

DIFFUSE OESOPHAGEAL SPASM AND RELATED DISORDERS

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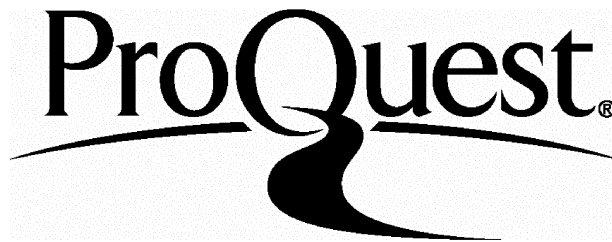
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ABSTRACT

A significant proportion of patients with non cardiac chest pain and/or dysphagia may have diffuse oesophageal spasm. Conventional techniques of endoscopy and barium studies had a low diagnostic yield for oesophageal motility disorders. Baseline oesophageal manometry using intraoesophageal microtransducers (Gaeltec) diagnosed diffuse oesophageal spasm in 66% of the patients. In view of the intermittent nature of the symptoms, provocative testing during manometry with a Bernstein acid perfusion test and edrophonium injection was used to increase the diagnostic accuracy. The edrophonium provocation test increased diagnostic yield by 34%.

Treatment was initially conservative and if this failed then balloon dilatation of the oesophagus was performed. Balloon dilatation relieved symptoms but reduced lower oesophageal sphincter pressure. Success was obtained in the absence of pathological reflux. Dilatation did not result in increased gastro-oesophageal reflux.

Many patients with the globus symptom have organic disease accounting for their symptoms. Spasm of the upper oesophageal sphincter secondary to gastro-oesophageal reflux and motility disorders of the oesophageal body have been postulated as causes for the globus sensation. Using the microtransducer system, it was possible to examine the upper oesophageal sphincter with greater accuracy. Patients with the globus symptom as a presenting symptom and normal pan-endoscopy were investigated with cine-barium, oesophageal manometry and ambulatory pH recording to assess oesophageal motility and reflux. The upper oesophageal sphincter complex was examined but all features, including coordination, were normal. An association between globus and gastro-oesophageal reflux has been demonstrated. No link could be shown between acid perfusion and upper oesophageal sphincter dysfunction. When compared to controls, the globus patients did not have increased psychological abnormality on two psychometry questionnaires. This suggests that the basis for globus may be related to a sensory abnormality in the pharynx in relation to reflux disease.

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STATEMENT OF ORIGINALITY

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university, or other institute of learning.

All work in this thesis is original, and was performed by me unless otherwise acknowledged.

This thesis was undertaken over a 2 year period whilst I was lecturer in surgery at Guy's Hospital, one year of which was spent in full time research.

J.C.LINSELL

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ABBREVIATIONS

C	Centigrade
cm	centimetre
F	French guage
in	inch
kg	kilogram
LOS	Lower oesophageal sphincter
µg	microgram
mg	milligrams
mls/min	millilitres per minute
mm	millimetre
mmHg	millimetres of mercury
N	Normal solution
n.s.	not significant
pH	degree of acidity or alkalinity of a substance
secs	seconds

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1: OESOPHAGEAL MANOMETRY

Interest in oesophageal motility disorders arose with the introduction of definitive motility studies in 1958 by Creamer et al, in 1960 by Olsen et al and in 1964 by Roth & Fleschler. The early systems used non-perfused catheters, which were highly compliant, to measure intraluminal pressures (Atkinson et al 1957, Winans & Harris 1967). Recent developments in instrumentation using low-compliance pneumohydraulic infusion pumps (Stef et al 1974, Arndorfer et al 1977) or miniature intra-oesophageal micro-transducers (Gaeltec), which minimise the damping effect, have allowed more accurate pressure measurements of the oesophageal body and lower and upper oesophageal sphincters.

There are many problems associated with the use of manometry.

These include:-

1. variations in the equipment and technique used to perform the manometric test which mean that no two centres' recordings are always strictly comparable;
2. lack of uniform criteria for defining the disorders;
3. The fact that motility disorders are defined by measuring pressures generated by intraluminal contractions which are the end point in a complex sequence of neuromuscular events. Oesophageal manometry records pressures simultaneously at several levels which permits evaluation of the oesophageal body as well as the proximal and distal sphincters. Thus, objective recording of pressures and swallowing wave patterns are obtained which can be compared to the normal. Pope (1974) described three areas where oesophageal

manometry had a role in the clinical evaluation of patients: first the preoperative documentation of patients with gastro-oesophageal reflux; second the evaluation of noncardiac chest pain and thirdly the diagnosis of those patients with suspected oesophageal motility disorders.

1.1.1: PHARYNGEAL FUNCTION.

Dodds et al (1975) measured pharyngeal contractions in human subjects using intraluminal strain gauges and found average pressures of 200mmHg with maximum pressures up to 600mmHg. Peristaltic wave speeds range from 9 to 25cm/sec. Frequently, before the single pharyngeal peak, an initial increase in pressure is observed: this is usually caused by the tongue thrust or the advancing bolus.

1.1.2: UPPER OESOPHAGEAL SPHINCTER FUNCTION

The upper oesophageal sphincter is a high pressure zone which separates the pharynx from the oesophagus. This sphincter corresponds anatomically to the cricopharyngeus muscle, a muscle sling attached posteriorly to both laminae of the cricoid cartilage exerting pressure mostly in an antero-posterior direction. Winans (1972) documented this asymmetry within the sphincter with 100mmHg pressures in the antero-posterior position and 33mmHg in the lateral orientation. When swallowing occurs, the tonic contraction of the sphincter disappears and the pressure falls to ambient resting pressure. At this time, pharynx and oesophagus become a common cavity and the rapidly progressing wave from the pharynx traverses the sphincter

area, pushing the bolus and closing the sphincter at the same time. The resulting pressures during sphincter closure are frequently double those of the resting pressures. When the peak pharyngeal contraction meets a totally relaxed sphincter area, normal coordination is said to be present.

1.1.3: OESOPHAGEAL BODY FUNCTION

An orderly, progressive contraction of the oesophageal body occurs in response to swallowing (primary peristalsis) or oesophageal distension (secondary peristalsis). Following the closure of the upper oesophageal sphincter, the oesophageal contraction travels down the oesophageal body at a speed of 2 to 5cm/sec. The contraction that occurs in response to deglutition progresses more slowly in the proximal striated muscle area and then becomes faster in the lower half, except just above the lower sphincter where it seems to slow again (Humphries & Castell 1977). In a similar fashion, peak contraction pressures are weak in the striated oesophagus and stronger in the distal oesophagus. Primary peristalsis or a normal peristaltic contraction in response to swallowing is seen in 95% of all swallows in the normal population (Richter et al 1987b). Secondary contractions occur more often in response to distension or irritation. Tertiary contractions may be an abnormal contraction in response to swallowing or may appear spontaneously in between swallows. The resting pressure in the oesophageal body reflects negative intrathoracic pressure. Obstruction, mechanical or functional, will result in increased resting pressures and abnormal body function.

1.1.4: THE LOWER OESOPHAGEAL SPHINCTER

The lower oesophageal sphincter is a zone of increased resting pressure 2 to 4cm⁽¹⁰⁻¹⁵⁾ located just proximal to the squamo-columnar junction in the distal oesophagus. Its main function is to act as a barrier to the reflux of gastric and duodenal content into the oesophagus. The level of basal tone recorded in the lower oesophageal sphincter is influenced by sphincter asymmetry (Winans 1977), oesophageal movement during contraction (Dodds et al 1974), the fasted state of the patient and the equipment used (Pope 1981, Meyer & Castell 1981a).

The normal resting sphincter pressure shows a range between 15 and 25 mmHg. During relaxation, which usually occurs immediately following swallowing, the pressure in the sphincter falls to ambient resting pressure. The sphincter remains open during the passage of the bolus from the oesophagus to stomach and it closes with the passage of the peristaltic wave. This creates a closing pressure following which the sphincter goes back to its normal resting pressure.

1.1.5: MANOMETRIC ABNORMALITIES IN ASYMPTOMATIC CONTROLS

The establishment of normality is obviously important as some features of the manometric pattern in diffuse oesophageal spasm may also be found in normal asymptomatic individuals. One of the problems in the diagnosis of abnormal oesophageal contractility has been the lack of studies on large numbers of normal healthy people. In general, diffuse oesophageal spasm affects patients over the

age of forty, whereas many of the control studies have been limited by small study populations and young age groups. Nagler & Spiro (1961), using a highly compliant system, found that non-peristaltic contractions could be recorded in young asymptomatic subjects (mean age 26 years). The most likely explanation for the high percentage of synchronous contractions in this study is that recordings were made after dry swallows.

Soergel et al (1964), studying 15 nonagenarians without gastro-oesophageal symptoms, found synchronous contractions in all of them with ten patients having 25% of swallows followed by a synchronous contraction. Cine-radiology showed abnormalities in 86%, with tertiary contractions being the most common. Abnormal X-ray and manometry findings in the asymptomatic elderly have produced further confusion in the diagnosis of diffuse oesophageal spasm. Hollis & Castell (1974) disagreed with Soergel's findings in elderly patients. They found a marked decline in amplitude of oesophageal contraction in healthy 80 year old patients but, unlike Soergel, found no increase in abnormal spontaneous motility. Many of Soergel's patients had dementia and this may be the explanation for his findings of disordered motility in the elderly population studied.

Richter et al (1987b) studied a group of 95 healthy controls with a mean age of 43 years and found that both distal mean contractile amplitude and duration of wet swallows significantly increased with age and peaked in the fifties. Triple peaked waves and wet swallow induced simultaneous contractions were seldom found and suggested an oesophageal

motility disorder. Double-peaked swallows were commonly found. Richter redefined abnormal amplitude in his laboratory as greater than 180mmHg calculated as the mean distal contraction amplitude + 2 standard deviation which has relevance for their definition of nutcracker oesophagus. Richter et al (1987b) found that 50% of their normal controls recorded spontaneous activity not associated with swallows during a rest period which they thought might be related to water perfusion via the manometry catheter.

1.1.6: WET OR DRY SWALLOWS

Even the use of wet (bolus of water) or dry (saliva) swallows has been shown to make a considerable difference to the recording. Dodds et al (1973) and Hollis & Castell (1975) have shown that wet swallows produce a complex of significantly greater amplitude and duration than do dry swallows. Wet swallows are usually associated with a higher incidence of normal peristaltic waves. Hollis & Castell (1975), using intraluminal transducers, found that peristaltic waves were produced following 97% of wet swallows and following only 71% of dry swallows. However, a 5ml bolus produced contractions of similar amplitude to a 20ml bolus. Richter et al (1987b), in a study of 38 normal controls, found that nonperistaltic contractions occurred after 18% of dry swallows and only 4% of wet swallows. This difference resulted from frequent simultaneous contractions after dry swallows. They recommended that wet swallows were used for the current evaluation of oesophageal peristalsis. It is therefore essential to use wet swallows (5ml boluses

of water) during manometric recordings.

SUMMARY:

The incidence of triplepeaked waves and simultaneous contractions is very low in asymptomatic controls as long as wet swallows are used. Double peaked waves are common. Normal control values over a wide age range need to be established for the equipment used. Most studies have shown that, although there is a large variation of results between individuals, the variation in repeated recordings on a single subject is not significant (Russell & Whelan 1987).

1.2: DIFFUSE OESOPHAGEAL SPASM

1.2.1: INTRODUCTION

"The differentiation between chest pain of cardiac origin and that of oesophageal origin may at times be difficult and may produce frustration for the doctor and anguish for the patient" (Evans 1952).

With the routine use of coronary arteriography it has become apparent that some patients, thought clinically to have coronary artery disease, have normal coronary arteries. The fact that changes in oesophageal motility may be associated with chest pain which mimics angina pectoris is well established (Castell 1984). The potential magnitude of this problem in the United States of America is calculated to be about 25,000 to 75,000 new cases of oesophageal motility disorders per year. Coronary angiograms are performed in about 500,000 patients with chest pain per year and normal coronary arteries are found in 10 to 30% of these patients. This latter group of patients has a low mortality but many remain severely disabled after investigation (Ockene et al 1980, De Caestecker et al 1985). The importance of making a diagnosis in these patients with chest pain and normal coronary angiograms is emphasised in a study by Ockene et al (1980). They followed up a group of patients with entirely normal angiograms and chest pain by questionnaire a mean of 16 months after their angiogram. All these patients had been informed that the investigations were normal and there was no evidence that their heart was responsible for symptoms. At follow-up 47% still described their activity as limited

by chest pain, 51% were unable to work and 44% still believed they had heart disease.

The identification of a non-cardiac source of pain may be of considerable benefit to these patients even if reassurance is the only available treatment (Katz & Castell 1984). It is estimated that up to 60% of patients with noncardiac chest pain will have an identifiable oesophageal abnormality (Blackwell & Castell 1984). With the increased interest in oesophageal investigation in Great Britain, oesophageal motility disorders may be diagnosed with increasing frequency.

Diffuse oesophageal spasm is characterised by symptoms of dysphagia and chest pain and occasionally may have characteristic appearances on barium swallow. The mainstay of diagnosis is oesophageal manometry.

1.2.2: HISTORICAL

The first reference to the disease was by Osgood in 1889. He described a group of patients with painful dysphagia and called the condition "oesophagismus". In 1934 Moersch and Camp described "Diffuse spasm of the lower part of the oesophagus". They found eight patients with intermittent dysphagia and chest pain who had similar abnormalities on radiology of multiple and variable abnormal contractions in the lower oesophagus. They considered this to be a separate condition from other causes of "oesophageal obstruction of neurogenic origin", for example achalasia.

1.2.3: CLINICAL FEATURES

The pain of diffuse oesophageal spasm varies from a mild substernal discomfort to a severe retrosternal crushing pain often misdiagnosed as myocardial infarction and is present in 80% of the patients. It may radiate into the neck, arms or through to the back. Eating and emotional stress are often triggers (Fleshler 1967). It may occur alone or in association with dysphagia. As the pain may be relieved by glycerine trinitrate it can be very difficult to distinguish clinically between angina and diffuse oesophageal spasm (Clouse et al 1985).

The patient may notice painful or painless dysphagia to both solids and particularly cold or carbonated liquids (Castell 1976). Almost half of a group of patients with dysphagia localised the problem to the cervical region above the suprasternal notch although the manometric abnormalities were in the distal oesophagus (Reidel & Clouse 1985). These symptoms are usually intermittent and seldom associated with weight loss (Waters & Demeester 1981).

1.2.4: RADIOLOGY

The radiological appearances on barium swallow are varied; they may be normal or they may show the characteristic simultaneous, nonperistaltic contractions that result in segmentation of the barium column in the lower half of the oesophagus. The primary peristaltic wave is halted at about the level of the aortic arch. When the lower two thirds of the oesophagus becomes passively distended with barium, a critical point is reached and then the lower oesophagus

diffusely contracts and barium passes into the stomach (McNally & Katz 1967). There may also be tonic segmental contractions with regurgitation back into the proximal oesophagus. The appearance may vary from a mild serration of the margins of the barium filled column (tertiary contractions) to more bizarre changes described as corkscrew oesophagus, curling, rosary bead oesophagus or pseudodiverticula, indicating that the contour is more irregular and the activity more erratic. The oesophagus remains narrow and the lower oesophageal sphincter functions normally in contrast to achalasia. One additional feature which is frequently present is the demonstration of thickening of the oesophageal wall due to muscular hypertrophy best shown on a lateral chest X-ray (Johnstone 1956, Henderson 1980) or more recently on CTscans of the chest (Reinig et al 1983). Similar appearances of irregular localised oesophageal contractions are sometimes seen in asymptomatic individuals particularly in the elderly, resulting in considerable diagnostic confusion (Templeton 1948). It seems unwise to use radiology alone to make the diagnosis.

1.2.5: MANOMETRIC CLASSIFICATION OF DIFFUSE OESOPHAGEAL SPASM

Technical advances have allowed more accurate pressure recordings and have facilitated the better identification and classification of motility disorders.

Because of the problems with making a diagnosis on manometric criteria, various different systems have been

developed over the years in an attempt to provide an international classification system. Richter & Castell (1984) reviewed twelve reported series of patients with diffuse oesophageal spasm looking at the criteria used for diagnosis. From this information and their large studies of normal individuals (Richter et al 1987b), they suggested that all patients with possible oesophageal symptoms i.e. dysphagia or chest pain must show simultaneous contractions after wet swallows on manometry for the diagnosis of diffuse oesophageal spasm to be considered. They suggested that an incidence of simultaneous contractions greater than 10% would be well above the average range of normal individuals. Simultaneous contractions must be interspersed with normal peristalsis to differentiate diffuse oesophageal spasm from vigorous achalasia. Repetitive contractions, spontaneous activity, contractions of high amplitude and long duration, and abnormalities of lower oesophageal sphincter function may be seen.

To try to avoid the situation described by Castell (1985) as "one man's spasm may be another man's nutcracker", Clouse & Staiano (1983) used a descriptive manometric classification based on manometric features observed in the oesophageal body. The patient's manometric records were first classified on the presence or absence of peristalsis. The group with peristalsis was subdivided, depending on abnormalities in the oesophageal body, into six groups. Group B (distal contraction abnormalities) was further divided depending on the presence of:-

1. increase in mean distal wave amplitude,

2. increase in mean distal wave duration,
3. number of abnormal motor responses (repetitive or simultaneous contractions),
4. the presence of triple peaked waves.

Severity was scored by the cumulative number of these abnormalities. 119 of 210 patients referred for manometry were found to have one or more abnormalities of distal contraction. Patients with all four abnormalities in group B, i.e. diffuse oesophageal spasm, represented less than five per cent of the patients. Symptoms were similar for all the distal contraction abnormalities. The authors thought their system allowed for recognition of the spectrum of distal contraction abnormalities without reliance on the present nomenclature. This may be useful for comparisons between studies but has not been shown to help with aetiology or treatment.

Vantrappen et al (1979) devised a system for analysis directed towards three parameters: oesophageal peristalsis(P), lower oesophageal sphincter relaxation(R) and the vigorous (V) or nonvigorous (v) character of the manometric response to a swallow. Vigorous characterised either a repetitive wave or a wave of amplitude of more than 70mm Hg or duration 6 seconds.

Using this scheme:-

Achalasia =pr: ie without peristalsis and without relaxation of LOS,

Diffuse oesophageal spasm =PR :ie with some peristalsis and relaxation of LOS.

Vantrappen devised this scheme using the manometric findings

in a group of patients with oesophageal motility disorder who had severe dysphagia requiring dilatation. A similar system was used by Henderson (1980 p186).

The advantages of systems adopted by Vantrappen et al (1979), Clouse & Staiano (1983) and Henderson (1980) are that the large number of patients whose manometry does not fit within the strict criteria of diffuse oesophageal spasm or achalasia can be classified and compared. However, the large variety of classification systems has made the situation confusing and Castell's manometric criteria for the diagnosis of diffuse oesophageal spasm ^{have} ~~has~~ become standard (Richter & Castell 1984).

1.2.6: MANOMETRIC FEATURES

Using a highly compliant system and mainly dry swallows, Creamer et al (1958) identified the manometric features in symptomatic and asymptomatic patients who had X-ray appearances of diffuse oesophageal spasm. They defined a simultaneous (synchronous) contraction as one where there was a difference of 0.2 secs or less in onset or peak of contractions recorded from orifices 5 cm apart. All the patients showed simultaneous contractions in the distal oesophagus and also prolonged duration of the contractions in this region. The simultaneous waves were interspersed with normal peristaltic contractions suggesting that the oesophagus had not completely lost its ability to function normally. The presence of symptoms was associated with an increased incidence of both simultaneous and repetitive contractions.

Mellow (1977), using dry swallows and a perfused catheter suggested that a mean oesophageal contraction duration of more than 7.5 seconds indicated diffuse oesophageal spasm in association with 30% abnormal responses either repetitive or synchronous contractions. The value 7.5 seconds was used as it was greater than 2 standard deviation from the mean of 20 randomly selected normal studies in his laboratory.

1.2.7: THE LOWER OESOPHAGEAL SPHINCTER

The lower oesophageal sphincter pressure and relaxation are normal in about 70% of patients with diffuse oesophageal spasm (Cohen 1979). Dimarino & Cohen (1974) found impairment of the lower oesophageal sphincter relaxation in 10 of 27 patients with diffuse oesophageal spasm. Nine of these patients also had a raised resting lower oesophageal sphincter pressure. These findings may suggest that diffuse oesophageal spasm belongs to a spectrum of motility disorders with achalasia as a common end point in some patients.

SUMMARY:

Wet swallows must be used under standard conditions and the diagnosis of diffuse oesophageal spasm should fulfil definite criteria. The correlation of symptoms with abnormal manometry would appear to be very important in view of abnormal findings in asymptomatic individuals and the present lack of evidence that chest pain is caused by certain manometric abnormalities.

1.2.8: INCIDENCE OF DIFFUSE OESOPHAGEAL SPASM.

Both Clouse & Staiano (1983) and Castell (1985) have found that diffuse oesophageal spasm is an uncommon diagnosis accounting for about 12% of all cases of oesophageal motility disorder. The percentage of cases defined as diffuse oesophageal spasm has decreased as the criteria for diagnosis have become more rigidly defined. Clouse & Staiano (1983) and Castell (1985) found that nutcracker oesophagus (high amplitude peristaltic contractions in the distal oesophagus) was found in about 34% of all patients with oesophageal motility disorders. Ten per cent of both groups had achalasia. The remaining categories of oesophageal motility disorders were hypertensive lower oesophageal sphincter 8% and the largest group, nonspecific motility disorders 36%. Katz et al (1987), in a retrospective review of 255 patients with noncardiac chest pain and abnormal manometry, found 48% had a nutcracker oesophagus and 10% had diffuse oesophageal spasm. However, in a group of 132 patients from the same unit with dysphagia, 36% had achalasia and 13% had diffuse oesophageal spasm. Nutcracker oesophagus was an infrequent finding (10%) in patients with dysphagia.

1.2.9: CORRELATION BETWEEN MANOMETRY AND OTHER METHODS OF INVESTIGATION

Roth & Fleshler (1964), using cine-radiology and simultaneous oesophageal manometry, found that a barium bolus in 7 of 9 patients with diffuse oesophageal spasm was at times kneaded backwards and forwards and even forced up

into the upper oesophagus. This coincided with manometry showing simultaneous contractions in the distal oesophagus. If the high amplitude pressure peaks were peristaltic then they were followed by normal oesophageal transit of barium. Richter et al (1983a) found similar results using oesophageal manometry and concurrent radionuclide transit studies. This has the advantage over cine-radiology in giving minimal radiation exposure. Richter et al (1983a) found that as long as the oesophageal contractions were peristaltic then the liquid bolus transit time was normal (8-12 seconds). Simultaneous contractions in patients with diffuse oesophageal spasm resulted in prolonged radionuclide transit (more than 50 seconds) and were associated with to and fro bolus movement. Drane et al (1987) performed radionuclide oesophageal scintigraphy and manometry within a week on 31 patients with nutcracker oesophagus diagnosed by mean distal amplitudes of greater than 120mmHg. They found delay in bolus transit in 81% of patients who had amplitudes more than 150mmHg and in only 20% of those below this level. Benjamin et al (1983) found prolonged radionuclide transit in the distal oesophagus in 94% of patients with nutcracker oesophagus. This was commonly related to chaotic bolus transit. They felt that this might be related to spontaneous simultaneous contractions which were seen in 50% of this group. These contrary findings may be related to the lack of simultaneous recordings so that manometry may have changed and raised doubts about the diagnosis of nutcracker oesophagus as opposed to diffuse oesophageal spasm. Richter & Castell (1984) have suggested that synchronous

contractions are likely to account for symptoms of dysphagia because of delayed bolus clearance. The initially favourable results using radionuclide transit studies in the diagnosis of motility disorders have not been maintained.

1.2.10: CORRELATION BETWEEN SYMPTOMS AND MANOMETRY

A definitive answer can be given only when the patient has an attack of typical chest pain during oesophageal manometry in conjunction with the appearance of a new manometric abnormality. There is no way to be sure that the chest pain is due to abnormal motility if the patient is asymptomatic during testing or the motility disorder occurs during both symptomatic and asymptomatic periods. The production of ambulatory manometry systems enables recordings of oesophageal motility during spontaneous chest pain.

Richter et al (1983b) have shown that edrophonium induced chest pain, in patients with normal coronary arteriograms, correlates with significant prolongation of oesophageal contraction duration during manometry. Brand et al (1977) have suggested that the amplitude of distal contractions may directly correlate with pain severity. Abnormal motor activity with repetitive or synchronous contractions may be responsible for pain if it occurs during symptomatic periods.

Unfortunately these abnormalities can also be found in asymptomatic subjects (Nagler & Spiro 1961) and therefore Clouse et al (1983) studied nine patients with daily attacks of chest pain. These patients were thought clinically to have chest pain secondary to oesophageal "spasms" as they

had normal cardiac investigations and 78% of the group also had dysphagia. The patients had had normal barium studies with negative endoscopy or oesophageal acid perfusion tests. Five of the patients had abnormalities on conventional manometry. These patients developed typical pain whilst undergoing prolonged manometry. Changes in the manometry pattern prior to and during an episode of pain were compared blindly with a control painfree period in the same patient. There was no significant difference observed in distal oesophageal wave duration or amplitude or in frequency of abnormal peristalsis during an attack of chest pain when compared with painfree periods during a mean monitoring time of 227 minutes. Clouse et al concluded that the presence or absence of motility abnormalities on standard manometry did not indicate that a patient's chest pain was due to this abnormality and they were unable to show an association between chest pain and manometric abnormality. These findings may indicate that high amplitude long duration spasms with abnormal peristaltic features are not the direct cause of chest pain in patients with suspected oesophageal pain. Worsening of the already abnormal control manometry does not seem to be responsible for the pain. Further support for this explanation is the lack of improvement in manometric findings with clinical improvement in symptoms on various medical treatments (Mellow 1982). Perhaps the easiest explanation is that, despite all the indications that oesophageal chest pain was the most likely finding in these patients, this was not the case.

One of the problems of correlation of manometric findings

with symptoms is the fact that symptoms are intermittent and therefore often absent during a standard manometric recording. The advent of ambulatory recording should help to show if there is correlation between symptoms and manometry. Peters et al (1988) studied 24 patients, who had daily substernal chest pain, with a 24 hour ambulatory oesophageal motility and pH system. Spontaneous chest pain episodes were correlated with pH less than 4 and abnormal motility changes which were different from the patient's baseline manometry. Twenty two patients experienced a total of 92 spontaneous chest pain episodes. 12% occurred with abnormal motility, 20% with pH less than 4 and 4% with both abnormalities. However, the majority of chest pain events, (64%), had no association with abnormal motility or change in pH. Abnormal high amplitude and long duration contractions were the motility changes most commonly associated with chest pain. They concluded that motility disorders were an infrequent cause of oesophageal chest pain and acid reflux was a more commonly identifiable cause.

Janssens et al (1986) used a similar combined ambulatory system to study 60 patients with non-cardiac chest pain. Only half of these patients experienced pain daily. Janssens et al compared the ambulatory results with those obtained with conventional non-ambulatory manometry.

An oesophageal origin for the pain was considered if :

- a. the usual pain was reproduced by an acid perfusion test,
- or b. the pain occurred during an episode of reflux,
- or c. the pain occurred with a motility abnormality,
- or d. with both reflux and a motility disorder.

The twenty four hour recordings showed a positive correlation of chest pain with pH less than 4 (22%) or a motor abnormality distinct from the baseline recording (50%) or both (28%). This group analysed the chest pain episodes associated only with oesophageal events i.e. severe motor abnormality or reflux episode. The 24 hour recording showed the oesophagus to be the likely cause of the pain in 35% of patients. Conventional manometry showed that an oesophageal origin for the pain was likely in 27% of patients. The combination of conventional and ambulatory recordings made an oesophageal origin of pain likely in 48% of patients.

SUMMARY:

Correlation between symptoms and manometry remains difficult particularly as symptoms tend to be intermittent and seldom occur during manometric recordings. This may be less of a problem with ambulatory recordings of longer duration allowing the patients to eat and drink and carry out other activities which may provoke symptoms although this may not help those patients whose symptoms occur only infrequently. The intermittent nature of symptoms has led to the development of provocation testing.

1.2.11: PROVOCATION TESTS

One of the problems with making the diagnosis of diffuse oesophageal spasm is the intermittent nature of symptoms and this has led to the development of various provocation tests to try to produce abnormal oesophageal motility and also to reproduce the patient's typical pain. Many patients report that they have intermittent chest pain but do not have

symptoms during a motility study which may show baseline abnormalities. If symptoms occur during an abnormal recording then a causal relationship is more easily made. Therefore a wide variety of provocation tests have been devised. The specificity, sensitivity and safety of a provocative agent must also be considered. The clinical usefulness of provocative testing in the evaluation of noncardiac chest pain is a difficult area to evaluate. The three major problems are those of patient selection, the choice of provocative agent and the lack of a "gold standard" (Lee et al 1987).

1.2.11a: ICE COLD LIQUIDS

Kaye et al (1987) found that boluses of ice cold water caused reduced amplitude, increased duration and reduced velocity of distal oesophageal contractions in normal controls and in two patients with diffuse oesophageal spasm when compared to water at room temperature. Some patients' symptoms are improved with cold water. Winship et al (1970) found similar results with cold water in normal controls. Meyer & Castell (1981) showed that swallows of cold ice cream (-5degrees C) decreased the peristaltic amplitude particularly in the mid-oesophagus. Continued ingestion of ice cream until chestpain developed was associated with a complete absence of motor activity in the distal oesophagus with a slow return to normal although this pain probably represents a different modality.

1.2.11b: HOT WATER

Winship et al (1970) found that hot water increased the speed of wave propagation, reduced the duration of contraction and produced a shorter period of relaxation of the lower oesophageal sphincter. They thought that the changes in motor function were probably secondary to changes in smooth muscle contractility with temperature variation as the upper oesophageal sphincter and most proximal oesophagus were unaffected by the temperature changes.

1.2.11c: ACID PERFUSION TEST

Bernstein & Baker (1958) proposed acid perfusion of the oesophagus as an objective test for the localization of chest pain. Reproduction of the patient's symptoms with acid perfusion constituted evidence for the oesophageal origin of these symptoms. Siegel & Hendrix (1963) found that acid perfusion of the oesophagus in patients with heartburn reproduced their symptoms and also produced manometric abnormalities in all patients. These consisted of increased amplitude of contractions, increased resting oesophageal pressure and the production of synchronous activity when the patients were symptomatic. The increase in resting pressure suggests that there was fluid retention in the oesophagus although this was not seen during a placebo perfusion with saline at the same rate or that acid induces spasm in an effort to clear the oesophagus of acid. Histological evidence of inflammation was found in 70% of cases. Four of 25 control subjects also produced some manometric abnormality in both the saline control and acid perfusion. Kjellen & Tibbling (1985), using a perfused system, studied

three groups of patients separated by their response to acid perfusion. Group 1 (asymptomatic during perfusion) showed no significant motility abnormality in response to 4 wet swallows before or after perfusion. Group 2 (heartburn during perfusion) and Group 3 (chest pain during perfusion) showed significant changes in motility which included higher peristaltic amplitude, longer contraction duration and slower peristaltic velocity. Lower oesophageal sphincter hypotension, measured prior to perfusion, was significantly commoner in groups 2 and 3 than 1 suggesting that heartburn and chestpain were secondary to reflux and not symptoms of motility disorders although acid induced spasm was a possibility. Interestingly, chest pain always developed after heartburn and remained after the perfusion had ceased. There was no temporal correlation between symptoms and manometric abnormality with symptoms occurring throughout the perfusion period and the manometric abnormality mainly shown in response to wet swallows. Atkinson & Bennett (1968) found that 60% of a group of patients with reflux oesophagitis had an overall increase of motility during acid perfusion compared to saline control which may be a protective response to clear acid. They found nonperistaltic contractions in the absence of pain and only in a minority could any change in manometry be detected at the onset of pain. Sodium bicarbonate infusion relieved the patient's pain without any effect on motility and propantheline abolished motility without relieving pain suggesting that motor changes are not an essential part of the pain mechanism.

Benjamin et al (1983a) performed intraoesophageal acid perfusion, with 0.1N Hydrochloric acid, in 23 patients with noncardiac chest pain who had abnormal baseline manometry. Gastro-oesophageal reflux had been excluded on symptoms and endoscopy. Perfusion produced substernal burning in three patients with a change in the motility pattern in one patient. Richter et al (1985c) found that a Bernstein test performed on 50 patients with chest pain was positive in 22% of patients. Seventeen had reproduction of their usual heartburn, 5 had their typical chest pain and 7 developed both heartburn and chest pain. Chobanian et al (1986) and De Caestecker et al (1988) studied patients with non-cardiac chest pain. 12-35 % produced a positive response after acid perfusion defined as symptom reproduction with or without abnormal motility. Katz et al (1987) reviewing 910 patients investigated for noncardiac chest pain found that only 6.7% had had their chest pain reproduced by acid infusion. All these patients had had cardiac investigations but it has been shown by Mellow et al (1983) that intraoesophageal acid perfusion can produce chest pain indistinguishable from coronary artery pain and may induce ST and T wave changes indicative of myocardial ischaemia and increased myocardial workload. Davies et al (1985) found that oesophageal perfusion with acid reduced the exertional angina threshold in patients with coronary artery disease especially if they experienced regular oesophageal symptoms. Therefore the Bernstein test should be interpreted with care in patients who have not had cardiac investigations. One should never accept gastro-oesophageal reflux as the only cause of chest

pain without ruling out cardiac disease.

1.2.11d: PENTAGASTRIN AND BETHANECHOL

Pentagastrin and Bethanechol, a cholinergic agonist, have also been tested as provocative agents. Bethanechol produced an increase in amplitude and duration of oesophageal contractions compared with saline control in a small study on normal subjects (Hollis & Castell 1976). Eckhardt & Weigand (1974) found that both subcutaneous and intravenous injections of pentagastrin when given to a patient with diffuse oesophageal spasm were followed by powerful spontaneous irregular contractions on manometry which were inhibited by atropine and abolished by nitroglycerine. They also found that, when pentagastrin was administered before a barium swallow, the classical appearances of diffuse oesophageal spasm were produced. They concluded that the pentagastrin effect was possibly mediated by acetyl choline release as it was inhibited by atropine. Orlando & Bozymski (1979) found that pentagastrin (6 μ g/Kg subcutaneously) produced an increase in mean lower oesophageal sphincter pressure, amplitude of contractions and repetitive wave forms in nine patients with diffuse oesophageal spasm diagnosed on either radiology or manometry and also produced chest pain or dysphagia in four of these. Placebo testing with saline failed to reproduce these abnormalities. To evaluate pentagastrin as a provocative test for diffuse oesophageal spasm, it was administered to twenty two patients with a possible clinical diagnosis of oesophageal motility disorder who had had nondiagnostic radiology and

manometry. In none of these patients did symptoms or abnormal manometry occur suggesting that these patients did not in fact have an oesophageal motility disorder.

Wexler & Kaye (1981) studied the effect of a continuous intravenous infusion of pentagastrin (1-10 μ g/Kg/hour) on oesophageal motility in six patients with diffuse oesophageal spasm. Unlike Eckhardt & Weigand (1974) and Orlando & Bozyski (1979) they found very few differences between contraction amplitudes and duration with pentagastrin and saline placebo. Two patients developed dysphagia and repetitive contractions during saline infusion and the lowest pentagastrin infusion which was thought to be due to inadequate clearance of wet swallows in the supine position. The most likely reason for their conflicting results is the different doses of pentagastrin used between a continuous infusion and a bolus injection. Mellow (1977) studied eight patients with diffuse oesophageal spasm as defined by the presence of some peristalsis and at least 30% abnormal repetitive or synchronous contractions. He compared the effect of injections of bethanechol (a cholinergic agonist), edrophonium (a cholinesterase inhibitor) and saline placebo on these patients with the effect on patients with heartburn and on normal controls. Both edrophonium and bethanechol produced an increase in contraction duration and amplitude in those patients with diffuse oesophageal spasm as opposed to the other patients. In those patients with diffuse oesophageal spasm, chest pain occurred in 6 of 8 patients after edrophonium and in 3 of 6 after bethanechol. None of the other patients experienced chest pain and no

pain occurred after placebo.

Benjamin et al (1983a) studied thirty four consecutive patients with a suspected oesophageal motility disorder who complained of chest pain and/ or dysphagia. Baseline manometry was followed by provocation with bethanechol, pentagastrin and edrophonium. Baseline recordings were abnormal in twenty three patients (nutcracker oesophagus 10 patients, nonspecific motility disorder 13 patients). Edrophonium was most effective as a provocative agent producing chest pain with new manometric abnormality in 18% of patients. Only one patient who had normal baseline manometry developed pain and a manometric abnormality after edrophonium. Pentagastrin produced chest pain with abnormal manometry in two patients and bethanechol in one. These 3 patients had also responded to edrophonium.

Conclusion: Injections of bethanechol and pentagastrin have been shown to amplify the motility abnormality in patients with a known diagnosis of diffuse oesophageal spasm but they have not been shown to be effective as provocative agents.

1.2.11e: ERGOMETRINE

Since the chest pain of diffuse oesophageal spasm can closely mimic angina, ergometrine has been used as a provocative agent for the diagnosis of diffuse oesophageal spasm. Ergometrine (ergonovine) can induce coronary artery spasm during cardiac catheterisation in patients with angina. Up to a third of these patients may develop chest pain following an injection of ergometrine without demonstrable coronary artery spasm or electrocardiographic

change. Fourteen patients who had received ergometrine during cardiac catheterisation without the production of coronary artery spasm underwent oesophageal manometry. Following an injection of ergometrine five of these patients developed their usual chest pain with an associated manometric abnormality of diffuse oesophageal spasm. Two of these five patients also developed marked ST segment elevation which was relieved by nitrates. Both these patients had had their coronary angiograms performed under nitrate cover which could have concealed that their chest pain was in fact due to coronary artery spasm. These findings suggest that certain patients may have a smooth muscle disorder of both the oesophagus and coronary arteries which renders them susceptible to both coronary artery and oesophageal spasm. Also of interest, two of the remaining patients and one of the controls developed a manometric abnormality of diffuse oesophageal spasm without symptom reproduction, suggesting a lack of specificity (Eastwood et al 1981).

Because of the potential hazards with ergometrine injection i.e. coronary artery spasm or even death, Davies et al (1982b) recommended that normal coronary angiography should be a prerequisite of its use together with careful cardiac monitoring. Eastwood et al (1981) suggested that ergometrine should be given only in a cardiac catheter laboratory in case intra coronary vasodilators are required, making it impractical for routine use. Following the use of ergometrine in forty two patients with non cardiac chest pain, twenty four had reproduction of their pain with

abnormal manometry. However 40% of the asymptomatic controls had ergometrine produced motility changes and 20% developed chest pain for the first time (Davies et al 1982b).

Conclusion: The production of abnormal motility and symptoms in previously asymptomatic normal controls as well as the potential hazards of ergometrine injection mean that it is not an ideal provocative agent.

1.2.11f: EDROPHONIUM

The effect of intravenous injections of edrophonium on normal human oesophageal peristalsis was studied by Hollis & Castell (1976). They found that following edrophonium there was a marked increase in amplitude of oesophageal contractions associated with a significant reduction in velocity of oesophageal peristalsis and also a significant increase in the duration of the contraction wave following a swallow. Increasing the dose of edrophonium resulted in significant increases in peristaltic amplitude with the maximal responses occurring at doses of 80 and 160 µg/Kg.

London et al (1981) showed that both edrophonium 10 mg and ergometrine provoked chest pain in association with high amplitude, long duration and repetitive contractions in 10 patients with ergometrine-induced chest pain without coronary artery spasm. This suggests that those patients who had a positive provocation test with ergometrine would also have a positive test with edrophonium.

Lee et al (1987) studied the effect of 10mg edrophonium on 120 patients with noncardiac chest pain and normal baseline manometry although high amplitude contractions were not

excluded. Patients with gastro-oesophageal reflux or a positive Bernstein test were excluded. A positive response required the production of chest pain associated with changes in manometry greater than two standard deviations from the control response to an intravenous bolus of saline. A positive response was observed in 34%, a negative response in 49% and an indeterminate response (either pain or manometric abnormality) in 17% of patients. Following edrophonium, the change in amplitude and duration, and number of repetitive contractions was significantly greater in positive responders. However, baseline manometry, including high amplitude contractions, did not predict a positive response.

Richter et al (1985c) found that edrophonium induced chest pain in 30% of patients with non-cardiac chest pain and normal coronary angiography, and increased the distal oesophageal amplitude and duration of peristaltic contractions. In this series no synchronous contractions were produced. The frequency of edrophonium-provoked chest pain was similar between the patients with normal baseline manometry and those with baseline oesophageal motility disorders. Those patients with a positive edrophonium test had a significantly higher incidence of heartburn and dysphagia than those with a negative result. Edrophonium (80µg/Kg of body weight intravenous bolus) increased oesophageal amplitude and repetitive contractions to a similar degree in both patients and controls but contraction duration was significantly greater in those patients who were edrophonium positive. This suggests that the manometric

response represents the cholinergic action of edrophonium on the oesophageal smooth muscle. Because no controls developed chest pain, Richter et al defined a positive test as one which reproduced the patient's symptoms.

Using this criteria, 29% of patients would have had a positive test in Benjamin's study instead of the 18% Benjamin et al report (1983a). Richter et al (1985c), in a further study of 125 consecutive patients with chest pain, found that 2 had chest pain after the placebo and 5 had chest pain after both the placebo and edrophonium giving a false-positive result of 6%.

De Caestecker et al (1988) performed oesophageal manometry, with provocation with edrophonium and with acid perfusion, on 60 consecutive patients with noncardiac chest pain. A positive response was defined, as with Richter et al (1985c), as symptom production with or without abnormal manometry. A positive response was present in 12 patients (20%) after edrophonium and 21 (35%) after acid perfusion. 92% of patients who responded to edrophonium also responded to acid perfusion. Positive responders recorded significantly greater increases in contraction duration after both edrophonium and acid perfusion. Richter et al (1985c) also noted that patients with a positive edrophonium test were likely to have a positive Bernstein test.

The specificity of edrophonium was assessed in 9 patients during cardiac catheterisation but no significant change was seen in coronary artery diameter, blood pressure or heart rate (Richter et al 1985c).

Mellow (1977), studying 8 patients with diffuse oesophageal

spasm, found that only 75% produced a positive edrophonium (100µg/Kg) provocation test. London et al (1981) found that 67% of patients with diffuse oesophageal spasm developed chest pain during provocation with both ergometrine and edrophonium. This may be because diffuse oesophageal spasm is an intermittent finding or edrophonium is not specific enough or powerful enough.

The different studies report different positive provocation results. This is partly due to the selection of the patient groups studied. These may be noncardiac chest pain groups after exclusion of gastro-oesophageal reflux (Lee), or included (Richter); with normal baseline manometry (Lee) or with manometry compatible with oesophageal motility disorder (Mellow, Benjamin, London) and with varying evidence of absence of cardiac disease. The use of either wet (Richter) or dry (Lee) swallows may explain the different manometric changes found after edrophonium injection in normal controls and patient groups. Note must also be taken of the dose of edrophonium used as this may affect the results produced. One major difference has been in the definition of a positive edrophonium provocation test. Richter and De Caestecker required only the production of typical chest pain for a positive result whereas Lee and Benjamin required both the production of chest pain and an alteration from baseline manometry for the provocation test to be positive. The mechanism of action remains unclear although the production of ischaemia by increase in mean contraction duration causing pain is a possibility. This hypothesis is weakened by the large overlap of peristaltic parameters in

all groups studied. Another possible explanation is that patients with high amplitude oesophageal contractions may be more sensitive to stimuli arising in the oesophagus. Studies by Vantrappen et al (1987) using 24 hour combined manometry and pH measurement have identified a group of patients who have positive edrophonium tests but who have gastrooesophageal reflux without motor disorder at the time of spontaneous chest pain. Irritability of the oesophagus may play a part in the production of chest pain. Since edrophonium is given systemically it is not possible to be certain that the oesophagus is the only source of chest pain.

Edrophonium has several advantages over ergometrine including specificity, relative safety, ease of administration and short duration. It seems to be relatively specific with no chest pain reported in controls (Richter et al 1985c). It also appears not to produce myocardial ischaemia or coronary artery spasm which is important when differentiating between a cardiac or oesophageal abnormality in patients with chest pain. Most studies report mild side effects after edrophonium including lightheadedness, nausea and abdominal cramps (London et al 1981, Benjamin et al 1983a, Richter et al 1985c).

SUMMARY:

To use edrophonium as an effective provocation agent, the dose must be standardised, wet swallows must be used and strict criteria for diffuse oesophageal spasm fulfilled, after excluding gastro-oesophageal reflux with 24hr pH testing. The whole oesophagus must be studied and the

requirements for a positive provocation test defined with the production of the patient's usual pain and change in manometry necessary.

1.2.11g: BALLOON DISTENSION

Recently balloon distension of the oesophagus has been suggested as a selective provocation test. Balloon distension was shown in 1955 (Kramer & Hollander and Baylis et al) to produce chest pain. Kramer found some patients with coronary artery disease could not distinguish between their angina and the oesophageal pain of distension despite showing no changes in their electrocardiograms during distension. In Kramer's study the balloon was distended with up to 40mls of water.

Barish et al (1986) studied the effect of a polyvinyl balloon placed 10cm above the lower oesophageal sphincter on 50 patients with noncardiac chest pain and 30 healthy controls. The balloon was inflated in 1 ml increments of air to a total of 10mls. Using a placebo-controlled design, pain response was recorded as well as associated balloon volumes. Pain occurred in 56% of the patients and 20% of the controls. Symptoms were unassociated with cardiograph changes and resolved completely on decompression of the balloon. Most of the patients experienced their usual symptoms at 8ml distension whilst the controls all experienced pain above 9ml distension. Therefore an abnormal response to balloon distension was considered if pain occurred at a cut off level of 8ml distension. The patients with chest pain also underwent provocation with acid

perfusion and edrophonium with reproduction of their symptoms in 12 patients with one or both agents. A positive balloon distension test occurred in 11 of these patients as well as identifying an additional 13 patients. Only 1 of the negative patients had another positive provocation test. There seems to have been good reproducibility from this study. It is recommended that balloon distension is performed only after a cardiac aetiology for the pain is excluded. This will avoid problems in those patients who might perceive the balloon distension pain as their typical symptom of angina.

Richter et al (1986a) found that patients with chest pain seemed to be more sensitive to smaller volumes of balloon distension than controls. They felt that the mechanism of pain production could be related to a lower pain threshold to distension in the chest pain patients which was independent of oesophageal contractions.

Edwards (1982) described a group of patients with painful dysphagia in whom symptoms could be reproduced by inflating a balloon at different points in the oesophagus. Not only was their pain duplicated but these patients were consistently sensitive to a balloon diameter unnoticed by normal subjects or patients with oesophagitis. He described this group of patients as those with a "tender oesophagus".

CONCLUSION:

Edrophonium at the present seems to be the best provocative agent available. It is relatively safe, has a short duration of activity and produces only mild transient side effects. It has a high specificity and in highly selected groups of

patients with diffuse oesophageal spasm the positive provocation test rate reaches 75%. Edrophonium does not affect the heart which could cause problems when differentiating between oesophageal and cardiac pain. Most studies have not produced symptoms in the control subjects although baseline manometry may alter, in particular producing increased peristaltic amplitude. Most studies have required the reproduction of symptoms as well as abnormal manometry for a positive test result.

The use of provocative agents has improved the diagnostic ability of Castell's unit in patients with noncardiac chest pain from 25% to 35% (Richter et al 1985c).

1.2.12: DIFFUSE OESOPHAGEAL SPASM AND ACHALASIA

Some researchers have considered that diffuse oesophageal spasm and achalasia represent two ends of a spectrum of motility disorders with predominant lower oesophageal sphincter dysfunction and aperistalsis (achalasia) at one end and predominant spastic activity (diffuse oesophageal spasm) at the other (Castell 1979). There is considerable evidence that these two diseases are interrelated. The methacholine test, once considered pathognomonic for achalasia, has been shown to be positive in 80% of patients with diffuse oesophageal spasm as measured by balloon-kymography (Kramer et al 1967a). In 1967(b) Kramer et al documented the manometric transition of a patient from diffuse oesophageal spasm to achalasia. Sanderson et al (1967) described a condition called vigorous achalasia which demonstrated a merging of features of both conditions.

Lower oesophageal sphincter abnormalities, similar to those of achalasia, have been found in some patients with diffuse oesophageal spasm (Dimarino & Cohen 1974). Many patients show clinical and manometric features of both diffuse oesophageal spasm and achalasia. These concepts are supported by Vantrappen et al's (1979) careful observations on a group of 156 patients with motility abnormalities and dysphagia in whom therapeutic dilatation was performed. 24% of these patients did not fit the criteria for either diffuse oesophageal spasm or achalasia. Six of the patients with diffuse oesophageal spasm followed over a period of several months showed a transition to achalasia adding further evidence for these disorders being related.

A further subset of nonspecific oesophageal motility disorder, characterised by high-amplitude peristaltic contractions and referred to as "nutcracker oesophagus", has been reported as a common primary motor disorder (Brand et al 1977, Benjamin et al 1979). It is unclear whether nutcracker oesophagus is a specific entity or just a variant of diffuse oesophageal spasm. Narducci et al (1985) have reported a case which shows transition from nutcracker oesophagus to diffuse oesophageal spasm during a year. Traube et al (1986) also reported a patient whose manometry changed from nutcracker oesophagus to diffuse oesophageal spasm. However, they diagnosed nutcracker oesophagus if there was peristalsis after more than 75% of wet swallows and if the amplitude was greater than 120mm Hg. Diffuse oesophageal spasm was diagnosed if simultaneous contractions occurred after more than 25% of wet swallows as long as some

peristalsis remained. Landau & Clouse (1982) found, on repeated studies of seven patients initially diagnosed as having nutcracker oesophagus, that two patients had developed repetitive or synchronous waves in response to more than 30% of swallows i.e. diffuse oesophageal spasm. Anggiansah et al (1990) report transition from nutcracker oesophagus to achalasia suggesting a possible pathophysiological relationship between nutcracker oesophagus and achalasia.

1.2.13: NUTCRACKER OESOPHAGUS

High amplitude peristaltic contractions referred to as nutcracker oesophagus are common findings in patients with angina like chest pain and normal cardiac catheter results. The manometric characteristics have altered as studies of large groups of older normal controls and more accurate equipment have increased the upper limit for normal contraction amplitude. Richter et al (1987b) have raised the diagnostic criteria for amplitude to more than 180mmHg. The relationship between high distal oesophageal pressures and chest pain appears to be tenuous at present (Koch 1988). Ferguson & Little (1988) found 23% of 123 consecutive patients to have high-amplitude peristaltic contractions either mean distal contraction greater than 120mmHg or maximal oesophageal amplitude greater than 200 mmHg during at least one contraction. A third of these patients had pathological gastrooesophageal reflux on 24hour pH monitoring. Despite this finding heartburn was not a major subsidiary symptom.

Drane et al (1987) and Dalton et al (1988) have shown a lack of reproducibility of manometric findings for the evaluation of nutcracker oesophagus. Dalton et al (1988) retrospectively reviewed the natural history of nutcracker oesophagus. When patients underwent repeated manometric testing over a 32 month period, the amplitude of distal oesophageal contractions frequently diminished and also showed significantly greater interstudy variability compared with normal control values. Indeed, at subsequent manometric studies the "nutcracker" could be shown only intermittently in 59% of subjects.

1.2.14: NONCARDIAC CHEST PAIN AND DIFFUSE OESOPHAGEAL SPASM

There is a large variation between studies depending upon patient selection; for example consecutive patients with chest pain or patients with chest pain where a cardiac cause has been excluded or the exclusion of patients with proven gastro-oesophageal reflux with or without ambulatory pH monitoring. Diffuse oesophageal spasm and gastro-oesophageal reflux were thought until recently to be the most common causes (Bennett & Atkinson 1966). Brand et al (1977) and Benjamin et al (1979) reported that high amplitude peristaltic contractions in the lower oesophagus, "nutcracker oesophagus", were more common than diffuse oesophageal spasm.

There may be considerable difficulty in diagnosis as diffuse oesophageal spasm may mimic cardiac disease (Brand et al 1977, Benjamin & Castell 1983). The relationship to chest pain is difficult to explain.

Davies et al (1982a) found that of 100 consecutive patients admitted to a medical unit with chest pain only 51 patients (61%) were found to have ischaemic heart disease. A further sixteen patients with negative exercise electrocardiograms had abnormalities demonstrated by oesophageal investigations. Eight of these patients had a positive provocation test reproducing their symptoms particularly with acid infusion. They suggested that in an unselected group of patients with angina like chest pain as many as 20% might have an oesophageal cause for the pain if investigated appropriately.

Brand et al (1977) studied fifty-eight patients with angina like chest pain. Forty three patients had no evidence of significant coronary artery disease on coronary angiology or exercise tests, the remaining patients were known to have coronary artery disease with symptoms possibly exacerbated by additional oesophageal disease. High amplitude contraction waves were the most frequently found abnormality (15 patients) with achalasia and diffuse oesophageal spasm accounting for two and three patients respectively. Only eight of the patients studied experienced their typical pain coincident with an abnormal manometric trace. Two further patients were observed to have proven reflux on ambulatory twenty four hour pH recording during episodes of pain. Seven patients experienced their typical pain but had normal manometry and the oesophagus was not thought to be the source of their symptoms. The oesophagus seemed to be the origin of the chest pain in 18% of those patients studied but the most common manometric abnormality was not diffuse

oesophageal spasm but nutcracker oesophagus.

Benjamin et al (1979) found seven patients with chest pain and dysphagia to have high amplitude contractions with a mean of 170 mmHg (range 225-430mmHg). They decided that recognition of these high amplitude contractions was related to the use of minimally compliant hydraulic-capillary infusion systems which enabled much higher amplitude contractions to be recorded than had been possible before. Acid perfusion produced peak pressures in one patient of more than 400 mmHg in association with heartburn. Three other patients experienced retrosternal burning and a further patient developed severe chest pain with acid perfusion. This was associated with a change to manometry consistent with diffuse oesophageal spasm.

Traube et al (1983) found thirteen patients with atypical chest pain to have high amplitude peristaltic contractions, six of whom also had symptoms of gastro-oesophageal reflux. Bernstein testing reproduced symptoms in these six patients and altered the motility tracing in two patients producing a tracing consistent with diffuse oesophageal spasm in one patient. These patients had some relief of symptoms with an antireflux regimen. These two studies suggest that gastro-oesophageal reflux may play a role in some patients in the development of chest pain. The use of ambulatory pH recording would allow the identification of those patients with gastro-oesophageal reflux.

Orr & Robinson (1982) found similar results in a group of 28 patients with chest pain. The mean lower oesophageal sphincter, peak and mean amplitudes and contraction

durations were all significantly elevated in the patients compared to controls. Interestingly 50% of patients had a positive Bernstein test.

De Caestecker et al (1985) in Edinburgh found oesophageal abnormalities in 60% of patients with noncardiac chest pain. The group found that manometry, ambulatory pH studies and radionuclide swallows were more sensitive than endoscopy and radiology. They were unable to produce the patients' symptoms using provocation tests and it is difficult to know if the abnormalities were responsible for the symptoms.

Katz et al (1987), in the largest study of 910 patients with noncardiac chest pain, found that 28% had abnormal motility. Nutcracker oesophagus was present in 48% of the abnormal tracings which they felt suggested it was a manometric marker for noncardiac chest pain. 27% of the whole group had their pain reproduced during provocative testing. The highest percentage of positive provocative responses occurred in patients with the nutcracker oesophagus on baseline manometry. Chobanian et al (1986) found that 74% of patients with noncardiac chest pain had abnormal oesophageal manometry. 59% were nutcracker oesophagus, 7% diffuse oesophageal spasm, 3% achalasia and the remainder non specific motility disorders. Wu et al (1982) found that 39% of patients with angina-like pain and a normal coronary arteriogram had abnormal oesophageal motility patterns. More than half had nutcracker oesophagus. Richter et al (1985b) reported the results of a double blind crossover study using nifedipine in patients with noncardiac chest pain and nutcracker oesophagus and found that

nifedipine markedly decreased lower oesophageal sphincter pressure and distal contraction amplitude. Despite the reduction in contraction amplitude, chest pain was not significantly improved which further questions the importance of high amplitude contractions in the aetiology of chest pain, particularly as all these patients had had normal coronary angiograms. It is possible that the dose of nifedipine used was not high enough to reduce the symptoms despite the reduction in amplitude. Cohen (1987) concludes that the hypothesis that high amplitude oesophageal contractions cause chest pain is not valid.

Three studies using 24hr ambulatory oesophageal motility and pH systems have produced some interesting results. Peters et al (1988), investigating every episode of chest pain, found that 64% were not associated with any motility or pH abnormality. These patients all had at least one other oesophageal symptom. They found that acid reflux was the most common identifiable cause of oesophageal chest pain (24% of chest pain events). Both Janssens et al (1986) and Peters et al (1988) felt that a chest pain episode should be attributed to abnormal motility only when similar pressure changes were absent during asymptomatic segments of a prolonged motility recording. This principle and the use of each patient as its own control was probably responsible for the low incidence of chest pain related to oesophageal motility disorders obtained. Only 2 patients had all their chest pain episodes associated with abnormal oesophageal events. Vantrappen et al (1987) found that similar episodes of chest pain were, in individual patients, sometimes

associated with gastro-oesophageal reflux alone, with oesophageal motility disorder alone or with both. However acid perfusion of the oesophagus could produce typical chest pain in patients who showed abnormal motility without reflux when they had spontaneous chest pain. Another group of patients had 24hour recordings which showed that spontaneous pain was accompanied by reflux alone but the edrophonium test was positive. They felt that in these groups of patients irritability of the oesophagus played an important part in the development of chest pain. They called this sensitivity to both acid and motor disorders "the irritable oesophagus" (Vantrappen & Janssens 1988). This concept may help to explain positive Bernstein tests with standard manometry in patients with diffuse oesophageal spasm and the positive edrophonium effect of chest pain production without manometric change.

1.2.15: CORONARY ARTERY AND OESOPHAGEAL SPASM

Rasmussen et al (1986) suggested an association between coronary artery spasm and oesophageal spasm. They found 60% of patients with coronary artery spasm, as shown by ST segment deviation on ECG with prolonged hyperventilation, to have simultaneous, repetitive contractions on baseline manometry. A further study during hyperventilation produced chest pain in all patients with ST segment deviation on ECG, aggravated the oesophageal spasms and increased the average amplitude and duration of the oesophageal contractions. A similar control group of patients with chest pain, but without coronary artery spasm, had normal baseline

manometry. Hyperventilation produced simultaneous contractions in one of this group without any ECG changes. These findings suggest a common pathogenesis for coronary and oesophageal spasm. They also emphasise that oesophageal and coronary artery spasm may coexist in a patient.

Mellow et al (1983) instilled hydrochloric acid into the oesophagus of 25 patients with coronary artery stenosis and in three patients pain and ECG changes developed when the rate pressure product (heart rate x systolic blood pressure) exceeded the figure at which ischaemic pain had previously occurred during exercise. They suggested that the sympathetic response to oesophageal pain had increased oxygen demand beyond a critical point. One patient was retested on β -blockade and, although he experienced pain with acid perfusion, the rate pressure product remained unchanged. Over half of the patients who developed pain on acid perfusion could not distinguish between this pain and their angina. They concluded that acid perfusion in patients with coronary disease which resulted in chest pain could induce myocardial ischaemia.

This idea was supported by Davies et al (1985) who found that instilling acid into the oesophagus of patients with exertional angina reduced the distance that 80% of patients could walk before their angina reappeared. Three possible explanations were postulated. The first was that there was increased sympathetic activity after acid perfusion although there was no significant increase in noradrenaline levels. The second was the possibility that oesophageal stimulation led to a viscerocardiac reflex mechanism which produced

coronary artery constriction although there was no ECG evidence that ischaemia occurred at an earlier point during the acid tests. Finally that the acid perfusion caused pain which mimicked angina pectoris.

1.2.16: GASTRO-OESOPHAGEAL REFLUX AND CHEST PAIN.

Demeester et al (1982) studied fifty patients with severe chest pain with normal angiology and found twenty three to have abnormal reflux on ambulatory pH monitoring. In twelve patients chest pain coincided with reflux episodes. All these patients responded well to anti reflux therapy, further suggesting that gastro-oesophageal reflux was the cause of their chest pain. Only two patients were shown to have a motility disorder, one diffuse oesophageal spasm and one scleroderma. Overall, 73% of patients with proven reflux had total abolition of chest pain following either medical or surgical antireflux therapy.

Further evidence for gastro-oesophageal reflux contributing to noncardiac chest pain is found in a paper by Schofield et al (1987). 52 patients with typical angina and normal coronary arteriograms underwent exercise testing on a treadmill during 24 hour pH monitoring. Eleven patients had significant reflux on 24 hour testing with ten also having exertional gastro-oesophageal reflux. In nine patients this was associated with their usual chest pain. A further thirteen patients had normal 24 hour pH result but had exertional reflux coincident with chest pain during exercise. The mean lower oesophageal sphincter pressure was lower in these groups than in the remainder without reflux.

These findings suggest that exertional gastro-oesophageal reflux may be a common finding in patients with chest pain and may be a more useful test than 24 hour recording.

Henderson et al (1978) found that in patients with atypical symptoms of gastro-oesophageal reflux diagnosed by radiology or Bernstein test, pain in the arm was frequent, pain precipitated by exercise occurred commonly and relief of pain by antacid administration was unreliable. Acid perfusion in the patients with atypical pain failed reliably to reproduce all components of their pain, especially not the pain in the arm. They felt that full cardiac and oesophageal investigations were important in these patients to avoid diagnostic errors.

Lee et al (1985) discussed the findings in nine patients with chest pain who were shown to have oesophageal motility disorder. Two patients had nutcracker oesophagus on baseline manometry. Both these patients had coexistent cardiac disease as one required a coronary artery bypass graft and the other suffered a myocardial infarct within two weeks of manometry. Four of the remaining patients had manometry showing diffuse oesophageal spasm. Methacholine provoked both the pain and manometric abnormalities in five patients who had normal baseline manometry. Methacholine also produced ischaemic changes on ECG in seven patients which were relieved by atropine suggesting that methacholine should be used only under close cardiac supervision. Simultaneous manometric and electrocardiographic abnormalities have also been reported by Eastwood et al (1981) and Davies et al (1982b).

SUMMARY:

The oesophagus can be the origin of chest pain which is indistinguishable from that of ischaemic heart disease. The oesophagus can be implicated only when the pain is reproduced either in association with a manometric abnormality known to cause chest pain or in response to provocation tests thought to act only on the oesophagus. Acid perfusion seems to reproduce pain in a significant number of patients with noncardiac chest pain but may also have effects on the heart. Endogenous acid reflux can also be shown to correspond with episodes of pain. Medical or surgical correction of reflux reduces chest pain suggesting that in these patients reflux is responsible for their symptoms. Although diffuse oesophageal spasm is said to be the oesophageal motility disorder most often found in patients with noncardiac chest pain, this would seem to be no longer the case. The advent of better equipment has allowed higher pressures to be recorded more accurately and therefore nutcracker oesophagus has been recognised. This seems to be more commonly found in these patients than diffuse oesophageal spasm. Whether these high pressure contractions produce chest pain remains controversial. As usual, the fact that manometry measures only the end point of a complex neuromuscular process does not help with its understanding. Ischaemic heart disease and oesophageal disease may occur together and pose a dilemma in diagnosis and management.

1.2.17: OESOPHAGEAL MOTILITY AND STRESS

Many patients with the nutcracker oesophagus have transient or labile high pressure distal oesophageal contractions. This may be a response to psychological or physical stimuli. Stacher et al (1979) have shown that acoustic stimuli provoke nonpropulsive oesophageal contractions in healthy subjects and that the amplitude of the contraction increased with stimulus intensity. On repetitive stimulation the number and amplitude of oesophageal responses decreased with increasing stimuli.

Rogers et al (1980) demonstrated that stress could provoke an increase in amplitude and spontaneous contractions in some highly anxious medical students. Rubin et al (1962) also found that synchronous contractions could be produced in normal controls in response to stress. Soffer et al (1988) were unable to show that mild stress had any effect on oesophageal motility in normal controls and patients with the irritable bowel syndrome.

Clouse & Lustman (1983) investigated a group of 50 patients referred for manometry to determine whether there was any association between psychiatric illness and oesophageal motility disorder. Using independently evaluated psychological questionnaires, 29 patients were diagnosed as having a psychiatric diagnosis. However, 21 of the 25 patients who fitted into Clouse's distal contraction abnormalities group had a psychiatric diagnosis making this the most common group. The frequent diagnoses of depression, anxiety disorder and somatic disorder were largely responsible for this high prevalence. The similar degree of

distress induced by oesophageal symptoms in all the manometric groups suggests that symptoms alone are not responsible for the psychiatric illness.

Whorwell et al (1981) observed a higher incidence of oesophageal motility disorders in patients with the irritable bowel disease than in healthy age-matched controls. Richter et al (1986b) compared the psychological profiles of 20 irritable bowel patients and twenty patients with noncardiac chest pain and the nutcracker oesophagus. Three control groups of people were also used. They were normal healthy hospital staff, normal healthy non-hospital workers and a group of patients with symptomatic peptic oesophageal strictures. A 150 item self-report questionnaire, developed to assess psychological impact of medical illness in a non-psychiatric population, was given to all subjects. The patients with the nutcracker oesophagus and irritable bowel disease differed significantly from the controls on scales of gastrointestinal susceptibility and somatic anxiety suggesting that these patients react to psychological stress with an increase in symptom frequency and severity. Patients with irritable bowel disease had a more generalised disorder as they had significantly higher scores than the other groups in depression and anxiety. They felt that emotional factors might modulate pain perception in patients with nutcracker oesophagus.

These findings suggest similarities between the irritable bowel disease and these oesophageal contraction abnormalities even to the extent that they may both be manifestations of a single entity, the "irritable gut".

Abnormalities of smooth muscle motility such as spastic contractions induced reflexly or by stress are reported in both syndromes. In both conditions there is an increased frequency in women and an association with psychiatric disturbances. There are also similar observations of abnormal perception of distension in irritable bowel disease and oesophageal disease (Schuster 1983, Richter et al 1986b).

1.2.18: PATHOLOGY

The cause of diffuse oesophageal spasm is unknown. It has been noted that these patients may have thickened oesophageal muscle. Gillies et al (1967) noticed that the oesophageal muscle was up to 2 cm thick when oesophagomyotomy was performed on seven patients with diffuse oesophageal spasm. Cassella et al (1965), using electron microscope studies on oesophageal tissue obtained at operation, found no apparent defects in the ultrastructure of the smooth muscle. Vagal nerve specimens exhibited generalised wallerian degenerative changes particularly in the afferent nerve fibres. The smooth muscle cells showed only minimal focal morphological changes. They proposed therefore that afferent vagal lesions were important in the development of diffuse oesophageal spasm. Ganglion cells are thought to be normal in diffuse oesophageal spasm. Serebro et al (1970) reported a case of diffuse oesophageal spasm secondary to gastric carcinoma. The tumour did not appear mechanically to obstruct the lumen. Histology of the resected specimen showed that many

of the nerve bundles supplying the myenteric plexus in the lower oesophagus were invaded by adenocarcinoma. They suggested that this further supported the view that the pathogenesis of achalasia and diffuse oesophageal spasm might be related.

Ischaemia of the oesophagus might account for the abnormal manometry and the associated chest pain in oesophageal motility disorder. Mackenzie et al (1988) measured the rewarming rate after a standardised cold challenge. They considered that oesophageal blood supply would be the main determinant of the rewarming rate and that changes in this rate would reflect oesophageal blood flow. They found that the rewarming rate was significantly longer in 9 patients with oesophageal motility disorder than in 21 normal controls. This might be a secondary effect or the primary cause of diffuse oesophageal spasm.

1.2.19: TREATMENT

The symptoms of diffuse oesophageal spasm are often more troublesome than incapacitating. Fear that the recurrent chest pain signals life threatening heart disease is common and the resulting anxiety may exacerbate oesophageal dysmotility. Understanding the interaction of oesophageal contractility and emotional tension is becoming more important as greater numbers of patients with noncardiac chest pain are studied.

The finding that motility disorders of the oesophagus are associated with elevated scores on measures of somatic anxiety and depression has led to the trial of psychiatric

therapy to treat these patients. Shabsin et al (1988) describe the successful use of a behavioural pain management programme in the treatment of refractory chest pain and dysphagia persisting after pneumatic dilatation and long oesophageal myotomy in a patient with vigorous achalasia. Clouse et al (1987) have reported a double blind placebo controlled trial, on patients with oesophageal motility disorders, of low dose trazodone, an antidepressant and anxiolytic which is said to have little or no effect on oesophageal motility. Upon completion of the treatment the trazodone group reported significantly greater improvement in oesophageal symptoms than the placebo group. Manometric changes observed during the trial were not influenced by treatment or by clinical response. There were remarkable reductions in ratings of chest pain in both treatment groups suggesting that the medical attention they were receiving was also responsible for some improvement. It would appear that symptom relief in patients treated behaviourally for chest pain of oesophageal origin is not necessarily related to long-term alteration in oesophageal motility.

1.2.19a: VASODILATORS

Experimentally glyceryl trinitrate diminishes abnormal motility but in clinical practice vasodilators are less effective. The effect of glycerine trinitrate and long acting nitrates on the oesophagus was studied on normal subjects. The administration of sublingual trinitrate produced a significant transient reduction in lower oesophageal sphincter pressure. There was no effect on

either amplitude or duration of contractions or on peristaltic wave velocity. Long acting nitrates had no effect on any of the parameters of oesophageal motility. (Swamy 1977, Kikendall & Mellow 1980). Swamy (1977) studied the effect of trinitrates on diffuse oesophageal spasm. The response to trinitrates was unpredictable in seven patients with significant gastro-oesophageal reflux, as recorded by a pH probe, in addition to diffuse oesophageal spasm. The remainder without gastro-oesophageal reflux had a good response remaining symptomfree on long-acting nitrates for up to four years.

Mellow (1982) studied the effect of isosorbide and hydralazine both on baseline manometry and on the effect of bethanechol provocation in five patients with diffuse oesophageal spasm. He found that neither agent affected baseline contraction amplitude or duration. However pretreatment with hydralazine significantly reduced the effect of bethanechol on contraction duration. Isosorbide was significantly less effective. Only one patient experienced pain in response to bethanechol when pretreated with hydralazine although all five patients experienced chest pain in response to bethanechol alone. Four patients who were subsequently placed on long term hydralazine therapy experienced improvement in chest pain and dysphagia with a reduction in amplitude and duration of oesophageal contractions.

1.2.19b: CALCIUM CHANNEL BLOCKING DRUGS

Recent interest has focused on the use of calcium channel

blocking drugs. Calcium is essential for oesophageal smooth muscle contraction. Experiments on muscle strips from the opossum oesophagus showed that calcium concentration affected the force of contraction. Calcium infusions in humans increase the contraction amplitude in the body of the oesophagus. Hongo et al (1984) showed in normal controls that sublingual nifedipine significantly decreased both lower oesophageal sphincter pressure and contraction amplitude in the body of the oesophagus. The effect on sphincter pressure required a lower dose of nifedipine and was more marked than that on contraction amplitude, where at least 30mg was required. The effects on both sphincter pressure and contraction amplitude correlated with plasma nifedipine levels. Richter et al (1985a) found that oral nifedipine produced a dose-dependent decrease in the amplitude and duration of contractions in the distal oesophagus in five normal controls and in 10 symptomatic patients with nutcracker oesophagus. These effects were maximal 15 minutes after ingestion and lasted for about 45 minutes and were significantly different from those with placebo. Significant decreases in amplitude were produced with 10 mg capsules. At doses of 30mg amplitude decreases of up to 86% were seen in individual patients with nutcracker oesophagus. Nifedipine had no effect on velocity or proximal oesophageal contractions. The differences between effects in this study and that of Hongo et al (1984) are probably related to different routes of administration of the drug. Plasma nifedipine levels after oral ingestion were nearly twice the values reported by Hongo et al (1984) after

similar doses sublingually.

Blackwell et al (1981) reported a reduction in both contraction frequency and in amplitude in both peristaltic and nonperistaltic contractions in patients with diffuse oesophageal spasm. He found that nifedipine reduced the frequency of symptoms in three patients with diffuse oesophageal spasm and was effective in reducing the severity of the pain when taken sublingually. Richter et al (1987a) compared the effects of oral nifedipine and placebo in 20 patients with non cardiac chest pain and the nutcracker oesophagus in a double blind crossover study. Interestingly, compared to placebo, nifedipine significantly decreased distal oesophageal contraction amplitude and duration. However, nifedipine was no better than placebo in the relief of daily chest pain frequency, severity, or index (frequency x severity). Despite these poor results, long term follow-up suggests that these patients do improve. Distal oesophageal contraction amplitudes significantly fell during the long term follow up but there was poor correlation with chest pain improvement. Nasrallah (1982) noted the transient return of peristalsis during manometry after acute administration of nifedipine and reported clinical improvement during a month trial of nifedipine in a patient with diffuse oesophageal spasm.

Traube et al (1984) found that nifedipine decreases lower oesophageal sphincter pressure in patients with achalasia to a similar extent in normal subjects and that plasma concentrations of nifedipine are comparable in both groups after sublingual administration. Nifedipine decreased both

lower oesophageal sphincter pressure and contraction amplitude in patients with nutcracker oesophagus to a greater extent than in normal subjects. Traube & McCallum (1984b) have suggested that a smaller dose of nifedipine may be needed to produce a reduction in contraction amplitude in patients with diffuse oesophageal spasm or nutcracker oesophagus than normals and this may be related to a greater sensitivity of the oesophagus with disordered motility. A more likely explanation would be that higher plasma levels are obtained by oral administration as shown by Richter et al (1987a).

There seems to be no consensus on the correct route or dose although Traube & McCallam (1984b) have suggested that 20mg significantly reduces contraction amplitude. There are only a few reports of the effects of verapamil and diltiazem on the oesophagus. Richter et al (1982) have shown that intravenous verapamil decreases lower oesophageal sphincter pressure and contraction amplitude in baboons. Richter et al (1984) also found that oral doses of diltiazem, in sufficient dosage to produce headaches, did not affect oesophageal contractions in normal controls. In patients with nutcracker oesophagus diltiazem decreased amplitude and duration of contractions but similar effects were produced by placebo. However, diltiazem significantly improved symptoms of chest pain and dysphagia when taken for eight weeks by seven patients. These results might well be a placebo effect especially as the patients were interviewed regularly and there may be benefits from frequent discussions between doctor and patient about their symptoms.

In general, controlled trials are absent.

1.2.19c: BALLOON DILATATION

In patients where symptoms are severe pneumatic dilatation may be considered. Blackwell & Castell (1984) have found that the patient with persistent and severe symptoms is uncommon and they have rarely had to resort to balloon dilatation or surgery. This probably reflects their pattern of referral as many of their patients seem to have noncardiac chest pain and not dysphagia, and severe dysphagia seems to have been the usual indication for dilatation. Craddock et al (1966) treated 7 patients with diffuse oesophageal spasm with dilatation using bougienage and the Negus hydrostatic dilator with relief of symptoms. Winters et al (1984) report interesting results using oesophageal bougienage in patients with the nutcracker oesophagus in a prospective double blind controlled trial. There were no significant differences between the results of bougienage with a therapeutic dilator (54-F) or with a placebo dilator (30-F) with respect to chest pain, dysphagia, lower oesophageal sphincter pressure or contraction amplitude. Chest pain scores at the end of the three month study period were significantly lower than baseline scores irrespective of the order in which the dilators were used. No subjective or objective improvement could be demonstrated when therapeutic bougienage was compared with placebo bougienage. This was probably related to the small size (54-F) of the dilator used for their

dilatation as the usual dilator used in achalasia is 90-120F. They were therefore not using a therapeutic bougienage but two placebo groups. They thought that the improvement in symptoms at the completion of the study could be related to close physician-patient interaction. Goldin et al (1982), in a retrospective study of 24 patients with high amplitude peristalsis treated with bougienage (50-60F), found that 83% reported symptomatic improvement following dilatation. 25% of a control group of untreated patients also reported improvement during the same period. The duration of remission in the treated group was very variable.

Rider et al (1969), using a flexible pneumatic dilator as a controlled expansion force (a Rider -Moeller Balloon), treated nine patients with diffuse oesophageal spasm primarily with chest pain but also with dysphagia. The smallest pneumatic dilator was distended to 300mm Hg and held in place for three minutes. The dumbbell shape of the dilator kept the lower section anchored in the stomach fundus and the upper part in the oesophagus with the central core at the cardia. None of these patients had any complications and they all achieved an excellent or good response. Rider, however, reports that the number of dilatations necessary to achieve symptomatic relief varied from 1 to 22 over several years. No comment is made on the effect of dilatation on actual symptoms or manometry or on the duration of response. There was no placebo and no clinical results are given as to whether there was lower oesophageal sphincter dysfunction or gastro-oesophageal reflux prior to dilatation. The description of the

dilatation suggests that the lower oesophageal sphincter received the maximum dilatation although this usually functions normally in diffuse oesophageal spasm. Of the two case histories given only one patient had manometry performed prior to dilatation. Both these patients had dysphagia to solid foods and chest pain but were symptom free after dilatation for up to a year.

Vantrappen & Hellemans (1980) performed pneumatic dilatation in a series of 156 patients with severe dysphagia. According to Vantrappen's criteria for diagnosis of oesophageal motility disorder 70% had true achalasia, 11% had diffuse oesophageal spasm and 17% had intermediate forms (17% pR and 2% Pr). The results after dilatation were good or excellent in 80% of the achalasia patients. "Excellent" meant free of symptoms and "good" included short duration of pain or dysphagia less than once a week. 78% of the intermediate group experienced good or excellent results. The results in the patients with diffuse oesophageal spasm were less successful with only 45% being classed as excellent or good results. No reasons are given for the poorer results obtained in the group with diffuse oesophageal spasm but the dilatations seem to have focused on the lower oesophageal sphincter which is not usually involved in diffuse oesophageal spasm.

Ebert et al (1983) reported the results of forceful pneumatic dilatation in nine patients with severe symptoms of diffuse oesophageal spasm and lower oesophageal sphincter dysfunction who were unresponsive to medical therapy and bougienage. Under X-ray screening the balloon was positioned

to straddle the diaphragmatic hiatus and inflated to 8-12 lb/sq in for 15 seconds. Manometry was repeated a mean of 14 months after dilatation. Pneumatic dilatation in these patients produced clinical improvement in 89% of patients followed for an average of 37 months. The improvement in oesophageal symptoms was associated with a sustained decrease in lower oesophageal sphincter pressure in most cases. There was no change in the percentage of lower oesophageal sphincter relaxation with swallowing or in the pattern of baseline oesophageal motility following clinically successful pneumatic dilatation. Dysphagia and regurgitation were the symptoms most improved by dilatation which is probably related to the decrease in lower oesophageal sphincter pressure. In most studies of diffuse oesophageal spasm the lower oesophageal sphincter function is normal but all these patients had incomplete relaxation with swallowing.

The deficiencies of the work so far published are:-

1. Some of their patients with diffuse oesophageal spasm had lower oesophageal sphincter dysfunction.
2. Lower oesophageal sphincter was dilated purposely but the oesophageal body was spared.
3. Many of the patients had chest pain as their prime symptom.
4. There was no attempt made to exclude refluxers or to assess whether dilatation made the patients more likely to reflux.
5. The size of the dilator used was inadequate.

1.2.19d: LONG OESOPHAGEAL MYOTOMY

Lortat-Jacob first reported the use in 1950 of a long oesophageal myotomy as surgical treatment for diffuse oesophageal spasm. This usually involves the longitudinal division of the full thickness of the oesophageal muscle leaving the mucosa intact from the gastro-oesophageal junction to the aortic arch or even higher if manometry shows that the motility abnormality extends above this. Dividing the muscle of the lower oesophageal sphincter raises the possibility of the production of gastro-oesophageal reflux. This has led to the use of an antireflux procedure in association with the myotomy. Leonardi et al (1977) have advocated the preservation of the lower oesophageal sphincter in those patients who have normal lower oesophageal sphincter function. The preservation of the lower oesophageal sphincter is worrying if diffuse oesophageal spasm may become achalasia in time. They describe a group of 11 patients treated in this way in whom 10 had clinical improvement after myotomy. The best results are obtained in patients in whom radiography and manometry are abnormal and who have muscle hypertrophy at operation. Ellis et al (1960) report that this is found in about 40% of patients. Craddock et al (1966) found the oesophageal muscle hypertrophied up to 15mm thickness. Henderson would not perform a myotomy unless oesophageal hypertrophy was present (1980).

Traube et al (1987) report the use of a long oesophageal myotomy from the aortic arch to the stomach in four patients with nutcracker oesophagus who underwent surgery because of

the severity of their symptoms and recalcitrance to various medical treatments. Manometry 1 to 5 years after surgery showed a reduction in amplitude and duration of contractions in the distal oesophagus with normal peristalsis in the proximal oesophagus. The lower oesophageal sphincter pressure was decreased in all patients. Three of the four patients received a modified Belsey antireflux procedure in addition to the myotomy. Three of the patients experienced mild heartburn and regurgitation postoperatively but only one patient had mild chest pain which was associated with the presence of peristalsis in the lower 10 cm of the oesophagus. Traube concluded that patients with the nutcracker oesophagus whose pain was resistant to medical treatment could be successfully treated with a myotomy. Richter and Castell (1987) disagreed with this policy in view of the poor understanding of the place of high amplitude contractions and associated symptoms such as chest pain and dysphagia. The four patients who underwent surgery did not produce pain at the time of their abnormal manometry. It remains controversial whether the high amplitude peristaltic contractions are the major cause of chest pain. The possible association between irritable bowel disease and nutcracker oesophagus suggested that psychiatric evaluation and treatment should be considered before embarking on major surgery. The natural history of these oesophageal symptoms seems to be that with reassurance the symptoms improve over a period of time. Interestingly, their large group of patients with nutcracker oesophagus have all responded to

medical treatment, psychotherapy or reassurance although no long term followup is available. No mention is made about the place of gastro-oesophageal reflux in the aetiology or treatment of nutcracker oesophagus.

1.2.20: SUMMARY

Diffuse oesophageal spasm seems to be a less common diagnosis than high amplitude peristaltic contractions (nutcracker oesophagus) when oesophageal manometry is performed in the investigation of noncardiac chest pain. The incidence of diagnosis of the two conditions is partly related to the referral pattern of an oesophageal manometry laboratory. Patients with chest pain should have coronary artery disease excluded before embarking on oesophageal investigation. The intermittent nature of the symptoms has led to the production of provocation tests. The best at present seem to be a Bernstein test and an edrophonium provocation test.

1.3: THE GLOBUS SENSATION

1.3.1: HISTORICAL

Globus Hystericus meaning "hysterical ball", or lump in the throat, was first mentioned by Hippocrates over two thousand years ago (Malcolmson 1968). Purcell in 1707 declared that this sensation was due to the contraction of the strap muscles of the neck pressing on the thyroid cartilage. Erasmus Darwin (1796) thought that the condition was due to a "retrograde movement of the oesophagus". Until recently this diagnosis was given to a sensation for which no organic cause could be found and was therefore considered to be psychogenic in origin. Globus sensation accounts for 3-4% of patients presenting to an otolaryngology clinic (Malcolmson 1968, Moloy & Charter 1982). Globus sensation occurred intermittently in 45% of the normal population (Thompson & Heaton 1982).

The history often extends over many months. The symptom is three times commoner in women than men below the age of fifty but has equal sex incidence above (Moloy & Charter 1982). The pharyngeal discomfort is usually midline, suprasternal and is more marked between meals. In the majority of patients there is no true dysphagia or weight loss. The prime requisite is the exclusion of primary pharyngolaryngeal and oesophageal malignancy.

Experimental and clinical studies have suggested that the upper oesophageal sphincter may be the origin of the globus sensation (Calderelli et al 1970, Winans 1972, Stanciu & Bennett 1974, Gerhardt et al 1978). Recently, improved

methods of investigation with cine-radiology and manometry (Sokol et al 1966) have focused attention on abnormalities of oesophageal motility (Flores et al 1981) and abnormal upper oesophageal sphincter function (Watson & Sullivan 1974).

1.3.2: THE ANATOMY OF THE UPPER OESOPHAGEAL SPHINCTER

The exact anatomical correlate of the upper oesophageal sphincter is uncertain but is currently thought to be the cricopharyngeal muscle with part of either the inferior constrictor or the upper fibres of the oesophageal muscle (Batson 1955, Palmer 1976). Asoh & Goyal (1978), using simultaneous manometry and electromyograms in the opossum, found that the upper oesophageal sphincter corresponded mainly to the cricopharyngeus and inferior constrictor muscles, which showed continuous activity on electromyography at rest in awake or anaesthetised animals and ceased to fire during swallowing. Cessation of the cricopharyngeal and inferior constrictor electrical activity by motor nerve section or administration of d-tubocurarine caused a marked reduction in upper oesophageal sphincter pressure. A small component of the resting upper oesophageal sphincter pressure appeared to be due to passive elasticity of the surrounding structures as this was not abolished by death of the animals. During swallowing the cessation of electrical activity in the sphincter muscles corresponded, on manometry, to the fall in the sphincter pressure to near atmospheric pressure. This fall was below the residual pressure observed after elimination of all myogenic activity

in the sphincter muscles and was associated with a burst of activity in the geniohyoid muscle. Contraction of the geniohyoid also caused a fall in the upper oesophageal sphincter pressure even when the cricopharyngeus and inferior pharyngeal constrictor were kept contracted. Asoh & Goyal postulated that the opening of the upper oesophageal sphincter was attributable to inhibition of the contraction of the cricopharyngeus and inferior constrictor and the forward displacement of the larynx by the geniohyoid muscle.

1.3.3: MANOMETRIC MEASUREMENT OF THE UPPER OESOPHAGEAL SPHINCTER

Upon swallowing, the upper oesophageal sphincter relaxes to cervical oesophageal baseline pressure; its relaxation phase totally encompasses pharyngeal contraction and is precisely coordinated with the contraction of the pharynx. Thus the upper oesophageal sphincter barrier function totally disappears with swallows, permitting ready passage of the oral bolus into the oesophagus (Ellis 1971, Hurwitz & Duranceau 1978).

1.3.4: UPPER OESOPHAGEAL SPHINCTER ASYMMETRY

It has been shown that the upper oesophageal sphincter has both radial and axial asymmetry. Stanciu & Bennett (1974) found that, in a small number of normal individuals, catheter openings arranged to record at 120 degrees showed a significant difference in sphincter pressure between the three readings, indicating that spatial orientation of catheter tips influences the pressure recorded. Berlin et al

(1977), using a six lumen catheter with openings at 60 degrees, found that the pressure in the upper oesophageal sphincter was non-uniform with a substantially greater pressure in the anterior-posterior direction with pressures of about 80mm Hg anteriorly and posteriorly. Greater resting pressures (average 100 mmHg) have been recorded from anterior and posterior catheter orifices than from the lateral orifices(33 mmHg) by Winans (1972) using an eight lumen catheter.

Welch et al (1979) compared the upper oesophageal sphincter manometry produced by three types of catheter. They were an eight lumen radially perfused probe similar to that used by Winans (1972), a conventional Honeywell three transducer probe and a circumferentially sensitive probe designed to measure upper oesophageal sphincter pressure without regard to probe orientation. The Honeywell probe produced significantly lower pressures than the other methods with wide intra subject variation. In contrast, upper oesophageal sphincter pressure measured by the circumferential probe was constant for each subject and was identical to the anteroposterior upper oesophageal sphincter pressure measured by the eight lumen probe. Computer analysis of the upper oesophageal sphincter pressure recorded by the eight lumen probe showed that the normal three dimensional map of the upper oesophageal sphincter was anteroposterior accentuation of peak pressures and also axial asymmetry with anterior peak pressures occurring 0.8cm closer to the pharynx (Welch et al 1979).

Kahrilas et al (1987a) used a modified Dent sleeve (1976) to

measure upper oesophageal sphincter pressure. The principle of the sleeve device is that it records the highest pressure acting at any site along its sensing membrane (Linehan et al 1985). The sleeve was 6cm in length and flat in cross section (3.3x7.2mm) so that it conformed to the slit-like upper oesophageal sphincter anatomy and held an anterior or posterior orientation. When compared to rapid pull-through measurement of upper oesophageal sphincter pressure using a standard manometry system, the sleeve sensor measured significantly lower upper oesophageal sphincter pressure with less variability between subjects suggesting that either the rapid pull-through technique or water perfusion into the upper oesophageal sphincter zone stimulates the upper oesophageal sphincter to contract. Simultaneous upper oesophageal sphincter recordings, using a sleeve sensor and a side-hole sensor during a station pull-through, produced almost equal pressure values at the peak of the high pressure zone but the side-hole sensor recorded significantly lower pressures than the sleeve sensor at 0.5 cm or more from the peak of the high pressure zone. During prolonged recording at the peak of the high pressure zone the sleeve recorded greater pressures than the side-hole sensor. This suggested that the side-hole sensor had a tendency to move relative to the peak upper oesophageal sphincter pressure. When stationary for 1 to 2 minutes both sensors recorded significantly lower upper oesophageal sphincter pressure, again suggesting that movement of the catheter stimulates the sphincter to contract. One limitation of the sleeve system was its relative inability

to record abrupt pressure increases. This meant that the duration of upper oesophageal sphincter relaxation was underestimated.

The anatomy of the cricopharyngeus explains the differential pressures recorded. The cricopharyngeal muscle originates from the lateral borders of the cricoid cartilage and then forms a continuous posterior sling for the upper oesophagus. There is no insertion into a median raphe (Lund 1965). Contraction causes flattening of the upper oesophagus against the cricoid arch in an anterior-posterior direction. This can be confirmed radiologically (Fyke & Code 1955). In 13 patients who underwent partial laryngectomy the upper oesophageal sphincter pressure fell after a cricopharyngeal myotomy. If no myotomy was performed, then the upper oesophageal sphincter pressure remained the same. There was no correlation between upper oesophageal sphincter pressure and ability to swallow as long as there was glottic competence (Berlin et al 1977). Studies of patients after total laryngectomy (Welch et al 1979) showed lower peak pressures (40% of control) with loss of radial pressure asymmetry. Three dimensional mapping showed that axial asymmetry had also vanished. It therefore appeared that the anatomical alterations produced by laryngectomy abolished upper oesophageal sphincter pressure asymmetry.

Peak upper oesophageal sphincter pressures are recorded in an antero-posterior direction. It is clear therefore that great care must be taken to ensure that the catheter orifices are uniformly positioned. Meaningful comparisons cannot be made between studies unless this convention is

observed.

1.3.5: THE FUNCTION OF THE UPPER OESOPHAGEAL SPHINCTER

The function of the high pressure zone appears to be two fold: to guard against the entry of air into the oesophagus and to prevent oesophageal contents entering the larynx. There is some evidence to support both these points (Winship 1983).

Prevention of air entering the oesophagus

Work in dogs by Levitt et al (1965) and Kawasaki et al (1964) on direct electromyographic studies on the cricopharyngeus shows that the muscle is active in inspiration and is quiescent during expiration. Goyal et al (1970) studied the influence of respiration on the intraluminal pressures in the region of the upper oesophageal sphincter in 25 patients with lower oesophageal symptoms. Inspiration was associated with a fall in pressure in the cervical oesophagus. As the catheter was withdrawn, the polarity of respiratory movements changed with the fall in pressure on inspiration in the oesophagus changing to a rise in the lower part of the upper oesophageal sphincter and then to a fall in the upper part of the upper oesophageal sphincter. In the pharynx, inspiration caused a significant drop in pressure. The inspiratory rise in pressure was most obvious at the peak pressure of the upper oesophageal sphincter which seemed to correspond to the horizontal fibres of the cricopharyngeus. A brief rise in pressure was seen in 25% of the patients in the maximal pressure region just prior to relaxation in response to

swallowing. Increased muscle activity in the sphincter, which can be demonstrated as a high pressure zone manometrically, prevents regurgitation of oesophageal contents into the pharynx.

Kahrilas et al (1987a), using a sleeve sensor in normal controls, found that the upper oesophageal sphincter pressure increased transiently with each respiration and was particularly noticeable during periods of rest and sleep. The upper oesophageal sphincter pressure increase was 180 degrees out of phase with the inspiratory drop of intraluminal pressure in the thoracic oesophagus. This was consistent with the hypothesis that function of the upper oesophageal sphincter is to exclude air from the oesophagus during respiration.

Prevention of oesophageal contents entering the larynx

Freiman et al (1981) studied in the dog the effect of bilateral vagosympathetic nerve blockade on the upper oesophageal sphincter responses to acid perfusion. Initial studies showed that the upper oesophageal sphincter in dogs has a similar asymmetry to the human sphincter with higher pressures anteriorly and posteriorly. Perfusion of acid at 0.5cc/min at the level of the upper oesophageal sphincter and below similarly produced an increase in pressures. This response was maximal on perfusion at the sphincter and decreased progressively with perfusion distally. Perfusion at a similar rate with saline or water failed to produce any change in sphincter pressure. Bilateral nerve blockade by cooling produced no change in resting upper oesophageal sphincter pressure or in the response of the sphincter to

swallowing. It produced abolition of the maximal sphincter response to acid.

Studies on normal subjects have shown that the upper oesophageal sphincter pressure rises in response to the presence of intraoesophageal fluid especially acid perfusion. Infusions of both saline and hydrochloric acid increased upper oesophageal sphincter pressure above a control period when no infusion occurred, suggesting that this was a volume response. However, the pressure rise was greater with the acid infusion suggesting a response to acid stimulus. In addition, the closer to the upper oesophageal sphincter the infusion was administered the greater was the increase in pressure recorded (Gerhardt et al 1978).

Wallin et al (1978) measured upper oesophageal sphincter pressure during infusion of 0.1N Hydrochloric acid (5ml/min) 5cm above the lower oesophageal sphincter in eight normal controls. There was a significant increase in the upper oesophageal sphincter pressure after one minute but this was not maintained. Stanciu and Bennett (1974) found that the upper oesophageal sphincter pressure showed no significant difference in normal controls and patients with gastro-oesophageal reflux. Within the reflux group there was no difference in upper oesophageal sphincter pressure between those with no oesophagitis and those with severe oesophagitis on endoscopy. There was no correlation between the severity of reflux as judged by 15 hour pH recording and the upper oesophageal sphincter pressure. Nine refluxers had 30mls of 0.1N Hydrochloric acid dripped into the oesophagus 10cm below the upper oesophageal sphincter at 10mls/min.

This produced no significant change in sphincter pressure. This may be related to the distance away from the upper oesophageal sphincter that perfusion occurred. The increased threshold to acid in the lower oesophagus may explain why Stanciu and Bennett (1974) and Wallin et al (1978) failed to demonstrate a consistent rise in upper oesophageal sphincter pressure in humans when acid was perfused into the oesophagus 10cm or more below the sphincter.

Gerhardt et al (1980) found that the mean peak upper oesophageal sphincter pressure in controls and patients with heartburn was significantly greater than in patients with oesophago-pharyngeal regurgitation. These patients all had an awareness of spontaneous movement of fluid from the oesophagus into the pharynx, most frequently at night. Nine controls responded to intraoesophageal perfusion with saline or acid with an increase in upper oesophageal sphincter pressure but the group with oesophago-pharyngeal regurgitation showed no change in pressure. They concluded that in these patients there was a breakdown of the normal mechanisms that serve as barriers to oesophago-pharyngeal regurgitation. Sondheimer (1983) found similar resting upper oesophageal sphincter pressures in infants with gastro-oesophageal reflux and controls. Oesophageal acidification produced a significant increase in mean upper oesophageal sphincter pressure in controls and refluxers.

Spontaneous episodes of gastro-oesophageal reflux did not produce any alteration in the upper oesophageal sphincter pressure which is at variance with experimental work. A possible explanation may be that in the experimental work

the duration and degree of acid exposure is much greater (Kahrilas et al 1987b).

Gerhardt et al (1978) suggest that the upper oesophageal sphincter functions as a dynamic barrier preventing oesophago-pharyngeal reflux and possible subsequent aspiration.

Kahrilas et al (1987b) used the sleeve sensor for prolonged overnight recording in normal subjects and found that with deep sleep the mean upper oesophageal sphincter pressure fell from roughly 40mmHg to about 10mm Hg. The swallow rate was also significantly less during sleep than awake periods. These findings may have significance as the fall in upper oesophageal sphincter pressure with sleep diminishes the barrier to nocturnal regurgitation and potential aspiration. Basal upper oesophageal sphincter pressure in awake subjects is sufficient to serve as an adequate barrier to prevent regurgitation because intraluminal oesophageal pressure resulting from gastro-oesophageal reflux rarely exceeds 10mmHg (Dent et al 1989).

Freiman et al (1981) also studied in the dog the effect of bilateral vagosympathetic nerve blockade on the upper oesophageal sphincter responses to intraoesophageal distension. Balloon distension at levels up to 20cm below the upper oesophageal sphincter produced a large increase in the sphincter pressure. The threshold for this response increased and the maximum response decreased as distension was performed more distally in the oesophagus. Bilateral nerve blockade by cooling produced a partial reduction in maximal upper oesophageal sphincter response to distension.

Similar results have been obtained in humans. Creamer et al (1956), using a nonperfused catheter, showed that the upper oesophageal sphincter pressure increased immediately after balloon inflation especially if the stimulus was in the upper two thirds of the oesophagus and was maintained for the period of distension. This was associated with a decrease in the lower oesophageal sphincter pressure. The oesophagus above the balloon contracted vigorously and repetitively but below the balloon there were very few contractions. Rapid distension of the upper oesophagus with 50mls of water also produced an increase in pressure in the upper oesophageal sphincter. Enzmann et al (1977) also found an increased pressure in the upper oesophageal sphincter in response to intraluminal balloon distension with resultant initiation of secondary peristalsis above the distension site which they felt comprised a highly integrated pressure barrier to regurgitation. Kahrilas et al (1987a), using the sleeve sensor, studied balloon distension in normal controls. Balloon distension in the oesophageal body caused a significant increase in upper oesophageal sphincter pressure. The increase was directly related to the balloon diameter and proximity to the sphincter. The maximal augmentation of upper oesophageal sphincter pressure, 214% above basal pressure, occurred with the balloon 5cm below the upper oesophageal sphincter, inflated to a diameter of 2.5cm. Using a similar technique, Kahrilas et al (1986) studied the effect on the upper oesophageal sphincter of belching in normal volunteers. Belching was preceded by complete upper oesophageal sphincter relaxation. Abrupt

oesophageal distension with air 8 cm below the sleeve produced upper oesophageal sphincter relaxation and secondary peristalsis and mimicked the effect of a belch. Increasing the volume of injected air significantly prolonged the duration of complete upper oesophageal sphincter relaxation. Saline injected at 3ml/second caused either no change in upper oesophageal sphincter pressure or an augmentation of upper oesophageal sphincter pressure. Mucosal anaesthesia did not change the response of the upper oesophageal sphincter to either rapid air distension or saline infusion. The use of a cylindrical balloon 15cm long to distend abruptly the proximal 75% of the oesophagus precipitated either partial or complete upper oesophageal sphincter relaxation in the small number of subjects tested. These findings suggest that the rapidity and spatial pattern of distension, rather than discrimination of the type of material causing the distension, determines whether or not upper oesophageal sphincter relaxation occurs.

1.3.6: HYPERTENSIVE UPPER OESOPHAGEAL SPHINCTER PRESSURE

Nine globus patients were found to have hypertensive cricopharyngeal sphincters with pressures ranging from 140 mmHg to 220 mmHg in a study by Watson & Sullivan (1974). They used a perfused catheter initially recording posteriorly but rotated to either side to measure the peak resting upper oesophageal sphincter pressure at any point. It may be that the catheter rotation in these globus patients caused the higher pressures recorded as Kahrilas et al (1987a) have shown that catheter movement increases the

sphincter pressure. These results are disputed by Calderelli et al (1970) who found no difference between cricopharyngeal resting pressures and duration of relaxation in globus patients and normal controls but they used a nonperfused catheter. Hunt et al (1970) recorded significantly raised resting cricopharyngeal pressures using non-perfused catheters in patients with heartburn and endoscopic oesophagitis. Successful surgical correction of reflux symptoms in nine patients restored the cricopharyngeal pressure to normal levels. They postulated that patients with gastro-oesophageal reflux had higher upper oesophageal sphincter pressures to prevent pharyngeal reflux. However, Winans (1972), using an eight lumen infused catheter, disputed these findings. He was unable to show any increase in pressures in patients with symptomatic gastro-oesophageal reflux although he recorded much higher pressures in all patients reflecting the antero-posterior orientation of his catheters. These apparently contradictory results probably reflect differences and inadequacies in measurement techniques and lack of orientation of catheters.

Berte & Winans (1977), reviewing 269 motility tracings, found that average and maximum upper oesophageal sphincter pressures were similar in patients with lower oesophageal sphincter pressures less than 10mm Hg or greater than 20mmHg, and in patients with and without gastro-oesophageal reflux as determined by an intraoesophageal pH electrode test. They used the mean pressure determined by averaging pressures from the three lateral orifices evenly distributed about the circumference of the lumen and used a perfused

catheter. This work seemed to cast doubt on Hunt's findings.

1.3.7: RELATIONSHIP OF GLOBUS TO GASTRO-OESOPHAGEAL REFLUX

Malcolmson (1968), in a retrospective review of 307 patients with globus who had all had barium studies, found that clinical and radiological examination revealed organic lesions in 79% of cases. In 92 of these cases abnormalities were found which were directly related to the throat, particularly osteophytes of the cervical spine. Four patients had a mediastinal abnormality and 104 of the remaining 146 patients had hiatus hernias although no comment is made on the presence or absence of gastro-oesophageal reflux.

Mair et al (1974) investigated 77 consecutive patients with the globus sensation. Sliding hiatus hernias were demonstrated in 13% with radiological reflux in all but one although this percentage may represent that found in a normal population. A further 34% had positive acid barium studies or gastroduodenal abnormalities. Examination 2 years later demonstrated symptomatic improvement in 50% of women and only 24% of men and bore no relationship to previous radiological findings. Only 11% of the group were asymptomatic but all the patients expressed gratitude in the interest being taken, leading the authors to conclude that psychogenic factors were at least partly contributory.

Hallewell & Cole (1970) showed reflux on radiology in all 14 of their patients with globus. Medical treatment of the reflux with antacids and bed head elevation produced complete relief of the globus sensation in 81% of these

patients. In several patients the symptoms recurred when therapy was stopped but were responsive to further courses of treatment. Freeland et al (1974) found acid sensitivity in 93% of globus patients which probably relates to the high false positive rate obtained with acid barium studies. Other studies have shown abnormal oesophageal motility in response to acid barium swallows (Donner et al 1966) and even reflux into the pharynx (Cherry et al 1970, Delahunty & Ardran 1970).

Delahunty (1972) found chronic inflammation of the posterior part of the larynx in a similar group of patients with globus and hoarseness. He was able to demonstrate oesophago-pharyngeal reflux on cinefluoroscopy. Chodosh (1977) reports a group of patients with globus who had erythema of the arthenoids which responded to simple anti-reflux measures. Cherry et al (1970) investigated 12 patients with globus and mild hoarseness who all had normal pharyngeal and laryngeal examinations. Eleven patients demonstrated abnormal oesophageal motility in response to acid barium. Three patients had a hiatus hernia and reflux of barium from the oesophagus to the hypopharynx was also observed in 3 patients. This may account for the patient's complaints of fluid in the pharynx and the laryngeal symptoms described.

Perfusion of the distal oesophagus with 0.1N HCl reproduced pharyngeal symptoms with motility abnormalities in the distal oesophagus in 80% of patients. These symptoms were abolished by saline perfusion. The remaining patients developed heartburn with acid perfusion. All patients

experienced either reduction or abolition of their symptoms with standard medical anti-reflux therapy. Most of these patients had significant symptoms of gastro-oesophageal reflux on further questioning after the completion of the study (Cherry et al 1970). Thompson and Heaton (1982) have found that heartburn occurs commonly in the normal population (33%).

These studies suggest that globus may be an atypical symptom of gastro-oesophageal reflux but they are mainly uncontrolled and have relied on clinical and radiological methods of diagnosis of gastro-oesophageal reflux. Twenty four hour ambulatory oesophageal pH recording is now available for monitoring gastro-oesophageal reflux accurately and objectively and may confirm the diagnosis in the presence of a normal barium swallow (Johnson & Demeester 1974). Wilson et al (1987), using prolonged ambulatory pH monitoring, found no abnormality of oesophageal acid exposure in globus patients.

Further aetiological factors postulated for the globus sensation include post nasal drip, maxillary sinusitis and osteophytes of the cervical spine (Ratnesar 1970, Flores et al 1981). Mills (1956) reported X-ray evidence of sinus infection in one or both maxillary sinuses in ten patients with globus. However, pus was found in only 40% on antral lavage. Maran & Jacobson (1977) reported a case of "globus" due to an anterior osteophyte at the C6/7 level in whom barium swallow and oesophagoscopy showed only external compression by this osteophyte. The patient was treated by removal of the exostosis and anterior cervical spinal

fusion. Following this, the "globus" improved and the barium swallow returned to normal.

Schatzki (1964) postulated that a common physiological rather than a psychological mechanism was responsible for the symptom. He thought that tension caused these patients to observe their swallowing of saliva and therefore to swallow repeatedly. This left them without saliva and therefore the throat became dry and hence a vicious circle developed. It has been suggested that the globus sensation is related to spasm of muscles attached to the hyoid bone secondary to postural malalignment in the lower cervical spine and may respond to local manipulation (Fletcher 1986).

1.3.8: RELATIONSHIP OF GLOBUS TO CRICOPHARYNGEAL DYSPHAGIA

Some researchers have used the term "pharyngo-oesophageal dysphagia" instead of globus but this implies that some of the patients have significant dysphagia, weight loss and aspiration (Henderson et al 1976, Ellis & Crozier 1981). Henderson et al (1976) studied 1000 consecutive patients with gastro-oesophageal reflux, referred for manometry, by history, x-ray and manometry. No pH recordings were performed. When questioned 513 patients had pharyngo-oesophageal dysphagia which was associated in 154 patients with aspiration, many having associated significant respiratory symptoms. In a further study of 200 patients with gastro-oesophageal reflux, 50% had pharyngo-oesophageal dysphagia. There was no significant difference in the severity of the reflux symptoms between those with and without pharyngo-oesophageal dysphagia. Twenty of the

patients with pharyngo-oesophageal dysphagia experienced this with every meal but in the remainder the symptoms were intermittent. Following surgical correction of reflux in these patients, 10% of those with pharyngo-oesophageal dysphagia had residual symptoms. In a few patients these have been severe enough to require a cricopharyngeal myotomy and they have shown marked improvement following this procedure. It is important to exclude persistent reflux before myotomy (Henderson & Marryatt 1977).

Henderson hypothesised that the symptoms were due to obstruction at the cricopharyngeus produced by intermittent motor inco-ordination since mechanical obstruction cannot be demonstrated endoscopically or radiologically. Henderson et al (1976), in a manometric study of 52 patients with gastro-oesophageal reflux and 10 normal controls, found that 20 of the refluxers showed inco-ordination of cricopharyngeal activity so that the pharyngeal wave arrived at the cricopharyngeus during the cricopharyngeal contraction and seemed to be related to premature cricopharyngeal contraction. Fourteen of these patients had some symptoms of dysphagia. None of the normal controls had inco-ordination or dysphagia. Since the disorder was correctable in the majority of patients by anti-reflux surgery, the motor change may be a direct response of the cricopharyngeus to the irritation of the refluxed bolus. Muscle biopsies of the cricopharyngeus at myotomy showed the presence of nemaline rods compatible with local irritation, possibly secondary to reflux irritation (Henderson et al 1983). Ellis and Crozier (1981) found 4 patients with

pharyngoesophageal dysphagia to have hypertensive upper oesophageal sphincters (mean 166 mmHg) and a hypopharyngeal bar on barium studies. Following myotomy, the sphincter pressure fell to a quarter of the pre-operative value with relief of dysphagia.

It would appear that Henderson's patient population is very different from those usually considered to have the globus syndrome particularly with regard to weight loss and aspiration.

1.3.9: MANOMETRIC ABNORMALITIES OF THE OESOPHAGEAL BODY

Flores et al (1981) found that twelve globus patients had abnormally high resting pressures in the body of the oesophagus. Nine of the group produced spontaneous, simultaneous and repetitive contractions of low amplitude in the lower oesophagus. Only one patient showed abnormal upper oesophageal sphincter function which was premature contraction of the cricopharyngeal muscle and he also showed gastro-oesophageal reflux on simultaneous pH recording. Flores proposed that the globus sensation was referred from the hypertonic and frequently inco-ordinate body of the oesophagus.

1.3.10: PSYCHOLOGICAL TESTING AND GLOBUS

Pratt et al (1976) describes a group of 99 patients with globus with normal direct laryngoscopy and normal barium studies who therefore had psychological assessment with the Minnesota multi-phasic inventory. The group consisted of 23 men and 76 women, 70% of each group were aged 20 to 50

years. The questionnaires were all analysed by computer. On the questionnaire result, 30% of both men and women were considered to need psychiatric evaluation. The group as a whole had elevated scores in the depression and hypochondriacal parts of the test. This finding was greater in the males.

1.3.11: CONCLUSION

Several studies have shown that medical treatment of gastro-oesophageal reflux with antacids and elevation of the head of the bed has abolished or improved the globus symptom (Hallewell 1970, Hunt 1970). Surgical correction of gastro-oesophageal reflux is also effective in relieving pharyngo-oesophageal dysphagia in most patients (Henderson et al 1976). The evidence so far available suggests that globus and gastro-oesophageal reflux may be related and that the diagnosis of "globus hystericus" should be made reluctantly and infrequently. Any patient with the globus sensation should therefore have at least a full ear nose and throat examination followed by a careful barium swallow and endoscopy, paying particular attention to the presence of an hiatus hernia and gastro-oesophageal reflux. Twenty four hour pH monitoring and manometry of the upper oesophageal sphincter should be reserved for those patients with negative findings. Treatment should be aimed at correction of any reflux present.

Discussion on the globus symptom is confusing with the use of different equipment and different groups of patients. The use of intraoesophageal microtransducers should enable

accurate recordings of the rapidly changing upper oesophageal sphincter to be made without the problems associated with perfused catheters such as increased swallowing and the need to stop perfusion in the pharynx to avoid coughing.

Some questions still remain to be answered. Is it possible to show crico-pharyngeal inco-ordination in patients with globus? What is the relationship between primary oesophageal motor disorders and globus? Is globus a symptom of gastro-oesophageal reflux? Twentyfour hour ambulatory pH monitoring is the most accurate way of assessing reflux but globus patients have not been studied. Is it a manifestation of a psychological disturbance? The following studies aim to answer some of these questions.

CHAPTER 2

AIMS

AIMS

The use of provocative agents in patients with noncardiac chest pain has improved the diagnostic ability of Castell's unit from 25% to 35% (Richter et al 1985c).

Deficiencies of the work so far have posed the following questions:-

1. What is the clinical significance of a positive edrophonium test?
2. What is the effect of edrophonium on the upper, middle and lower oesophagus?
3. What is the relationship between edrophonium and Bernstein tests?
4. Is edrophonium a nonspecific oesophageal provocative agent?

My aims are :-

1. To determine the usefulness of edrophonium in clinical practice in the diagnosis of diffuse oesophageal spasm with regard to predicting long term success of treatment.
2. To determine the effect of edrophonium on the whole oesophagus and to assess its reproducibility.
3. To compare the effectiveness of Bernstein testing with edrophonium in this group of patients.

There is little evidence of the natural history of motility disorders and virtually no information about the place of balloon dilatation in the management of diffuse oesophageal spasm with reference to:- a. symptom relief; b. long term effects on motility; c. effects on lower oesophageal

sphincter and thus d. effects on gastro-oesophageal reflux.

My aims are:-

1. To assess the effect of a standard pneumatic dilatation in patients with diffuse oesophageal spasm, dilating the area of spasm and preserving the lower oesophageal sphincter function.
2. To measure gastro-oesophageal reflux pre- and post-dilatation in order to determine lower oesophageal sphincter function.
3. To identify those patients who respond to pneumatic dilatation of the body of the oesophagus.
4. To investigate the relationship of gastro-oesophageal reflux to the effect of dilatation on diffuse oesophageal spasm.

The evidence so far available suggests that globus and gastro-oesophageal reflux may be related. Abnormalities of both the upper oesophageal sphincter and oesophageal body have been reported in globus patients.

My aims are:-

1. To assess the relationship between oesophageal motility of the upper oesophageal sphincter, oesophageal body and lower oesophageal sphincter and globus.
2. To explore the association of globus with gastro-oesophageal reflux using ambulatory pH monitoring and to investigate the effects of acid perfusion on the upper oesophageal sphincter complex.
3. To consider the possibility of globus as a manifestation of a psychological disturbance.

CHAPTER 3

MATERIALS AND METHODS

GENERAL MATERIALS AND METHODS

3.1: HISTORY

All patients presenting in the oesophageal laboratory with symptoms of chest pain, dysphagia or globus had a full history taken with particular reference to specific symptoms, length of complaint and drug therapy (see history sheet in appendix). A clinical diagnosis was made taking into account results of previous endoscopy and barium studies. A full explanation of the investigations to be performed was given and oral consent was obtained.

3.2: BARIUM STUDIES

All patients underwent barium swallow and meal and/or had a cine bread barium swallow. If the X-rays had been performed at the referring hospitals they were all reviewed.

3.3: ENDOSCOPY

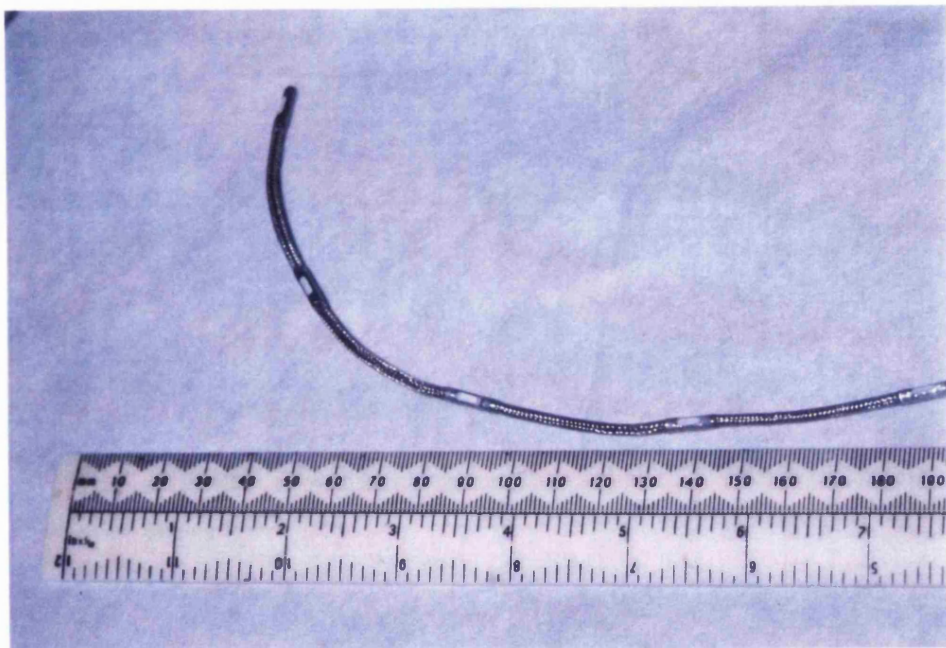
All patients with diffuse oesophageal spasm underwent oesophago-gastroscopy and all the globus patients had indirect and direct laryngopharyngoscopy and gastroscopy.

3.4: OESOPHAGEAL MANOMETRY

Oesophageal manometry was performed on all patients using a fully computerised Gaeltec system (Dussek 1987). The manometry catheter (figure 3.1) is 2.5mm in diameter which compares well with the Arndorfer catheter of 4.5mm diameter. It has six miniaturised pressure transducers arranged at 5cm intervals along the catheter with the first at the catheter

FIGURE 3.1

THE MANOMETRY CATHETER



Photograph showing catheter with its miniaturized pressure transducers. Note its curved appearance with the transducers pointing in the left lateral position.

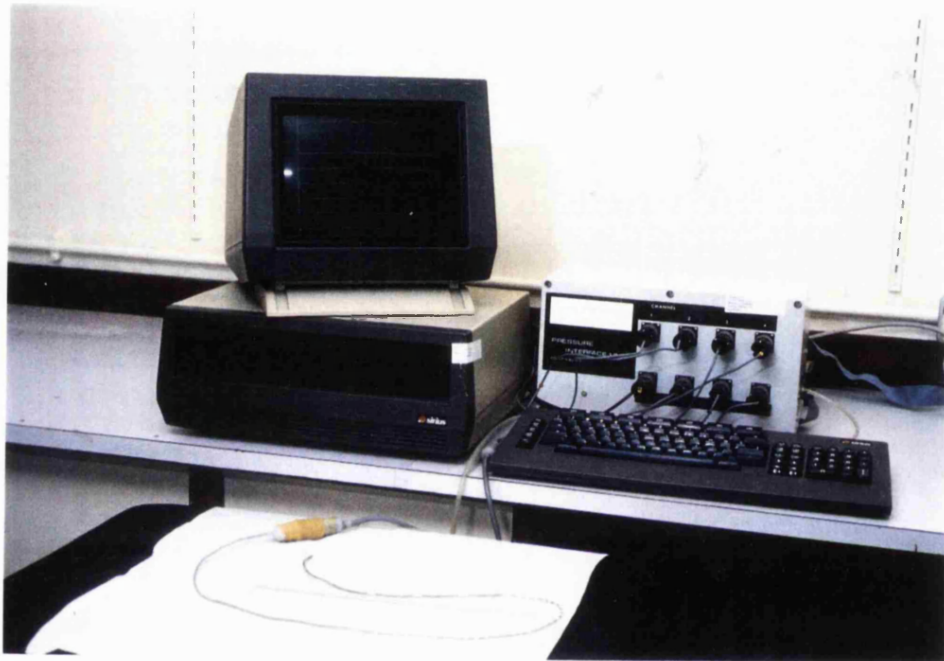
tip. These sensors measure intra-oesophageal pressure at each level without the use of the fluid filled catheter, infusion pump and external transducer required in other systems (Humphries & Castell 1977). The advantages are the simplicity of the measuring system; freedom from catheter damping effects; very high frequency response and lack of resonance effects due to plumbing compliance and air bubbles in the system (Stef et al 1974, Dodds et al 1975, Dodds et al 1976). Thus the system measures pressure over a 25 cm length at 5 cm intervals and can store the information recorded during 1 hour when sampling rate of 8 samples/second is used (6 samples/second is the minimum sampling rate for oesophageal body peristaltic activity) (Castell et al 1980).

The pressure transducers are based on a metal diaphragm which contains a thin-filmed strain gauge. This is a thin copper alloy plate photochemically machined to form a rigid outer area and a very thin deformable centre. This diaphragm, which typically measures 1.6mm wide by 4mm long, is then mounted on a medical-grade stainless steel housing which forms a pressure measuring sensor. The transducers are all parallel to the long axis of the catheter in the same radial alignment. The tube is bonded to stainless steel braid and inserted into a silicone rubber catheter to produce a flexible, compliant catheter which is radio-opaque.

Pressure signals from the transducers are converted in the interface unit to a digital form for processing (Castell et al 1984). Data can be recorded at different sampling rates

FIGURE 3.2

GAELTEC COMPUTERISED OESOPHAGEAL MANOMETRY



Photograph showing the Gaeltec manometry catheter, interface unit and Sirius computer used for analysis and storage.

of up to 64 samples per second which makes this system very suitable for recording from areas of rapidly changing pressure such as the pharynx and cricopharyngeus. A Sirius computer (figure 3.2) processes the pressure changes which are then displayed and finally stored on floppy discs.

Prior to use, the transducers and reference pressure transducer within the interface unit were calibrated. This allowed the computer to provide any necessary correction during data recording to ensure that accurate pressure values were recorded. The Gaeltec system uses a negative pressure calibration technique. By applying a negative pressure to the inside of the catheter (which is referenced to atmospheric pressure during use) the same pressure differential can be generated across the transducer diaphragm as would be generated by applying a positive pressure to the outside of the catheter. During calibration air is introduced and withdrawn to produce a pressure range from -30 to 300 mmHg whilst the catheter is at 37 degreesC. The transducers are then zeroed lying flat in a tray of fluid at body temperature. After calibration, the catheter is inserted into a cylinder of water to check that all the transducers are reading correctly.

The catheter was introduced through the nose using lubricating jelly on an unседated fasted patient in the semi-recumbent position (figure 3.3). Although this position for recording allows gravity to assist with swallowing, it is a much more physiological position for normal swallowing to occur. Babka et al 1973 found a significant difference between the lower oesophageal sphincter pressure measured in

FIGURE 3.3

INSERTION OF THE MANOMETRY CATHETER



Photograph showing the "patient" swallowing water to facilitate the insertion of the manometry catheter into the oesophagus.

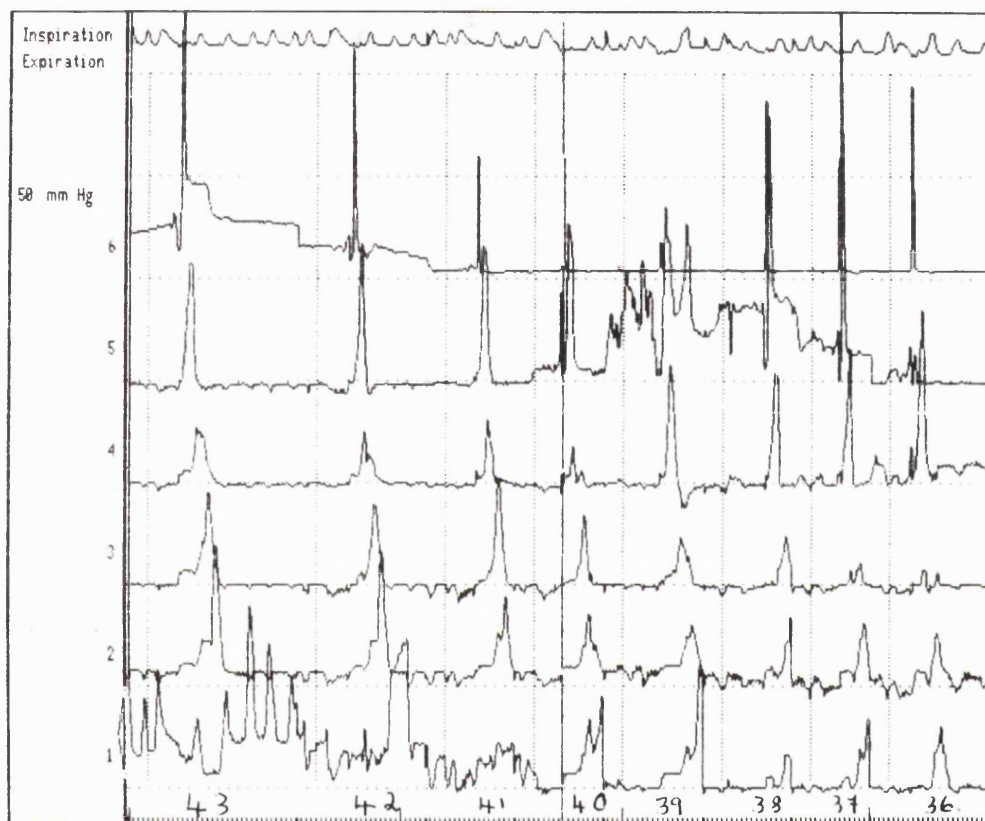
the supine and sitting positions. All studies were performed in the semi-recumbent position. The catheter was introduced until at least two transducers were found to be in the stomach as shown by a positive pressure change with inspiration. The patient was then allowed to rest for a few minutes before recording was commenced. The computer was programmed to collect pressure recordings from all six transducers simultaneously which ideally allowed the whole of the oesophagus including cricopharyngeus and the lower oesophageal sphincter to be visualised on the display screen at the same time if the lower oesophageal sphincter was exactly 20 or 25cm from the upper oesophageal sphincter. Respiration was recorded by a sensor fastened to the chest which recorded chest wall movements.

3.4.1: LOWER OESOPHAGEAL SPHINCTER

The lower oesophageal sphincter pressure was recorded using the station pull-through technique (figure 3.4) (Dodds 1976a, Welch & Drake 1980). The catheter was inserted so that at least two sensors were below the sphincter. With the patient trying to avoid swallowing during recordings, the catheter was withdrawn 1cm at a time holding at each position for at least four respiratory cycles. All pressures were recorded as end expiratory readings. Gastric pressure was recorded as allowance would need to be made when calculating lower oesophageal sphincter pressure if gastric pressure was not zero. As the catheter was withdrawn, the high pressure zone of the lower oesophageal sphincter appeared. Its relationship to the diaphragm could be shown by the point where the respiratory positive deflection in

FIGURE 3.4

STATION PULL-THROUGH MEASUREMENT OF LOWER AND UPPER
OESOPHAGEAL SPHINCTER PRESSURES



Photograph of manometric trace with the catheter withdrawn 1 cm. at a time starting with recording 1 at 43 cm. from the nose. The trace shows full relaxation of the lower oesophageal sphincter (recording 1) and the upper oesophageal sphincter (recording 5).

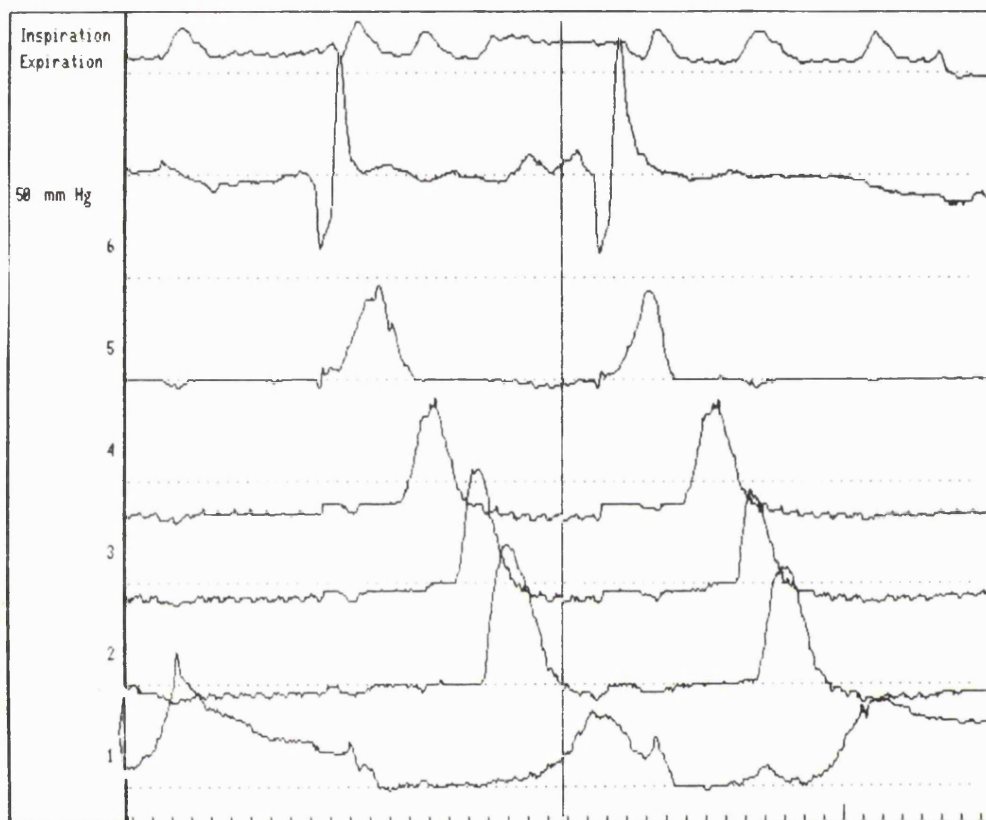
the abdomen changed to a respiratory negative deflection in the intrathoracic oesophagus, the respiratory inversion point (Harris 1966). In patients with hiatus hernias, variations in the position of the respiratory inversion point are of diagnostic value. If the respiratory inversion point moves during a recording, the high pressure zone will fluctuate, changing from respiratory positive to respiratory negative, i.e. double respiratory reversal. These fluctuations reflect the incompetence of the junction and are a diagnostic feature of hiatal hernia (Henderson 1980). The length and position of the sphincter could also be recorded. The peak end-expiratory resting lower oesophageal sphincter pressure was recorded by each sensor as it was withdrawn (Boyle et al 1985), the gastric pressure was subtracted and a mean of all values calculated. The lower oesophageal sphincter has been shown to be asymmetrical, with pressures measured in the left lateral position being twice that to the right (Winans 1977, Welch 1980). The Gaeltec catheter was always inserted via the nose with the transducers pointing to the left lateral position so that the recording was standardised for radial assymetry. Attempts to twist the catheter whilst in the patient resulted in one of the transducers being destroyed.

3.4.2: OESOPHAGEAL BODY

Further recordings with the patient swallowing 5ml boluses of water delivered by syringe into the patient's mouth (wet swallows) were then made. Wet swallows are necessary to produce consistent results (Richter 1987). Dry swallows, swallowing saliva, give very variable volumes to swallow and

FIGURE 3.5

MANOMETRY OF THE NORMAL OESOPHAGUS

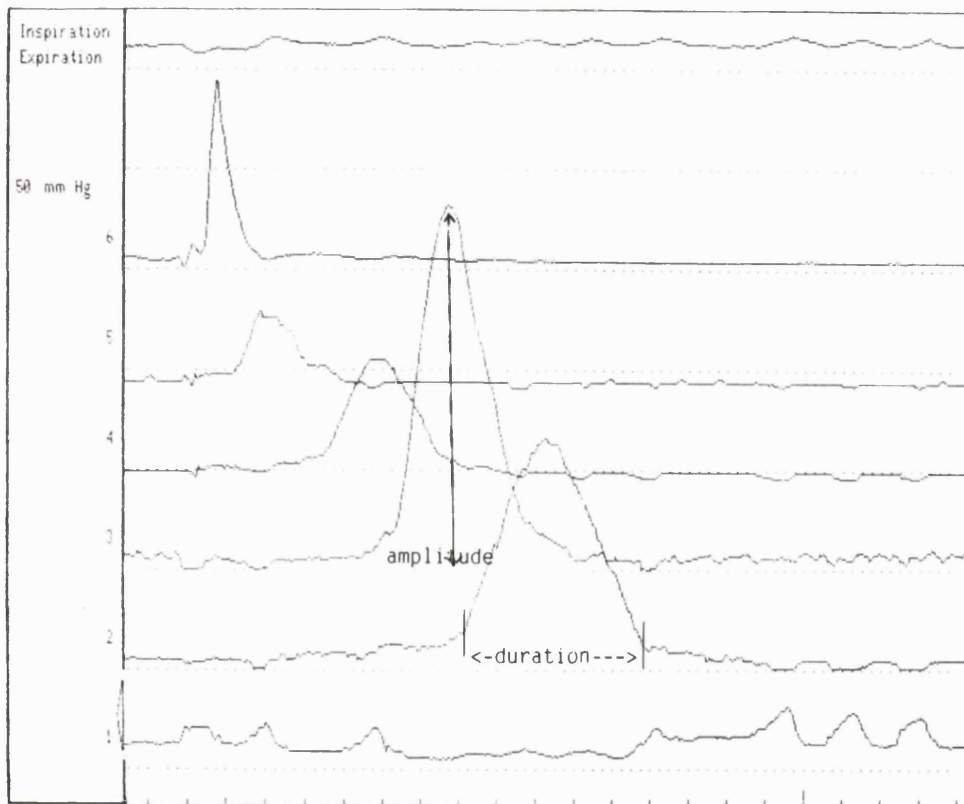


The trace shows the upper oesophageal sphincter relaxation in response to a wet swallow followed by normal peristaltic contraction down the body of the oesophagus with full relaxation of the lower oesophageal sphincter.

Recording 1 is at the level of the lower oesophageal sphincter; recording 6 is at the level of the upper oesophageal sphincter; the remaining recordings are arranged at 5 cm. intervals between them.

FIGURE 3.6

MANOMETRIC MEASUREMENT OF AMPLITUDE AND DURATION OF CONTRACTIONS

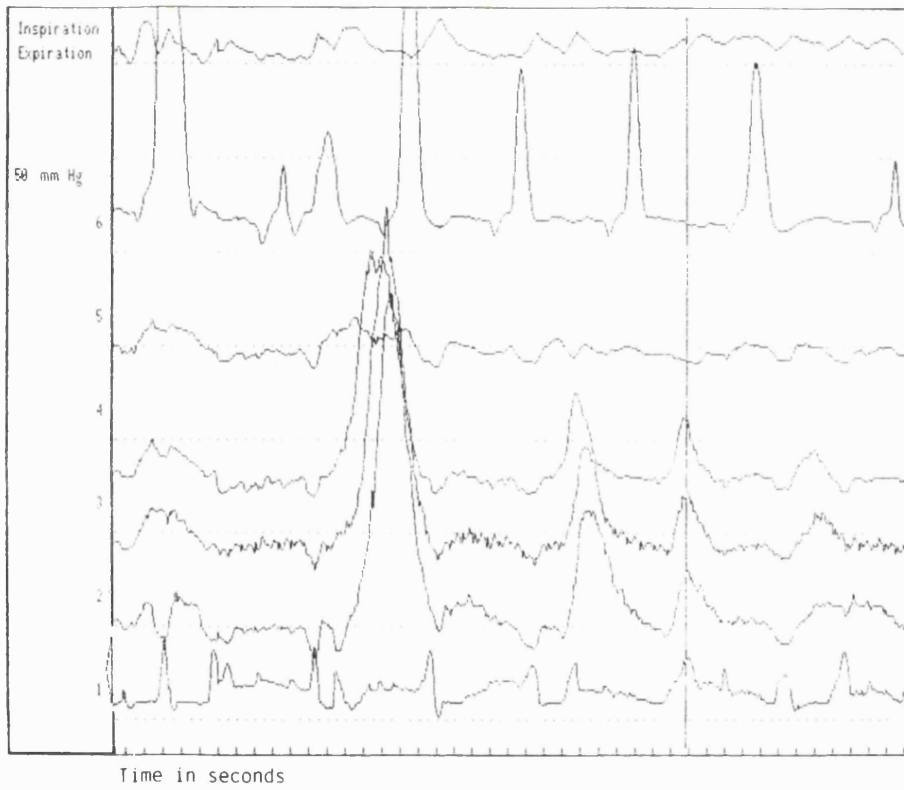


Amplitude (mmHg) was measured from the baseline intraoesophageal pressure to the peak of the contraction. Duration (seconds) was measured from the onset of the major upstroke to the end of the contraction.

are therefore often followed by nonperistaltic contractions (Hollis & Castell 1975). 5ml boluses have been shown to produce good amplitude peristaltic contractions in normal subjects without giving too large a total volume to drink during a complete recording. A wet swallow in a control subject should produce a pharyngeal contraction to pump the bolus down followed by cricopharyngeal relaxation. A peristaltic propagated wave must be present in the body of the oesophagus to propel the bolus down to the lower oesophagus and, finally, there should be coordinated relaxation of the lower oesophageal sphincter (figure 3.5). The results from 10 wet swallows were used to produce mean results. Contraction amplitude and duration (figure 3.6) could be measured directly from the screen using various computer functions. Wave amplitude (mmHg) was measured from the mean intraoesophageal baseline pressure to the peak of the wave. Duration (seconds) was measured from the onset of the major upstroke to the end of the wave. In wet swallow induced contractions the upstroke generally rose from an initial pressure plateau, which resulted from fluid entering the oesophagus (Ingelfinger 1958), and the onset was therefore taken as the intersection between the initial pressure plateau and the upstroke of the wave. Particular attention was paid to abnormal contractions. These included:- 1) synchronous contractions (figure 3.7) defined as simultaneous (or less than 0.5 seconds difference) onset or simultaneous peak of waves recorded by adjacent recording sites; 2) repetitive contractions (figure 3.8) with at least 3 peaks and separated by at least 1 second from the previous

FIGURE 3.7

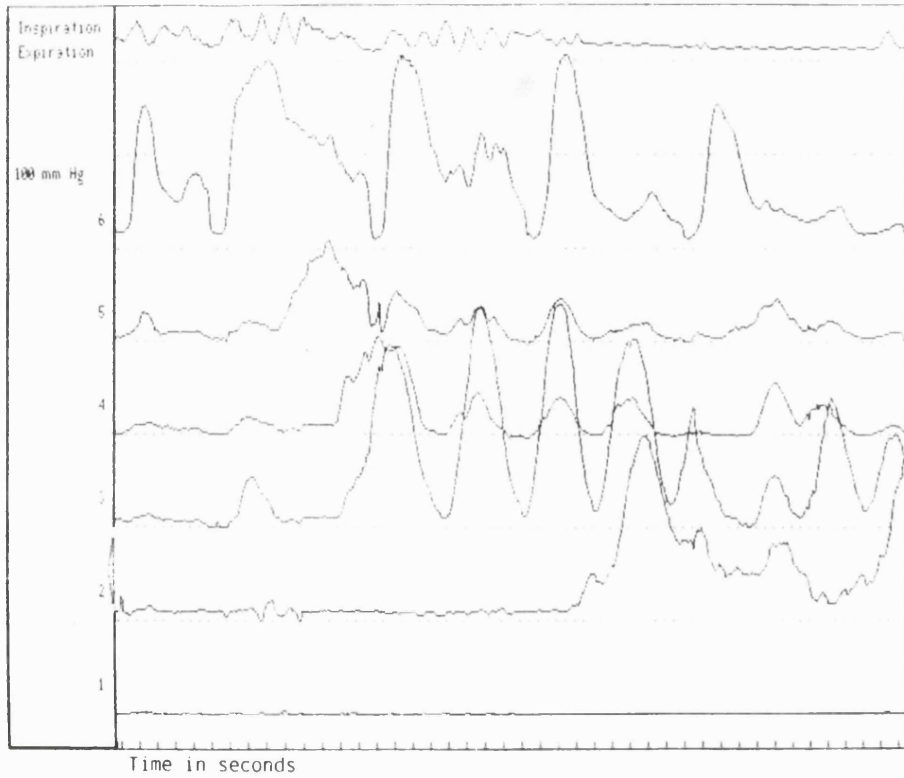
MANOMETRIC TRACING SHOWING SYNCHRONOUS CONTRACTIONS



Tracing showing simultaneous contractions in response to wet swallows in recordings 2 to 4.

FIGURE 3.8

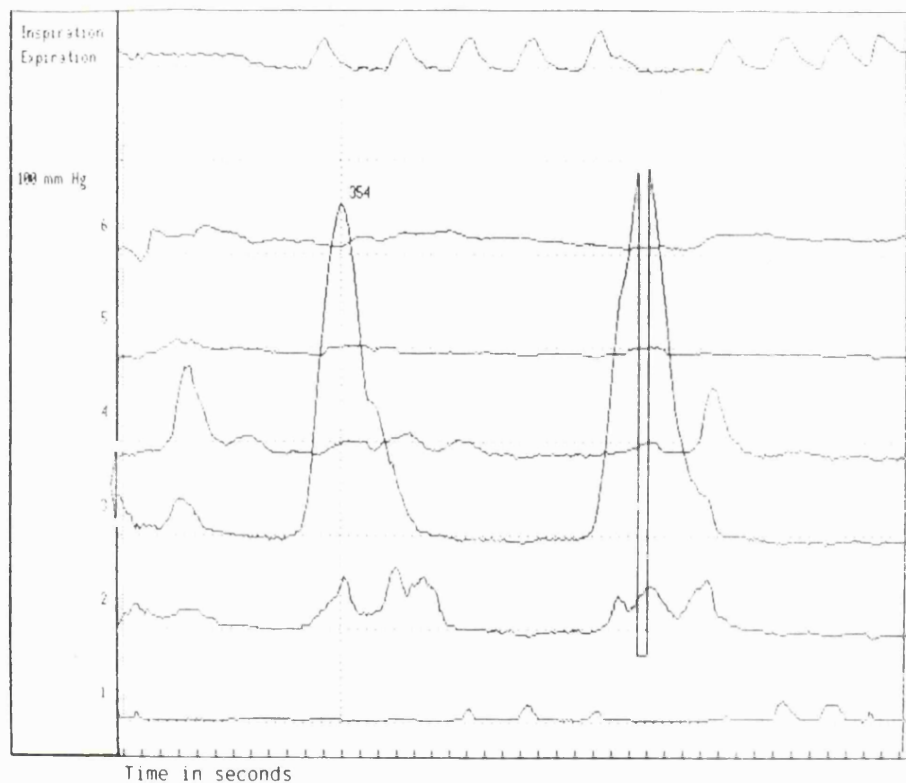
MANOMETRIC TRACING SHOWING REPETITIVE CONTRACTIONS



Tracing showing a multi-peaked contraction in recording 3 in response to a wet swallow.

FIGURE 3.9

MANOMETRIC TRACING SHOWING SPONTANEOUS CONTRACTIONS



Tracing showing spontaneous contractions in recording 3 occurring without a swallow. The amplitude of the second contraction exceeded the upper limit of calibration of 400mmHg. Note the change of scale to 100mmHg.

wave; 3) retrograde contraction sequences; or 4) spontaneous contractions (figure 3.9) not generated by a swallow.

3.4.3: UPPER OESOPHAGEAL SPHINCTER

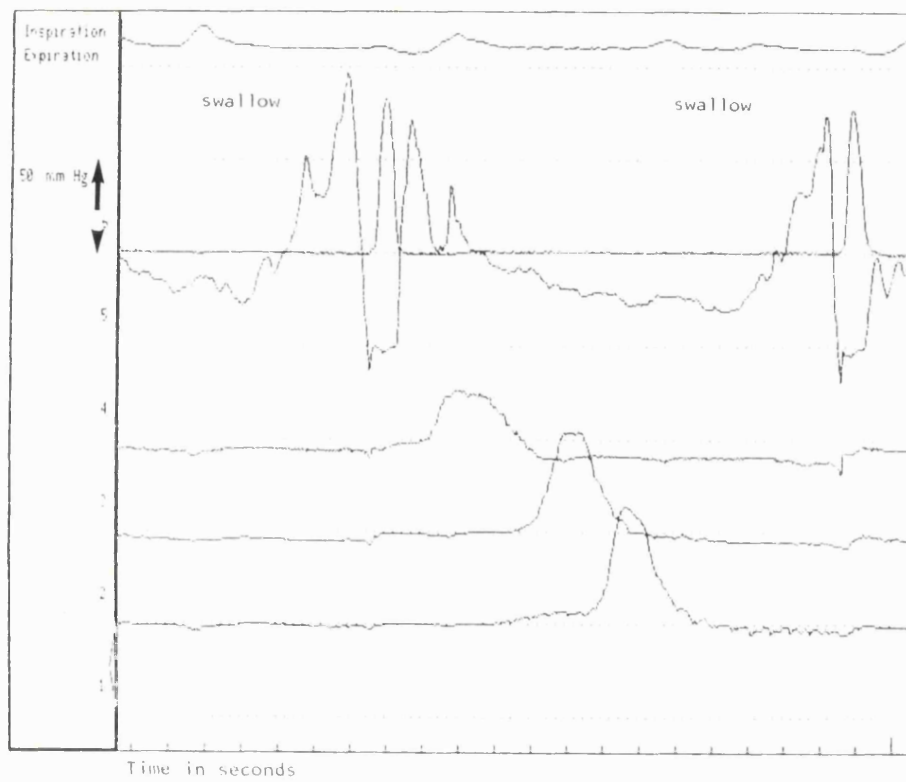
The tracing could also be magnified to allow more accurate analysis of the upper oesophageal sphincter mechanism (figure 3.10). The amplitude of peak pharyngeal contraction, cricopharyngeal contraction and resting cricopharyngeal pressure were easily calculated as was the duration of relaxation of the high pressure zone. Henderson et al (1976) have suggested that the sensation of food sticking in the upper oesophagus may be related to cricopharyngeal incoordination. They found that the pharyngeal contraction arrived at the cricopharynx during the period of cricopharyngeal contraction above the resting pressure in some patients with hiatus hernias and appeared to represent incoordination. They used a perfused catheter which made recordings in the upper oesophagus technically difficult. The use of the Gaeltec catheter should enable more accurate recordings to be obtained. Any incoordination between pharyngeal contraction and cricopharyngeal relaxation could be shown by analysis of the time between peak pharyngeal contraction and the start of cricopharyngeal contraction.

3.5: MANOMETRIC DIAGNOSIS

Diffuse oesophageal spasm (figure 3.11) was diagnosed in patients who had symptoms of dysphagia and/or chest pain and whose manometry showed both a. more than 10% simultaneous contractions in response to wet swallows and b. retention of peristalsis to differentiate diffuse oesophageal spasm from

FIGURE 3.10

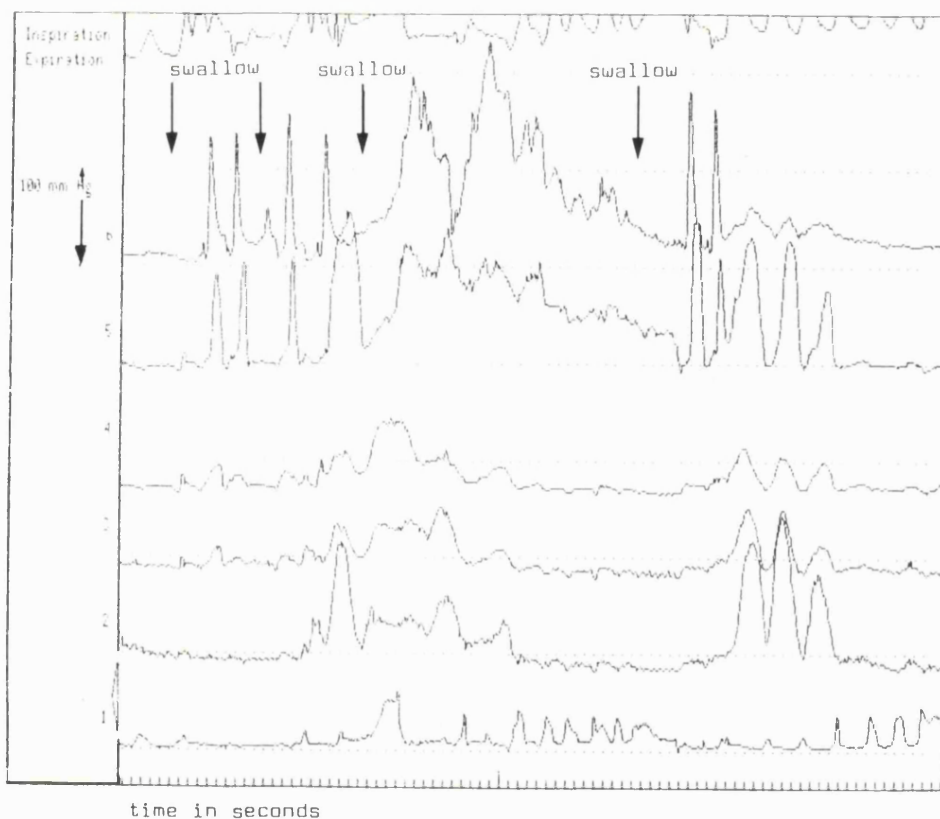
UPPER OESOPHAGEAL SPHINCTER MANOMETRY



Photograph showing upper oesophageal sphincter relaxation (recording 5) in response to a pharyngeal contraction (recording 6) following a wet swallow.

FIGURE 3.11

MANOMETRIC TRACING OF DIFFUSE OESOPHAGEAL SPASM



Photograph showing repetitive synchronous contractions in response to wet swallows with normal lower oesophageal function.

Recording 1 is at the level of the lower oesophageal sphincter with the other recordings at 5 cm. intervals above the sphincter. Normal peristalsis is seen elsewhere in the recording.

achalasia. Additional optional features were:- 1. amplitude of contraction of more than 200mmHg, 2. duration of contraction of longer than 7 seconds (figure 3.12) and 3. repetitive activity (Richter 1984).

Achalasia (figure 3.13) was diagnosed if there was:-
a. incomplete lower oesophageal sphincter relaxation,
b. aperistalsis in the oesophageal body, c. an elevated lower oesophageal sphincter pressure, (although the lower oesophageal sphincter pressure can be normal), and
d. increased intraoesophageal baseline pressure relative to intragastric pressure.

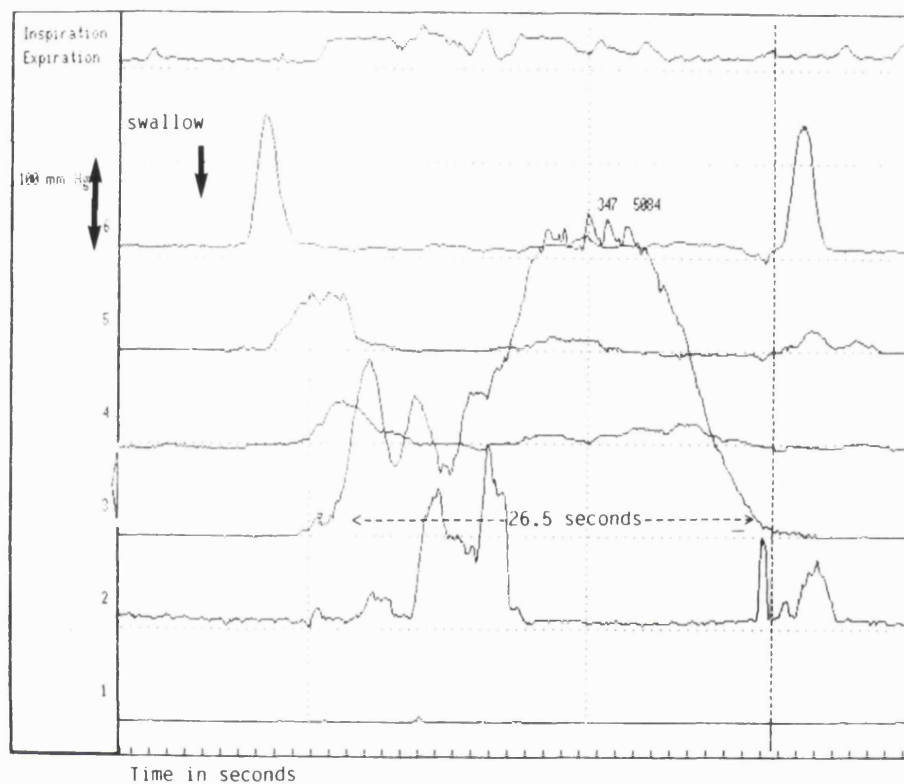
Nutcracker oesophagus (figure 3.14) was diagnosed when a normal peristaltic sequence was recorded with mean peristaltic amplitude in the distal oesophagus greater than 180mmHg and often an increase in mean duration of contractions (Benjamin & Castell 1983, Richter et al 1987).

3.6: BERNSTEIN TEST

The oesophagus was perfused with normal saline , without the patient's knowledge, at 10 mls/min for five minutes via a subsidiary catheter placed 5cm above the lower oesophageal sphincter as control. Any symptoms or alteration in manometry were recorded. The perfusate was then changed to 0.1N hydrochloric acid at the same rate for a further 10 minutes, again without the patient's knowledge, to test for acid sensitivity by provoking the patient's symptoms (Bernstein 1958). In those patients with globus the manometric pattern of the upper oesophageal sphincter was specifically examined.

FIGURE 3.12

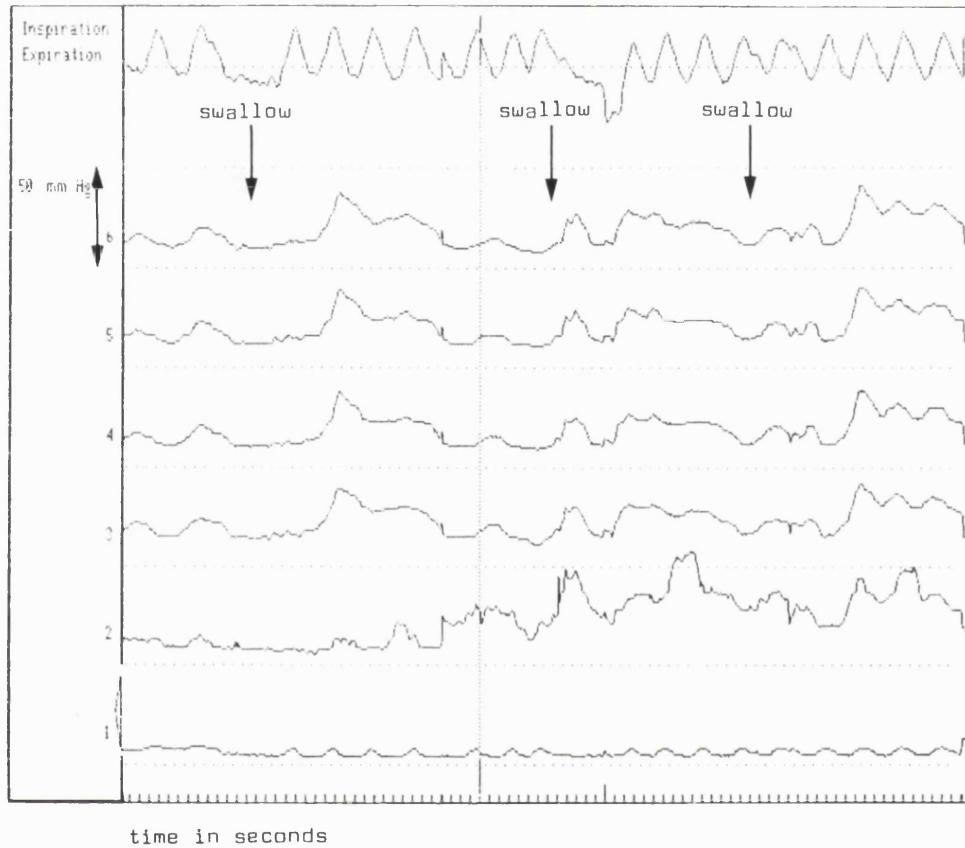
MANOMETRIC TRACING OF A HIGH AMPLITUDE, LONG DURATION CONTRACTION



Tracing showing a contraction with an amplitude of 347mmHg and 26.5 second duration in response to a wet swallow in recording 3. This recording occurred in a patient with diffuse oesophageal spasm and was associated with severe chest pain.

FIGURE 3.13

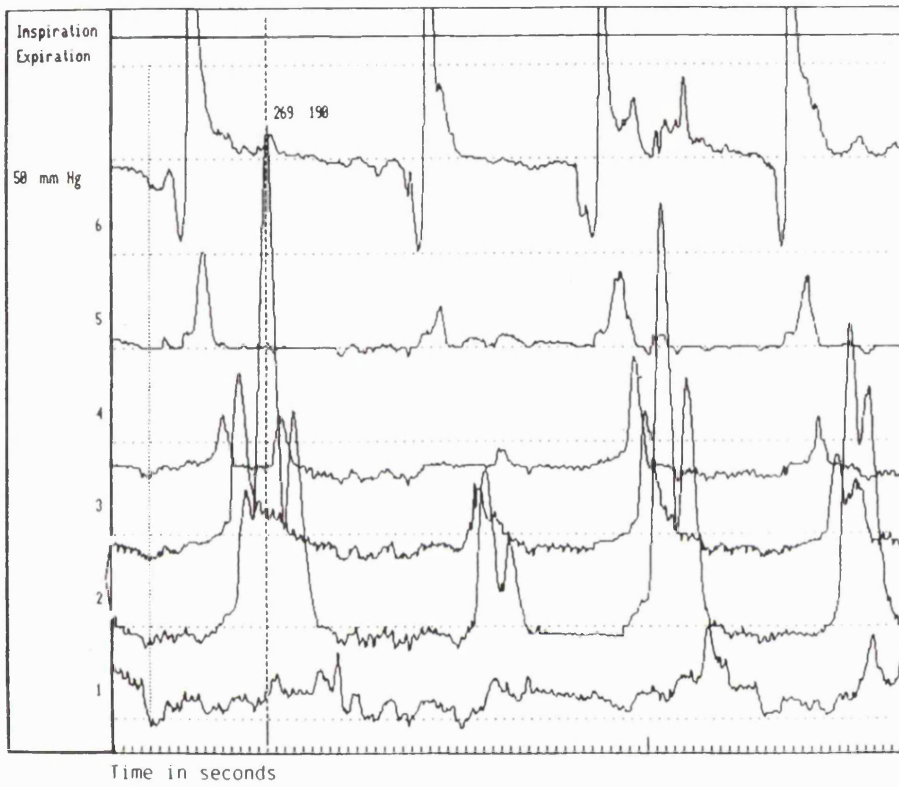
MANOMETRIC TRACING OF ACHALASIA



Tracing shows raised intraoesophageal pressure with loss of peristalsis and absent lower oesophageal relaxation. Recording 1 shows intragastric pressure. Recording 2 is at the level of the lower oesophageal sphincter with the other recordings at 5 cm. intervals above the sphincter.

FIGURE 3.14

MANOMETRIC TRACING OF NUTCRACKER OESOPHAGUS



Tracing showing high amplitude (269mmHg maximum) peristaltic contractions in response to wet swallows.

3.7: EDROPHONIUM PROVOCATION TEST

The majority of patients were then given a 10mg intravenous bolus of edrophonium chloride (Tensilon Roche). This dose has been shown to produce a maximal response in oesophageal contractions (London 1981). Patients received a placebo injection of normal saline prior to edrophonium. Immediately after the injection, further wet swallows were recorded and the patient's symptom response was noted, with particular reference to chest pain and dysphagia and how these symptoms compared with the patient's usual symptoms. A positive test reproduced the patient's symptoms with the production of a manometric abnormality of diffuse oesophageal spasm (Benjamin 1983).

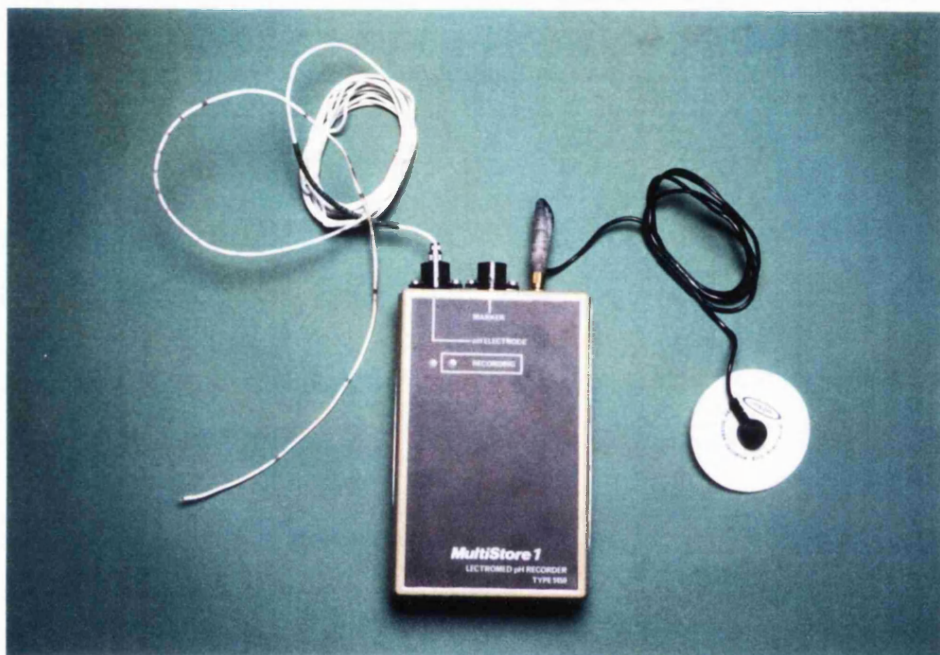
Following the recording, the catheter was removed, soaked in Cidex (activated gluteraldehyde solution: Johnson and Johnson) for 10 minutes and rinsed in water prior to further use.

3.8: TWENTYFOUR HOUR AMBULATORY pH MONITORING

Ambulatory pH monitoring produces both a qualitative and quantitative way of assessing objectively how much acid reflux a patient has and allows correlation of symptoms with episodes of acid reflux into the oesophagus (Tuttle & Grossman 1958, Johnson 1974, Demeester 1980, Johnson 1985). The Ormed system (figure 3.15) consists of a glass pH electrode, a recording device and a skin reference electrode. The system requires calibration with buffers of pH 4 and 7 prior to use. The glass pH electrode was inserted via the nose and fixed so that it recorded 5 cm above the

FIGURE 3.15

TWENTYFOUR HOUR AMBULATORY pH MONITORING SYSTEM



Photograph showing the glass pH electrode, recording device and skin reference electrode.

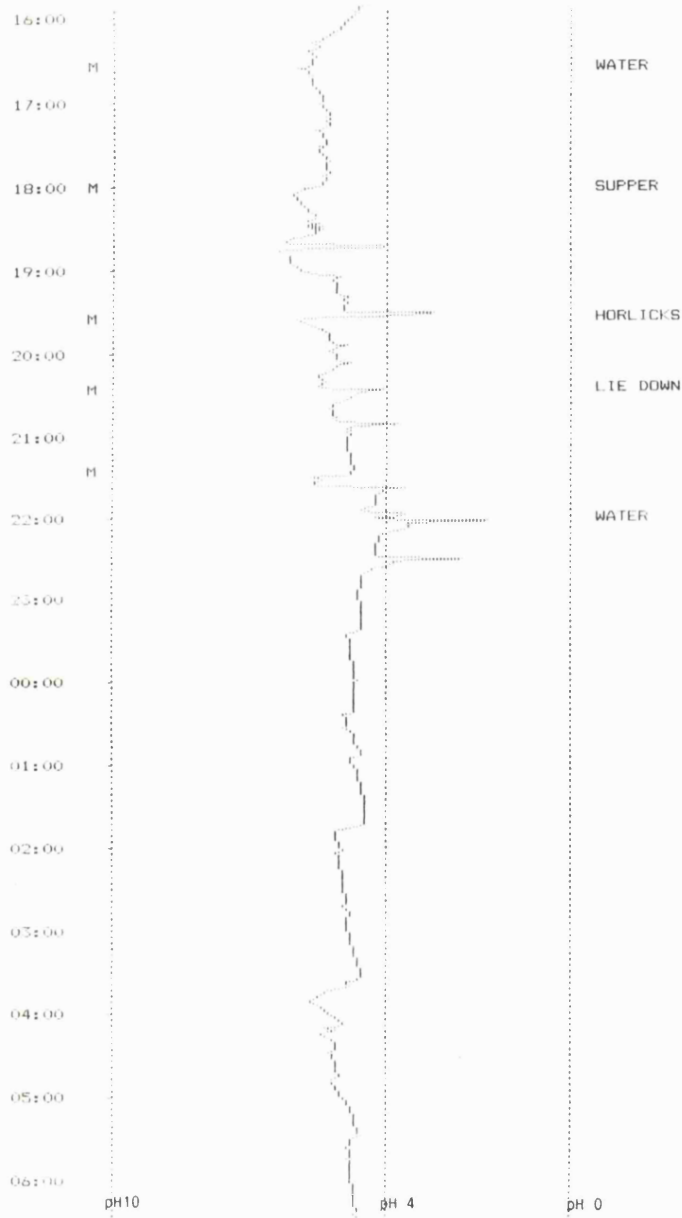
upper margin of the lower oesophageal sphincter as determined by manometry. The electrode was connected to a recorder worn by the patient around the waist and a skin reference electrode, attached to the patient's chest, was also attached to the recorder.

A marker on the recorder allowed the patient to record changes in position from supine to upright and also symptoms and events such as eating and drinking. A timed diary (see appendix) was also completed for the period of study. A reasonably normal diet was taken with the exclusion of particularly acid foods which might bias the results although de Caestecker et al (1987) have shown that oesophageal pH changes from ingested acid food are so transitory that the effect is minimal. This test was performed as an outpatient procedure and the patient was encouraged to go home and continue with his normal activities, particularly those known to produce his usual symptoms.

After twenty four hours the probe was removed and the recorder was attached to a BBC computer for analysis. Reflux was deemed to have occurred when the pH in the oesophagus became less than 4. The percentage time that the pH was less than 4 was determined for the whole 24 hours and for the time spent in the upright and supine positions. In addition, the total number of single reflux events, the number of episodes longer than five minutes and the time of the longest reflux episode were obtained from the recording. The use of the diary and the marker button with the tracing allowed positive or negative correlation between symptoms

FIGURE 3.16

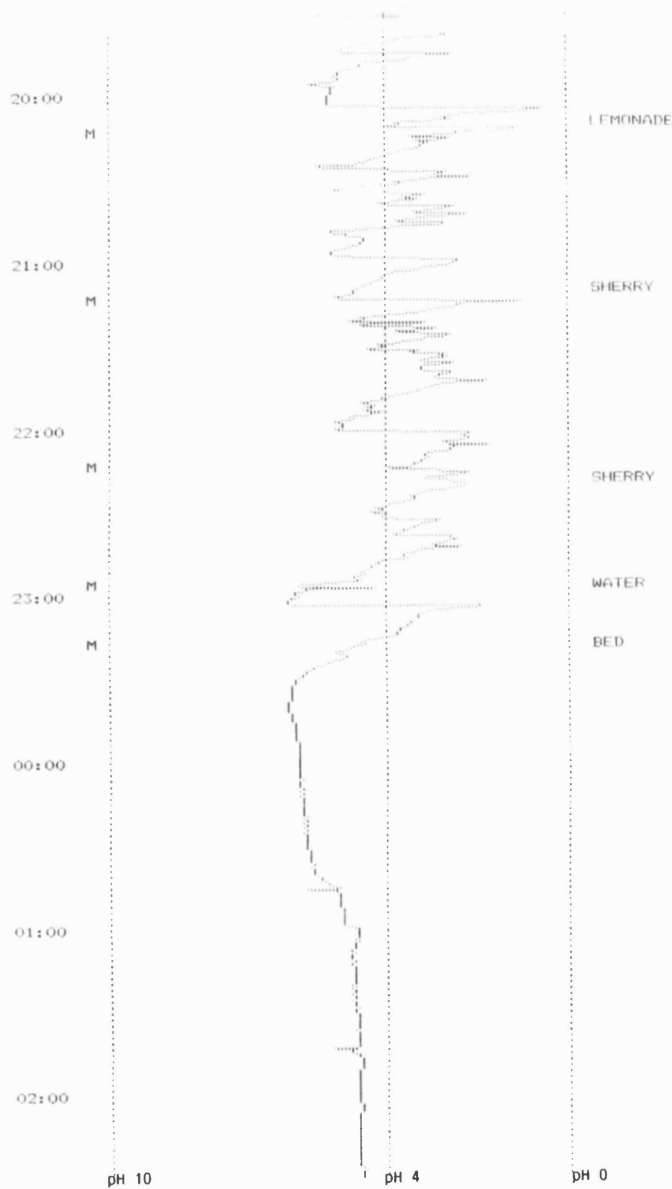
NORMAL TWENTYFOUR HOUR AMBULATORY pH MONITORING



Recording of ambulatory pH recording showing physiological episodes when the pH recorded fell below pH 4. The recording shows the diary entries and pH 0, 4 and 10.

FIGURE 3.17

TWENTYFOUR HOUR AMBULATORY pH MONITORING SHOWING SEVERE UPRIGHT GASTRO-OESOPHAGEAL REFLUX



Tracing showing many episodes of reflux of acid into the oesophagus with the pH falling to less than 1. No reflux is demonstrated in the supine part of the recording.

and reflux episodes (figures 3.16 and 3.17).

3.9: PSYCHOMETRIC TESTING

At the completion of the ambulatory pH monitoring the patients were asked to complete two questionnaires (see appendix), the Eysenck Personality Inventory and a modified General Health Questionnaire (Goldberg 1979), as Pratt (1976) has suggested that patients with the globus sensation have a tendency to depression and hypochondriasis.

The Eysenck personality inventory (Eysenck 1972) was designed to assess extroversion and neuroticism. It is a reliable and well validated test which has been used in studies investigating the contribution that personality may make to physical illness (Stockton 1985). It consists of a 24 item extroversion scale, a 24 item neuroticism scale and a lie scale of 9 items. The patient is asked to score 'yes' or 'no' to all items and must therefore make a decision in answer to each question.

The general health questionnaire is a self-administered screening questionnaire aimed at detecting patients with diagnosable psychiatric disorders (Goldberg 1986). It comprises questions about symptoms which best differentiate psychiatric patients as a group from those who consider themselves well and therefore focuses on the fine distinction between psychological illness and health. It considers two main topics: inability to carry out one's normal healthy functions and the appearance of new phenomena of a distressing nature. The modified 28 item questionnaire consists of 4 subscales, somatic symptoms, anxiety and

insomnia, social dysfunction and severe depression. The patient is required to underline the most appropriate answer for each question with respect to health in the recent past, and present illness. Each answer is then scored on both the general health questionnaire method (0,0,1,1) and the Likert method (0,1,2,3). A score of 5 or more with the general health method suggests psychiatric abnormality. When compared with psychiatric interview, the modified questionnaire had 88% sensitivity and 84% specificity. These two questionnaires were administered to the patients as soon as the pH probe was removed.

3.10: STATISTICAL ANALYSIS

Nonparametric statistical methods have been used throughout for analysis with results expressed as median and range. For the analysis of paired samples Wilcoxon's rank sum test has been used. For analysis of two independent samples, Mann-Whitney U test was used and for analysis of three related samples, Freidman's two way analysis of variance was used. A p value of 0.05 or less was accepted as denoting statistical significance. All calculations have been performed using the Systat programme on an Apple Macintosh computer.

3.11: METHOD DIFFUSE OESOPHAGEAL SPASM

All patients referred to the oesophageal laboratory had a careful history taken with particular reference to symptoms of chest pain and dysphagia. Barium studies and gastroscopy were performed as previously documented (3.2 & 3.3).

A provisional diagnosis was made on the results of the symptoms and barium studies.

Oesophageal manometry was then performed using the Gaeltec system as detailed in the general method (3.4). The lower oesophageal sphincter pressure was measured using a station pull through technique and then oesophageal contractions were recorded in response to 5 ml boluses of water (wet swallows). The mean values from 10 wet swallows were calculated for the maximum amplitude and mean amplitude of contractions 5 cm, 10 cm and 15 cm above the lower oesophageal sphincter region and similarly for the maximum duration and mean duration. The percentage of synchronous contractions in response to wet swallows was recorded and the presence of triple peaked contractions and spontaneous contractions documented. A standard Bernstein test was performed using a saline control perfusion. The provisional diagnosis was reviewed before and after the edrophonium provocation test.

Patients were then given edrophonium chloride 10 mg as an intravenous bolus with a control intravenous bolus of 1 ml of 0.9% saline. Immediately after the injection, further wet swallows were recorded and the patient's symptom response was recorded noting in particular chest pain and dysphagia and how these symptoms compared with the patient's usual

symptoms. A positive test reproduced the patient's symptoms with the production of a manometric abnormality of diffuse oesophageal spasm. The mean values for maximum and mean amplitude and duration were calculated as before and the percentage of synchronous contractions recorded.

24 hour ambulatory pH monitoring was then carried out as described in the general method (3.8) to exclude patients with primary gastro-oesophageal reflux.

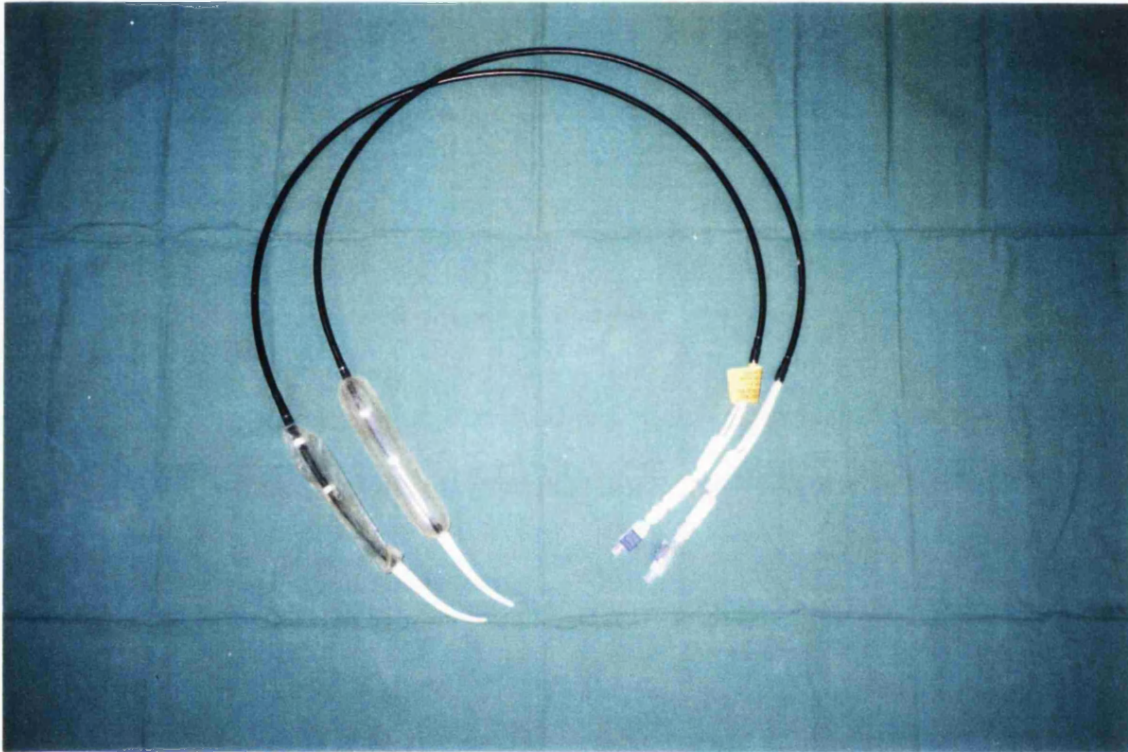
3.12: METHOD BALLOON DILATATION

The diagnosis was made as described in the section on manometric criteria (3.4) either before or after the edrophonium test (3.7). Initial treatment of all patients was conservative and consisted of reassurance, calcium channel blocking drugs (nifedipine Adalat Retard Bayer) and anti-reflux therapy in those patients with coexisting significant gastro-oesophageal reflux. Although the results of conservative treatment were disappointing, symptoms in 21 patients were tolerable. Seventeen of the 38 patients found the symptoms sufficiently distressing to need further treatment and they were therefore treated by balloon dilatation after full explanation of the technique, the potential benefits and the risks, including the possibility of oesophageal rupture.

BALLOON DILATATION

The dilatations were performed by Dr J.D.Irving under neuroleptanalgesia (Midazolam, Hypnovel Roche and Fentanyl, Sublimaze Janssen). Under fluoroscopic control, in the left lateral position, an angiographic catheter was passed into the stomach per ^{or}um and a guide wire 0.038in. (0.97mm) in diameter and 200cm in length was introduced through the catheter so that the flexible tip lay well within the stomach. The angiographic catheter was changed over the guide wire for a "Rigiflex" balloon catheter (Microvasive), the balloon being 30 or 35mm in diameter and 8 cm in length (figure 3.18). The oesophagus was dilated from the lower oesophageal sphincter to above the level of the aortic arch, no attempt being made to dilate the lower oesophageal >pa

FIGURE 3.18
BALLOON DILATOR



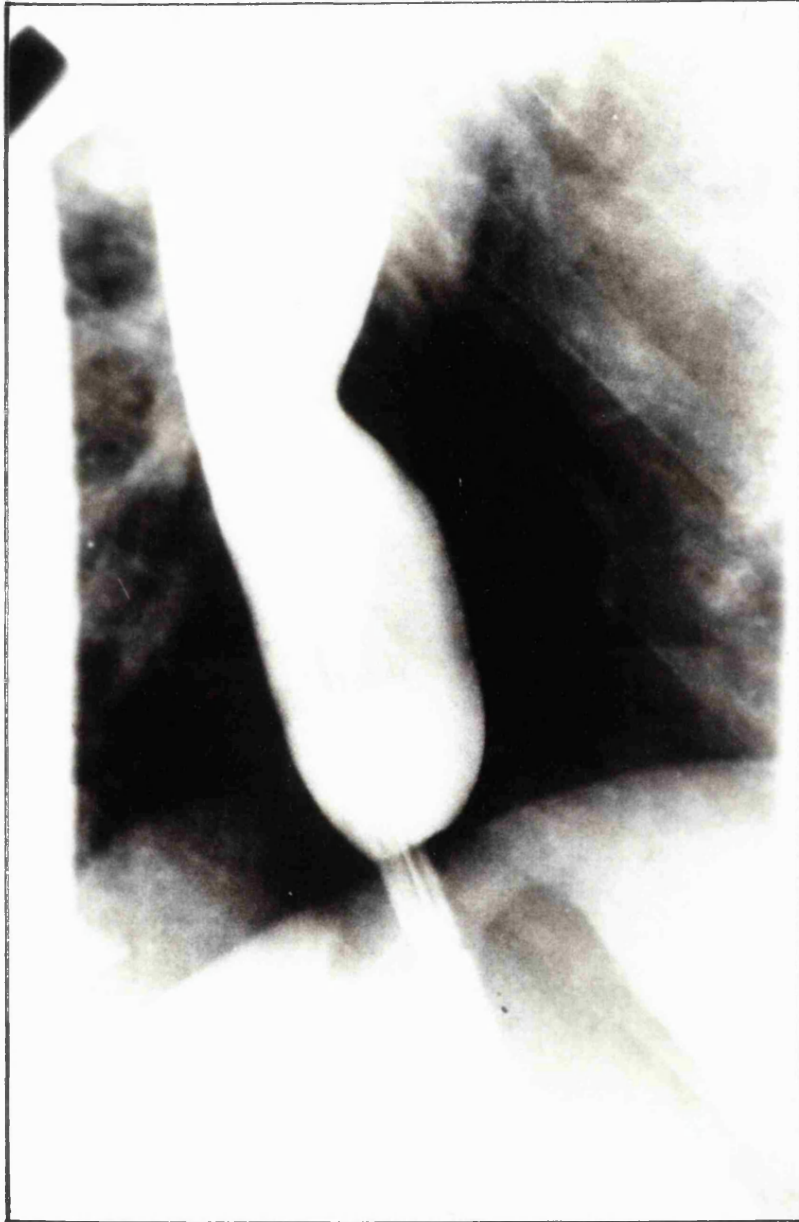
Photograph of the "Rigiflex" balloon catheter deflated and fully inflated.

sphincter itself in contrast to achalasia. Using dilute contrast medium in a 60ml syringe, the balloon was inflated with hand pressure (figure 3.19), the patient's reaction being closely observed. If pain was produced, inflation of the balloon was continued with increased care. Full inflation of the balloon (figure 3.20) was usually possible with only moderate discomfort but, if severe pain was produced then the dilatation was terminated at that point. In most cases a 30mm diameter balloon was used initially and the 35mm balloon was used for repeat dilatation if symptoms persisted after the initial dilatation. The balloon catheter was then withdrawn into the upper oesophagus, the guide wire was removed and non-ionic contrast medium (Iohexol-Nycomed) injected through the end hole of the catheter to exclude oesophageal perforation. The catheter was removed and the patient observed overnight (Irving et al 1992).

Symptomatic relief of pain and dysphagia obtained by the patients after balloon dilatation was gauged by the patient, and expressed on a digital scale of 1-10, 0/10 indicating complete symptomatic relief, 10/10 implying no relief at all.

FIGURE 3.19

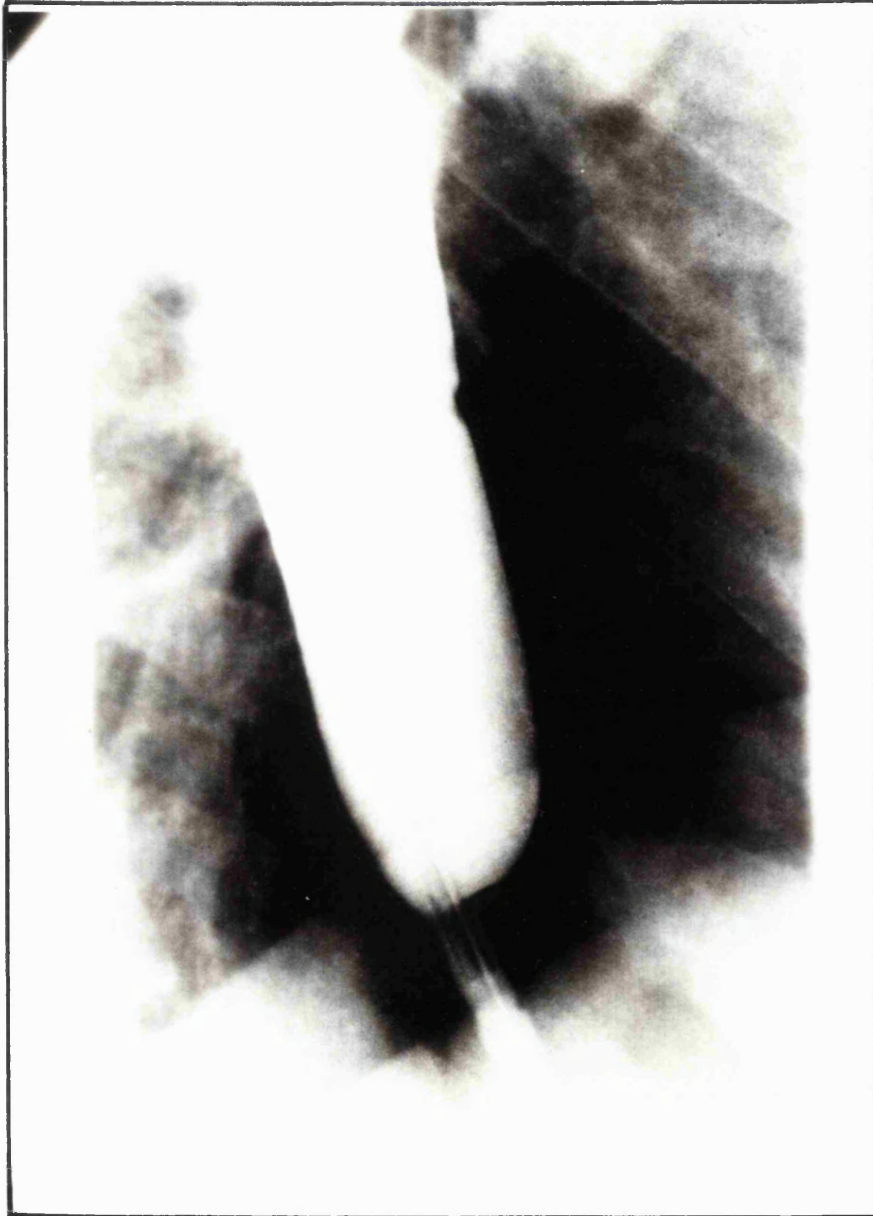
X-RAY SHOWING BALLOON DILATOR DURING DILATATION



Note the localized "waisting" in the balloon occurring 6-8 cm. above the gastro-oesophageal junction during dilatation of patient with diffuse oesophageal spasm.

FIGURE 3.20

X-RAY SHOWING BALLOON FULLY INFLATED



The "waisting" has disappeared during dilatation in diffuse oesophageal spasm patient.

3.13: METHOD GLOBUS PATIENTS

A study was made of twenty four consecutive patients with globus which was defined as a feeling of a lump in the throat present most of the time and often improved with swallowing. A careful history was taken with particular reference to the description of globus and the presence or absence of associated symptoms of dysphagia to solids or liquids, chest pain, heartburn, reflux and hoarseness. Patients with definite dysphagia producing weight loss were excluded. Past medical history and drug history were also recorded.

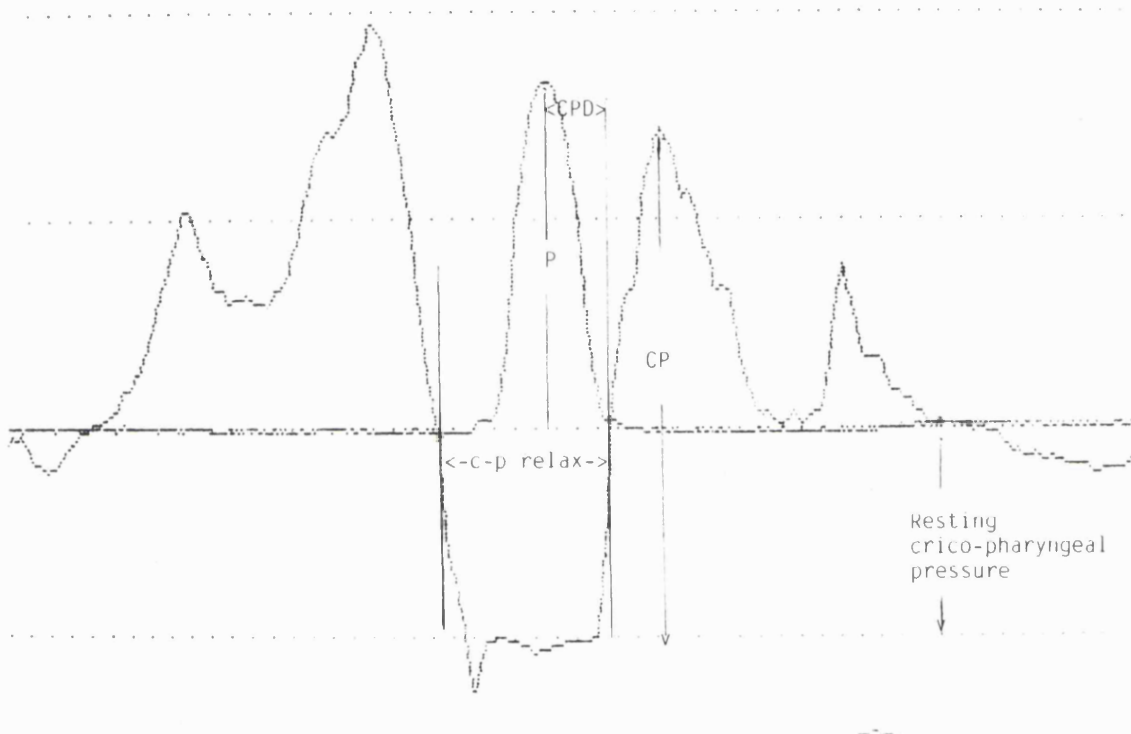
All patients underwent gastroscopy and indirect laryngoscopy. Barium swallows were performed with cinebread barium swallows in some patients.

Oesophageal manometry was then performed as described in the general methods (3.4). The mean lower oesophageal sphincter pressure was measured using a station pull through technique and the percentage of sphincter relaxation in response to wet swallows was recorded. The manometric pattern in the oesophageal body was recorded and the upper oesophageal sphincter region was then examined in detail. The recording was expanded so that the following measurements could be made of the mean of ten wet swallows (Figure 3.21):

1. the mean resting cricopharyngeal pressure,
2. upper oesophageal sphincter length,
3. peak pharyngeal contraction,
4. peak cricopharyngeal contraction,
5. cricopharyngeal relaxation time,
6. time between peak pharyngeal contraction and the start of

FIGURE 3.21

ASSESSMENT OF THE UPPER OESOPHAGEAL SPHINCTER COMPLEX IN GLOBUS PATIENTS AND CONTROLS



1. Mean resting cricopharyngeal pressure.
2. P = amplitude of peak pharyngeal contraction.
3. CP = amplitude of peak cricopharyngeal contraction
4. c-p relax = time of cricopharyngeal relaxation from the resting pressure to start of cricopharyngeal contraction.
5. CPD = time from peak pharyngeal contraction to start of cricopharyngeal contraction following relaxation.

the cricopharyngeal contraction following relaxation to assess if there was incoordination.

The oesophagus was then perfused with saline followed by 0.1N hydrochloric acid or acid followed by saline 15 cm below the upper high pressure zone without the patient's knowledge and the measurements repeated. Twentyfour hour ambulatory pH monitoring was then performed (3.8) and finally the patients completed the two questionnaires immediately following the removal of the pH probe (3.9).

CHAPTER 4

RESULTS

INTRODUCTION

The results relate to patients studied in the oesophageal laboratory at Guy's hospital. The diagnosis of diffuse oesophageal spasm was made using the criteria set out above (3.5) and the patients with severe symptoms were treated with balloon dilatation. Twenty four patients complaining of globus were also studied.

4.1: DIFFUSE OESOPHAGEAL SPASM

4.1.1: PATIENTS' DETAILS

During this time 438 patients were studied of whom 394 patients (90%) received an edrophonium provocation test. Final diagnoses in the 438 patients studied were:- 57% had gastro-oesophageal reflux, 23% had no oesophageal abnormality and 20% had oesophageal motility disorders including achalasia and scleroderma.

Thirty eight patients were diagnosed on either manometric criteria or positive edrophonium provocation test as having diffuse oesophageal spasm. There was an equal sex ratio and a wide age distribution as shown below.

<u>Patient Details</u>	<u>Median Age (range)years</u>
Total=38	51 (14 to 79)
Males=19	56 (14 to 79)
Females=19	43 (25 to 71)

4.1.2: PATIENTS' SYMPTOMS

All patients complained of dysphagia and/or chest pain.

The group had had symptoms for a median of 51 months (range

6 weeks to 20 years).

Number of Patients (percentage) Symptom

31 (82%)	Chest pain
25 (66%)	Dysphagia
18 (47%)	Chest pain and dysphagia
16 (42%)	Heartburn
9 (24%)	Acid reflux

The time between first consultation and definitive diagnosis was 3 to 6 years and on average they had visited 4 different hospitals. Ten patients were smokers.

4.1.3: BARIUM SWALLOW RESULTS

Sixteen patients had abnormal barium swallows of whom 12 had possible peristaltic abnormalities. Tertiary contractions were only seen in 16% of patients.

Number of Patients Barium Swallow Findings

22	normal
4	hiatus hernia
1	gastro-oesophageal reflux
1	low amplitude peristalsis
1	epiphrenic diverticulum
6	tertiary contractions
3	retrograde peristalsis
4	delayed emptying distal oesophagus

4.1.4: GASTROSCOPY RESULTS

<u>Number of Patients</u>	<u>Gastroscopy Findings</u>
25	normal
4	hiatus hernia
1	oesophageal diverticulum
1	food residue in oesophagus

CONCLUSION

Thirteen patients of the group (34%) therefore had a provisional diagnosis made of an oesophageal motility disorder on the basis of their symptoms and gastroscopy and/or radiological findings.

4.1.5: MANOMETRY RESULTS

4.1.5a: LOWER OESOPHAGEAL SPHINCTER

The median lower oesophageal sphincter pressure was 16 mmHg (range 3 to 43 mmHg) and was not significantly different from the median lower oesophageal sphincter pressure of the control group which was 12mmHg (range 5-22). The lower oesophageal sphincter completely relaxed to gastric pressure in all patients but, in 3 patients, the lower oesophageal sphincter relaxation was not completely coordinated with the peristaltic contraction.

4.1.5b: OESOPHAGEAL BODY

Synchronous contractions, present with more than 10% of wet swallows, were demonstrated in 25 patients (66%). The median percentage of synchronous contractions was 30% in the patients and 0% in the controls ($p < 0.0001$). None of the controls had synchronous contractions in excess of 10% of

wet swallows. The median maximum amplitude over the length of the oesophagus was 147 mmHg (range 32 to 343 mmHg). The median maximum duration in the diffuse oesophageal spasm patients was 6.3 secs and 5.4 secs in the controls ($p < 0.01$) (Table 4.1). The results for the upper, middle and lower thirds of the oesophagus are shown in Table 4.2. The median amplitude increased and the median duration lengthened the closer to the lower oesophageal sphincter the recording was made.

Nine patients had contractions of amplitude in excess of 200 mmHg and 2 patients had contractions of duration greater than 10 seconds. Two patients has spontaneous contractions, not in response to a swallow, 11 had triple-peaked contractions and one patient had repetitive activity of 5 to 6 peaks.

CONCLUSION

A diagnosis of diffuse oesophageal spasm was made following baseline manometry in 25 patients (66%) using Richter's criteria (Richter & Castell 1984).

4.1.6: BERNSTEIN TEST

This was performed in 33 patients and was positive in only 8 people. In one patient high amplitude contractions were recorded during acid perfusion.

4.1.7: EDROPHONIUM PROVOCATION TEST

Following edrophonium injection, synchronous activity greater than 10% was seen in 29 patients with a median of 37%. The median maximum amplitude increased to 221 mmHg

Table 4.1

CONTROLS AND DIFFUSE OESOPHAGEAL SPASM PATIENTS

Results of manometric studies on normal controls and diffuse oesophageal spasm patients.

Lower oesophageal sphincter pressure mmHg (LOSP), percentage of synchronous contractions % (SYN), maximum amplitude (MAXAMP), amplitude 15, 10, 5 cm above LOS (AMPTOP, AMPMID, AMPBOT) (mmHg), maximum duration (MAXDUR), duration 15, 10, 5cm above LOS (DURTOP, DURMID, DURBOT) (sec). Median and range. Analysis Mann-Whitney U.

	<u>Controls</u>	<u>Patients</u>	<u>p value</u>
LOSP	12 (5-22)	16 (3-43)	n.s.
SYN	0 (0-5)	70 (20-100)	p<0.0001
MAXAMP	134 (43-145)	147 (32-343)	n.s.
AMPTOP	44 (31-92)	39 (22-98)	n.s.
AMPMID	55 (34-82)	59 (19-164)	n.s.
AMPBOT	88 (30-127)	82 (26-203)	n.s.
MAXDUR	5.4 (3.5-5.8)	6.3 (3.3-15.5)	p<0.01
DURTOP	3.4 (2.4-3.8)	3.1 (2-5.9)	n.s.
DURMID	2.9 (2.5-4.4)	3.3 (2.3-5.9)	n.s.
DURBOT	4 (2.9-5.4)	4.2 (2.5-8.2)	n.s.
Number	10	38	

Table 4.2

BASELINE AMPLITUDE AND DURATION

Results of baseline amplitude and duration (median & range) in patients with diffuse oesophageal spasm recorded 5, 10 and 15 cm from the lower oesophageal sphincter (LOS). Wilcoxon rank sum test.

<u>Distance from LOS</u>	<u>Amplitude (mmHg)</u>	<u>Duration (sec)</u>
15 cm	39 (22-98)	3.1 (2-5.9)
10 cm	58.5 (19-164)	3.3 (2.3-5.9)
5 cm	81.5 (26-203)	4.2 (2.5-8.2)
Maximum	147 (32-343)	6.3 (3.3-15.5)
Number	38	38

Amplitude 5 to 10cm	p<0.001	Duration 5 to 10cm	p<0.001
10 to 15cm	p<0.001	10 to 15cm	p<0.005
5 to 15cm	p<0.001	5 to 15cm	p<0.001

(range 37 to 368 mmHg) ($p < 0.001$) and the median maximum duration to 10.3 secs (range 3.8 to 27.2 secs) ($p < 0.001$). The median amplitude and duration in the three regions of the oesophagus were significantly increased following edrophonium as shown in Tables 4.3 and 4.4 ($p < 0.001$) (Figures 4.1 and 4.2).

A positive edrophonium test required both a manometric abnormality compatible with diffuse oesophageal spasm and the production of the patient's usual symptoms. The results of the provocation test are shown in table 4.5. No patients developed symptoms or change in manometry following placebo injection of saline.

The remaining patients did not satisfy the manometric criteria of diffuse oesophageal spasm and all had negative edrophonium provocation tests.

Before the edrophonium injection, 25 of the 38 patients had baseline manometry which was diagnostic of diffuse oesophageal spasm. Ten of these patients with positive manometry experienced their usual symptoms of chest pain or dysphagia with worsening of their manometric abnormality following the injection of edrophonium and 11 had a negative provocation test as their symptoms were not reproduced by the edrophonium although 3 patients had worsening of manometry. Four patients did not receive edrophonium. The remaining 13 patients (34%) had normal manometry initially. Following edrophonium, they developed their usual symptoms and produced a manometric pattern compatible with diffuse oesophageal spasm. Without edrophonium provocation testing 34% of the patients would

Table 4.3

AMPLITUDE BEFORE AND AFTER EDROPHONIUM PROVOCATION TEST

Comparison of amplitude mmHg (median & range) before (Baseline) and after edrophonium provocation testing at levels 5, 10 and 15 cm above the lower oesophageal sphincter (LOS) in diffuse oesophageal spasm patients.

Wilcoxon rank sum test

<u>Distance LOS</u>	<u>Baseline</u>	<u>Edrophonium</u>	<u>p value</u>
15 cm	39 (22-98)	49 (19-164)	p<0.001
10 cm	58.5 (19-164)	93.5 (21-196)	p<0.001
5 cm	81.5 (26-203)	114 (23-339)	p<0.001
Maximum	147 (32-343)	221 (37-368)	p<0.001
Number	38	34	

Table 4.4

DURATION BEFORE AND AFTER EDROPHONIUM PROVOCATION TEST

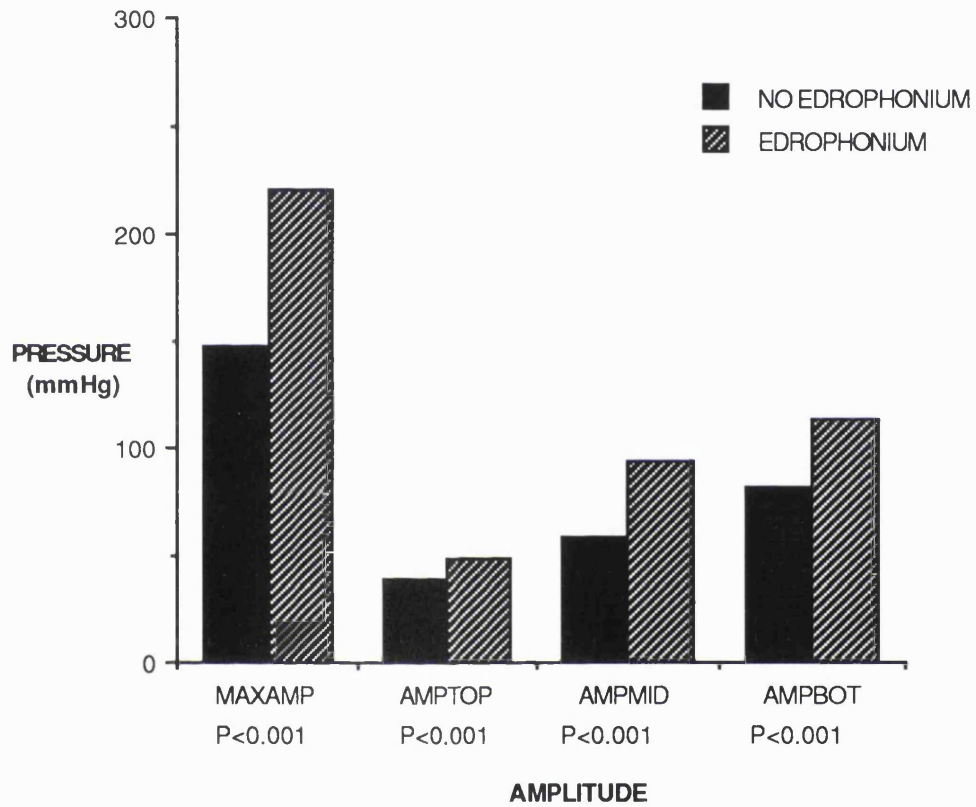
Comparison of duration secs (median & range) before (Baseline) and after edrophonium provocation testing at levels 5, 10 and 15 cm above the lower oesophageal sphincter (LOS) in diffuse oesophageal spasm patients.

Wilcoxon rank sum test.

<u>Distance LOS</u>	<u>Baseline</u>	<u>Edrophonium</u>	<u>p value</u>
15 cm	3.1 (2-5.9)	3.7 (1.9-7.3)	p<0.001
10 cm	3.3 (2.3-5.9)	5.2 (2.4-15)	p<0.001
5 cm	4.2 (2.5-8.2)	6.5 (2.8-16.9)	p<0.001
Maximum	6.3 (3.3-15.5)	10.3 (3.8-27.2)	p<0.001
Number	38	34	

FIGURE 4.1

AMPLITUDE PRE AND POST EDROPHONIUM



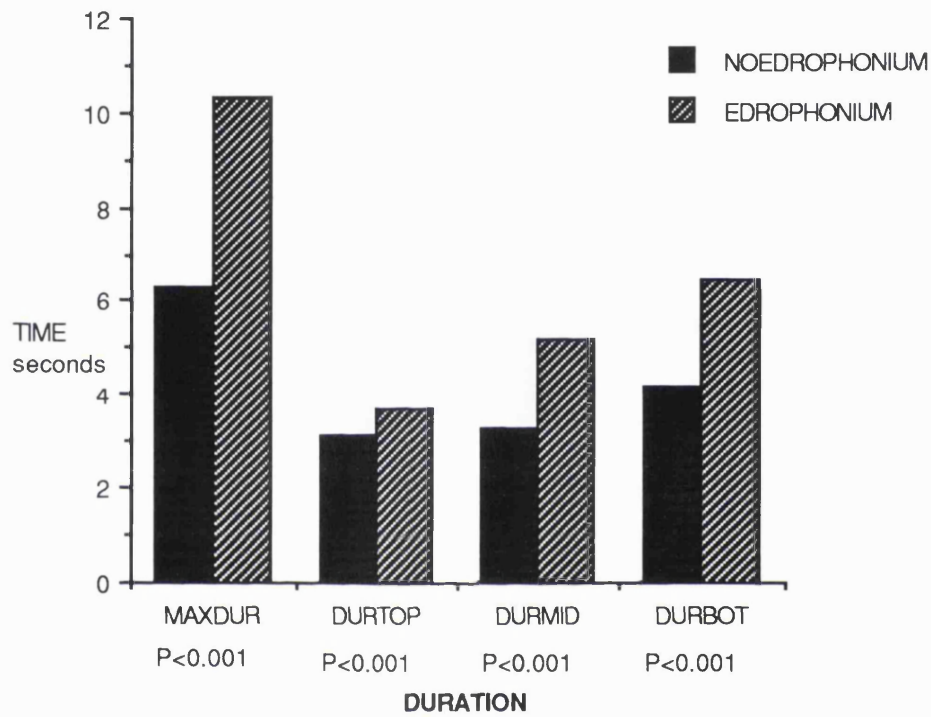
COMPARISON OF MEDIAN AMPLITUDE BEFORE AND AFTER EDROPHONIUM IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM.

MAXIMUM AMPLITUDE (MAXAMP), AMPLITUDE 15cm (AMPTOP), 10cm (AMPMID), 5cm (AMPBOT) ABOVE LOWER OESOPHAGEAL SPHINCTER.

STATISTICAL ANALYSIS WILCOXON RANK SUM TEST

FIGURE 4.2

DURATION PRE AND POST EDROPHONIUM



COMPARISON OF MEDIAN CONTRACTION DURATION BEFORE AND AFTER EDROPHONIUM IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM. MAXIMUM DURATION (MAXDUR), DURATION 15cm (DURTOP), 10cm (DURMID), 5cm (DURBOT) ABOVE THE LOWER OESOPHAGEAL SPHINCTER
STATISTICAL ANALYSIS WILCOXON RANK SUM TEST

Table 4.5

MANOMETRY AND EDROPHONIUM PROVOCATION TEST

Results of manometry and edrophonium provocation tests in the diagnosis of diffuse oesophageal spasm.

	<u>Manometry*</u>	<u>Manometry**</u>
	<u>Positive</u>	<u>Negative</u>
Edrophonium+ Positive	10	13
Edrophonium++ Negative	11	0
Total	21	13

4 patients did not receive edrophonium.

Chi-squared with 1 degree freedom using Yates correction factor $p < 0.005$.

*=baseline manometry positive for diffuse oesophageal spasm.

**=baseline manometry negative for diffuse oesophageal spasm.

=symptoms and abnormal manometry following edrophonium injection.

+=no symptoms or abnormal manometry following edrophonium injection.

not have been diagnosed as having diffuse oesophageal spasm. There were no significant side effects from the edrophonium injection although several patients experienced transient abdominal colic or blurred vision.

Five patients who had a positive edrophonium provocation test also had a positive Bernstein test and 3 who were edrophonium negative were Bernstein positive (Table 4.6) which would fit with Vantrappens' suggestion of an "irritable oesophagus" (Vantrappen et al 1987). There was an equal sex distribution between those patients with a positive and a negative edrophonium test. There was no significant age difference between the two groups. 73% of those patients who were edrophonium negative complained of dysphagia compared to 57% of the edrophonium positive group.

	<u>Edrophonium</u> <u>Positive</u>	<u>Edrophonium</u> <u>Negative</u>
Female	12	5
Male	11	6
Chest Pain	22	7
Dysphagia	13	8
Dysphagia & Chest Pain	12	4
Heartburn	11	5
Reflux	2	4
Number	23	11

The manometry results on those patients who received edrophonium were further analysed to determine any baseline manometric features which might predict a positive result.

Table 4.6

BERNSTEIN AND EDROPHONIUM PROVOCATION TEST

Results of Bernstein and edrophonium provocation tests in the diagnosis of diffuse oesophageal spasm.

	<u>Bernstein</u> <u>Positive</u>	<u>Bernstein</u> <u>Negative</u>
Edrophonium Positive	5	14
Edrophonium Negative	3	8
Total	8	22

8 patients excluded as both tests not performed.

Chi-squared test with Yates correction factor was not significant.

There was no significant difference between the age or lower oesophageal sphincter pressure of the two groups. There was a significant difference ($p < 0.0001$) between the percentage of synchronous contractions in the group who were edrophonium positive (median 9%) and the group that was edrophonium negative (median 70%) (Figure 4.3). The medians between the groups for duration and amplitude were very similar with only the amplitude results for the middle and lower oesophagus reaching significance ($p < 0.05$) (Table 4.7). There was a significantly greater increase in the amplitude and duration of contractions post compared to pre edrophonium in the edrophonium positive group ($p < 0.001$) (Tables 4.8 and 4.9).

CONCLUSION

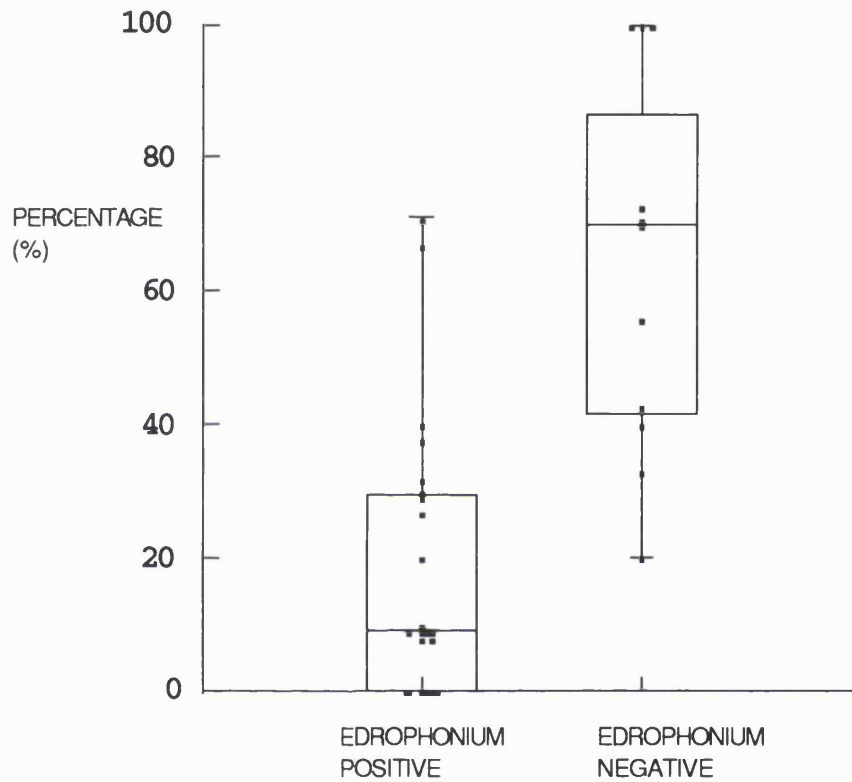
Without edrophonium provocation testing 34% of patients would not have been diagnosed as having diffuse oesophageal spasm.

4.1.8: TWENTYFOUR HOUR AMBULATORY pH MONITORING

In the early part of the series gastro-oesophageal reflux was excluded on the basis of radiology, endoscopy and biopsy. When ambulatory 24 hour pH monitoring became available 23 of the 38 patients had this performed. Ambulatory pH monitoring was normal in 13 subjects, showed either minimal upright or supine reflux in 5 patients and significant upright and supine reflux in 5 others. Analysis showed that the results for patients and controls were very similar although the longest episode of reflux was significantly longer in the patients than the controls

Figure 4.3

SYNCHRONOUS CONTRACTIONS PRIOR TO EDROPHONIUM



$P < 0.0001$

PERCENTAGE OF SYNCHRONOUS CONTRACTIONS IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM PRIOR TO EDROPHONIUM INJECTION IN THOSE PATIENTS WHO HAD A POSITIVE EDROPHONIUM TEST AND THOSE WHO HAD A NEGATIVE EDROPHONIUM TEST.
ANALYSIS MANN-WHITNEY U TEST.
HORIZONTAL BARS SHOW MEDIAN, INTERQUARTILE AND RANGE.

Table 4.7

EDROPHONIUM POSITIVE AND NEGATIVE STUDIES

Results of edrophonium positive and edrophonium negative studies prior to injection of edrophonium in diffuse oesophageal spasm patients.

Lower oesophageal sphincter pressure mmHg (LOSP), percentage of synchronous contractions % (SYN), maximum amplitude (MAXAMP), amplitude 15, 10, 5 cm above LOS (AMPTOP, AMPMID, AMPBOT) (mmHg), maximum duration (MAXDUR), duration 15, 10, 5cm above LOS (DURTOP, DURMID, DURBOT) (sec). Median and range. Analysis Mann-Whitney U.

	<u>Edrophonium</u> <u>Positive</u>	<u>Edrophonium</u> <u>Negative</u>	<u>p value</u>
Age	43 (25-66)	56 (25-75)	n.s.
LOSP	15 (3-27)	18 (7-43)	n.s.
SYN	9 (0-71)	70 (20-100)	p<0.0001
MAXAMP	146 (61-343)	135 (32-246)	n.s.
AMPTOP	39 (22-68)	39 (25-98)	n.s.
AMPMID	59 (31-132)	46 (19-85)	p<0.05
AMPBOT	95 (28-185)	44 (26-164)	p<0.05
MAXDUR	6 (3.3-13.6)	7.4 (3.5-15.5)	n.s.
DURTOP	3 (2-5.1)	3.4 (2.3-5.9)	n.s.
DURMID	3.7 (2.5-5.3)	3.3 (2.3-5.9)	n.s.
DURBOT	4.4 (2.7-8.2)	4.2 (2.5-6)	n.s.
Number	23	11	

Table 4.8

EDROPHONIUM POSITIVE STUDIES BEFORE AND AFTER EDROPHONIUM

Results of edrophonium positive studies before and after injection of edrophonium in diffuse oesophageal spasm patients.

Percentage of synchronous contractions % (SYN), maximum amplitude (MAXAMP), amplitude 15, 10, 5 cm above LOS (AMPTOP, AMPMID, AMPBOT) (mmHg), maximum duration (MAXDUR), duration 15, 10, 5cm above LOS (DURTOP, DURMID, DURBOT) (sec). Median and range. Analysis Wilcoxon sum rank test.

	<u>Before</u>	<u>After</u>	
	<u>Edrophonium</u>	<u>Edrophonium</u>	<u>p value</u>
SYN	9 (0-71)	30 (10-91)	p<0.005
MAXAMP	146 (61-343)	239 (72-360)	p<0.001
AMPTOP	39 (22-68)	50 (32-132)	p<0.001
AMPMID	59 (31-132)	99 (31-196)	p<0.001
AMPBOT	95 (28-185)	120 (48-264)	p<0.001
MAXDUR	6 (3.3-13.6)	10.7 (4.6-27.2)	p<0.001
DURTOP	3 (2-5.1)	3.7 (2-7.3)	p<0.001
DURMID	3.7 (2.5-5.3)	5.2 (2.4-13.1)	p<0.001
DURBOT	4.4 (2.7-8.2)	6.6 (2.8-13.4)	p<0.001
Number	23	23	

Table 4.9

EDROPHONIUM NEGATIVE STUDIES BEFORE AND AFTER EDROPHONIUM

Results of edrophonium negative studies before and after injection of edrophonium in diffuse oesophageal spasm patients.

Percentage of synchronous contractions % (SYN), maximum amplitude (MAXAMP), amplitude 15, 10, 5 cm above LOS (AMPTOP, AMPMID, AMPBOT) (mmHg), maximum duration (MAXDUR), duration 15, 10, 5cm above LOS (DURTOP, DURMID, DURBOT) (sec). Median and range. Analysis Wilcoxon rank sum test.

	<u>Before</u>	<u>After</u>	
	<u>Edrophonium</u>	<u>Edrophonium</u>	<u>p value</u>
SYN	45 (0-100)	70 (20-100)	n.s.
MAXAMP	120 (37-368)	135 (32-246)	n.s.
AMPTOP	45 (19-164)	39 (25-98)	n.s.
AMPMID	64 (21-187)	46 (19-85)	p<0.05
AMPBOT	87.5 (23-339)	44 (26-164)	p<0.05
MAXDUR	7.3 (3.8-18.9)	7.4 (3.5-15.5)	n.s.
DURTOP	3.4 (1.9-6.4)	3.4 (2.3-5.9)	n.s.
DURMID	5.3 (2.9-15)	3.3 (2.3-5.9)	p<0.05
DURBOT	5.9 (2.9-16.9)	4.2 (2.5-6)	p<0.05
Number	11	11	

($p < 0.05$) (Table 4.10). The results for the edrophonium positive and edrophonium negative group showed that the total time the pH was below 4 in the positive group was significantly greater than in the negative group ($p < 0.05$) (Figure 4.4). The number of reflux episodes was also significantly greater in the positive group ($p < 0.05$) (Table 4.11).

4.1.9: CONCLUSION

Diffuse oesophageal spasm was diagnosed in 38 of 438 patients studied.

1. Provisional diagnosis of diffuse oesophageal spasm was made on the basis of symptoms, gastroscopy and radiology in 34% patients.

2. Baseline manometry, using Richter's criteria (Richter & Castell 1984), increased the diagnostic yield to 66%.

3. Thirteen patients who had normal baseline manometry developed symptoms and abnormal manometry in response to the edrophonium provocation test.

4. Following the edrophonium injection there was a significant increase in contraction amplitude and duration over the whole oesophagus.

5. The patients who were edrophonium positive had significantly more total acid reflux, on twentyfour hour ambulatory pH monitoring, than the edrophonium negative group.

Table 4.10

TWENTYFOUR HOUR AMBULATORY pH MONITORING

Twentyfour hour ambulatory pH results for diffuse spasm patients and controls.

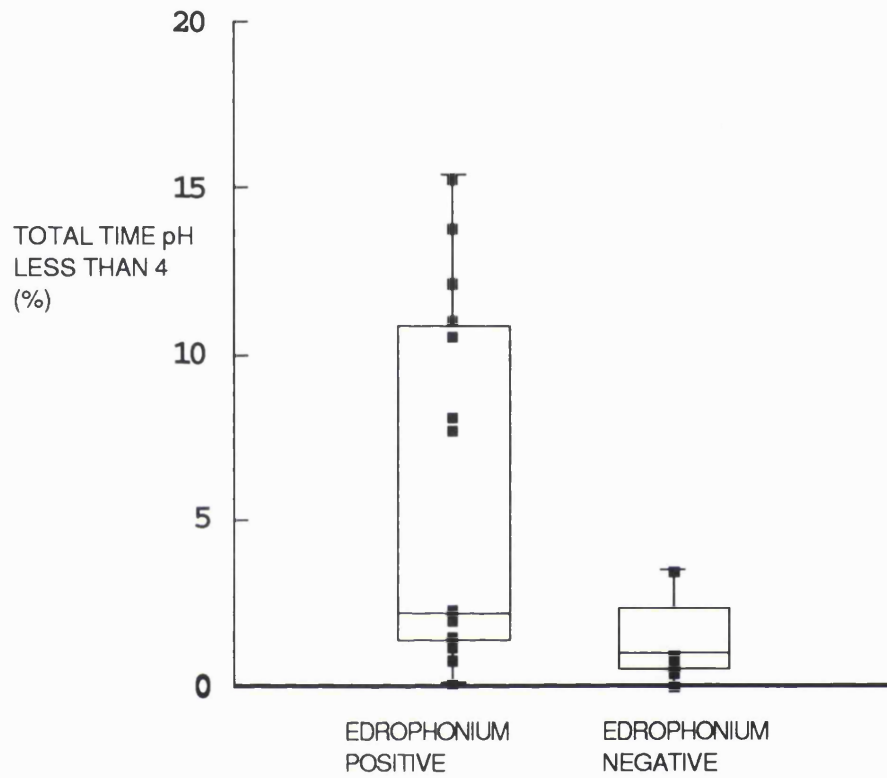
Percentage time pH less than 4 for total, supine, upright recording, number of reflux episodes, the number greater than 5 minutes and the longest (minutes). Median and range.

Analysis Mann-Whitney U.

<u>pH Results</u>	<u>Patients</u>	<u>Controls</u>	<u>p value</u>
Total reflux	2 (0-15.4)	2 (0.1-5)	n.s.
Supine reflux	0 (0-17.2)	0 (0-2.1)	n.s.
Upright reflux	2.5 (0-16.1)	1.7 (0.1-5.8)	n.s.
Reflux episodes	10 (0-48)	6 (2-27)	n.s.
Greater 5 min	1 (0-12)	1 (0-3)	n.s.
Longest	8.3 (0-53.9)	3.9 (1-12.3)	p<0.05
Number	23	11	

Figure 4.4

TOTAL REFLUX IN DIFFUSE OESOPHAGEAL SPASM PATIENTS



P<0.05

TOTAL TIME pH LESS THAN 4 IN PATIENTS WHO HAD A POSITIVE AND A NEGATIVE EDROPHONIUM PROVOCATION TEST.
ANALYSIS MANN-WHITNEY U TEST.
HORIZONTAL BARS SHOW MEDIAN, INTERQUARTILE AND RANGE.

Table 4.11

TWENTYFOUR HOUR AMBULATORY pH MONITORING IN EDROPHONIUM POSITIVE AND NEGATIVE PATIENTS

Twentyfour hour ambulatory pH results for the diffuse oesophageal spasm edrophonium positive and edrophonium negative patients.

Percentage time pH less than 4 for total, supine, upright recording, number of reflux episodes, the number greater than 5 minutes and the longest (minutes). Median and range. Analysis Mann-Whitney U.

	<u>Edrophonium</u> <u>Positive</u>	<u>Edrophonium</u> <u>Negative</u>	<u>p value</u>
Total reflux	2.2 (0.1-15.4)	0.9 (0-6.1)	p<0.05
Supine reflux	0.2 (0-17.2)	0 (0-0.8)	n.s.
Upright reflux	3.2 (0.2-16.1)	0.9 (0-7.3)	n.s.
Reflux episodes	13.5 (2-48)	3 (0-30)	p<0.05
Greater 5 min	1 (0-12)	1 (0-6)	n.s.
Longest	10.1 (1.1-53.9)	6.1 (0-26.7)	n.s.
Number	16	7	

4.2: BALLOON DILATATION

4.2.1: PATIENT DETAILS

All patients were initially treated with conservative measures. 23 patients were given Cimetidine 400 mg b.d. but only 9 patients experienced improvement in symptoms. Nifedipine 20mg b.d. was prescribed for 24 patients but only 7 had their symptoms improved. 17 patients, 9 women and 8 men, with a median age 52 years (range 34- 79), therefore underwent balloon dilatation.

4.2.2: SYMPTOMATIC RESULTS

Virtually complete symptom relief (0-1/10) was seen in 7 patients. Significant improvement (2-5/10) was obtained in a further 5 patients. 5 patients experienced little or no improvement in symptoms.

<u>Results of Balloon Dilatation</u>	<u>Number of Patients</u>
1. Complete symptomatic relief	7
2. Significant improvement	5
1 dilatation	3
2 dilatations	2
3. Little or no improvement	5

Three were then treated with a long oesophageal myotomy and 2 had no further treatment either because the patient refused surgery or because an oesophageal myotomy was not considered justified. Of the successful group, ten were treated by a single dilatation and two by two dilatations. The failures, having had no improvement after two dilatations, were not subjected to a further attempt.

Six patients, who underwent balloon dilatation, were diagnosed as having diffuse oesophageal spasm on the basis of a positive edrophonium provocation test as they had normal baseline manometry. A good result to dilatation was obtained in 66% suggesting that the edrophonium provocation test was diagnosing true cases of diffuse oesophageal spasm.

4.2.3: LONG TERM RESULTS

The 12 patients in whom balloon dilatation was regarded as successful have been followed for between 1 and 6 years (median 3.4 years). Two patients successfully dilated have died of unconnected illnesses several years after the procedure. Subjective improvement in symptoms of dysphagia and chest pain has been the criteria used for success or failure.

CASE HISTORY

The effectiveness of balloon dilatation is demonstrated by the following case history: A 71year old lady with 20 years of severe chest pain and dysphagia, who had seen at least 18 doctors, finally had a diagnosis of diffuse oesophageal spasm made on oesophageal manometry. She had complete resolution of her symptoms following balloon dilatation.

4.2.4: THE IRVING SIGN

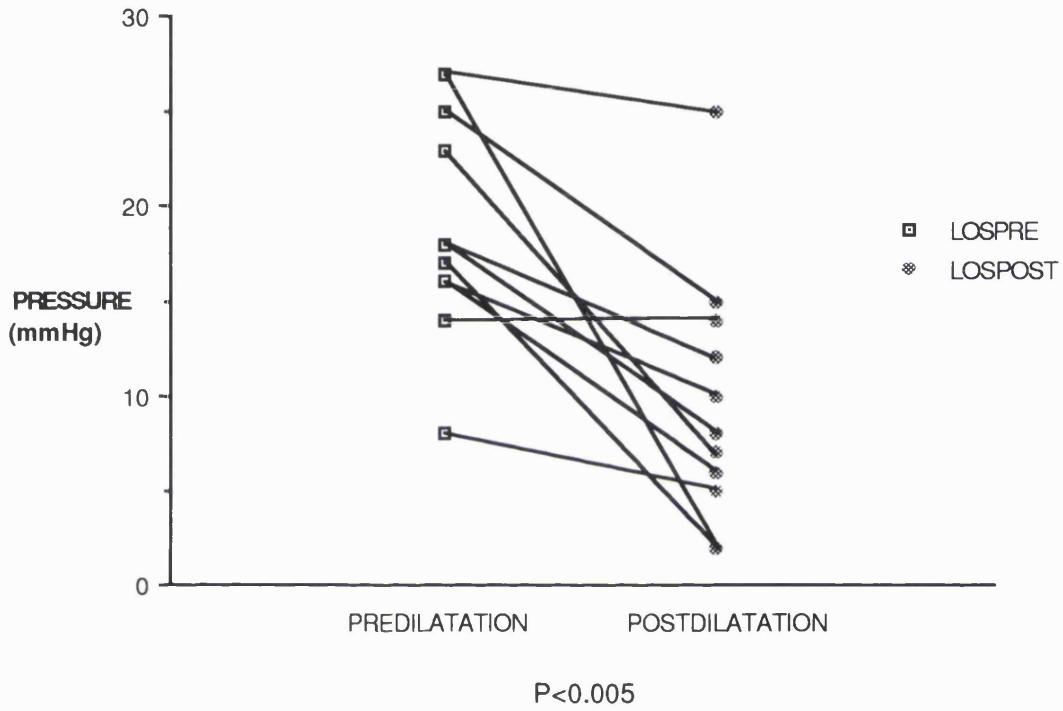
In all cases treated by balloon dilatation, a constant eccentric "waisting" was seen anteromedially at a point 6-7 cm above the gastro-oesophageal junction. Its dilatation was accompanied by discomfort, although performed without difficulty. The level was constant in all cases, and no similar narrowing was seen at any other point in the oesophagus. None of these patients had an hiatus hernia and in all the gastro-oesophageal junction was below the level of the diaphragm. There appears to be no anatomical correlation to this waisting and it is not seen in patients with achalasia when the balloon is distended.

4.2.5: MANOMETRIC RESULTS

Manometric data following dilatation is available on only 11 patients as several patients who obtained symptomatic relief refused a repeat manometry. Despite efforts to avoid dilation of the lower oesophageal sphincter, the median (range) lower oesophageal sphincter pressure prior to dilatation was 18mmHg (8-27) and following dilatation was 8mmHg (2-25) ($p < 0.005$) (Figure 4.5). Following dilatation the median percentage of synchronous contractions increased from 20% to 38%, the median maximum amplitude decreased (126 mmHg to 73 mmHg n.s.) and the median maximum duration decreased (7.4 secs to 4.7 secs n.s.) see Table 4.12. There is a trend but it does not reach statistical significance (Figures 4.6 and 4.7). Further analysis of the manometry results, depending on whether a good or poor result was

FIGURE 4.5

LOWER OESOPHAGEAL SPHINCTER PRESSURE PRE AND POST DILATATION



MEAN LOWER OESOPHAGEAL SPHINCTER PRESSURE BEFORE (LOSPRE) AND AFTER (LOSPOST) BALLOON DILATATION IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM.
ANALYSIS WILCOXON RANK SUM TEST.

Table 4.12

OESOPHAGEAL MANOMETRY BEFORE AND AFTER BALLOON DILATATION

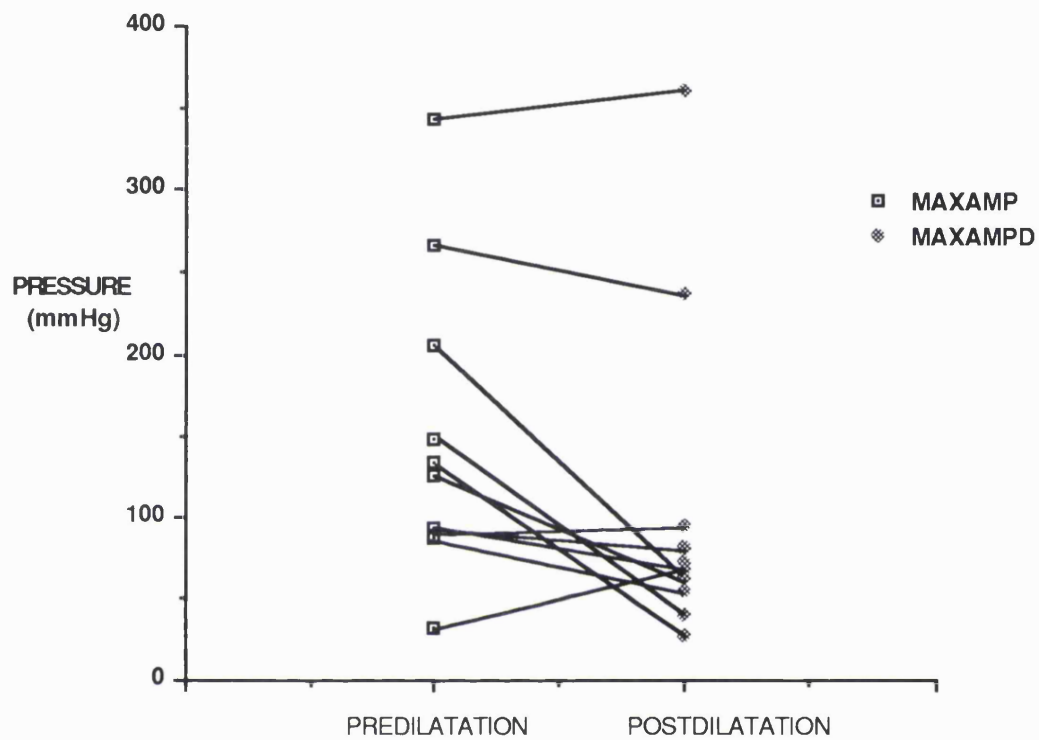
Results of oesophageal manometry before and after balloon dilatation.

With reference to lower oesophageal sphincter pressure mmHg (LOSP), percentage of synchronous contractions % (SYN), maximum amplitude (MAXAMP), amplitude 15, 10, 5 cm above LOS (AMPTOP, AMPMID, AMPBOT) (mmHg), maximum duration (MAXDUR), duration 15, 10, 5cm above LOS (DURTOP, DURMID, DURBOT) (sec). Values expressed as median and range with analysis by Wilcoxon rank sum test.

<u>Manometry</u>	<u>Predilatation</u>	<u>Postdilatation</u>	<u>p value</u>
LOSP	18 (8-27)	8 (2-25)	p<0.005
SYNC	20 (0-100)	38 (0-100)	n.s.
MAXAMP	126 (32-343)	73 (28-362)	n.s.
AMPTOP	33 (26-52)	53 (16-78)	p<0.05
AMPMID	43 (25-129)	45 (15-177)	n.s.
AMPBOT	62 (26-185)	38 (15-252)	n.s.
MAXDUR	7.4 (3.5-9.7)	4.7 (3-15.5)	n.s.
DURTOP	2.9 (2.3-5.9)	3.3 (2.6-4.3)	n.s.
DURMID	3.1 (2.3-5.9)	3.3 (2-5.6)	n.s.
DURBOT	3.6 (2.5-8.2)	3.9 (2.6-8.5)	n.s.
Number	11	11	

FIGURE 4.6

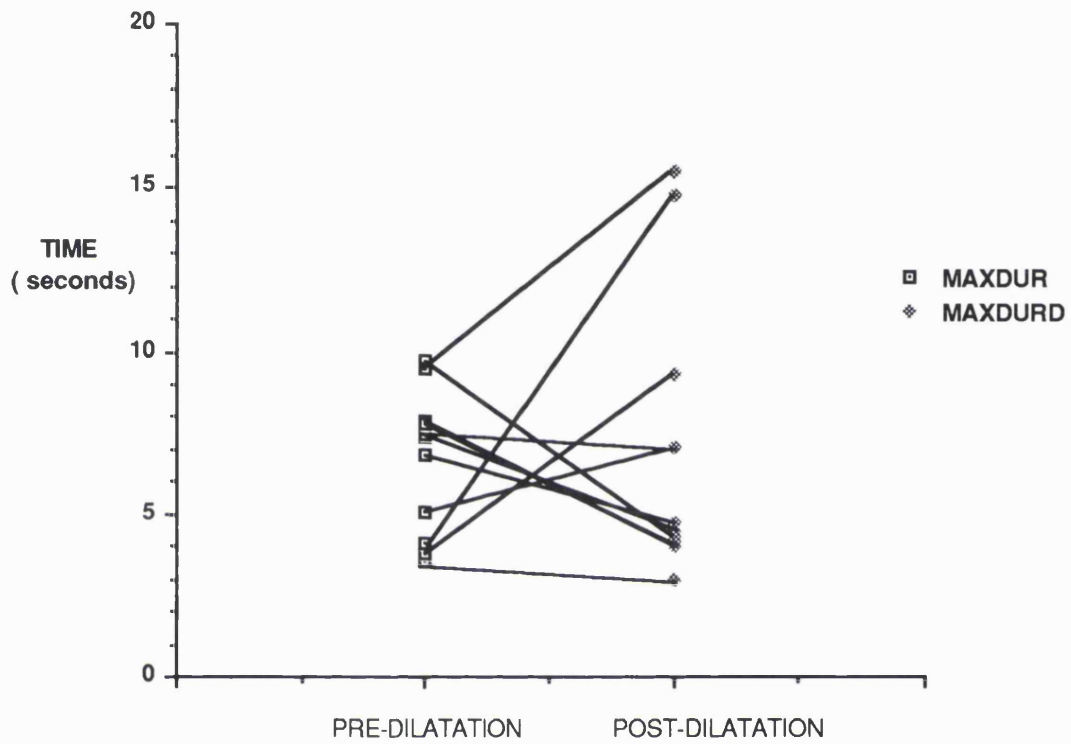
MAXIMUM AMPLITUDE PRE AND POST DILATATION



MAXIMUM AMPLITUDE BEFORE (MAXAMP) AND AFTER (MAXAMPD) DILATATION IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM. WILCOXON RANK SUM TEST NOT SIGNIFICANT

FIGURE 4.7

MAXIMUM DURATION PRE AND POST DILATATION



MAXIMUM DURATION BEFORE (MAXDUR) AND AFTER (MAXDURD) BALLOON DILATATION IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM. WILCOXON RANK SUM TEST NOT SIGNIFICANT.

obtained following dilatation, showed no significant difference between the groups, (Table 4.13). There was a significant decrease in the lower oesophageal sphincter pressure following dilatation as compared to predilatation in both the good and poor result groups ($p < 0.05$). There was no significant effect on synchronous activity, amplitude or duration of contractions in either group comparing results before and after dilatation. Balloon dilatation made no difference to the effects of edrophonium on the post dilatation manometry in the small numbers studied.

4.2.6: TWENTYFOUR HOUR AMBULATORY pH MONITORING

Following dilatation in the small number studied there was no increase in gastro-oesophageal reflux, (Table 4.14) (Figure 4.8).

Among the patients who were failures of balloon dilatation, gastro-oesophageal reflux, as diagnosed by 24 hour ambulatory pH monitoring, was present in 80% of patients, whereas in the 8 patients, in whom dilatation was successful and who were examined by pH monitoring, reflux was present in only one. There was a significant difference in the pre-dilatation percentage of total, supine and upright reflux ($p < 0.05$) between those that had a good result and a poor result from dilatation, (Table 4.15) (Figure 4.9).

No complications were seen in this group although one patient since the end of this study experienced an oesophageal perforation which necessitated repair and long oesophageal myotomy. In this case the dilatation was

Table 4.13

MANOMETRY RESULTS OF PATIENTS WITH A GOOD OR POOR RESULT FROM DILATATION

Manometry results before and after dilatation in those patients who had a good result and a poor result from dilatation.

Lower oesophageal sphincter pressure mmHg (LOSP), percentage of synchronous contractions % (SYN), maximum amplitude (MAXAMP), amplitude 15, 10, 5 cm above LOS (AMPTOP, AMPMID, AMPBOT) (mmHg), maximum duration (MAXDUR), duration 15, 10, 5cm above LOS (DURTOP, DURMID, DURBOT) (sec). Median & range analysis Mann-Whitney U.

Predilatation

<u>Manometry</u>	<u>Good Result</u>	<u>Poor Result</u>	<u>p value</u>
LOSP	18 (14-27)	17 (8-25)	n.s.
SYN	26 (0-100)	20 (0-53)	n.s.
MAXAMP	91.5 (32-205)	148 (87-343)	n.s.
AMPTOP	34 (26-52)	33 (27-45)	n.s.
AMPMID	43 (25-80)	69 (36-129)	n.s.
AMPBOT	51.5 (26-99)	102 (35-185)	n.s.
MAXDUR	7.5 (3.5-9.7)	6.8 (4.1-9.5)	n.s.
DURTOP	3 (2.3-5.9)	2.6 (2.6-4.2)	n.s.
DURMID	2.9 (2.3-5.9)	3.8 (2.9-4.1)	n.s.
DURBOT	3.6 (2.5-8.2)	4.4 (3-6.4)	n.s.
Number	6	5	

continued

Postdilatation

<u>Manometry</u>	<u>Good result</u>	<u>Poor Result</u>	<u>p value</u>
LOSP	11 (2-25)	6 (2-15)	n.s.
SYN	40.5 (0-100)	38 (0-100)	n.s.
MAXAMP	77 (28-95)	62 (40-362)	n.s.
AMPTOP	50.5 (16-78)	57.5 (33-64)	n.s.
AMPMID	48.5 (15-17.7)	42 (15-152)	n.s.
AMPBOT	31.5 (15-58)	40 (15-252)	n.s.
MAXDUR	4.4 (3-9.3)	7.1 (4-15.5)	n.s.
DURTOP	3.3 (2.9-4.3)	3 (2.6-3.5)	n.s.
DURMID	3.2 (2-5.6)	4.5 (3.3-5.1)	n.s.
DURBOT	3.9 (2.6-6.2)	5.1 (3.3-8.5)	n.s.
Number	6	5	

Table 4.14

AMBULATORY pH MONITORING PRE AND POST DILATATION

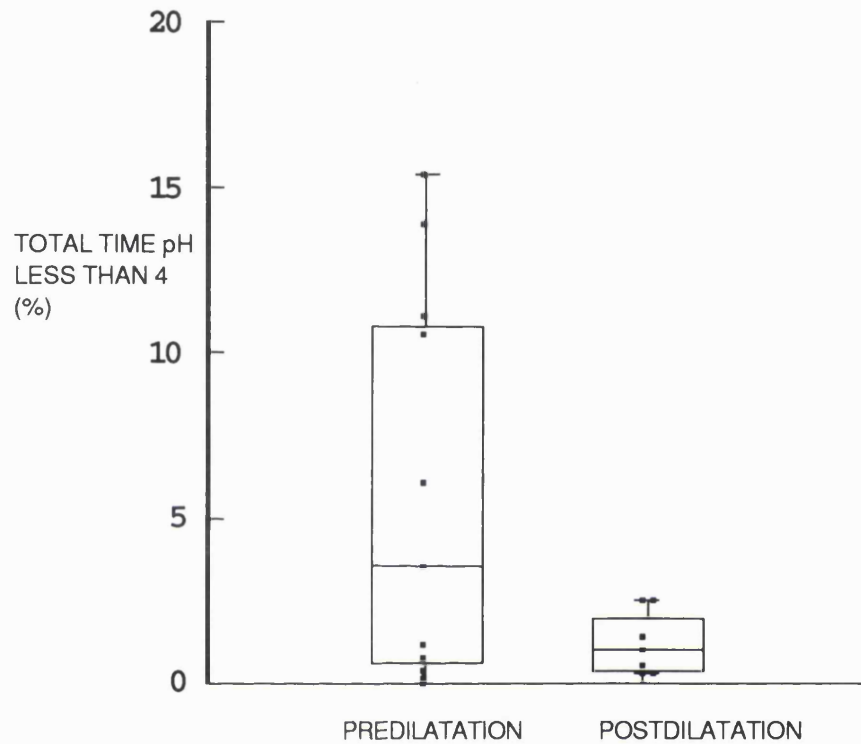
Twentyfour hour ambulatory pH monitoring pre and post balloon dilatation.

Results showing percentage time that the pH was less than 4 for total time, the upright and supine positions, the number of reflux episodes, the number of episodes lasting longer than 5 minutes and the longest reflux episode measured (minutes). Median and range with analysis using Wilcoxon rank sum test

<u>pH Results</u>	<u>Predilatation</u>	<u>Postdilatation</u>	<u>p value</u>
Total Reflux (%)	3.5 (0-15.4)	1 (0.3-2.5)	n.s.
Upright Reflux (%)	5.6 (0-15)	0.8 (0.4-3.8)	n.s.
Supine Reflux	0 (0-17.2)	0 (0-6)	n.s.
No reflux episodes	6 (0-30)	7 (3-19)	n.s.
Reflux episodes >5m	2 (0-8)	0 (0-2)	n.s.
Longest	9.6 (0-45)	6.1 (2.1-30.7)	n.s.
Number	11	7	

Figure 4.8

TOTAL REFLUX BEFORE AND AFTER DILATATION IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM



TOTAL PERCENTAGE TIME pH LESS THAN 4 IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM BEFORE AND AFTER BALLOON DILATATION. HORIZONTAL BARS SHOW MEDIAN, INTERQUARTILE AND RANGE. ANALYSIS WILCOXON RANK SUM TEST =NOT SIGNIFICANT.

Table 4.15

AMBULATORY pH MONITORING IN PATIENTS WITH A GOOD AND POOR RESULT FROM DILATATION

Results of twentyfour hour ambulatory pH monitoring before and after balloon dilatation in the patients with a good result from dilatation and those with a poor result.

With reference to percentage total reflux time, upright and supine time, number of reflux episodes, number of reflux episodes longer than 5 minutes and longest period of reflux (minutes). Median and range with analysis by Mann-Whitney U.

Predilatation

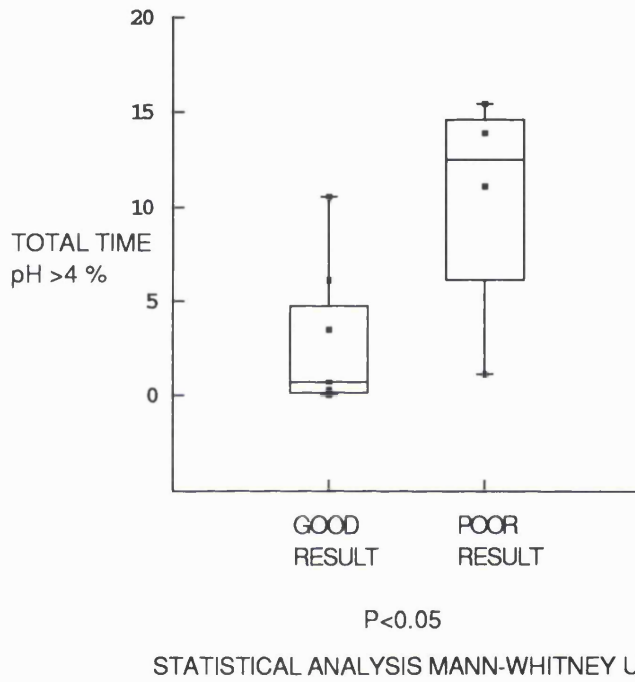
	Good Result	Poor Result	p value
Total Reflux	0.8 (0-10.6)	12.5 (1.2-15.4)	p<0.05
Upright Reflux	1 (0-7.6)	12.8 (2-15)	p<0.05
Supine Reflux	0 (0-14)	12.1 (0-17.2)	p<0.05
No Reflux episodes	3 (0-30)	15 (6-30)	n.s.
Reflux episodes >5m	1 (0-8)	6 (1-7)	n.s.
Longest	9.6 (0-45)	22.3 (7.2-43.5)	n.s.
Number	7	4	

Postdilatation

Total Reflux	0.5 (0.3-2.5)	1.8 (1-2.5)	n.s.
Upright Reflux	0.7 (0.4-2.4)	2.6 (1.4-3.8)	n.s.
Supine Reflux	0 (0-6)	1 (0.4-1.5)	n.s.
No Reflux episodes	6 (3-7)	14.5 (10-19)	n.s.
Reflux episodes >5m	0 (0-2)	1 (0-2)	n.s.
Longest	3.7 (2.1-30.7)	12.1 (9.1-15)	n.s.
Number	5	2	

FIGURE 4.9

AMBULATORY pH MONITORING PRIOR TO BALLOON DILATATION
IN PATIENTS WITH A GOOD OR POOR RESPONSE TO DILATATION



GRAPH SHOWING PERCENTAGE TOTAL TIME pH LESS THAN 4 PRIOR TO BALLOON DILATATION IN PATIENTS WITH DIFFUSE OESOPHAGEAL SPASM WHO HAD A GOOD OR POOR RESPONSE TO DILATATION. BARS SHOW MEDIAN, INTERQUARTILE RANGE AND RANGE.

performed under general anaesthetic because of the patient's anxiety.

4.2.7: CONCLUSION

1. Balloon dilatation was effective in 71% of patients and their response to treatment was sustained.
2. "Waisting" was noticed during dilatation in all patients.
3. Balloon dilatation produced a significant reduction in the lower oesophageal sphincter pressure.
4. The patients who had a poor response to dilatation had significantly more reflux on ambulatory pH monitoring.

4.3: GLOBUS RESULTS

4.3.1: PATIENTS DETAILS

Twenty four patients, fourteen women and ten men, with the globus sensation were investigated. The female patients were aged 26 to 71 (median 51.5 years) and the male patients aged 40 to 76 (median 54 years). The time from onset of symptoms to investigation was a median of 20 months with a range from 3 months to 10 years with 19 of the patients having the symptom for over a year before presentation. 13 patients were referred from otolaryngologists and the remainder from general surgeons, probably reflecting a known interest in the problem.

4.3.2: PATIENTS SYMPTOMS

The symptom of globus was defined as a feeling of a lump in the throat present most of the time but usually improved by swallowing. The patients variously described it as a tightness, dryness, a crumb, a choking or burning sensation. All patients had globus as their primary symptom. In addition, on direct questioning, 10 patients had occasional intermittent dysphagia to solids which tended to catch just above the suprasternal notch although the globus sensation was generally improved by swallowing. The dysphagia was not associated with weight loss and was not severe enough to fit with Henderson's finding of crico-pharyngeal dysphagia (Henderson et al 1976). Associated symptoms were chest pain, heartburn, acid reflux and hoarseness.

Associated Symptoms

<u>No of Patients(percentage)</u>	<u>Symptom</u>
10 (42%)	dysphagia
4 (17%)	chest pain
14 (58%)	heartburn
4 (17%)	acid reflux
6 (25%)	hoarseness
3 (12%)	weight loss
4 (17%)	weight gain

Three patients experienced weight loss of 7 pounds but 4 patients reported recent increase in weight. Two patients were asthmatic and 9 were smokers.

4.3.3: GASTROSCOPY

All patients underwent upper gastrointestinal endoscopy. Patients were biopsied at approximately 5cm above the oesophagogastric junction to exclude microscopic oesophagitis. Endoscopy was normal in all but one case where oesophageal reflux was found with biopsy proven evidence of oesophagitis.

4.3.4: LARYNGOSCOPY

All patients had indirect laryngoscopy on which one patient had erythema of the hypopharynx and ary-epiglottic folds. The remainder were normal.

4.3.5: BARIUM SWALLOW STUDIES

On barium swallows, half of the group had at least one abnormality of the oesophagus and stomach.

<u>Number of Patients</u>	<u>Barium Swallow Result</u>
12	Normal
4	Hiatus hernia
5	Gastro-oesophageal reflux
4	Motility disorder including, a.tertiary contractions, b.delayed clearance of bread barium
2	Spasm of cricopharyngeus
1	Pharyngeal diverticulum.

4.3.6: MANOMETRY

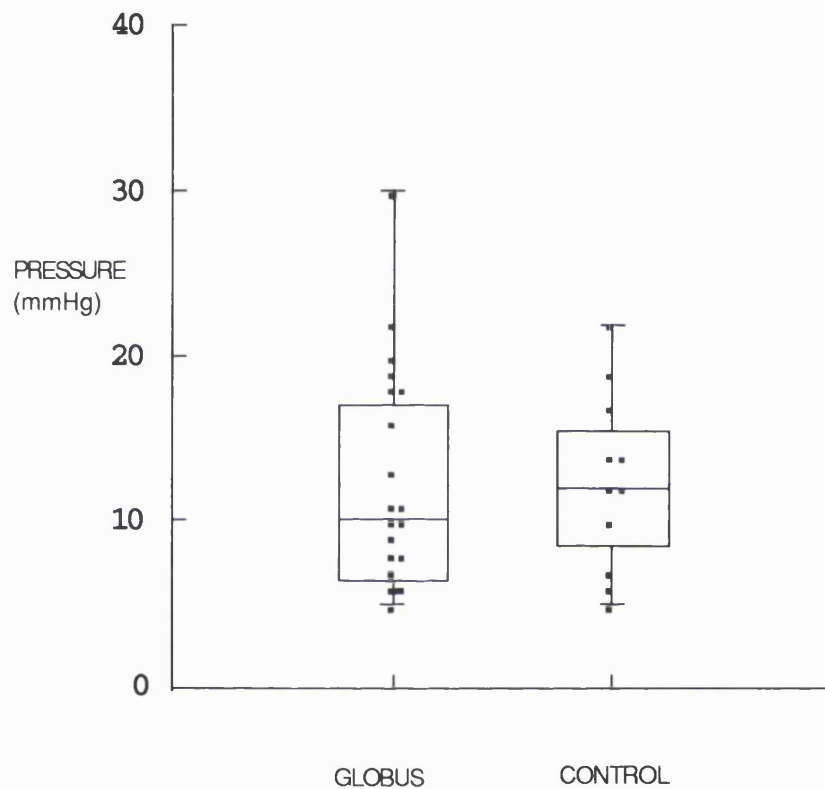
A group of 11 asymptomatic volunteers underwent manometry and acted as a control group. Their median age was 52 years and the group consisted of 3 men and 8 women.

4.3.6a: LOWER OESOPHAGEAL SPHINCTER

The median lower oesophageal sphincter pressure of the globus patients was 10mmHg with a range 5 to 30 mmHg. There was no significant difference when compared to the median lower oesophageal sphincter pressure of the controls of 12mmHg (range 5-22) (Figure 4.10). Six patients had lower oesophageal sphincter pressures of 6mmHg or less. The lower oesophageal sphincter relaxation was coordinated in all patients and there was complete relaxation to gastric pressure.

FIGURE 4.10

MEAN LOWER OESOPHAGEAL SPHINCTER PRESSURE IN GLOBUS PATIENTS AND CONTROLS



MEAN LOWER OESOPHAGEAL SPHINCTER PRESSURE IN GLOBUS PATIENTS AND CONTROLS . HORIZONTAL BARS SHOW MEDIANS, INTERQUARTILES AND RANGE. ANALYSIS MANN-WHITNEY U =NOT SIGNIFICANT.

4.3.6b: OESOPHAGEAL BODY

Sixteen patients had entirely normal motility in the oesophagus, 4 had peristaltic contractions of amplitude less than 50 mmHg which may be found in patients with gastro-oesophageal reflux. The remaining 4 patients had motility abnormalities, 2 compatible with the diagnosis of diffuse oesophageal spasm having 30-40% synchronous contractions to wet swallows and spontaneous contractions, and 2 with the diagnosis of nonspecific motility disorder.

4.3.6c: UPPER OESOPHAGEAL SPHINCTER

As shown in Table 4.16 there was no significant difference in resting upper oesophageal sphincter pressure between globus patients and controls with a large range of results in both groups. The length of the upper oesophageal high pressure zone was similar in both the globus patients and the controls. The findings were also similar for the pharyngeal contraction pressure, cricopharyngeal contraction pressure, time of cricopharyngeal relaxation and delay between pharyngeal and cricopharyngeal contractions in both globus patients and controls. The Mann-Whitney U test was used for analysis of two independent samples. Double pharyngeal contractions were recorded in 3 patients which appeared to be related to difficulty in swallowing water on demand with the catheter in situ.

There was no significant difference in the results obtained with reference to upper oesophageal sphincter function between baseline manometry, saline perfusion or acid perfusion, (Table 4.17) (Figure 4.11). Freidman's two way analysis of variance was used for three related samples.

Table 4.16

UPPER OESOPHAGEAL SPHINCTER MANOMETRY IN GLOBUS PATIENTS

Upper oesophageal sphincter results in control and globus groups.

With reference to the resting cricopharyngeal pressure (REST CP), length of upper oesophageal sphincter region (UOS), peak pharyngeal contraction (PC), peak cricopharyngeal contraction (CPC), cricopharyngeal relaxation (CPR) and pharyngo-cricopharyngeal delay (PCPD). Results are median & range using Mann-Whitney U test for p value.

<u>Manometry</u>	<u>Control</u>	<u>Globus</u>	<u>p value</u>
REST CP mmHg	28 (18-63)	39 (17-66)	n.s.
UOS cm	3 (2-4)	3 (2-4)	n.s.
PC mmHg	70 (30-101)	57.5 (23-124)	n.s.
CPC mmHg	89 (46-145)	77 (47-149)	n.s.
CPR sec	0.9 (0.7-1.1)	0.9 (0.1-1.2)	n.s.
PCPD sec	0.4 (0.2-0.5)	0.4 (0.2-0.8)	n.s.
Number	11	24	

Table 4.17

THE EFFECT OF SALINE AND ACID PERFUSION ON THE UPPER OESOPHAGEAL SPHINCTER

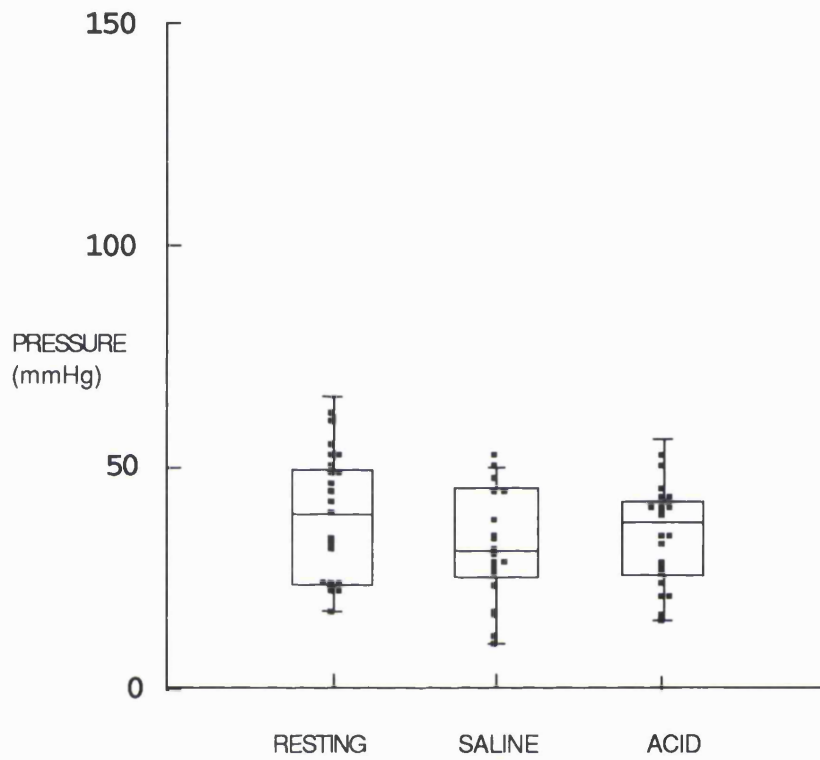
Upper oesophageal sphincter results comparing baseline results with saline and acid perfusion in patients with globus.

With reference to the resting cricopharyngeal pressure (REST CP), length of upper oesophageal sphincter region (UOS), peak pharyngeal contraction (PC), peak cricopharyngeal contraction (CPC), cricopharyngeal relaxation (CPR) and pharyngo-cricopharyngeal delay (PCPD). Results shown as median and range using Freidman test for analysis.

	Baseline	Saline	Acid	p value
REST CP	39 (17-66)	31 (10-132)	37.5 (15-84)	n.s.
PC mmHg	57.5 (23-124)	58 (19-110)	61 (20-89)	n.s.
CPC mmHg	77 (47-149)	76.5 (53-150)	72.5 (46-152)	n.s.
CPR sec	0.9 (0.1-1.2)	1 (0.7-1.2)	0.9 (0.6-1.2)	n.s.
PCPD sec	0.4 (0.2-0.8)	0.4 (0.1-0.6)	0.4 (0.2-0.8)	n.s.
Number	24	22	24	

Figure 4.11

UPPER OESOPHAGEAL SPHINCTER PRESSURE AT REST AND WITH SALINE AND ACID PERFUSION



COMPARISON OF MEAN CRICOPHARYNGEAL PRESSURE AT REST AND AFTER SALINE AND ACID PERFUSION IN PATIENTS WITH THE GLOBUS SENSATION. HORIZONTAL BARS SHOW MEDIAN, INTERQUARTILE AND RANGE. ANALYSIS FREIDMAN TEST = NOT SIGNIFICANT.

4.3.7: BERNSTEIN TEST

None of the patients developed any of their usual symptoms during the saline control perfusion. However seven patients developed heartburn in response to acid perfusion of the oesophagus (Bernstein positive) and two developed their globus symptom which was more severe than usual in one patient. Two further patients did not develop symptoms but their manometry became abnormal with the development of both spontaneous and synchronous contractions.

4.3.8: TWENTYFOUR HOUR AMBULATORY pH MONITORING

10 patients had no evidence of reflux on ambulatory pH monitoring using normal values of total reflux less than 4%, upright reflux less than 6% and supine reflux less than 1%. 6 patients had upright reflux alone, 5 had supine reflux alone and 3 had both upright and supine reflux. Analysis of the group shows that the globus group had significantly more total reflux, upright reflux, reflux episodes and longer reflux episodes than the controls ($p < 0.05$), (Table 4.18) (Figure 4.12) .

4.3.9: PSYCHOMETRY

Nineteen of the globus patients completed both of the questionnaires. A group of 16 patients undergoing varicose vein and hernia surgery was used as a control group. There was no significant difference between the controls and the globus patients for neuroticism or extroversion on the Eysenck personality inventory. The control group had significantly more somatic symptoms and anxiety and

Table 4.18

AMBULATORY pH MONITORING IN GLOBUS PATIENTS

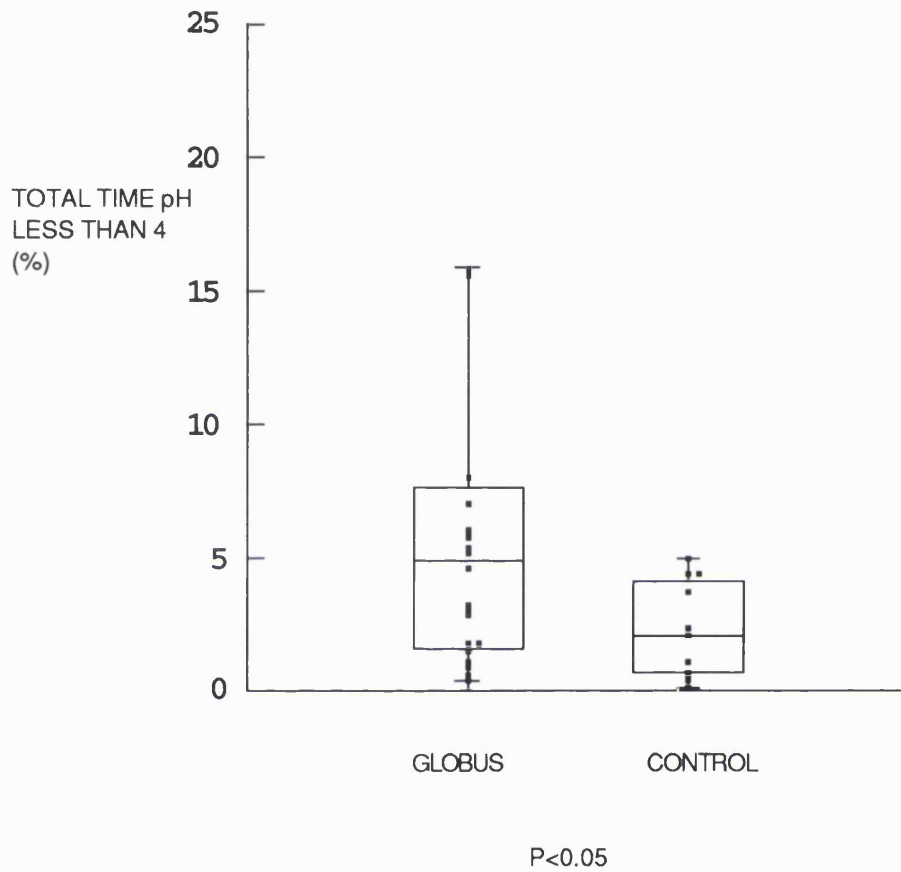
Twentyfour hour ambulatory pH monitoring in controls and globus patients.

Results showing percentage time that the pH was less than 4 for total time, the upright and supine positions, the number of reflux episodes, the number of episodes lasting longer than 5 minutes and the longest reflux episodes measured. Results shown as median and range using Mann-Whitney U test for analysis.

<u>pH Results</u>	<u>Globus</u>	<u>Control</u>	<u>p value</u>
Total reflux (%)	4.9 (0.4-22.6)	2 (0.1-5)	p<0.05
Upright reflux (%)	4.7 (0.7-29.2)	1.7 (0-5.8)	p<0.05
Supine reflux (%)	0.15 (0-31)	0 (0-2.1)	n.s.
No reflux episodes	16.5 (2-49)	6 (3-27)	p<0.05
Reflux episodes >5min	2 (0-10)	1 (0-3)	n.s.
Longest episode (min)	9.6 (1.5-152)	3.9 (1-12.3)	p<0.05
Number	24	11	

Figure 4.12

TOTAL REFLUX IN GLOBUS PATIENTS AND CONTROLS



PERCENTAGE TOTAL TIME pH LESS THAN 4 DURING TWENTYFOUR HOUR AMBULATORY pH MONITORING IN GLOBUS PATIENTS AND CONTROLS. HORIZONTAL BARS SHOW MEDIAN, INTERQUARTILE AND RANGE. ANALYSIS MANN-WHITNEY U TEST.

insomnia. Six of the globus group scored 5 or more on the General health questionnaire which suggests psychiatric illness. Nine of the control group however scored more than 5 and, using the Likert method of scoring, the controls were significantly more psychiatrically disturbed than the patients with globus, (Table 4.19).

4.3.10: CONCLUSION

1. There was no change in manometry of the upper oesophageal sphincter in response to saline or acid perfusion in the globus patients.
2. Twentyfour hour ambulatory pH monitoring revealed significantly more reflux in the globus patients than in the controls.
3. Psychometric tests suggested that the globus patients had less psychiatric illness than the controls.

Table 4.19

PSYCHOMETRIC RESULTS

General Health Questionnaire and Eysenck personality inventory in globus and control group.

The results of the general health questionnaire scored using the Likert and GHQ method with a=somatic symptoms, b=anxiety and insomnia, c=social dysfunction and d=depression. Median and range with analysis using Mann-Whitney U.

	Globus	Control	p value
GENERAL HEALTH QUESTIONNAIRE			
LIKERT a	4 (1-10)	7.5 (1-13)	p<0.05
LIKERT b	3 (0-18)	8 (3-14)	p<0.05
LIKERT c	7 (3-17)	8.5 (1-13)	n.s.
LIKERT d	1 (0-8)	1 (0-12)	n.s.
LIKERT TOTAL	15 (6-53)	27 (12-44)	p<0.01
GHQ a	0 (0-4)	3 (0-4)	p<0.05
GHQ b	0 (0-6)	2 (0-6)	p<0.05
GHQ c	0 (0-7)	1.5 (0-6)	n.s.
GHQ d	0 (0-2)	0 (0-5)	n.s.
GHQ TOTAL	1 (0-19)	7 (0-16)	n.s.
EYSENCK			
Lie	4 (1-7)	4.5 (1-7)	n.s.
Neuroticism	11 (0-22)	12.5 (5-23)	n.s.
Extraversion	11 (2-17)	13.5 (7-20)	p<0.05
Number	19	16	

CHAPTER 5

DISCUSSION

5.1: DIAGNOSIS OF DIFFUSE OESOPHAGEAL SPASM

Diffuse oesophageal spasm was diagnosed in about 9% of the patients referred to the oesophageal laboratory. Clouse & Staiano (1983), Castell (1985) and Katz et al (1987) reported diffuse oesophageal spasm accounting for a similar percentage (12%) of oesophageal motility disorders in patients with non cardiac chest pain and this percentage probably relates to the similar criteria used for diagnosis. All the patients diagnosed as having diffuse oesophageal spasm had symptoms of chest pain and/or dysphagia with nearly half the patients having both symptoms. Dysphagia was much more common in this study than other reported studies (Richter et al 1985c). This is because referrals came mainly from gastroenterologists rather than cardiologists. The presence of dysphagia makes an oesophageal disorder more likely. There was a large variation in age with a median in the fifth decade but no sex bias in the group studied. Many of the patients had suffered severe symptoms, which were a major interference with their lives, for more than 4 years and had visited several hospitals prior to the correct diagnosis being made. The identification of a non-cardiac source for the pain is of considerable benefit to these patients (Katz & Castell 1984).

5.1.1: BARIUM SWALLOW and ENDOSCOPY

In general, gastroscopy was unhelpful, although it played an important part in excluding oesophagitis or malignant oesophageal disease particularly in patients with dysphagia.

Sixteen patients had abnormal barium swallows. Only 13 of the 38 patients had any suggestion of peristaltic abnormality on barium examination with tertiary contractions found on only 6 patients' barium swallows. Tertiary contractions are a frequently reported finding on barium swallow but are probably non-specific. Henderson (1980 p183) also found that the radiological diagnosis was correct in only 43% of his patients with diffuse oesophageal spasm despite retrospective review of the films.

Thirteen patients (34%) therefore had a provisional diagnosis made of an oesophageal motility disorder on the basis of their symptoms, gastroscopy and barium findings. In only a third of the patients studied could the correct diagnosis have been made without the facilities of an oesophageal laboratory.

5.1.2: MANOMETRY

Dimarino and Cohen (1974) found abnormalities of lower oesophageal sphincter pressure and relaxation in about 30% of their patients with diffuse oesophageal spasm. In the present study the median lower oesophageal sphincter pressure of the patients was not significantly different from the controls. Relaxation to gastric pressure was complete in all the spasm patients but relaxation was not coordinated with the peristaltic contraction in 3 patients. This incoordination might suggest a similar pathophysiology to achalasia and may explain the various documented cases of transition from diffuse oesophageal spasm to achalasia (Kramer et al 1967b, Vantrappen et al 1979).

From their review of twelve reported series of patients with diffuse oesophageal spasm, Richter & Castell (1984) suggested that all patients with possible oesophageal symptoms, i.e. dysphagia or chest pain, must show simultaneous contractions after wet swallows on manometry for the diagnosis of diffuse oesophageal spasm to be considered. Their large study of normal individuals showed that an incidence of simultaneous contractions greater than 10% would be well above the average range of normal individuals (Richter et al 1987b). Simultaneous contractions must be interspersed with normal peristalsis to differentiate diffuse oesophageal spasm from vigorous achalasia. Repetitive contractions, spontaneous activity, contractions of high amplitude and long duration, and abnormalities of lower oesophageal sphincter function may be seen. Therefore, to make the diagnosis of diffuse oesophageal spasm in this study, the presence of synchronous contractions in response to at least 10% of wet swallows was required and was found in 66% of the group studied. Using the Gaeltec system, the upper limit of normal amplitude is 200mmHg which is higher than is usually obtained using a water-perfused system. Other researchers might consider amplitudes of this magnitude to be in the nutcracker oesophagus range (Ferguson & Little 1988). All the patients with diffuse oesophageal spasm had synchronous contractions associated in some cases with high amplitude contractions and did not therefore fulfil the criteria for the nutcracker oesophagus.

Thirteen patients had contraction durations in excess of 7.5

seconds which was considered by Mellow (1977) to suggest diffuse oesophageal spasm. Eleven patients had contractions of amplitude greater than 180mmHg, considered by Richter et al (1987b) to be outside of their normal range. The median amplitude and duration of contractions was significantly greater the nearer to the lower oesophageal sphincter the recording was made. Similar findings are seen in Richter et al's study of normal volunteers (1987b).

Using baseline manometry, a diagnosis of diffuse oesophageal spasm was made in 66% of the patients. Benjamin et al (1983a), studying patients with suspected oesophageal motility disorders, found a similar percentage to have abnormal baseline manometry although these were diagnosed as nutcracker oesophagus and nonspecific motility disorder.

If synchronous contractions in response to 30% of wet swallows as opposed to 10% had been chosen for diagnostic criteria, as used by Dimarino & Cohen (1974) and Mellow (1977), then diffuse oesophageal spasm would have been diagnosed on baseline manometry in 53% of patients as opposed to 66% using the 10% cut-off. Two patients, one edrophonium negative and one who did not receive edrophonium, would not have been diagnosed. Two patients, who were edrophonium positive with 10% synchronous contractions, would have developed symptoms but not a manometric abnormality in response to edrophonium, ie would have become edrophonium negative. The change to 30% synchronous contractions would have made a difference to the diagnosis in only two patients.

5.1.3: BERNSTEIN TEST

The Bernstein test was positive in only 24% of patients. The perfusion of acid altered the manometric pattern in only 1 patient. Studies by other researchers have found similar results. Richter et al (1985c) found that a Bernstein test was positive in 22% of patients with chest pain reproducing both heartburn and chest pain. Chobanian et al (1986) and De Caestecker et al (1988) found 12-35% of patients with noncardiac chest pain had symptom reproduction after acid perfusion. Benjamin et al (1983a) found that acid perfusion in patients with oesophageal motility disorders could produce altered manometry even though gastro-oesophageal reflux had been excluded by symptoms and endoscopy.

5.1.4: EDROPHONIUM PROVOCATION TEST

The intravenous injection of edrophonium had no significant effect on the proportion of synchronous contractions recorded in response to wet swallows. On the other hand, Richter et al (1985c), in their study of patients with noncardiac chest pain, recorded no synchronous contractions after edrophonium. In the present study, there was a very significant increase in the median amplitude and duration of contractions at all levels of the oesophagus following the edrophonium injection. Hollis & Castell (1976) found similar results in normal controls following injection of edrophonium with the maximum response occurring at the dose used in this study of 80ug/Kg. Richter et al (1985c) found that edrophonium increased the distal oesophageal amplitude and duration of peristaltic contractions in patients with

non cardiac chest pain.

Various definitions have been used for a positive provocation test. Lee et al (1987) required the production of chest pain associated with changes in manometry greater than two standard deviations from the control response for a positive test whereas Richter et al (1985c) and De Caestecker et al (1988) defined a positive test as requiring only the reproduction of the patient's symptoms because none of the controls developed chest pain after edrophonium injection. The production of symptoms with the additional development of manometric abnormality suggests that the oesophagus may be the source of the problem. Therefore the definition used in this study for a positive provocation test required both the reproduction of symptoms and the production of typical manometry of diffuse oesophageal spasm or worsening of the manometric pattern.

A positive result was observed in 67% and a negative result in 33% of the patients with 3 of the negative group producing worsening of manometric pattern without symptoms. Eleven of the patients who had positive baseline manometry had a false negative provocation test. This may be related to the intermittent nature of symptoms. Only 10 patients (48%) who had diffuse oesophageal spasm on baseline manometry had a positive edrophonium test. Mellow (1977) and London et al (1981) found that 67-75% of their patients with diffuse oesophageal spasm on baseline manometry had positive edrophonium tests. Both these studies had a very small number of patients with diffuse oesophageal spasm and used a larger dose of edrophonium. The finding of less than 100%

positive edrophonium provocation test in patients already diagnosed on manometry as having diffuse oesophageal spasm suggests that edrophonium is not specific enough or the dose used is too small. The 13 patients, who initially had normal manometry and then had a positive provocation test, might be considered to represent false positive results. This study would refute this for several patients had the typical radiology of diffuse oesophageal spasm in addition to a positive provocation test. The injection of edrophonium rapidly produced their typical symptoms with associated manometric abnormality of diffuse oesophageal spasm although, prior to the injection, they had been asymptomatic with normal manometry. Without edrophonium provocation testing, 34% of patients would not have been diagnosed as having diffuse oesophageal spasm.

Analysis of the groups which were edrophonium positive and those which were edrophonium negative showed no significant difference in age or sex ratio. The edrophonium negative group contained more patients with dysphagia, although Richter et al (1985c) found a significantly higher incidence of dysphagia in the edrophonium positive group. The edrophonium positive group had a median synchronous contraction percentage of 9%, prior to the edrophonium injection, as compared to the negative group of 70% which was highly significant ($p < 0.0001$). The large proportion of synchronous contractions may explain the high incidence of dysphagia in the edrophonium negative group. The finding of the large proportion of synchronous contractions in the edrophonium negative group may suggest that edrophonium is a

better provocative agent for those patients with chestpain rather than those with dysphagia. The change in both amplitude and duration of contractions before and after edrophonium was significantly greater in the edrophonium positive group and agrees with the findings of Richter et al (1985c) and Lee et al (1987).

Richter et al (1985c) have suggested that the mechanism of edrophonium induced symptoms may be related to prolongation of contraction duration. In this study edrophonium produced a very significant increase in both amplitude and duration of contractions in the edrophonium positive group but, as in other studies, there was a large overlap of results. Several of the patients developed gigantic contractions (amplitude greater than 300 mmHg) which were associated with symptom production.

In this study only 5 patients (16%) had both positive Bernstein and edrophonium provocation tests (n.s. chi-squared). This is a very much smaller percentage than was found by Richter et al (1985c) and De Caestecker et al (1988). This difference may be related to the small numbers of diffuse oesophageal spasm patients in their groups of non cardiac chest pain patients and the presence of large numbers of refluxers.

5.1.5: TWENTYFOUR HOUR AMBULATORY pH MONITORING

Gastro-oesophageal reflux was not a predominant feature as judged by the Bernstein acid perfusion test and ambulatory 24hr pH testing, with no significant difference between the pH results for the spasm group and the controls. These

patients were considered to have primary spasm as those who appeared to have secondary spasm had been excluded.

When the pH results were analysed further depending on the result of the edrophonium provocation test, those who had a positive edrophonium test had significantly more total reflux and reflux episodes than those who were edrophonium negative ($p < 0.05$). Studies by Vantrappen et al (1987), using 24 hour manometry and pH recording, have identified a group of patients who experience similar episodes of chest pain sometimes with gastro-oesophageal reflux alone, with oesophageal motor disorders alone, or with both. Bernstein testing produced typical pain in some patients who showed only a motility disorder without reflux at the time of spontaneous pain. Edrophonium produced chest pain with motility abnormality in patients who showed only reflux without motility abnormality at the time of spontaneous pain. Vantrappen et al felt that irritability of the oesophagus played an important part in the production of chest pain perhaps due to a lowered oesophageal pain threshold. The discovery that those patients who were edrophonium positive had significantly more total reflux may well reflect some patients with the "irritable oesophagus".

5.1.6: CONCLUSION

It is often difficult to prove a causal relationship between a manometric abnormality and the patient's symptoms unless these occur during the recording. Edrophonium provocation testing seems to increase the likelihood of this happening. In this study over 30% of patients would not have been

diagnosed as diffuse oesophageal spasm without provocation testing as their baseline manometry was normal. The edrophonium provocation test has been found to be well tolerated by a large number of patients and its routine use is recommended in conjunction with manometry in the investigation of oesophageal motility disorders.

If the patients who have normal baseline manometry and a positive edrophonium provocation test improve with treatment for diffuse oesophageal spasm, then this will lend further credence to the edrophonium test. Future experiments would include attempting correlation between a positive edrophonium test and 24 hour manometry.

5.2: BALLOON DILATATION

Balloon dilatation has been used regularly for the treatment of achalasia. There are few reports of its use in diffuse oesophageal spasm. Blackwell & Castell (1984) found patients with persistent and severe symptoms were uncommon and they rarely had to resort to balloon dilatation or surgery. Their pattern of referral seems different from that of this study as many of their patients had noncardiac chest pain and not dysphagia. Severe dysphagia has been the usual indication for dilatation. The presence of dysphagia further suggests that the chest pain is likely to be of oesophageal origin.

Winters et al (1984) described the use of mercury-filled bougies 24-F (8mm) and 54-F (18mm) for dilatation in patients with nutcracker oesophagus. The usual dilator used for the treatment of achalasia is 90-120F and they were therefore not performing therapeutic bougienage but had two placebo groups. They concluded that temporary relief of chest pain could be obtained by both sizes of bougie and suggested that symptomatic relief was due to a close patient-physician interaction. Vantrappen & Hellemans (1980) performed pneumatic dilatation of the lower oesophageal sphincter in 18 patients with diffuse oesophageal spasm and severe dysphagia. Only 45% had a good response which was much less than their results for similar treatment on achalasia patients. Ebert et al (1983) reported balloon dilatation in 9 patients with diffuse oesophageal spasm. All these patients had dysfunction of the lower oesophageal sphincter in addition to other manometric criteria for diffuse oesophageal spasm and Ebert et al dilated the lower

oesophageal sphincter region. They used a balloon inflated to 8-12lbs/sq in for 15 seconds. Marked improvement in dysphagia occurred in 89% of patients. There was a significant reduction in the lower oesophageal sphincter pressure following dilatation. The presence of lower oesophageal sphincter abnormalities in all these patients with diffuse oesophageal spasm suggests that they might actually have had an early form of achalasia.

The treatment in this study was quite different as it involved balloon dilatation to 90-120 F. All the patients treated had fulfilled the manometric criteria for diffuse oesophageal spasm. Four of the patients had lower oesophageal sphincter pressures greater than the normal range with two of these having incoordinated relaxation of the sphincter. These results have been obtained by dilating the body of the oesophagus rather than the lower oesophageal sphincter as in the studies of Vantrappen & Hellemans (1980) and Ebert et al (1983).

5.2.1: LOWER OESOPHAGEAL SPHINCTER

Despite dilating the body of the oesophagus there was a significant reduction in lower oesophageal sphincter pressure following dilatation ($p < 0.005$). Considering separately those patients who had a good response and a poor response, there was still a significant decrease in the lower oesophageal sphincter pressure following dilatation. One possible explanation is that the sphincter region itself was inadvertently dilated but against this is the fact that the balloon dilatation was performed under screening and the

oesophagus was dilated from above the sphincter to above the aortic arch. Another explanation is that dilatation of the body of the oesophagus is responsible for a lowering of the sphincter pressure, possibly by interference with the myenteric plexuses or nerve supply.

Following dilatation the percentage of synchronous contractions increased. The median maximum amplitude and duration of contractions decreased. After dilatation the amplitude of contraction in the upper third of the oesophagus increased significantly but there was no other significant change in amplitude or duration in the rest of the oesophagus. There was considerable overlap of results both before and after dilatation.

5.2.2: TWENTYFOUR HOUR AMBULATORY pH MONITORING

The reduction in sphincter pressure following dilatation was not associated with an increase in gastro-oesophageal reflux as might be expected. There was no significant difference in the values obtained from ambulatory pH recording for all patients before and after dilatation. However, when the results were further analysed, the group that had a poor response to dilatation had significantly more total, supine and upright reflux prior to dilatation. This finding suggests that the primary problem in patients with diffuse oesophageal spasm and gastro-oesophageal reflux is the reflux. The numbers of patients who had pH testing following dilatation were very small but dilatation did not increase gastro-oesophageal reflux. This finding may explain the lack of reflux produced by dilating the lower oesophageal

sphincter in cases of achalasia.

5.2.3: THE IRVING SIGN

It is difficult to explain the finding of the eccentric localized narrowing of the balloon during inflation in all cases. An oesophageal ring is unlikely since a Schatzki's ring (Schatzki 1963) is usually found lower down the oesophagus at the squamo-columnar junction. In all cases the waisting was incomplete and eccentric whilst oesophageal rings are complete. Although lower oesophageal sphincter pressure fell following dilatation, the waisting was too far up the oesophagus for this to be the sphincter region. Endoscopy has also shown no abnormality at this level. Interestingly this waisting has not been seen in other types of oesophageal strictures during balloon dilatation although dilatation of the oesophageal body to 30 or 35mm is not used in these cases. The waisting may represent a localised area of muscle spasm where the circular muscle is particularly marked and this may be responsible for dysphagia. This lower oesophageal ring may cause functional obstruction and pain and, given the intermittent nature of symptoms, it may be difficult to record an abnormality on standard manometry. Twentyfour hour manometry may help to elucidate this finding.

5.2.4: CONCLUSION

It is not clear why balloon dilatation is effective in improving symptoms of chest pain when no alteration in manometry is produced. It is possible that the amplitude in

the oesophageal body decreased in some patients but the numbers are too small to show a difference. Perhaps dilatation is effective only on patients with impaired lower oesophageal sphincter function. Follow-up studies over several years have shown consistent improvement in symptoms. It was considered unethical to insert the balloon into the oesophagus and not inflate it. Winters et al's (1984) work on the nutcracker oesophagus suggests that passage of even a very small bougie may have a therapeutic effect on the patient's symptoms although it would appear to have no such effect on the oesophagus.

Significant symptomatic improvement in 12 of 17 patients (71%) suggests that the majority of diffuse oesophageal spasm patients with severe symptoms will benefit from balloon dilatation and thus avoid surgical intervention. The sustained effect of balloon dilatation shows it is not a placebo effect. The next step would be a double blind trial of a 90F balloon against a 40F balloon dilatation. The finding of significant gastro-oesophageal reflux in the poor responders suggests that balloon dilatation should not be performed on patients who reflux, although it is unlikely to make reflux worse.

5.3: THE GLOBUS SENSATION

5.3.1: METHODOLOGY CRITIQUE

The use of intra oesophageal mini-transducers with their ability to record at 32 samples per second and high frequency response with less damping should produce more accurate recording of a rapidly contracting region such as the cricopharyngeus. In a typical Arndorfer system (Arndorfer et al 1973) the infusion fluid tends to make pharyngeal and cricopharyngeal recording difficult as the fluid tends to stimulate swallowing, which should not be a problem with the Gaeltec system of mini-transducers. Winans (1972) has shown that the upper oesophageal sphincter is radially and axially asymmetrical with a fixed relationship between the pressures recorded in the antero-posterior and lateral directions. Using an eight-lumen perfused catheter, the greatest pressures (mean 100mmHg) were recorded from orifices directed anteriorly and posteriorly, and lowest pressures (mean 33mmHg) were detected by orifices pointing to the subject's right or left. The catheter used for the present study had only one transducer at each level. This catheter, because of its shape after a few uses, always entered the oesophagus at the same orientation which was with the sensor pointing to the left lateral position. This means that the recording is not of the peak upper oesophageal sphincter pressure which has been shown by Winans to be found in the anterior and posterior axes. Since all the recordings were made with the transducer recording in the same direction, inter-patient and intra-patient

comparisons can be made of mean resting pressures and the inability to record in several directions has no effect on coordination of contractions. Attempts to twist an earlier catheter in the oesophagus failed to produce any movement of the catheter in the oesophagus but did destroy one of the sensors. The development of a sleeve catheter, as described by Dent (1976) and Kahrilas (1987a), may further improve recordings from the upper oesophageal sphincter as contraction of the cricopharyngeus and the movement of swallowing does tend to cause the whole catheter to be tugged into the patient which can make keeping the transducer at the correct recording point for the peak upper oesophageal pressure difficult.

5.3.2: SYMPTOMS

Globus was the presenting symptom in all the patients studied in the group which had a female bias. The age distribution was similar for both sexes. Thompson & Heaton (1982) recorded globus in 45% of apparently healthy individuals questioned during a survey of bowel symptoms. Globus occurred in almost equal proportions of those with and without heartburn. Associated symptoms of mild dysphagia, chest pain, heartburn, acid reflux and hoarseness in the group studied suggest that physical disease in the oesophagus may be related to the symptom. The finding of heartburn and reflux in common association with globus suggests that gastro-oesophageal reflux may be the origin of the globus symptom. However, both heartburn and reflux are very common symptoms throughout the population, experienced

by most people at some time in their lives. Studies in the United States of America found 7% of the population experienced gastro-oesophageal reflux daily (Nebel et al 1976) and a Gallup survey found that 61 million adult Americans, or 44% of the population, experienced reflux monthly (Gallup 1988). Hoarseness may also be due to reflux of acid up to the larynx, further suggesting gastro-oesophageal reflux. Cherry et al (1970), Delahunty (1972) and Chodosh (1977) reported the association of hoarseness with globus which they felt was related to oesophago-pharyngeal reflux demonstrated on barium swallows.

5.3.3: LARYNGOSCOPY

Only one patient had any abnormality on indirect laryngoscopy when erythema of the hypopharynx and ary-epiglottic folds were found. Similar findings have been reported by Delahunty (1972) and Chodosh (1977) with demonstration of free reflux of barium into the pharynx. To obtain further information laryngeal biopsies could be performed.

5.3.4: BARIUM SWALLOW AND GASTROSCOPY

The barium swallows revealed a variety of results with 5 patients having radiological gastro-oesophageal reflux. Other studies have found reflux on barium studies in 13-100% of globus patients (Mair et al 1974, Hallewell & Cole 1970). Twentyfour hour ambulatory pH monitoring is a more accurate way of assessing gastro-oesophageal reflux and may confirm the diagnosis in the presence of a normal barium swallow.

Despite the presence of symptoms suggestive of oesophagitis, the majority of the gastroscopies were normal.

5.3.5: MANOMETRY

Lower oesophageal sphincter pressure was not found to be significantly different from that in the control group. Wilson et al (1987) found similar results in their study of globus patient. This finding does not exclude gastro-oesophageal reflux as reflux patients can have lower oesophageal sphincter pressures in the normal range and there is a large overlap of results between refluxers and nonrefluxers (Thurer et al 1974).

Most of the globus patients had entirely normal manometry of the oesophageal body. However, 16% had low amplitude peristalsis which may be associated with gastro-oesophageal reflux (Richter & Castell 1982). A further two patients had manometry compatible with diffuse oesophageal spasm and two compatible with a nonspecific motility disorder. Flores et al (1981) found disordered motor activity in the oesophageal body on manometry in 75% of their patients with the globus symptom. This consisted of spontaneous, synchronous and repetitive contractions although no attempt was made to define the motility disorders further. No mention is made of other symptomatology in these patients who appear to have abnormal motility compatible with diffuse oesophageal spasm on the recordings included in the review.

5.3.5a: UPPER OESOPHAGEAL SPHINCTER

There was no significant difference between resting cricopharyngeal pressure in the globus patients and controls

with a wide variation in the results recorded in both groups. The median pressure recorded was very similar to that recorded by Winans (1972) in the lateral position and gives further credence to the fact that the Gaeltec catheter consistently recorded laterally. Watson & Sullivan (1974) found elevated resting cricopharyngeal pressure in globus patients compared to controls whereas Calderelli et al (1970) found the pressures to be similar. These differences seem to be due to catheter orientation and the presence or absence of a perfused catheter which may be eliminated by the use of intra-oesophageal mini-transducers which are more able to respond to the rapid pressure changes found in the upper oesophageal sphincter region. Watson & Sullivan twisted the catheter in the oesophagus to obtain peak pressure but movement has been shown by Kahrilas et al (1987a) to increase the upper sphincter pressure. The large range of values measured probably relates to the difficulty in keeping the catheter in the maximum of the upper high pressure zone. A sleeve catheter might aid this. The measurements of pharyngeal and cricopharyngeal contraction amplitude and cricopharyngeal relaxation were not significantly different in both groups.

Incoordination of the cricopharyngeal relaxation with the pharyngeal contraction was reported by Henderson et al (1976) to be found in patients with gastro-oesophageal reflux and pharyngo-oesophageal dysphagia. In this study of globus patients no incoordination has been demonstrated and Henderson et al's findings would appear to relate to a completely different group of patients with dysphagia, i.e.

not true globus.

5.3.5b: SALINE AND ACID PERFUSION

Gerhardt et al (1978) have shown that in normal people the upper oesophageal sphincter pressure increases with instillation of saline and acid into the oesophagus and that the pressure rise is greater following acid infusion, although Stanciu & Bennett (1974) and Wallin et al (1978) were unable to demonstrate any sustained increase in pressure following acid perfusion. Gerhardt et al (1980) found that patients with oesophago-pharyngeal reflux had a lower resting upper oesophageal sphincter pressure than both normal controls and patients with heartburn. The last two groups showed an increase in upper oesophageal sphincter pressure in response to saline and acid perfusion but the group with oesophago-pharyngeal reflux showed no change in pressures. They concluded that in these patients the normal protective mechanism to prevent regurgitation had been lost. No increase in upper oesophageal sphincter pressure has been found in this group of globus patients comparing baseline manometry to saline and acid infusion. This may be related to the speed of infusion or the distance from the sphincter to the point of infusion, although this appears to have been 15cm from the upper oesophageal sphincter in most of the studies. Gerhardt et al (1978 & 1980) used a water-perfused catheter as opposed to the intraoesophageal microtransducers used in this study and the difference may be due to additional fluid retention in the oesophagus with the perfused catheter.

Saline perfusion did not produce symptoms in any of the

patients. Seven patients (30%) had a positive Bernstein test in response to acid perfusion with the development of the globus symptom in 2 patients. Cherry et al (1970) found 80% of their patients developed globus following acid perfusion.

5.3.6: TWENTYFOUR HOUR AMBULATORY pH MONITORING

Fourteen patients (58%) had evidence of pathological reflux on pH testing. Twenty four hour ambulatory pH monitoring showed that the total percentage time that the pH was less than 4 was significantly greater ($p < 0.05$) in the globus patients than in the controls. The findings were similar for upright reflux percentage ($p < 0.05$) but there was no significant difference in the supine group. There were significantly more reflux episodes in the globus group and the longest episode was also greater in the globus patients. The latter result is skewed by one patient who had a reflux episode that lasted 152 minutes. Wilson et al (1987) found no difference between globus patients and controls in the mean time the pH was below 4 using ambulatory pH recording but one control group contained patients with noncardiac chest pain and with heartburn. Similar percentages of globus patients in both studies complained of heartburn. A difference in patient selection seems the most likely reason for the differences obtained with the present study having a smaller younger group of controls.

5.3.7: PSYCHOMETRY

The results of the psychometric questionnaires are interesting as there was no evidence of psychological

disturbance in the globus patients. Hernia and varicose vein patients were chosen as they had been shown to be an acceptable control group by Stockton et al (1985). When the scaled general health questionnaire was used as a screening test, Goldberg & Hillier (1979) felt that the simpler "GHQ scoring method" (0.0.1.1) gave better results than the Likert method. When the GHQ scoring method was used, three of the globus patients in this study had a significant score for depression on the general health questionnaire, with 6 patients having a total score of more than 5. However, the higher scores of the control group would suggest that they were more psychiatrically disturbed than the globus patients. Therefore, it would seem appropriate to drop the term "globus hystericus".

5.3.8: CONCLUSION

One problem associated with the investigation of globus symptom and its cause is the intermittent nature of the symptom. Only a few of the patients have actually experienced the symptom during recording although acid perfusion in a few patients has reproduced their symptoms of globus. Several others have experienced their symptoms during the ambulatory pH monitoring allowing a causal relationship to be suggested. The finding that at least half of the patients studied also had symptoms of heartburn and reflux might suggest that these patients had gastro-oesophageal reflux anyway. However, their main complaint was of globus and the other symptoms were obtained only on direct questioning and were very mild and intermittent. The

finding of gastro-oesophageal reflux associated with the globus symptom in 58% of patients may suggest that:- a. acid in these people refluxes into the pharynx, b. oesophageal acid clearance is reduced or, more probably, c. there is hypersensitivity to acid in the pharynx, i.e. that it is a sensory difference rather than a motor problem. To investigate the possibility of a sensory change to stimulus, further plans could include investigation of neurophysiological changes with acid sensitivity testing or balloon distension. Ambulatory pH monitoring simultaneously at multiple levels in the oesophagus may enable acid to be recorded refluxing from the lower oesophagus into the pharynx.

CHAPTER 6

CONCLUSION

Diffuse oesophageal spasm although uncommon is important in that it produces severe disabling symptoms which may be indistinguishable from cardiac disease. There may be great difficulty in making the diagnosis with radiology being positive in only a third of patients. These patients therefore may consume a large amount of medical time. The use of strict manometric criteria is necessary for the diagnosis of diffuse oesophageal spasm as is the exclusion of gastro-oesophageal reflux.

Diffuse oesophageal spasm was diagnosed in 9% of 438 patients studied. Baseline manometry, using Richter's criteria (Richter & Castell 1984), showed diffuse oesophageal spasm in 66% of patients. In view of the intermittent nature of symptoms the edrophonium provocation test was performed. Thirtyfour percent of patients who had normal baseline manometry developed symptoms and abnormal manometry in response to the edrophonium provocation test. Without the use of the edrophonium provocation test these patients would not have been diagnosed as diffuse oesophageal spasm.

The patients who were edrophonium positive had significantly more total acid reflux, on twentyfour hour ambulatory pH monitoring, than the edrophonium negative group which may reflect an "irritable oesophagus" as suggested by Vantrappen et al (1987).

Treatment can be given for diffuse oesophageal spasm and is successful. Seventyone percent of patients with severe symptoms benefited from balloon dilatation with lasting

relief of dysphagia and chest pain following dilatation of the lower oesophageal body directly above the lower oesophageal sphincter and thus avoided surgical intervention. Dilatation was effective in patients with primary diffuse oesophageal spasm but not in patients with gastro-oesophageal reflux and secondary spasm. A concentric narrowing of the lower oesophageal body, "waisting", was seen in all patients with diffuse oesophageal spasm during dilatation and was quite separate from the lower oesophageal sphincter.

There was a close correlation between symptom eradication with balloon dilatation and the absence of gastro-oesophageal reflux prior to dilatation. Balloon dilatation caused a significant reduction in lower oesophageal sphincter pressure and a tendency towards reduction in amplitude of peristalsis of the lower oesophagus.

Globus is a very common symptom. Previous studies postulated different causes for the symptom including spasm of the upper oesophageal sphincter, incoordination of the upper oesophageal sphincter, an association with gastro-oesophageal reflux and motility disorders of the oesophageal body.

These results reinforce the dropping of the term "globus hystericus" as psychometric tests suggested that the globus patients had less psychiatric illness than the controls. No abnormality of the upper oesophageal sphincter complex could be identified. Twentyfour hour ambulatory pH monitoring revealed significantly more reflux in the globus patients

than in the controls.

One possible explanation for the sensation may be a sensory change in pharyngeal threshold to acid reflux.

APPENDIX

1. OESOPHAGEAL SYMPTOM SHEET
2. 24 HOUR AMBULATORY pH RECORDING DIARY
3. GENERAL HEALTH QUESTIONNAIRE
4. EYSENCK PERSONALITY INVENTORY

OESOPHAGEAL INVESTIGATION UNIT
DEPARTMENT OF SURGERY, GUY'S HOSPITAL
ADULT MANOMETRY AND pH MONITORING

Patient : Test date :
Hosp. No : DOB :
Telp : Sex :
Address : Referred by :

HISTORY

Main complaint :

Dysphagia : duration what level

type of food solid liquid

Chest pain : position on swallowing

Heartburn : duration worse on bending

worse in bed pillow

bed propped up

felt temperature of food or drink

Vomiting Regurgitation belching

ENT symptoms : odynophagia globus

hoarseness laryngitis

throat clearing sore throat

Pulmonary symptoms : asthma chronic cough
night cough choking sensation

Weight loss :

Habits : smoking alcohol

Prior studies : Radiology :

Endoscopy :

Cardiac :

Prior UGI Surgery :

Present Medication :

pH study :

Single channel :

Location of sensor :

Dual channel :

Gastric and oesophageal pH : location of sensors : cm. cm

Oesophageal and Pharyngeal pH : location of sensors : cm. cm

Pre-test calibration : pH 7 : pH 1 : water :

post- test calibration :pH 7 : pH 1 : water : .

24-HOUR AMBULATORY pH RECORDING DIARY

IF PROBLEMS PLEASE RING BETWEEN 9AM AND 5PM ON 071 955 4053

NAME:

DATE:

DISTANCE FROM NARES TO pH TIP:

RECORD EVERYTHING YOU EAT AND DRINK BELOW. RECORD ANY PAIN YOU EXPERIENCE ALSO WHEN YOU LIE DOWN AND GET UP.

PRESS THE MARKER BUTTON EVERY TIME YOU EAT, DRINK, EXPERIENCE PAIN, LIE DOWN OR GET UP.

AVOID THE FOLLOWING: FRUIT JUICE, YOGHOURT, CITRUS FRUITS AND LEMONADE. RECORD ALL COFFEE, TEA AND CIGARETTES.

GENERAL HEALTH QUESTIONNAIRE

Please read this carefully:

We should like to know if you have had any medical complaints, and how your health has been in general, **over the past few weeks**. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those you had in the past. It is important that you try to answer ALL the questions. Thank you very much for your cooperation.

HAVE YOU RECENTLY:

A1. Been feeling perfectly well and in good health?	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2. Been feeling in need of a good tonic?	Not at all	No more than usual	Rather more than usual	Much more than usual
A3. Been feeling run down and out of sorts?	Not at all	No more than usual	Rather more than usual	Much more than usual
A4. Felt that you are ill?	Not at all	No more than usual	Rather more than usual	Much more than usual
A5. Been getting any pains in your Head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A6. Been getting a feeling of tightness or pressure in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A7. Been having hot or cold spells?	Not at all	No more than usual	Rather more than usual	Much more than usual

B1. Lost any sleep over worry?	Not at all	No more as usual	Rather more than usual	Much more than usual
B2. Had difficulty in staying asleep once you are off?	Not at all	No more than usual	Rather more than usual	Much more than usual
B3. Felt constantly under strain?	Not at all	No more than usual	Rather more than usual	Much more than usual
B4. Been getting edgy and bad-tempered?	Not at all	No more than usual	Rather more than usual	Much more than usual
B5. Been getting scared or panicky for no good reason?	Not at all	No more than usual	Rather more than usual	Much more than usual
B6. Found everything getting on top of you?	Not at all	No more than usual	Rather more than usual	Much more than usual
B7. Been feeling nervous and strung-up all the time?	Not at all	No more than usual	Rather more than usual	Much more than usual

C1. Been managing to keep yourself busy and occupied?	More so than usual	Same as usual	Rather less than usual	Much less than usual
C2. Been taking longer over the things you do?	Quicker than usual	Same as usual	Longer than usual	Much longer than usual
C3. Felt on the whole you were doing things well?	Better than usual	About the same	Less well than usual	Much less well
C4. Been satisfied with the way you have carried out your task?	More satisfied	About same as usual	Less satisfied	Much less satisfied
C5. Felt that you are playing a useful part in things?	More so than usual	Same as usual	Less useful than usual	Much less useful
C6. Felt capable of making decisions about things?	More so than usual	Same as usual	Less so than usual	Much less capable
c7. Been able to enjoy your normal day-to-day activities?	More so than usual	Same as usual	Less so than usual	Much less than usual

D1. Been thinking of yourself as a worthless person?	Not at all	No more as usual	Rather more than usual	Much more than usual
D2. Felt that life is entirely hopeless?	Not at all	No more than usual	Rather more than usual	Much more than usual
D3. Felt that life isn't worth living?	Not at all	No more than usual	Rather more than usual	Much more than usual
D4. Thought of the possibility that you might make away with yourself?	Definitely not	I don't think so	Has crossed my mind	Definitely have
D5. Found at times you couldn't do anything because your nerves were too bad?	Not at all	No more than usual	Rather more than usual	Much more than usual
D6. Found yourself wishing you were dead and away from it all?	Not at all	No more than usual	Rather more than usual	Much more than usual
D7. Found that the idea of taking your own life kept coming into your mind?	Definitely not	I don't think so	Has crossed my mind	Definitely has

EYSENCK PERSONALITY INVENTORY

by H. J. Eysenck and Sybil B. G. Eysenck

PERSONALITY QUESTIONNAIRE

FORM A

NAME..... *Master Copy* AGE.....

OCCUPATION..... SEX.....

N=

E=

L=

Instructions

Here are some questions regarding the way you behave, feel and act. After each question is a space for answering "YES" or "NO".

Try to decide whether "YES" or "NO" represents your usual way of acting or feeling. Then put a cross in the circle under the column headed "YES" or "NO". Work quickly, and don't spend too much time over any question; we want your first reaction, not a long-drawn out thought process. The whole questionnaire shouldn't take more than a few minutes. Be sure not to omit any questions.

Now turn the page over and go ahead. Work quickly, and remember to answer every question. There are no right or wrong answers, and this isn't a test of intelligence or ability, but simply a measure of the way you behave.



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- | | YES | NO |
|---|------------------------------------|------------------------------------|
| 1. Do you often long for excitement? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 2. Do you often need understanding friends to cheer you up? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 3. Are you usually carefree? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 4. Do you find it very hard to take no for an answer? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 5. Do you stop and think things over before doing anything? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 6. If you say you will do something do you always keep your promise, no matter how inconvenient it might be to do so? | <input checked="" type="radio"/> L | <input type="radio"/> |
| 7. Does your mood often go up and down? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 8. Do you generally do and say things quickly without stopping to think? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 9. Do you ever feel "just miserable" for no good reason? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 10. Would you do almost anything for a dare? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 11. Do you suddenly feel shy when you want to talk to an attractive stranger? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 12. Once in a while do you lose your temper and get angry? | <input type="radio"/> | <input checked="" type="radio"/> L |
| 13. Do you often do things on the spur of the moment? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 14. Do you often worry about things you should not have done or said? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 15. Generally, do you prefer reading to meeting people? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 16. Are your feelings rather easily hurt? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 17. Do you like going out a lot? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 18. Do you occasionally have thoughts and ideas that you would not like other people to know about? | <input type="radio"/> | <input checked="" type="radio"/> L |
| 19. Are you sometimes bubbling over with energy and sometimes very sluggish? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 20. Do you prefer to have few but special friends? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 21. Do you daydream a lot? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 22. When people shout at you, do you shout back? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 23. Are you often troubled about feelings of guilt? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 24. Are <i>all</i> your habits good and desirable ones? | <input checked="" type="radio"/> L | <input type="radio"/> |
| 25. Can you usually let yourself go and enjoy yourself a lot at a lively party? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 26. Would you call yourself tense or "highly-strung"? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 27. Do other people think of you as being very lively? | <input checked="" type="radio"/> E | <input type="radio"/> |

- | | YES | NO |
|--|------------------------------------|------------------------------------|
| 28. After you have done something important, do you often come away feeling you could have done better? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 29. Are you mostly quiet when you are with other people? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 30. Do you sometimes gossip? | <input type="radio"/> | <input checked="" type="radio"/> L |
| 31. Do ideas run through your head so that you cannot sleep? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 32. If there is something you want to know about, would you rather look it up in a book than talk to someone about it? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 33. Do you get palpitations or thumping in your heart? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 34. Do you like the kind of work that you need to pay close attention to? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 35. Do you get attacks of shaking or trembling? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 36. Would you always declare everything at the customs, even if you knew that you could never be found out? | <input checked="" type="radio"/> L | <input type="radio"/> |
| 37. Do you hate being with a crowd who play jokes on one another? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 38. Are you an Irritable person? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 39. Do you like doing things in which you have to act quickly? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 40. Do you worry about awful things that might happen? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 41. Are you slow and unhurried in the way you move? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 42. Have you ever been late for an appointment or work? | <input type="radio"/> | <input checked="" type="radio"/> L |
| 43. Do you have many nightmares? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 44. Do you like talking to people so much that you never miss a chance of talking to a stranger? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 45. Are you troubled by aches and pains? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 46. Would you be very unhappy if you could not see lots of people most of the time? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 47. Would you call yourself a nervous person? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 48. Of all the people you know, are there some whom you definitely do not like? | <input type="radio"/> | <input checked="" type="radio"/> L |
| 49. Would you say that you were fairly self-confident? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 50. Are you easily hurt when people find fault with you or your work? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 51. Do you find it hard to really enjoy yourself at a lively party? | <input type="radio"/> | <input checked="" type="radio"/> E |
| 52. Are you troubled with feelings of inferiority? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 53. Can you easily get some life into a rather dull party? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 54. Do you sometimes talk about things you know nothing about? | <input type="radio"/> | <input checked="" type="radio"/> L |
| 55. Do you worry about your health? | <input checked="" type="radio"/> N | <input type="radio"/> |
| 56. Do you like playing pranks on others? | <input checked="" type="radio"/> E | <input type="radio"/> |
| 57. Do you suffer from sleeplessness? | <input checked="" type="radio"/> N | <input type="radio"/> |

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL THE QUESTIONS

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