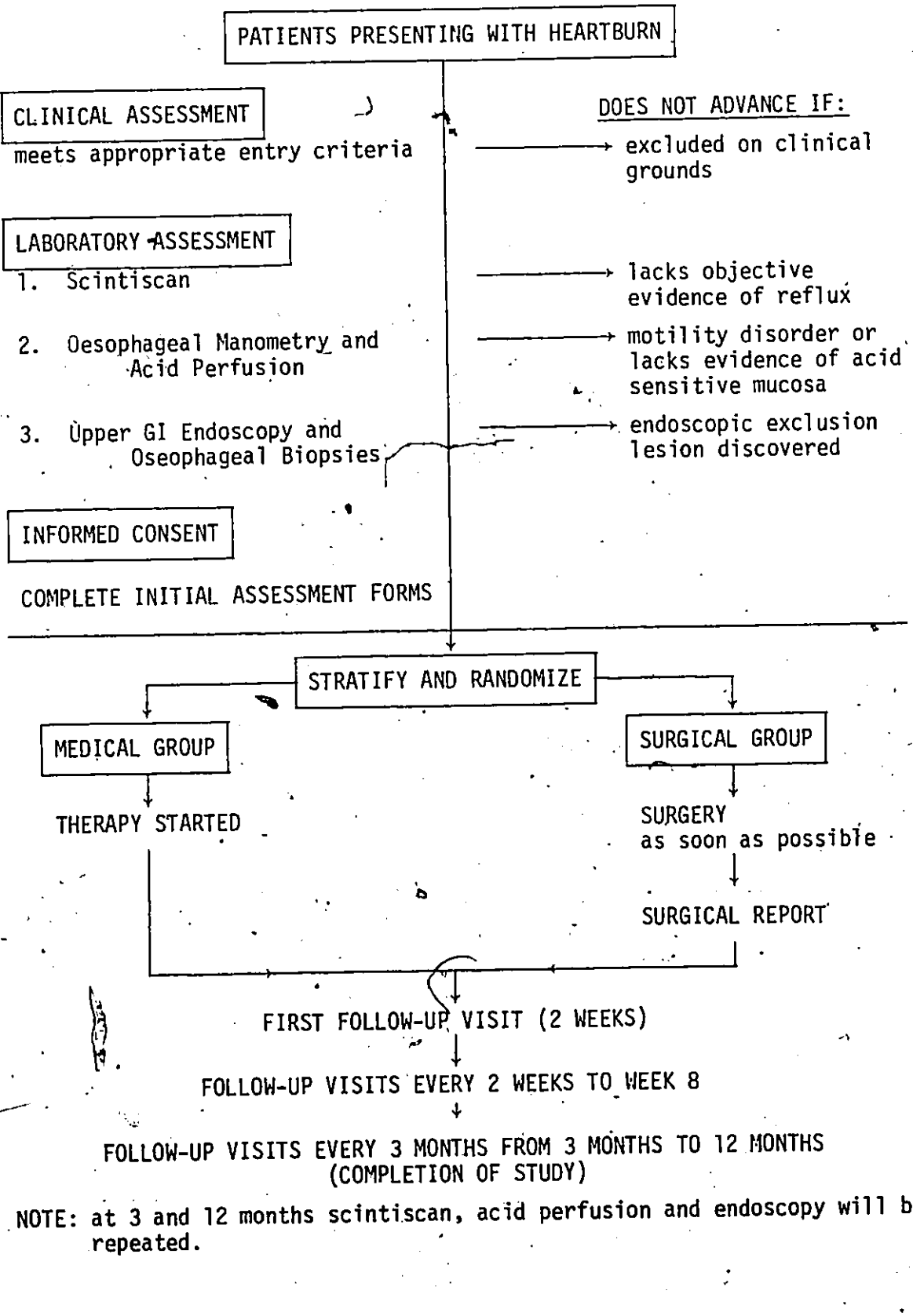
A summary of the *intervention study design* can be seen presented in a flow diagram form on the next page. The reader can trace a patient's path through the initial clinical assessment, laboratory assessment, into the study and to its completion.

3.13 Getting It All Started

3.13.1 The Feasibility Meeting

With the protocol written, the work for the study commences with a feasibility meeting involving staff from all the participating hospitals and the Methods Centre. At this meeting, the precirculated protocol will be discussed. Decisions will be made concerning its adequacy, in terms of definitions, criteria, ethics and design. If

SUMMARY STUDY DESIGN FLOW DIAGRAM



NOTE: at 3 and 12 months scintiscan, acid perfusion and endoscopy will be repeated.

agreement can be reached on these points, and centres believe that they will have sufficient numbers of patients, a further session will be organized to discuss and reach consensus on the precirculated data collection documents. During this time period the questionnaire will be assessed by both gastroenterologists and patients with heartburn for face validity and after any necessary alterations individual items on it rated (see sections 4.5.4 and 4.5.6).

3.1.3.2 Planning Meeting

Once consensus is reached on these items and the documents altered accordingly a *planning meeting* will be held to go over these forms and to discuss them with the data management staff prior to having them printed for the pilot study.

3.13.3 The Pilot Study

The Pilot Study will afford an opportunity to determine whether, among other things, the projected patient numbers from each centre are truly available. It will also be used to determine what percentage of the patients who present with heartburn and undergo the beginning of the investigative work up actually make it through the assessment process and remain eligible to enter the randomization step.

The pilot study will have two phases. The initial or *preliminary phase* will be carried out as follows:

(i) All patients attending the clinic will be eligible. Patients will not be exluded from progressing through the initial clinical and investigative work up. Patients will not be randomized to a

therapeutic group but will be followed while being treated as their clinicians direct.

(ii) The initial pretesting by sufferers of heartburn of the questionnaire will occur at this time (see section 4.5.4 and 4.5.5 for details.) The opportunity will be taken to utilize the responses on this form to extensively document the symptom status of all patients. I am particularly interested in determining at this stage, whether the majority of patients can be categorized into one of many (perhaps a dozen) "clusters" of symptoms. If so then it becomes feasible to develop a health utility status as an outcome variable. For details of this manoeuvre in the use of the questionnaire, see section 4.5.2.

(iii) *All data collection forms* will be pretested at this stage. For some this will enable the investigators an opportunity to gain familiarity with their use and slight modifications to some are anticipated at this field testing stage. For others (e.g., the self administered questionnaire) this will be the main opportunity to extensively test this instrument for reliability - by repeating its administration after a 2 week interval before therapy is instituted, to see which items stand up well to this test-retest procedure. This pretest will determine whether extensive rewording or merely minor modification of this form will be required before further use.

(iv) This pilot study will be used to pretest *all the investigative procedures* and afford an opportunity to do observer variation studies on many of them - assessors will be asked to read coded oesophageal motility tracings, scintiscan outputs and oesophageal biopsies in a "blinded fashion". Such checks will be used to determine

whether there is a need to change definitions of terms, nature of report forms, etc., on these tests as well as on the endoscopy and acid perfusion measurements. If the amount of variation from observer to observer or within observers is unacceptably large then "training" sessions will be instituted in order to attempt to reduce this source of measurement error before beginning the main study. Having made whatever modifications were found necessary to the documents and procedures - some may need to be dropped if training still leaves us with unacceptable variation in measurement techniques - a small pilot study proper can be performed.

The *pilot study proper* will test the now pretested questionnaire, the randomization step and the data management aspects of the study. During this phase observer variation studies and data collection form pretesting will continue to check if the training programmes have been effective. The data collection flow procedures from pick up through manual editing and computer processing will be checked.

Chapter IV

Data Management Considerations

4.1 Data Collection and Processing

The data collected for this study will be recorded on forms, (see Appendix, sections C, D, E and F) supplied to the participating hospitals from the central office. Separate forms shall be used for entry documentation and subsequent follow-up assessment.

The data management considerations for this study are outlined on the Data Management-Time Line Diagram (see section 4.2). This illustrates the steps that will be undertaken to co-ordinate this study under the control of the data manager. The Diagram is divided into 3 sections - the initial planning steps, the pilot study and the randomized controlled trial. At each step the personnel predominately involved are mentioned and the anticipated time span is indicated.

4.1.1 Initial Planning Stage

It can be seen that there will be a major input from a wide variety of people at this stage with designing, revising and rewarting, after consultation, will be their major activities.

4.1.2 The Pilot Study

The pilot study, the details of which appear in section 3.13, will hopefully be the training ground which will pave the way for a

successful trial. The data manager will no doubt have his biggest headaches at this time. He will need to keep closely in touch with both clinical and data handling staff during this time. He needs to become aware of problems as they arise and smoothly co-ordinate any changes needed on the run. The results of the pilot test will be extensively studied prior to settling on the documents and procedures for the actual study.

4.1.3 The Intervention Trial

The data management aspects involve the distribution of forms to each centre then the checking of these forms both at the participating centres and centrally for completeness. The data preparation and editing procedures under the supervision of the data manager, are designed to check all data for accuracy and to get it into the data base in a valid form. Errors detected at this stage will be checked against the original documents and if necessary validated or altered by contact with the participating hospital. Among the reports generated from the data base at monthly intervals will be an assessment by institution of the number of patients entered, the number followed-up, the number who missed follow-up and the number of withdrawals.

It is proposed to enter patients from the 5 centres over a 12 month period and to follow them up for another 12 months.

From the records kept by the clinic registrar (see section 3.2) it will be possible to determine at each institution: (i) the number of patients presenting with heartburn, (ii) the number of patients eligible but not randomized, and (iii) number of patients who enter therapy.

Efforts will be made to trace the outcomes of all these patients at the completion of the study. The clinic registrar will be asked also to keep a list updated every week of all anti-reflux procedures performed at his centre during the period of the study. The accuracy of this list can be checked by the research nurse against the medical records librarian's accounts of all operations. The record librarian's list is updated as each patient is discharged.

Each clinical investigator will be responsible for informing the referring physician of the entry of each patient in his hospital into a controlled clinical trial. This will be done by phone call followed by a letter (see Appendix, H). He will be responsible for securing co-operation of the referring physician to aid in achieving high compliance by the patient with his allocated therapy and follow-up examinations. Any additional therapy administered by the family physician should be reported to the clinical investigator either by the patient himself or by the referring physician.

There are potential problems with relying on the chief clinical investigator at each centre to be responsible for checking data collection documents when he himself will be entering patients. To reduce problems with this step, it can be seen that they will first be checked by a research nurse assistant. In addition, as participating centres are all in the same city, there will be regular pick ups and telephone reminders to each centre to keep co-operation going. Thus it is anticipated that the lag time between completion of forms and arrival at the central office will be relatively brief. A large responsibility will rest on the shoulders of the 3 people centrally who will be manually

checking forms. Here the forms will go from the research associate to the principal clinical investigator, to the principal methods investigator. Initialing with the date will be required at each step to indicate that the form has been checked by the appropriate person. Incomplete forms will be completed where possible by telephone check up. Only extensive lack of information will require returning of the form to the centre for completion. The monthly report will flag records still awaiting specific laboratory reports, etc.

4.2 Data Management - Time Line Diagram

4.2.1 Initial Planning Steps

	PERSONNEL*	TIME
1) Design the study protocol, including documents for data collection	PCI, DM	zero
2) Hold a feasibility meeting, to discuss and estimate: - the adequacy of the protocol - the inclusion and exclusion criteria - the investigations proposed - the ethics of the study - the projected number of cases if this meeting reaches a satisfactory conclusion, move to the:	PCI, DM clinicians (all CCIs)	
3) The data collection forms discussion meeting - the initial clinical assessment form - the patient self assessment questionnaire - the laboratory report forms - the dietitian's report form - the follow-up report forms - the consent and withdrawal forms - the surgical report forms - the coding forms	PCI, DM and computer staff	
4) Design the data management requirements - write the external reference specifications - review with the computer centre personnel - revise and rewrite	PCI, DM and computer staff	
5) Hold a planning meeting with clinical and data management personnel to: - agree on the specifics of the study including the above forms	Everyone involved RA hired	
6) Printing forms for Pilot Study		

4.2.2 Pilot Study (Preliminary Phase)

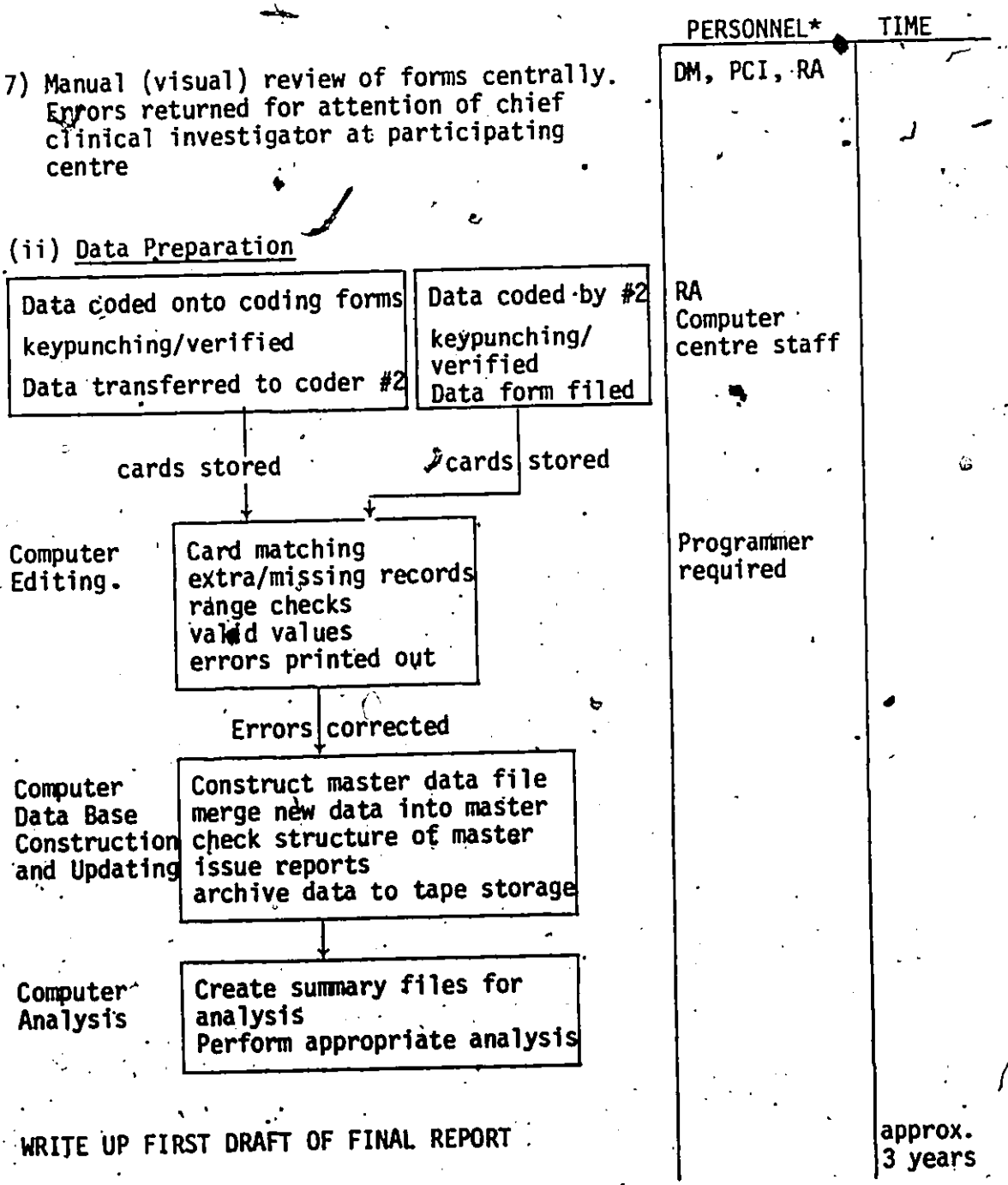
1) Pretest all procedures - do observer variation studies on these - if necessary have training studies for agreement	Clinical and data management staff	6 months

	PERSONNEL*	TIME
2) Pretest all documents - the questionnaire for suitability, timing, validity and reliability. Check it against the physician assessment, scintiscan and perfusion - the other data collection forms and coding forms	Clinical and data management staff	6 months
(Formal Phase)		
3) Test revised pretested documents and procedures		
4) Pretest data preparation and computer services - keypunching, filing, editing, data base construction, updating, report generating and archiving		
5) Revise all forms and all procedures		12-18 months
6) Have documents printed and contracts signed to start the study		

4.2.3 The Randomized Controlled Trial

(i) Data Collection Organization

1) Sent forms to participating centres	DM, RA	18 months after onset of plans
2) Data forms completed at participating centres	Clinicians Patients Research Nurse	
3) Review forms at participating centres for completeness, eligibility, etc. - corrected locally	CCI and Research Nurse at participating centre	
4) Stratification (preliminary) at Methods Centre	RA, PCI	
5) Randomization by phone call to central office		
6) Transport of all completed forms to central office		



* PCI = Principal Clinical Investigator
CCI = Chief Clinical Investigator at participating centres
DM = Data Manager (Principal Methods Investigator)
RA = Research Associate

4.3 Sample Size Requirements

4.3.1 The Basis for the Calculations of Sample Size

This is a study with a variety of outcomes of interest being assessed at several points in time. The major ones are clinical and therefore the sample size calculations will be based on these. The easiest to measure, with the least controversy, will be the attainment of the pain free state. This certainly will be the only definitive end-point. However, in addition a reduction in heartburn severity is considered a worthwhile clinical outcome and thus this also will be included in the sample size determination. Since some patients are predominately nocturnal refluxers while others have most of their problems during the day, particularly in relationship to meals, it will be necessary to assess these outcomes separately.

As indicated in section 2.5.2.2, the results published from a double blind multi-centre trial of medical therapy (Behar, et al. 1978) indicate that there is an expected reduction in average symptom severity of some 35% of the baseline levels on placebo (which included antacid for symptom relief). Medical therapy would be expected to improve this to 50% of baseline values. The pain free state (defined as absence of heartburn while on medication) was achieved *during the day* in 30% of patients on medical therapy (20% on placebo) and at night in 70% of medical therapy patients (25% on placebo).

Sample size determination to demohstrate (i) improvement in the surgical group, which is twice as good as the results expected in the medical group, for the end point of achieving the pain free state *during the daytime* and (ii) reduction in symptom severity in the surgical group

which is at least 1 1/2 times better than that achieved in the medical group have been computed for these patients presenting with heartburn. These calculations assume a similar response rate in the medical group as occurred in this published trial (Behar, et al. 1978). It is also likely that the medical rates of improvement are likely to be less after the first 8 weeks (when follow up intervals lengthen and compliance rates will likely fall) - unless continued weight reduction in the obese reduces reflux significantly - and surgical relapses will occur but at a presumed lower rate. Thus the sample size to demonstrate such a difference at 8 weeks should also be more than adequate by the end of 1 year.

The accompanying tables, 4.3.2 and 4.3.3, show the sample sizes required to show different levels of surgical benefits. The estimated level of surgical benefit is of course difficult to pin down. Surgeons rarely publish results of any procedure which is less than 85% successful and the absence of independent (blinded) assessment of the post surgical state leads to a tendancy for published figures to underestimate both recurrences and side effects.

It can be seen that to achieve twice as good a result in the surgical group in attainment of the daytime pain free state, a total of approximately 100 patients will be required. With this sample size an assessment will almost certainly not be able to be performed for night time heartburn since the medical regimen (containing cimetidine) is particularly effective in producing a favourable outcome at night. Surgery would need to result in relief of heartburn at night in virtually every patient to produce a significant margin of improvement

with this size sample. With regard to the outcome of reduction in pain severity, as perceived by the patient, a total sample size of approximately 150 will be sufficient to demonstrate a 50% improvement over medical therapy.

It is believed that this number of patients will be available for study. Since the follow-up period is to be of 12 months duration, it is important to enter as many patients as possible into the study as quickly as possible. Efforts to generate larger numbers would mean a longer period of entry (meaning that some patients would still be entering the study as the first group were completing their follow-up period). This drawing out of the entry period may well influence referral patterns to the extent of producing a form of entry bias. Of course a larger number could be entered by using more centres but this adds to organizational problems and I would anticipate reduced efficiency in data collection.

These sample size calculations indicate the number of patients for which outcomes can be assessed. Since some patients will be lost to follow-up, for a variety of reasons, it is necessary to increase the number of patients admitted to the study to compensate for this potential loss - in these calucations 15% has been added to allow for these losses.

Why Choose This Sample Size?

A 1 1/2 to 2 times better result for the surgical group in relief of heartburn or reduction in its severity is considered relevant. The magnitude of this difference has to be sufficient to allow for an expected higher level of moderately severe incapacity (due to the post

operative state) among the surgical patients compared to the medical therapy group members.

The surgical literature (DeMeester, et al. 1974, Behar, et al. 1975[2], Woodward, 1978), suggests that surgical improvement may well be better than twice the improvement rate in the medically treated group.

4.3.2 Table 1

Sample size required in *each of the two* treatment groups to show surgical benefits of varying size in attaining the Pain Free State during daytime.

Surgical Benefit	Medical Success Rate	Surgical Success Rate	Required Sample Size	
20%	30%	50%	120 + 15%	= 138
*30%	30%	60%	58 + 15%	= 67
40%	30%	70%	34 + 15%	= 39
50%	30%	80%	22 + 15%	= 25

* represents twice the improvement achieved in the medical therapy group based on a Chi-square Analysis using a one tailed test with $\alpha = 0.05$ and $\beta = 0.10$ (Fleiss, 1973).

4.3.3 Table 2

Sample size required in *each of the two* treatment groups to show surgical benefits of varying sizes of reducing Heartburn Severity (day or night)

Surgical Benefit	Medical Improvement	Surgical Improvement	Required Sample Size		
10%	50%	60%	420 + 15%	=	483
20%	50%	70%	100 + 15%	=	115
*25%	50%	75%	63 + 15%	=	72
30%	50%	80%	41 + 15%	=	62
40%	50%	90%	21 + 15%	=	24

* represents improvement 1 1/2 times as good as that achieved with medical therapy based on an unpaired one-tailed t-test of the significance of any detected differences between the two groups in terms of alteration in heartburn severity in each group from pretreatment to post therapy periods. (Cochran and Cox, 1957, Colton, 1974).

4.4 Data Analysis

The data will be analysed in the following manner:

4.4.1 In Relationship to the Major Endpoint Measurements

The primary objectives of the research question and thus the outcome variables chosen to be measured as endpoints relate to (a) the *attainment of pain free state* and if that is not achieved then (b) *a reduction in its severity*. Assessments will be made of each of these features (the presence of heartburn, an estimate of its severity) both at entry into the study and at the major checkpoints 3 months and exit (in addition to intermediate time periods during the study). For severity, the change between entry and the checkpoint in this value, will be computed. The significance of any differences between the two groups (i) in the achievement of the pain free state will be analysed

using a one tailed chi-square analysis (Fleiss, 1973), (ii) in the values for alteration in severity will be analysed using a one tailed unpaired t-test (Colton, 1974). If the data gives indication of violation of the normality and/or homogeneity of variance assumptions of the t-test, the Wilcoxon Rank Sum Test (Hollander & Wolfe, 1973) will be used for the analysis.

4.4.2 In Relationship to Overall Function

Each patient will have been allotted a utility value based on the data collected regarding symptoms occupational, social and emotional function. Index values thus will be available for both the pre-therapy and post-therapy assessments. The change in this value from entry to each checkpoint will be computed and a mean change for each group (medical and surgical) calculated. Any difference between mean values for each group will be compared using an unpaired t-test (Colton, 1974). Again, if the t-test is inappropriate the Wilcoxon Rank Sum Test will be used.

4.4.3 In Relationship to Secondary Endpoints

How will I assess the influence of therapy on a variety of other items such as number and duration of heartburn episodes and other symptoms such as regurgitation? How does one analyse the influence of therapy on the non-clinical outcomes such as the investigative tests?

These are difficult questions to answer. They raise the problems

of independence of these items from one another and of multiple testing of the data. There will be 10 items (4 clinical, 6 non-clinical) tested in this fashion. Although the same type of analyses will be performed, items significant at levels more extreme than $p = 0.005$ (i.e., $0.05 \div 10$) will only be considered of importance. These secondary analyses will be predominately descriptive in nature and can be used to determine if other research of an explanatory nature is worthy of consideration for future studies.

4.5 The Self Administered Questionnaire

4.5.1 Introduction

This data collection instrument is believed to be an important part of the assessment measurements used in this clinical trial. Since symptoms are the major reason for therapy, since the nature of the therapeutic alternatives make it difficult if not impossible to keep the medical observer "blinded" to the patients therapy, this form will be used to allow the patient an opportunity to rate his own symptoms on a document which will not be seen by the clinician who is supervising his therapy.

The form (a copy of which is found in the Appendix, section C) is designed to gather data on the patient's symptoms - the frequency, duration and severity of his heartburn - and the degree to which it may interfere with his social, emotional, occupational and physical functioning. For economy of space, responses are put across the page. In the form to be used by patients, in the pretest, responses will be placed vertically down the page.

This data collection instrument will be administered at each clinic visit. One person (most likely the research nurse or clinic Registrar) will be responsible for giving it to the patient, explaining its function, checking the responses for completeness and placing it in an envelope, which is sealed prior to the patient being seen by his clinician. At the completion of each clinic, all questionnaires will be forwarded to the Methods Centre, where the Research Associate will scrutinize it and if found complete, determine the patient's preliminary stratification status. Then the form will enter the data processing

stream.

4.5.2 The Questionnaire - How will it be used?

The questionnaire items will be used as follows:

(i) To record items that will be used directly as *outcome variables*. Information such as frequency and severity of heartburn and the presence or absence of associated symptoms will be recorded before and during therapy. Any changes developing in these measures can be computed at the analysis stage.

(ii) To determine the preliminary stratification status of each patient - subject to confirmation or adjustment of the severity stratum when the endoscopic results are known.

(iii) To construct a *utility measure* (social preference rating) of the clinical states associated with the before and after conditions of patients in the trial.

4.5.2.1 How Will This Utility Index Be Constructed?

As noted in the preliminary study outline, it is proposed to review all the questionnaire responses to form an exhaustive list of answers. This will include all the possible combinations of before and after symptom variables - symptoms of the disease and those of the side effects of therapy as well. From this we can gain an overview of the possible range of positive responses. Then a series of profiles in scenario form will be constructed to capture the information contained in the most frequently occuring combinations. Hopefully, these will not number more than about 10 clusters. Then utilizing the time trade

off technique (Torrance, et al. 1972) utility measures for each of these states will be determined. It is proposed to determine a value for each cluster on a random sample of primary care physicians (located in the Melbourne Branch of Australian College of Family Practice). They will be asked to perform this exercise from the point of view of themselves as the person suffering from the health disability states. In addition, samples of patients who have suffered from heartburn and who have been followed closely in the preliminary study, will be asked to rate the scenarios. Lastly, patients with heartburn who have not undergone a treatment programme will be sampled.

The determined utility values then will be applied to the individual patient's data within the study by two assessors who will be unaware of the patients identity, whether treated medically or surgically or whether the state under consideration was a pretreatment or post therapy condition. Thus the effectiveness of therapy can be judged by the degree of change in the value of this utility index from before to after the institution of either surgical or medical therapy.

4.5.3 Construction of the Questionnaire

The items in the questionnaire have been constructed in an attempt to gather both historical and attitudinal information. The former relates to facts such as the frequency, duration and circumstances associated with episodes of heartburn. The latter attempts to estimte the patient's level of physical, occupational, social and emotional dysfunction relating to his heartburn in addition to his judgement of its severity. There are 11 items which relate to a description

of heartburn; 5 items on physical function; 6 on social and 7 on emotional function. Lastly there are 17 items concerning other associated symptoms which may accompany heartburn or the therapy of this disorder.

4.5.4 Preliminary Viewing of the Form

The form is currently, as constructed, answered by using check marks against the appropriate responses. Precoding has not as yet been attempted as it is likely many items may need to be altered as a result of pretesting.

These questions are now ready to be viewed by a group of experts (gastroenterologist and a group of patients with heartburn) to determine the face validity of each item. At a preliminary pretesting, they will be asked (i) to determine whether the length of time that it takes to complete this form is acceptable and (ii) what degree of difficulty is experienced with the wording of questions and meaning of words. At this time, half of the questionnaires will be requiring to be answered using a check mark - the remaining half by circling a response. Scrutiny of the completed forms will determine which type of presentation appears to create less problems to the respondent. Also, at this check, space will be provided for the respondents to write in their reactions and any suggested changes. Their overall reactions in terms of what did they like, dislike or want modified will be sought. The returns from this initial trial run will be checked for items left blank, misinterpretations and possible ambiguities. Then the questionnaire where necessary will be revised and reworded. Once the ques-

tionnaire has been reorganized, it will be ready for formal pretesting and evaluation.

4.5.5 Evaluation of the Questionnaire

During a pilot study to precede the main effectiveness study, extensive pretesting of this document will be undertaken. Prior to and during the preliminary aspect of the pilot study, item evaluation for validity and reliability will occur.

4.5.5.1 Tests for Validity

Validity here refer to the efficiency with which the questionnaire measures what it purports to measure in terms of *relevance, completeness* and *accuracy*. (Bennett, et al. 1975).

From among the many types of validity usually spoken about in medical questionnaires *face validity* and *content (comprehensiveness) validity* will be checked for by scrutiny of a panel of experts (e.g. gastroenterologists) during initial preliminary viewing of the form.

Concurrent validity, that is how well the questionnaire agrees with an independent measure of some variables being investigated by the questionnaire (Bennett & Ritchie, 1975) will be sought in both a clinical and criterion dimension.

Clinical validity in the concurrent sense will be sought by comparing the patient's responses within each category - symptom complex, physical, occupational, social and emotional functioning - with the clinician's rating of the patient on these same categories. Criterion validity will be checked for by comparing the items concerning severity

of the symptom of heartburn with the results of the two investigative procedures - the scintiscan and the acid perfusion test.

4.5.5.2 Test For Reliability

i) *Repeatability*. A test-retest will be performed by repeating the administration of the questionnaire, some 2 weeks later, on a random sample of patients who completed the initial form. This will be done, however, prior to the patient starting on definitive therapy. Particular notice will be taken concerning whether the responses are similar in those patients who have stated that their heartburn is stable and whose antacid consumption between the two tests is also stable.

ii) *Internal consistency* will be sought by seeking consistency in responses to repeated but differently worded questions.

4.5.5.3 How Important Are These Issues of Reliability and Validity?

Internal consistency is a desirable characteristic of any questionnaire. However, the situation in which it appears to be most important is in the construction of an instrument in which a series of items within a single construct category (e.g. social health) are required to be reliable indications of that category.

Clinical validity is also highly desirable. However, since physician judgement is not to be used as an outcome variable, the information on the questionnaire can be used as designed in the absence of this. It is possible that the pretesting procedure and the associated discussion workshop around this instrument (described in the pilot trial) will increase the likelihood of achieving acceptable clinical

validity.

Concurrent criterion validity as judged by correlation with the objective tests of oesophageal function would help support the hypothesis that the severity of the patient's symptoms relate to the degree of reflux and the extent of its effects on the oesophageal mucosa. Failure to achieve this type of criterion validity will not invalidate the use of the questionnaire in the intervention trial. The statistical procedure used to evaluate individual items in the questionnaire will be the chi-square procedure for linear trend. Items which display a significant "overall chi-square as well as a significant chi-square for linearity, with a non-significant residual will be judged as valid items". (Sackett, et al. 1977).

4.5.6 Scoring of the Questionnaire

Many items in the questionnaire relate to the collection of historic data on items such as heartburn duration, frequency, etc., and as such do not require a scoring system. They can be used directly as outcome variables. However, the items which relate to symptom severity, occupational function, social and emotional function, require further attention. The layout of the response sets is such that it has an interval scale. As they currently stand these response sets are considered to represent equal interval scoring responses. As such they could be scored directly by giving each possible response a numerical value (e.g. 1-5 for symptoms items, 0-4 for social items and 0-5 for emotional items). An individual's score for any category could be determined by summating his scores for each item within that category. However, each

item need not, and indeed perhaps should not, be considered of equal worth. Prior to pretesting the document to determine if a weighting (scaled value) system needs to be used, a panel of judges (gastroenterologists) will be asked to rank each item within each category (that is, symptom complex, social function, etc.). A Thurstone-type procedure (Isaac, 1971) will be used to create a scale value for each item. The score attached to any item can then be used to compare with the clinician's judgement in the pilot trial when testing for concurrent clinical validity of that item. It should be noted that responses do not require scale values to be used directly for the wording of the scenario profiles in the construction of the health utility index.

4.5.7 Discussion on Use of Questionnaire

4.5.7.1 Why This Variety of Approaches?

The clinical evalution of a symptom complex, that is not associated with hard clinical endpoint such as stroke or death, is associated with a strong possibility that observer bias will influence both the direction and magnitude of the response. This problem is particularly difficult to overcome when the observer cannot be blinded to the patient's treatment group while making his subjective assessment. This study where there is no placebo therapy and where one treatment is surgical and the other is medical illustrates well such a situation if clinicans are to be used to assess symptoms.

In addition it is likely that as a result of the intervention, patients will fall into a series of categories: (i) heartburn completely relieved, (ii) heartburn eased, (iii) new symptoms due to the therapy,

or (iv) some combination of the first 3. Therefore, measurement of outcome variables alone, without taking into account the differing quality of life values for each of these states, would fail to adequately measure the success or failure of each therapy.

Any judgement that is placed on a symptom or the quality of life that a patient "enjoys" who suffers from that symptom must be a value judgement. However, such judgements often need to be made daily in clinical practice. While recognizing that there are value differences involved, I have preferred to go the route of squarely facing up to this. However, I have selected more than one endpoint measure in an effort to see whether the results vary if we use a fairly simple outcome measure - change in symptoms - versus the results from a utility measure approach. While not directly related to this study, the use of functional outcomes and utility values should allow comparisons to be made with other disease states.

In setting up this study, attention was given to the methods of collection of information concerning symptoms with the highest possible accuracy and the least bias. The concepts of using a "blind" interviewer who was not part of the assessment or treatment team was considered. Such a person could do the before and after ratings without information which related to the treatment regimen. However, there are also disadvantages to using an interviewer. (Orlich, 1978).

Among the advantages of the self-administered questionnaire are that each patient would receive identical questions, answers should be able to be given without fear of embarrassment, interviewer bias can be avoided, and the technique is inexpensive. The usual disadvantage of

non-respondence can be avoided by having a staff member check to see that the instrument has been completed. Some of the disadvantages which relate to complex design or question meaning can hopefully be minimized by extensive pretesting. As the data to be collected concern predominately historical rather than attitudinal information, the advantages of an interview technique - opportunity for discussion, assessment of motivation, non-verbal behaviour, probing and high respondent numbers - are less important here. The disadvantages (the cost of interview training, interviewer bias scheduling of interviews for convenience of staff and patient, time taken) can be avoided with the questionnaire technique. The clinician can still be kept "blind" by not allowing him to assess the questionnaire responses. I finally decided to use a self-administered questionnaire rather than the "blind" interviewer technique because, in addition to the problems previously mentioned, I believe that it would be difficult to:

i) ensure that the patient did not reveal his treatment status to the interviewer - if even accidently, e.g., "Since my operation ..."

ii) train 5 interviewers, one for each participating institution in Melbourne, who could be always available when needed with sufficient expertise and acceptable inter-interviewer consistency for this study.

4.5.8 Summary

It can be seen from the foregoing that the major role for the questionnaire's attitudinal items is the gathering of sufficient information from which the health utility status profiles can be constructed.

The utility index itself can be tested for reliability by repeating the scaling a year later to see if it maintains an adequate coefficient of reliability. Validity is difficult to test in terms of whether actual health care decisions made by individuals were consistent with their health state preferences. However the validity of the measurement technique could be tested against another method of measurement, e.g. the standard gamble technique. The reliability of the historical information gathered on the questionnaire could be checked against their primary care physician's records. However, physician's records are at times themselves, notoriously unreliable.

Appendix

A) Details of Investigations Utilized to Assess Oesophageal Function

B) Descriptions of Surgical Procedures

C) Questionnaire

D) Initial Clinical Assessment Form

E) Follow up Clinical Assessment Form

F) Surgical Report

G) Withdrawal Form

H) Letter to Patient's Local Medical Officer

I) Consent Form

J) Information for Patient

K) References

A) Details of Investigations: Utilized to Test Oesophageal Function

1) Acid Perfusion Test

This test - the Bernstein test (Bernstein, et al. 1958) is performed as follows. With the patient in the seated position, the perfusing opening of the tube assembly is postitioned 6-10 cms. above the gastro-oesophageal sphincter zone. As this test is to be done immediately following the manometry measurement, the position of the sphincter zone will be accurately known. Firstly normal saline is infused at a speed of up to 8 ml./minute (120 drops on a standard infusion set) for approximately 5 minutes. Then without the patient's knowledge that the perfusing solution has been changed, 0.1N HCL is infused by turning off the saline and on the acid utilizing a Y connection assembly. Acid is perfused until the patient experiences heartburn or until 20 minutes have elapsed, which ever occurs first. The time taken to reproduce heartburn with the acid solution is recorded. Saline is again infused and the time which elapses till the heartburn disappears is noted. The results are recorded as:

A *POSITIVE TEST* - when the initial saline perfusion does not produce heartburn, the acid perfusion does and the second saline perfusion is associated with symptom relief.

A *NEGATIVE TEST* - when neither saline nor acid produce symptoms.

An *INDETERMINATE RESULT* - when saline produces symptoms usually not heartburn and acid infusion likewise produces discomfort but not heartburn.

For the purpose of this study an indeterminate result will be read as negative in the analyses although recorded as indeterminate.

2) Upper Gastrointestinal Endoscopy

Fibreoptic endoscopic examination of the upper gastrointestinal tract will be performed using standard instruments (eg., Olympus GIF series). The appearance of the oesophageal mucosa (Behar, et al. 1978) is recorded as:

Grade 1. - normal or diffuse erythematous colour.

Grade 2. - friable or with exudate on the surface.

Grade 3. - presence of ulceration or erosions.

Grade 4. - severe ulceration or stricture formation with haemorrhage or mucosal denudation.

In addition the gastric and duodenal mucosa will be examined for the presence of peptic ulcers. These latter 2 conditions will lead to exclusion of the patient from the study.

3) Oesophageal Mucosal Biopsy

At the endoscopy session suction biopsies will be taken from the mucosal surface between 2 and 8 cms. above the lower oesophageal sphincter zone. All samples after orientation, fixation, processing will be coded and read independently by 2 individuals in a central laboratory. Each sample will be scored as normal or abnormal according to current criteria for oesophagitis on histological grounds (Ismail-Beigi, et al. 1970). Intra- and interobserver disagreements will be resolved prior to final assessment by use of a training workshop with discussion to achieve consensus.

4) Oesophageal Manometry

This test will be performed using a four lumen tube assembly, infused catheter system with the three recording catheters arranged to

measure pressures through side orifices 5 cm. apart. Perfusion rate is to be 2 ml./minute. Pressure recordings will be made during a "slow pull through" procedure with the assembly moving 1 cm. at a time across the lower oesophageal sphincter. Lower oesophageal sphincter pressure will be measured at the mid-respiratory excursion point. The mean gastric pressure will be used as zero reference by subtracting its value from these oesophageal values, and the mean, for all orifices, designated the oesophageal sphincter pressure, (mmHg.). Belt pneumographs over the larynx and around the chest will monitor swallowing and respiration. Two observers will review each record and the final LES pressure will be the mean of the two results.

5) The Scintiscan

The equipment required for this includes a gamma camera with scintigraphic data analyser and Tc-sulphur (99) colloid. After an overnight fast the patient ingests 300 uc 99mTc sulphur colloid diluted in 300 mls. water and is positioned under the collimetor of a gamma camera in the supine position. Timed counts are displayed on the console of the gamma camera and photographs are taken as desired. Data from the camera are stored in and processed by the data analyser. The gastro-oesophageal pressure gradient is increased in increments of 20 mm Hg (from 0-100 mm.) by inflating an abdominal binder. (This raises the gradient across the gastro-oesophageal junction from 10 to 35 mm Hg). A scintiscan is obtained at a 30 second exposure for each pressure recording. If no reflux is seen on the screen during this procedure after 20 minutes wait, the test is repeated with 300 uc in 150 cc 0.IN HCL diluted in 150 ml. orange juice. The GE reflux index

is computed employing the formula $RI = [(E-E_B)/G_0)] \times 100$, in which RI represents the gastro-oesophageal reflux index as a percent of gastric counts; E, oesophageal counts; E_B, oesophageal background counts; and G_0, maximal gastric counts.

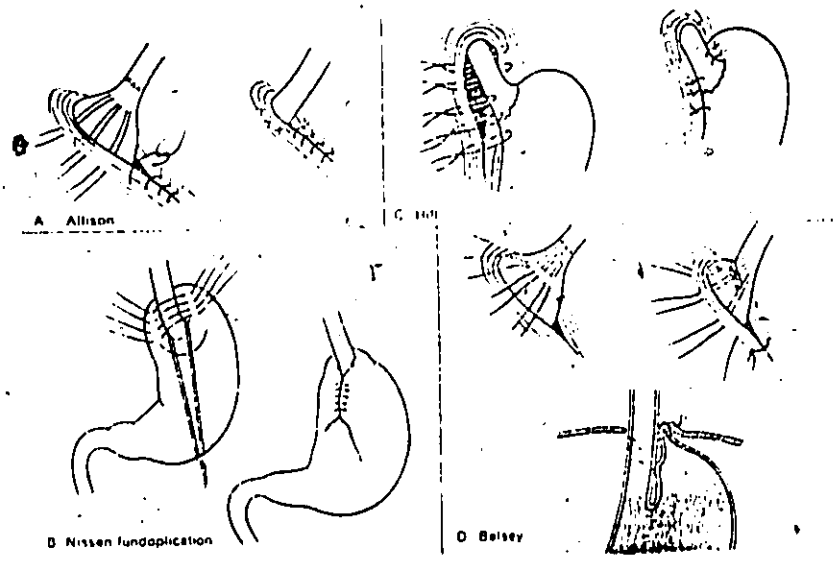
B) The Anti-reflux Operations

The *Nissen* is performed (Nissen, 1961) through a transabdominal approach. The gastric fundus is wrapped 360 degrees around the distal 4 cms. of oesophagus, both to maintain it below the diaphragm and to buttress it. The diaphragmatic crura are approximated together allowing space for the insertion of the distal phalanx of the surgeon's index finger through the reconstructed oesophageal hiatus. *Belsey* (Woodward, 1978) developed a technique to mobilize the distal oesophagus and oesophagogastric junction through a left thoracotomy incision. He approximates the gastric fundus to the distal oesophagus in a beltlike fashion using 3 layers of sutures. The oesophagogastric junction is then thrust below the diaphragm. This procedure has the obvious disadvantage of requiring the thoracic cavity to be opened. The *Hill* procedure (1967) was first proposed by its creator in 1961. In this technique, the posterior aspects of the crura are approximated to the oesophagus and the oesophagogastric junction is sutured to the lesser gastric curvature and the median arcuate ligament.

In all these 3 operations, the procedure is done around a 30Fr. tube to maintain an adequate lumen.

Diagrammatic Illustrations of

4 Anti-reflux Procedures



from R. Earlam (1976) "Clinical Tests of Oesophageal Function"

A) *Allison* Repair

B) The *Nissen* Fundoplication

C) The *Hill* Gastropexy

D) The *Belsey* Repair

The QUESTIONNAIRE

Gastro-oesophageal Reflux Symptom Assessment

Dear Patient:

We wish to ask you some questions about your illness and for you to record your answers on this form. We need this information in order to keep track of your condition while you are under treatment. Your answers will form part of the method by which we will decide just how well this form of treatment suits you. It is important that you complete every question as accurately as possible. Please take your time in answering these following items. It should take you about 20 minutes to complete. It will be checked for completeness by the Clinic Registrar when you have finished.

Thank you for your trouble.

Respectfully yours

Clinic Director

Study Director
(41-0221, Ext. 695)

INSTRUCTIONS FOR COMPLETING THIS FORM

The majority of questions on this form can be answered by placing a mark (x) in the space provided. Some require a number to be put in the space to indicate how long you have had the problem or how frequent episodes of heartburn are occurring. In other circumstances special instructions will accompany the question.

These first 4 questions are about your heartburn since it first began.

1) How many years have you been getting heartburn? ____ years

2) Since you first developed your illness, have you had any days or nights when you have been free of heartburn?

____ yes ____ no

If yes,

3) What is the longest period of time that you have been completely free of heartburn?

____ months or ____ years

4) Looking back from today, how many months or years have you had heartburn at least once a day?

____ months ____ years

Questions 5 to 11 are about the heartburn you are having now.

5) Over the past 2 weeks has your heartburn occurred

____ at night time only
____ during the daytime only
____ both at night and during the daytime
____ neither at night or during the daytime

If you have not had any heartburn in the last 2 weeks, Skip to Question 24.

6) Over the last 2 weeks, would you say that your heartburn is

____ staying the same
____ improving
____ getting worse

7) Over the past 2 weeks, which of the following have brought on your heartburn?

____ eating
____ bending over
____ lying down
____ none of the above

To complete Questions 8 to 11,

- *Answer Part A if your heartburn occurs only at night time;*
- *Answer Part B if your heartburn occurs during the daytime only;*
- *Please answer both Part A and Part B if your heartburn occurs both at night and during the daytime.*

8) In a 24 hour period, on the average, how many episodes of heartburn would you say you have? (over the past 2 weeks)

A) ____ episodes at night time
B) ____ episodes during the daytime

9) Over the past 2 weeks, how long would an average episode of heartburn last? (indicate whether it is hours, minutes or seconds)

A) At night time they last
____ hours
____ minutes
____ seconds

B) During the daytime they last
____ hours
____ minutes
____ seconds

We would now like you to tell us how severe your heartburn is by marking (x) the answer which best describes the severity of your current heartburn.

10) A) Over the past 2 weeks, my average episode of heartburn at night is:

____ mild
____ not very severe
____ somewhat severe
____ moderately severe
____ very severe

10) B) During the past 2 weeks, my <u>average</u> episode of <u>daytime</u> heartburn is:

____ mild
____ not very severe
____ somewhat severe
____ moderately severe
____ very severe

11) A) Over the past 2 weeks, my <u>worst</u> episode of heartburn <u>at night</u> was:

____ mild
____ not very severe
____ somewhat severe
____ moderately severe
____ very severe

11) B) Over the past 2 weeks, my <u>worst</u> episode of <u>daytime</u> heartburn was:

____ mild
____ not very severe
____ somewhat severe
____ moderately severe
____ very severe

Questions 12 to 16 are about the effect that your heartburn has on many of your usual daily activities. Please answer them by placing the check mark (x) in the space which best describes the amount to which your heartburn interfere with these activities. (work=usual daily occupation)

12) Over the past 2 weeks, my heartburn has interfered with my work:

____ not at all
____ slightly
____ somewhat
____ moderately
____ a great deal

13) Over the past 2 weeks, my heartburn has interfered with my hobbies:

____ not at all
____ slightly
____ somewhat
____ moderately
____ a great deal

14) Over the past 2 weeks, my heartburn has interfered with my ability to enjoy my food:

____ not at all
____ slightly
____ somewhat
____ moderately
____ a great deal

15) Over the past 2 weeks, my heartburn has interfered with my going out to visit friends:

____ not at all
____ slightly
____ somewhat
____ moderately
____ a great deal

16) Over the past 2 weeks, my heartburn has interfered with my other favourite social activities:

____ not at all
____ slightly
____ somewhat
____ moderately
____ a great deal

Please identify these activities:

---

17) Over the past 2 weeks, have you lost any time from work due to your heartburn?

____ yes, if so how many days ____
____ no

18) Over the past 2 weeks, how much antacid would you say you have taken, on average, in a 24 hour period for the relief of your heartburn?

___ mls., if you use a liquid (a bottle contains 200 mls.)

___ tablets, if you use tablets

---

19) Over the past 2 weeks, have you been able to dress yourself?

____ yes

____ yes, with difficulty

____ no

20) Over the past 2 weeks, have you been able to put on your shoes?

____ yes

____ yes, with difficulty

____ no

If you do not do regular household activities, please Skip to Question 24.

21) Over the past 2 weeks, have you been able to make the beds?

____ yes

____ yes, with difficulty

____ no

22) Over the past 2 weeks, have you been able to clean the bath?

____ yes

____ yes, with difficulty

____ no

23) Over the past 2 weeks, have you been able to clean the floors?

____ yes

____ yes, with difficulty

____ no

Questions 24 to 33 contain a list of some of the other symptoms that people with heartburn may at times develop. Please use a check mark (x) to indicate the ones that you have had.

24) ____ difficulty swallowing solid food or fluids

25) ____ nausea

26) ____ vomiting

27) ____ regurgitation (the sudden appearance of bitter or sour tasting fluid in your mouth which you have not vomited up. This fluid may be bile stained, a green colour)

28) ____ belching up large amount of gas (flatulence)

29) ____ difficulty belching up gas

30) ____ diarrhoea

31) ____ swelling of the abdomen

32) ____ passing excessive gas through the bowel

33) ____ a persistent cough

If you don't have any difficulty with regurgitation, Skip to Question 39.

If you have suffered from <u>regurgitation</u>, please use a check (x) mark to indicate whether it occurs:

34) ____ after bending or lifting objects

35) ____ after large meals

36) ____ after lying down following meals

37) ____ after lying down not following meals

38) ____ during sleep

If you don't have any difficulty swallowing, Skip to Question 44.

If you have difficulty swallowing, please indicate with a check mark (x) whether it occurs:

39) ____ occasionally after solid meals

40) ____ with cool liquids

41) ____ after the first bite

42) ____ with a need to drink liquids for relief

43) ____ with a need to go to hospital for relief ~~of the blockage~~

---

44) Everything considered, would you describe your health these days as

____ very good
____ pretty good
____ not so good
____ quite poor

Some people with heartburn have problems with other aspects of their general health. For the next 7 Questions, please mark (x) the answer which best applies to you.

45) Over the past 2 weeks, how have you been feeling in general?

____ in excellent spirits
____ in very good spirits
____ in good spirits mostly
____ I have been up and down in spirits a lot
____ in low spirits mostly
____ in very low spirits

46) Over the past 2 weeks, have you been bothered by nervousness?

____ extremely so
____ very much so
____ quite a bit
____ some -- enough to bother me
____ a little
____ not at all

47) Over the past 2 weeks, have you felt so sad, discouraged or had so many problems that you wondered if anything was worthwhile?

____ extremely so
____ very much so
____ quite a bit
____ some -- enough to bother me
____ a little bit
____ not at all

48) Over the past 2 weeks, how happy, satisfied or pleased have you been with your personal life?

____ extremely happy
____ very happy
____ fairly happy
____ satisfied -- pleased
____ somewhat dissatisfied
____ very dissatisfied

49) Over the past 2 weeks, have you been anxious, worried or upset?

____ extremely so
____ very much so
____ quite a bit
____ some -- enough to bother me
____ a little bit
____ not at all

50) Over the past 2 weeks, have you been waking up fresh and rested?

____ every day
____ most every day
____ fairly often
____ less than half the time
____ rarely
____ none of the time

51) Over the past 2 weeks, have you felt down hearted and blue?

____ all of the time
____ most of the time
____ a good bit of the time
____ some of the time
____ a little of the time
____ none of the time

INITIAL CLINICAL ASSESSMENT FORM

1. Identification Information

1.1) Patient's Name: _____
surname *given name* *other*

1.2) Marital Status: Married _____
Single _____
Other _____

1.3) Address: _____

_____

_____

1.4) Telephone Number: _____ _____
area code *local*

1.5) Information concerning a close friend or relative, not living with the patient, but who will always know the patient's whereabouts.

Name: _____
surname *given name* *other*

Address: _____

_____

_____

Telephone Number: _____ _____
area code *local*

Relationship to patient: _____

2. General Information

2.1) Date of clinical assessment: _____ _____ _____
day month year

2.2) Institution: _____

2.3) Attending Physician: _____ /Surgeon: _____

2.4) Sex: _____ _____ (2.5) Race: _____
male female

2.6) Age (in years): _____ (2.7) Date of birth: ___ _____ _____
day month year

2.8) Employment status:

employed: _____ unemployed: _____

nature of work: _____ how long: _____ _____ _____
years months days

does it involve:-

bending? ___ ___
yes no

lifting? ___ ___
yes no

is it full time? ___
yes

or part time? ___
yes

previous employment: _____

specify reason for unemployment:

_____

_____

_____

if part time, specify reason:

_____

2.9) Does the patient have regular hobbies? _____ _____
yes no

if *yes*, do they involve:

bending? ___ ___
yes no

lifting? ___ ___
yes no

3. Brief Summary of Oesophageal Disease

3.1) Please summarise the main features of this patient's reflux history. Include comments on the presence or absence of heartburn, dysphagia, regurgitation, nausea, vomiting and flatulence.

Has the patient experienced any of the following complications?

3.2) Stricture ____ ____ (yes / no) Date of onset: (if yes) ____ ____ ____ (day / month / year)

3.3) Haemorrhage ____ ____ (yes / no) Date of onset: (if yes) ____ ____ ____ (day / month / year)

3.4) Other ____ ____ (yes / no)
please specify: _____ Date of onset: ____ ____ ____ (day / month / year)

3.5) Antacid Use: ____ ____ (yes / no)
if used Name of preparation _____
unit dose for an episode _____
average frequency of use _____
average total daily amount _____

4. Health Status Form

Using whatever clinical information you have available (but not the completed patient self assessment questionnaire) please complete this form.

4.1) Today, the total health of this patient is:

_____ poor _____ fair _____ good

4.2) Today, this patient's social functioning is:

_____ poor _____ fair to good

_____ poor to fair _____ fair _____ good

4.3) Today, this patient's emotional functioning is:

_____ poor _____ fair to good

_____ poor to fair _____ fair _____ good

4.4) Today, this patient's physical functioning is:

_____ poor _____ fair to good

_____ poor to fair _____ fair _____ good

4.5) If the patient is incapacitated in social, emotional or physical function, do you consider that it is due to disorders other than the patient's oesophageal disease?

_____ Yes _____ No

If yes, please specify your reasons:

4.6) How would you rate the severity of this patient's oesophageal condition?

_____ mild

_____ not very severe

_____ somewhat severe

_____ moderately severe

_____ very severe

5. Further History

5.1) Medical problems other than gastro-oesophageal reflux.

Has the patient had any of the following: ____ yes ____ no

(if yes, indicate where applicable)

		Date of onset and comments
Gall bladder disease	____	
gastric surgery	____	
vagotomy	____	
gastric ulcer	____	
duodenal ucler	____	
angina pectoris	____	
scleroderma	____	
recent weight loss	____	
other (specify)	____	

5.2) Medications.

Treatment for Gastro-oesophageal Reflux within the Last Month

	Drug Name	*Dose/Frequency*	*From*	*To*
1.				
2.				
3.				

Other medications? yes ____ (if so complete below) no ____

(particularly if the patient has been taking steroids, analgesics or anti-inflammatory drugs include in the list below)

	Drug Name	*Dose/Frequency*	*From*	*To*	*Indication*
1.					
2.					
3.					

5.3) Smoking Habits

Non Smoker _____ Pipe/Cigar smoker _____

ex-Smoker _____ Years smoked _____ Average no. daily _____

Years stopped ____

Cigarette now ____ Years smoked _____ Average no. daily _____

5.4) Drinking Habits

(use 10 ml spirits (1/3 oz) = 3.2G alcohol
100 ml beer = 4.0G alcohol)

non-drinker ____

ex-drinker _____ years imbibed _____ Daily average (Gms. alcohol) _____

years stopped _____

current drinker ____ years imbibed _____ Daily average (Gms. alcohol) _____

6. Physical Examination

6.1) Date of physical: ____ ____ ____
day *month* *year*

6.2) Height _____ (cms.) (6.3) Weight _____ (kgms.)

6.4) Blood pressure _____ mmHg (syst.) _____ mmHg. (diast.) _____ arm.

6.5) has the patient any evidence of liver disease? ____ yes _____ no

if yes, specify: _____

_____

_____

OESOPHAGEAL FUNCTION STUDIES

7. Acid Perfusion Study

7.1) Date of procedure _____ _____ _____
day *month* *year*

7.2) Where was the procedure performed?
Hospital _____
Address _____
_____

7.3) Was the procedure technically satisfactory? _____ _____
yes *no*

7.4) Was the result positive _____
negative _____
indeterminate _____

if positive duration of acid perfusion _____ minutes.
duration of second saline perfusion _____ minutes.
if indeterminate specify reason _____
_____

8. Oesophageal Manometry

8.1) Date of procedure _____ _____ _____
day *month* *year*

8.2) Where was the procedure performed?
Hospital _____
Address _____
_____

8.3) Was the procedure technically satisfactory? _____ _____
yes *no*

(include copy of gastroenterologist's report).

9. Upper Gastrointestinal Endoscopy

9.1) Date of the procedure: _____ _____ _____
day *month* *year*

9.2) Where was the procedure performed?

Hospital: _____

Address: _____

Endoscopist: _____

9.3) Was the procedure technically adequate? _____ _____
yes *no*

9.4) Did the appearance of the oesophageal represent?

Grade 1. _____ - normal or diffuse erythematous colour.

Grade 2. _____ - friable or with exudate on the mucosal surface.

Grade 3. _____ - presence of ulceration or erosions.

Grade 4. _____ - severe ulceration or stricture formation with haemorrhage or mucosal denudation.

9.5) Were there any of the following seen? _____ _____
yes *no*

Gastric ulcer _____ Duodenal ulcer _____

Other lesion _____ if so, specify: _____

9.6) Were oesophageal biopsies taken? _____ _____
yes *no*

if *yes*, was the result Abnormal _____ Normal _____

if *no*, why not: Specify: _____

_____

10. Scintiscan

10.1) Date of procedure: _____ _____ _____
day *month* *year*

10.2) Where was the procedure performed?

Hospital: _____

Address : _____

_____

10.3) Was the procedure technically adequate? _____ _____
yes *no*

10.4) Was the result: *Positive* _____ *Negative* _____
(please include copy of the report)

11. Procedure for Entering a New Patient Into the Study

Once the preceding items have been completed and a tentative date for surgery identified, please complete the following items and then call the Methods Centre.

11.1) Patient's Name: _____

11.2) Patient's Study Number: _____

11.3) Name of Participating Centre: _____

11.4) Age of Patient: _____ years

11.5) Were exclusion lesions found at Endoscopy? _____ _____
(see item 9.5 in Initial Clinical Assessment Form) *yes* *no*

11.6) Endoscopy Grading of Oesophagitis: _____
(see item 9.4 in Initial Clinical Assessment Form)

Now proceed with the randomization schedule

Procedure of Randomization

11.7) Date of Randomization: _____ _____ _____
day *month* *year*

Call Methods Centre: St. Vincent's Hospital, Melbourne, Victoria
03-41 0221

Repeat Information 11.1 to 11.6

11.8) You will be given the patient's randomization category:

_____ surgical _____ medical

11.9) If Surgical

Name of Surgeon: _____

Date of surgery: _____

Send in Form 1: Initial Clinical assessment Form with copies of all reports.

Arrange for first follow-up visit.

11.10) If Medical

Send in Form 1: Initial Clinical Assessment Form with copies of all reports.

Initiate medical therapy.

Arrange for first follow-up visit.

11.11) This form has been completed and submitted by:

_____

(Signature)

FOLLOW UP CLINICAL ASSESSMENT

1. Identifying Information

1.1) Patient's Name: _____
surname *given name* *other*

(complete the rest of this page ONLY IF CHANGED from last assessment)

1.2) Address: _____

_____

_____

1.3) Telephone Number: _____ _____
area code *local*

1.4) Information concerning a close friend or relative, not living with the patient, but who will always know the patient's whereabouts.

Name: _____
surname *given name* *other*

Address: _____

_____

_____

Telephone Number: _____ _____
area code *local*

Relationship to patient: _____

2. General Information

2.1) Date of assessment: _____ _____ _____
day *month* *year*

2.2) Institution: _____

2.3) Attending Clinician: _____

2.4) Sex: _____ _____ (2.5) Race: _____
male *female*

2.6) Age (in years):_____

2.7) Employment status:

_____ unchanged from last assessment (*skip to next page*)

_____ changed from last assessment (*complete this section*)

employed: _____ unemployed: _____

nature of work: _____ how long: _____ _____ _____
years *months* *days*

does it involve:-

stooping? ___ ___ (*yes* *no*)

bending? ___ ___ (*yes* *no*)

lifting? ___ ___ (*yes* *no*)

full time? _____

part time? _____

previous employment: _____

specify reason for unemployment:

_____

_____

_____

2.8) Usual daily activities (including hobbies)

do they involve: stooping? _____ _____ (*yes* *no*)

bending? _____ _____ (*yes* *no*)

lifting? _____ _____ (*yes* *no*)

3. Brief Interim Summary

3.1) *Please note the items commented upon in the last assessment and indicating their progress. Information should be obtained from the patients diary as well as the patient.*

Has there been a change in the following since last assessment?

yes _____ *no* _____ *(if yes complete the following)*

Has the patient experience any of the following complications?

3.2) Stricture ____ ____ (*yes* / *no*) Date of onset: (if *yes*) ____ ____ ____ (*day* / *month* / *year*)

3.3) Haemorrhage ____ ____ (*yes* / *no*) Date of onset: (if *yes*) ____ ____ ____ (*day* / *month* / *year*)

3.4) Other ____ ____ (*yes* / *no*) Date of onset: ____ ____ ____ (*day* / *month* / *year*)

please specify: _____

4. Health Status Form

Using whatever clinical information you have available (but not the completed patient self assessment questionnaire) please complete this form.

4.1) Today, the total health of this patient is:

_____ poor _____ fair _____ good

4.2) Today, this patient's social functioning is:

_____ poor
_____ poor to fair
_____ fair
_____ fair to good
_____ good

4.3) Today, this patient's emotional functioning is:

_____ poor
_____ poor to fair
_____ fair
_____ fair to good
_____ good

4.4) Today, this patient's physical functioning is:

_____ poor
_____ poor to fair
_____ fair
_____ fair to good
_____ good

4.5) If the patient is incapacitated in social, emotional or physical function, do you consider that it is due to disorders other than the patient's oesophageal disease?

_____ *Yes* _____ *No*

If *yes*, please specify your reasons:

4.6) How would you rate the severity of this patient's oesophageal condition?

_____ mild

_____ not very severe

_____ somewhat severe

_____ moderately severe

_____ very severe

5. Further History

5.1) Other Medical Problems (*either new or continuing*)
since the last assessment has the patient had any of the following: _____ *yes (check only where applicable)* _____ *no*

		Date of onset and comments
Gall bladder disease	____	_____
Gastric surgery	____	_____
Vagotomy	____	_____
Gastric ulcer	____	_____
Duodenal ulcer	____	_____
Angina pectoris	____	_____
Scleroderma	____	_____
Recent weight loss	____	_____
Other (*specify*)	____	_____

5.2) Current Medications. *Yes* ____ *(complete below) No* ____

	Drug Name	*Dose/Frequency*	*From*	*To*
1.	_____	_____	_____	_____
2.	_____	_____	_____	_____
3.	_____	_____	_____	_____

5.3) Smoking Habits. *any change since last assessment?*

Yes _____ *(provide details below) No* _____

_____

_____

_____

5.4) Drinking Habits: *any change since last assessment?*

Yes _____ *(provide details below) No* _____.

_____

_____

_____

5.5) Study Medication Consumption.

ANTACID

Volume prescribed ..... _____ mls. Date prescribed __/__/__ *dy mo yr*

Volume remaining ..... _____ mls. Date of visit __/__/__ *dy mo yr*

CIMETIDINE

Number of tablets prescribed _____ Date prescribed __/__/__ *dy mo yr*

Number remaining _____ Date of visit __/__/__ *dy mo yr*

6. Physical Examination

6.1) Date of physical: _____ *day* _____ *month* _____ *year*

6.2) Height _____ (cms.) (6.3) Weight _____ (kgms.)

6.4) Blood pressure _____ mmHg (syst.) _____ mmHg. (diast.) _____ arm.

6.5) *Has the patient any evidence of liver disease?* ___ *yes* ___ *no*

if yes, specify: _____

_____

_____

SURGICAL REPORTS

1. Patient's name: _____
   surname *given name* *other*

2. Date of operation: _____ / _____ / _____
   day *month* *year*

3. Name of surgeon: _____

4. Type of anaesthesia: _____

5. Type of procedure: _____

6. Duration of anaesthesia: _____

7. Volume of blood used: _____

8. Surgical complications
   (*within 30 days of procedure*)

Yes		*No*
_____	Wound Infection	_____
_____	Pulmonary Infection	_____
_____	Dysphagia	_____
_____	Pulmonary Embolism	_____

9. Duration of Hospitalization: _____ days

This form is completed and submitted by

_____ ____/____/____
(Signature) *day* *month* *year*

PATIENT WITHDRAWAL FORM

1. Patient's name: _____
   surname *given name* *other*

2. Patient's Study Number: _____

3. Date of withdrawal: ____ / _____ / _____
   day *month* *year*

4. Reason for withdrawal:

   (a) Patient's decision

   Unco-operative _____

   Loss to follow-up _____

   Other _____

   Specify: _____

   (b) Physician's decision

   Unco-operative _____

   Loss to follow-up _____

   Other _____

   Specify: _____

   (c) Protocol Violation

   Antireflux surgery in patient assigned to medical group _____ Date: ___ / ___ / ___
   dy *mo* *yr*

   (d) Death _____ Date: ___ / ___ / ___
   dy *mo* *yr*

   Specify cause of death and attached autopsy report if available.

   _____

   _____

   (e) Serious illness _____ Date of Onset: ___ / ___ / ___
   (preventing follow-up) *dy* *mo* *yr*

   Specify: _____

   _____

   _____

(f) If more than one reason for withdrawal, list below in descending order of importance.

(g) Any further details concerning withdrawal?

Date of Report: ____ / ____ / ____
day / month / year

Submitted by: _____
(Signature)

STUDY OF GASTRO-OESOPHAGEAL REFLUX THERAPY

Information for Family Physicians

The best possible form of therapy for your patient's reflux has yet to be established. Currently it is not known with certainty if medical or surgical therapy, a combination of both or neither comprises the best treatment.

For these reasons, this and a number of other hospitals in Melbourne are participating in a study of its management. Both therapeutic regimens are known to give symptom relief and can be administered with little risk to the patient.

Your patient has agreed to participate in this study and the randomization process has selected that he/she be entered into the Medical group. This does not imply that he/she has been denied a surgical procedure known to be of superior benefit.

He/she is to receive therapy with Cimetidine 300mg. Q.I.D. in addition to dietary advice, elevation of the head of the bed and antacids.

Your patient will be seen every 2 weeks for 8 weeks and then at 3,6,9, and 12 months afterwards. Regular reports will be sent to you following each visit.

If you have any queries, if any difficulties arise, or if your patient must *withdraw* from the study, *for any reason*, please let us know.

_____
(Signature)

_____
(Hospital)

NOTE:-

If the patient is randomized into the surgical group, all paragraphs are the same except for the 3rd, which becomes:

Your patient has agreed to participate in the study and the randomization process has selected that he/she be entered into the Surgical group. An antireflux has been/will be performed by Dr. _____ *on* _____, *19*___.

INFORMED CONSENT DOCUMENT

Gastro-oesophageal Reflux Study

The undersigned has been fully informed that _____ (Miss, Ms., Mrs., Mr.) has been enrolled as a volunteer patient in the above named study.

The undersigned has been told that his symptoms are caused by reflux of stomach contents into the oesophagus (gullet). He has been told that a surgical procedure, that is well established, is available to reduce this reflux and in many patients it results in relief of symptoms. He has been told that the *surgery is not experimental*. However it is not known for sure whether it is superior to drug medication in relieving symptoms.

The patient has been told that a random selection process will indicate whether or not surgery will be performed and that this is the only technique that is known to conclusively demonstrate whether the benefits of surgery significantly exceed its side effects. *This is the only aspect of the study that is experimental.*

The patient has been told that the complications of surgery can include a small risk of death and among others difficulty vomiting, belching and swallowing and the usual anaesthetic risks which attend all surgery of this type.

The volunteer understands that his consent may be withdrawn at any time and that participation in the study discontinued and in that event he will continue to receive the best known medical care. If the treatment does not include surgery, the patient knows that he will receive treatments also known to be of value in symptom relief. He knows that the follow-up includes a visit every 2 weeks for 8 weeks and then visits at 3,6,9, and 12 months. He is aware that it is proposed to repeat the investigations at 3 months and 12 months after the beginning of treatments.

The volunteer understands that *complete confidentiality* will be kept both in terms of the hospital and clinic records, and that the records will be put together with similar records from all cooperating hospitals at the University of Melbourne.

_____ *Signature of Witness*

_____ *Signature of Patient*

_____ *Address and date*

_____ *Hospital number, address, phone number*

I, the undersigned, have defined and fully explained the study to the above volunteer patient

_____ *Signature of Investigator*

Date: ____ / ____ / ____ *Day / Month / Year*

INSTRUCTIONS FOR PATIENTS REGARDING REFLUX STUDY

Thank you for agreeing to participate in this important study. Here are some simple things concerning your part in the study.

1. Your doctors will have described the study to you. If you wish to have any more information, please don't hesitate to ask.

2. Please record in the diary provided any symptoms you may experience. Please note the time in the space provided for that date.

3. Bring the diary with you to each follow-up visit.

4. You will be given medicines for your condition by your gastroenterologist. Please continue to take them for as long as he prescribes for you. If you run out, please contact him.

5. If you change your address, please notify your gastroenterologist immediately.

6. If, for any reason, you can no longer pariticpate in the study, please notify your gastroenterologist immediately.

YOUR HELP IS GREATLY APPRECIATED!

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