Review Articles

Motility Disorders of the Oesophagus

M. I. El Mouzan

Saudi Medical Journal 1992; 13(4): 275-282

تسبب الأمراض الحركية للمريء اعراضا عديدة. ومع ان هذه الامراض معروفة عند الكبار، الا ان بعض الدراسات تشير الى اصابة الاطفال بأنواع كثيرة منها.
تحتوي هذه المقاله على مراجعة شاملة للتطورات الحديثة في تشخيص وعلاج هذه الامراض.

Oesophageal motility disorders are recognized causes of oesophageal symptoms. Although adults are more commonly affected, reports indicate that all types of motility disorders may occur in children. In this article, a comprehensive review is presented in order to update physicians on recent developments in the diagnosis and treatment of oesophageal motor dysfunction.

Oesophageal motor dysfunction occurs in all age groups. It is a recognized cause of oesophageal symptoms such as dysphagia, gastro-oesophageal reflux, and chest pain. Recent advances in diagnostic techniques such as manometry have improved the understanding of these functional disorders. Consequently, diagnostic criteria and therapeutic strategies are being developed and investigated more precisely. In Saudi Arabia, adequate diagnostic facilities are available only in a few centres that are usually inaccessible to the general population. The purpose of this review is to update the reader on the importance of motility disorders in the genesis of many distressing symptoms. Adequate anatomic and physiologic knowledge which is required for the understanding of these disorders will be briefly presented. Manometry, which is no longer a research tool, is now considered the most accurate diagnostic modality and will be described in more detail. It is hoped that this approach will stimulate the interest of physicians in these disorders and help the establishment of motility studies in major hospitals in the Kingdom.

Anatomy of the oesophagus

The oesophagus is a hollow structure extending from the pharynx to the stomach. It consists of three major parts: the upper oesophageal sphincter (UES), the oesophageal body, and the lower oesophageal sphincter (LES). The gross anatomy of the oesophagus and its nervous system are depicted in Fig. 1.

The UES

The UES is located between the pharynx and upper oesophageal body. It consists of an intraluminal

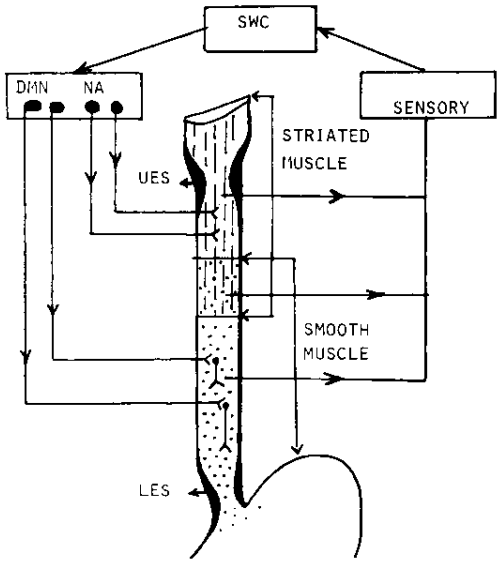

Figure 1. Anatomy of the oesophagus. SWC = swallowing centre, DMN = dorsal motor nucleus, NA = nucleus ambiguus, UES and LES = upper and lower oesophageal sphincters.

Social Insurance Hospital, PO Box 42142, Riyadh 11541, Saudi Arabia
MOHAMMED I. EL MOUZAN MD FAAP, Professor

high pressure zone most probably due to contraction of the cricopharyngeus and the lower part of the inferior pharyngeal constrictor muscles.[1] Both of these striated muscles are innervated by somatic nerves originating from the nucleus ambiguus and dorsal motor nucleus of the vagus nerve. These lower motor neurones reach the sphincter by the superior and recurrent laryngeal nerves.

The oesophageal body

The oesophageal body extends from the UES to the LES. Its length varies with age and individuals. The wall of the oesophagus is composed of mucosa, muscularis mucosa, submucosa, and muscularis propria. The mucosa consists of stratified squamous epithelium. The finding of columnar epithelium in the oesophagus is abnormal and characterizes Barret's oesophagus. The muscularis mucosa consists of longitudinal smooth muscle throughout the length of the oesophageal body. The muscularis propria includes an inner circular and an outer longitudinal muscle layer. The proximal 4–5 cm of the oesophagus is formed by striated muscles in both the circular and longitudinal layers, followed by another zone of 4–5 cm where a mixture of striated and smooth muscles is found. After this point, the muscularis propria consists of smooth muscles which constitute approximately the distal half of the oesophagus.[2] The innervation of the oesophagus includes extrinsic nerves that connect the intrinsic nerves of the body of the oesophagus to the central nervous system (Fig. 1). The intrinsic nerves have their cell bodies either in the submucosa (Meissner's plexus) or between the circular and longitudinal muscles (Myenteric or Auerbach's plexus). Most of the extrinsic nerve fibres leave the vagus high in the neck to form an oesophageal plexus at the mid-oesophageal body which explains why vagotomy performed for peptic ulcer disease does not affect oesophageal functions.

The LES

The LES consists of a high pressure zone that is anatomically distinct from the rest of the oesophagus. It lies between the negative pressure of the oesophageal body and the positive intragastric pressure. The motor nerve supply of the LES is similar to that of the oesophageal body.

Physiology of the Oesophagus

Development of sucking and swallowing

Although sucking and swallowing movements have been identified *in utero*, prematures have ineffective sucking and swallowing at the time of birth. Effective sucking followed by coordinated swallows (one swallow after about four sucks) can be seen after several weeks when the birthweight of these infants approaches 2000 g. In infants born near term, however, the rate of maturation of sucking and swallowing is faster, and many infants are able to have effective sucking and coordinated swallowing and oesophageal peristalsis by 5 days of postnatal age.[3]

Deglutition

The deglutition reflex refers to a stereotyped involuntary sequence of events that produces primary peristaltic contractions propelling ingested material into the stomach. The act of swallowing may be divided into three stages: the voluntary or oral stage, the pharyngeal or involuntary stage, and the oesophageal stage.

The voluntary stage starts with the placement of the material in the middle of the tongue which forces the bolus into the pharynx by coordinated contractions of several muscles. Once the bolus reaches the orophagynx, receptors are stimulated and the involuntary phase starts. The soft palate is pulled upward opposing the posterior pharyngeal wall. The palatopharyngeal folds are pulled medially, the vocal cords close and the epiglottis falls backwards and downwards. The larynx is pulled upward and forward by the muscles attached to the hyoid bone stretching the opening of the UES. The total duration of this phase is about 1 second. During this phase, motor impulses responsible for closure of the UES are abolished and the pressure falls shortly after the onset of swallowing for 0.5–1.2 s. The oesophageal stage of deglutition is the longest and lasts between 7 and 10 s. Sequential contractions of the circular muscle layers form the peristaltic waves that propel the bolus through the oesophageal body. Primary peristalsis is the continuation of the pressure wave that originated in the pharynx and secondary peristalsis is the pressure wave produced by distension of the oesophageal lumen by the bolus. The latter is an important mechanism for clearing ingested or refluxed material from the oesophagus. Tertiary waves are non-peristaltic and, therefore, non-propulsive. They may occur spontaneously or during swallowing. The LES relaxes simultaneously with UES or 2–3 s after the initiation of swallowing to allow passage of the bolus in the stomach. This relaxation precedes the peristaltic wave and lasts from 5 to 10 s.

Regulation of oesophageal peristalsis

The swallowing centre controls the pharyngeal musculature, the striated portion of the oesophagus, and partially the contractions of the oesophageal smooth muscles. In addition, this centre which is found in both sides of the reticular formation near the fourth ventricle, interacts with the respiratory centre and area controlling speech to produce

inhibition of respiration and speech during deglutition. The pharyngeal phase of swallowing is completely under central nervous system (CNS) control. In view of the precise coordination required within a short period of time, neuromuscular diseases affecting this area may produce nasal regurgitation, aspiration, or dysphagia.[4,5] The striated muscle portion of the oesophagus is also under complete CNS control. Sequential activation of the nucleus ambiguus, transmitted through vagal nerve fibres to the striated muscle fibres, induce sequential contractions. High cervical vagotomy abolishes both primary and secondary peristalsis in the striated oesophageal segment. However, in view of the intrinsic and extrinsic innervation of the smooth muscle part of the oesophagus, peristalsis may also be produced by peripheral mechanisms.[5] The LES remains closed between swallows not because of continuous nerve stimulation as in the UES, but because of intrinsic properties of the sphincter muscle. The resting LES tone, however, may be modulated by hormonal, mechanical, myogenic, or neural factors. Relaxation of the LES during swallows is under CNS control through vagal nerve fibres and intramural fibres that release an inhibitory neurotransmitter that remains to be identified.

Clinical Presentation of Oesophageal Motility Disorders

Patients with oesophageal disease usually present with a limited number of symptoms. A detailed history is necessary to define the precise type of complaint in order to develop an appropriate differential diagnosis and plan appropriate investigations.

Dysphagia

This refers to the subjective sensation of obstruction as food passes from the mouth to the stomach. Patients may complain that food or liquids get 'hung up' or stuck after swallowing. Patients having only pain with swallowing do not have true dysphagia. Dysphagia should also be differentiated from the globus hystericus syndrome which refers to a permanent 'lump' in the throat. Further distinction should be made between oropharyngeal and oesophageal dysphagia. The former refers to difficulty in initiating a swallow or in transfer of food from the mouth to the oesophagus. These patients are likely to have a neuromuscular disease, and nasal or oral regurgitation, dysphonia, and dysarthria may be associated symptoms. When food and drink leaves the mouth without problems, oesophageal dysphagia is more likely and may be caused by mechanical obstruction, neuromuscular disease or oesophageal inflammation.

Odynophagia

This refers to pain on swallowing. Between swallows, the patient is pain free. Odynophagia is usually caused by severe inflammation of the oesophageal mucosa (oesophagitis) associated with infections, gastro-oesophageal reflux, ingestion of caustic substances, and skin diseases such as bullous pemphigoid and epidermolysis bullosa. Odynophagia should be differentiated from *pyrosis* (heartburn) which is defined as burning-like sensations that radiate from the epigastrium to the throat, sometimes ending with regurgitation. Pyrosis is not associated with the act of swallowing. It is a classical symptom of reflux in older children and adults.

Chest pain

Chest pain of oesophageal origin may closely mimic that of coronary artery disease and differentiation may at times require special studies such as manometry or catheterization.

Regurgitation

This refers to effortless, sudden return of small amounts of gastric contents into the pharynx, whereas, vomiting or retching refers to projection of gastric contents from the mouth, always associated with vigorous contraction of the abdominal muscles. This distinction is important in the differential diagnosis of motor disorders.

Diagnostic Methods in Motility Disorders

A variety of techniques are potentially useful. Barium swallow has the advantage of being readily available. It is useful in the initial investigation to exclude obstructing lesions. Fluoroscopy or cinefluoroscopy is also useful and has been reported to be almost as sensitive as manometry.[6] However, both these radiological studies do not provide quantitative information. Oesophageal scintigraphy consists of studying the oesophageal clearance of swallowed radioactive material. The method provides quantitative data, its sensitivity is high.[7] However, its use as a screening test for oesophageal motility disorders has been questioned in view of the limited sensitivity for non-specific motility disorders.[8] Other methods such as the acid perfusion test (Bernstein test), endoscopy and biopsy, and electromyography have special indications and will not be discussed here. Manometry, however, remains the method of choice and will be reviewed in some detail.

Oesophageal Manometry

The equipment necessary for the performance of oesophageal manometry is illustrated in Fig. 2. In summary, variations in intraluminal pressure are transmitted to pressure transducers directly

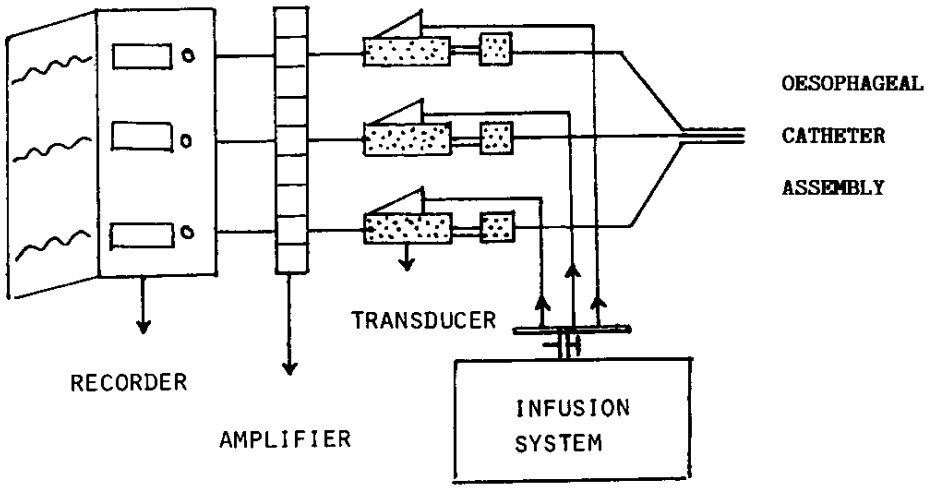

Figure 2. Equipment for manometry.

(proximal transducers), or through the fluid filled catheters (distal transducer as in Fig. 2). The signal is amplified and displayed either on a screen, or on a recorded paper. Pressures are recorded in kiloPascals (kPa) or millimetres of mercury (mmHg). The system is perfused by a pneumo-hydraulic capillary apparatus. The catheter assembly may contain up to eight small catheters with lateral openings at variable distances from each other depending on the needs. Before starting the study, all the equipment must be checked and calibrated.

After an overnight fast, the catheter assembly is passed through the nose or throat with the patient in the sitting position. The catheter assembly is then advanced until all the catheter openings are in the stomach. The patient is now put in a supine position and recording is started. At this point, recording of all intragastric channels should show gastric pressure waves as well as identical respiratory excursions. The catheter assembly is then slowly pulled back, 1 cm at a time and recording is observed in all channels for three to five respirations. The LES is first recorded by the most proximal (upper) channel as a high pressure recording. The LES pressure is then recorded by the next two channels as the catheter assembly is slowly withdrawn. Failure to observe this sequence requires an explanation and correction of the problem before proceeding any further.

The next step is the study of oesophageal peristalsis. This is accomplished by slow withdrawal of the catheter assembly 1–2 cm at a time and asking the patient to swallow one or more times at each recording step. The UES is studied at the end of the procedure. The most important step is the evaluation of the co-ordination of UES relaxation with pharyngeal contractions. The LES pressure may be measured by two methods, station pull-through (SPT) and rapid pull-through (RPT). Each method has advantages and limitations. It is, therefore, recommended to perform at least three pull-through measurements with either SPT or RPT, as both methods yield reasonable assessments of LES pressure.[9] Modifications of the equipment or procedure are sometimes indicated in special studies such as simultaneous pH measurements, respiration, heart rate, and acid perfusion studies (Bernstein test). It should be noted that reduction in LES pressure without pH confirmation is not sufficient for the diagnosis of reflux.[10] The pattern

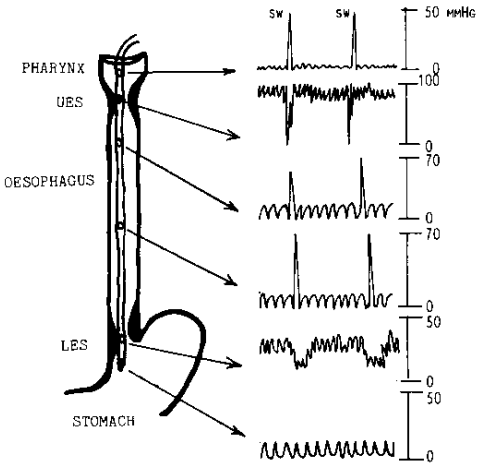

Figure 3. Normal oesophageal manometry recorded simultaneously from the pharynx to the stomach.

of normal manometry is illustrated in Fig. 3. The pharyngeal phase of swallowing is recorded as a single pressure wave of varying amplitude depending on the technique. Upon swallowing and coincident with the pharyngeal spike, the UES relaxes and pressure drops to the baseline oesophageal pressure. Immediately below the UES, the primary peristaltic wave of the oesophageal body can be recorded simultaneously or briefly after UES relaxation. The amplitudes of these waves are 7.98–10.64 kPa (60–80 mmHg), 6.65–9.31 kPa (50–70 mmHg), and 5.32–7.98 kPa (40–60 mmHg) in the distal, proximal and mid-oesophagus respectively. The duration of these waves varies between 2 and 6 s being shortest in the proximal and longest in the distal part of the oesophagus. The basal LES pressure varies from one patient to another, it also varies with time in the same patient. In general, the resting LES pressure averages 1.33–3.99 kPa (10–30 mmHg). Relaxation of the LES usually begins 1.5–2.5 s after the onset of deglutition, it reaches intragastric pressure levels and persists for about 8 s.

Motility Disorders of the Oesophagus

Disorders of oesophageal motility may be primary (affecting only the oesophagus) or secondary when oesophageal involvement is associated with a systemic disease. A tentative classification of these disorders is presented in Table 1.

Achalasia of the oesophagus

This is a rare disorder of unknown cause. The disease affects all age groups although the majority of patients present between the ages of 20 and 40 years. The most common presenting symptom is dysphagia for both liquids and solids. Chest pain and regurgitation may occur, whereas some patients may be diagnosed before symptoms appear when mediastinal widening is detected in a chest X-ray taken for other reasons. Nocturnal asthma-like symptoms and recurrent pneumonia may occur and weight loss becomes evident with worsening of obstruction. Achalasia is characterized by three manometric abnormalities: Increased resting tone of the LES, marked reduction or absence of peristalsis in the oesophageal body, and incomplete to absent relaxation of the LES on swallowing (Fig. 4). Pathologic findings such as absence of myenteric ganglion cells, degenerative changes of nerve fibres, thickening of circular muscle, and decreased number of cells in the dorsal motor nucleus of the vagus, have been described in many patients.[11,12] No relationship, however, was found between basal LES pressure, length, relaxation and histopathologic findings.[13] Treatment of achalasia mainly consists of instrumental dilatation or oesophagomyotomy. However, in the early stages of the disease, medical measures aimed at reduction of LES pressure such as long-acting nitrates and calcium channel blockers may be effective.

Table 1
Classification of oesophageal motility disorders

Primary Motility Disorders
Achalasia, diffuse oesophageal spasm, hypertensive LES, nutcracker oesophagus, non-specific motility disorder
Secondary Motility Disorders
Neurologic disease (central, peripheral), myasthenia gravis, polymyositis, muscular dystrophy, scleroderma, Chagas's Disease, diabetes mellitus, oesophageal atresia
Gastro-oesophageal Reflux

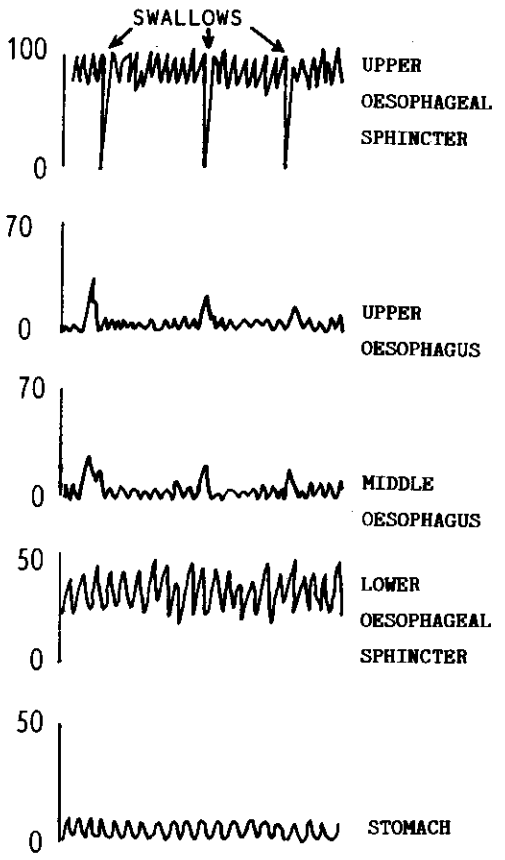

Figure 4. Idiopathic achalasia. Note low amplitude waves, elevated resting LES pressure without relaxation on swallowing.

Diffuse oesophageal spasm (DES)

This functional disorder of oesophageal smooth muscle may occur at any age although it is considered to be more common in patients over 50 years of age. The cause is unknown and symptoms

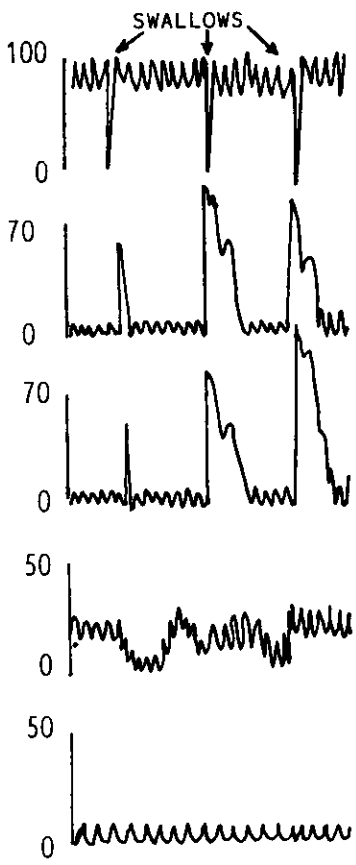

Figure 5. Diffuse oesophageal spasm. The first swallow is normal but the second and third show simultaneous high amplitude, long duration, non-peristaltic waves.

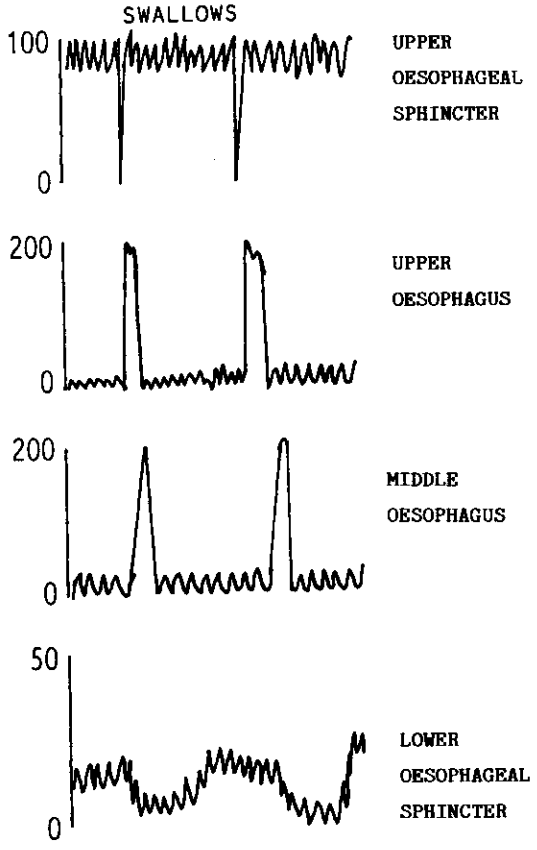

Figure 6. Nutcracker oesophagus. High amplitude, long duration, but peristaltic waves.

consist of episodic pressure like chest pain that may mimic coronary artery disease. Dysphagia for liquid and solids may also be intermittent. Barium studies of the oesophagus may show segmental contraction in advanced cases, resulting in a picture called corkscrew oesophagus. Manometry reveals the following motility disorders. (1) Simultaneous contractions (non-peristaltic) occurring in more than 10% of wet swallows. This is the most important finding. (2) Other findings include high amplitude contractions of more than 23.94 kPa (180 mmHg), repetitive contractions ($\geqslant$3 peaks), and prolonged duration (>6 s). The LES is usually normal and relaxes with swallows although this relaxation may be incomplete (Fig. 5). Therapeutic measures include reassurance that chest pain is not of cardiac origin, antacids when reflux is associated with DES, nitrates, or calcium channel blockers. Surgical measures such as pneumatic dilatation and myotomies are rarely required.

The nutcracker oesophagus

This entity is defined by markedly increased amplitudes of oesophageal contraction usually between 29.93–57.19 kPa (225–430 mmHg). These waves are peristaltic contrasting with the non-peristaltic waves in DES (Fig. 6). Patients usually complain of dysphagia and chest pain and many of them have positive responses to provocative tests (Tensilon, Bernstein tests). Other patients may have features of other motility disorders such as achalasia or DES. Furthermore, patients with this disorder may have lower intestinal complaints or a psychological profile suggestive of irritable bowel syndrome.[14-16] The diagnosis is confirmed by manometry and treatment modalities are similar to those used in DES.

Hypertensive lower oesophageal sphincter

In some patients with dysphagia or chest pain, isolated increased LES pressure has been found. Manometric criteria for the diagnosis of this entity are increased LES pressure of more than 5.99 kPa (45 mmHg)

with normal relaxation and absence of other motility abnormalities. It should be emphasized, however, that most patients with raised LES pressures have additional motility abnormalities. Therapy consists of reducing the LES pressure by medical means.

Non-specific oesophageal motility disorders (NEMD)

Patients with symptoms such as dysphagia, chest pain, and abnormal manometric findings that do not fit in any of the well known primary motility disorders. The most common motility abnormality is probably high amplitude, long duration but normally transmitted waves. The cause of this entity as well as the benefits of medical treatment remain unknown.

Scleroderma (progressive systemic sclerosis)

This disease is characterized by involvement of several systems by fibrosis and clinically manifests itself by tightness of the skin and Raynaud's phenomenon. Oesophageal motility disorders, presenting as intermittent dysphagia, are found in about 70% of the cases and may precede the other manifestations. Scleroderma occurs in all age groups although the disease is considered rare in children.[17] Pathological changes are limited to the distal smooth muscle of the oesophagus and consist of increased collagen in the lamina propria and submucosa with atrophy of the muscularis propria.[18] Barium swallow may show delayed emptying of the lower oesophagus, distal oesophagitis or ulcerations and stricture formation. In later stages, the radiologic picture is similar to achalasia. Endoscopy may reveal hypoperistaltism, oesophagitis and patulous LES. Manometry is, however, more sensitive and findings characteristic of scleroderma include marked reduction or absence of peristaltic activity in the lower oesophagus associated with marked decrease or loss of LES pressure (Fig. 7). The basic disease process is not reversible. Treatment is aimed at oesophagitis if present.

Other collagen vascular diseases such as systemic lupus erythematosus, polymyositis, and mixed connective tissue diseases, rheumatoid arthritis and Sjogren's syndrome may have a variety of oesophageal motility disorders. Similarly, diabetes mellitus, Chagas's disease, and chronic intestinal pseudo-obstruction may be associated with secondary motility disorders.

Cricopharyngeal dysphagia

Systemic disorders affecting the striated muscle of the oesophagus frequently affect the muscles of the pharynx and oral cavity, disturbing the co-ordination of events of deglutition. Consequently,

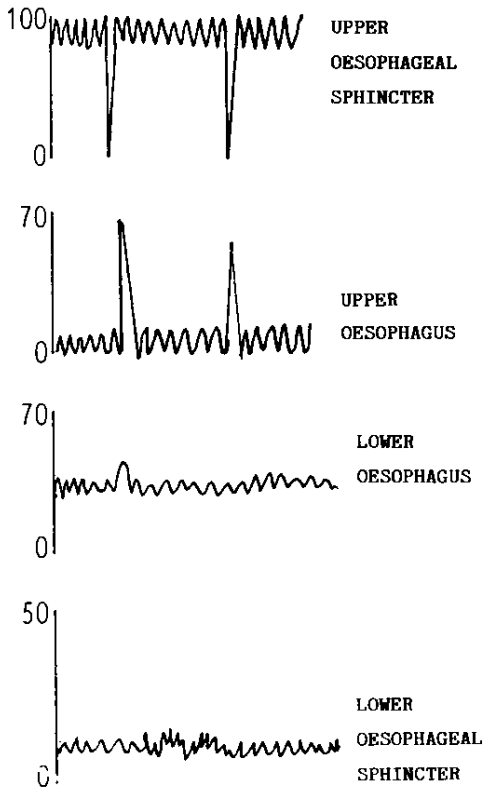

Figure 7. Scleroderma. Normal upper oesophageal peristalsis, but low to absent lower oesophageal peristalsis and low to absent LES tone.

these disorders may be associated with vomiting, dysphagia with difficulty in initiating a swallow, cough or aspiration after swallowing, nasal or oral regurgitation, and dysarthria. These symptoms may be part of a central nervous system disease such as various congenital abnormalities in infants (microcephaly, cerebropalsy, meingomyelocele), familial dysautonomia, or acquired diseases such as cerebral vascular accidents. In addition, cricopharyngeal dysphagia may be caused by diseases of peripheral nerves, or of the neuromuscular junction such as myasthenia gravis or disease of striated muscles such as polymyositis and muscular dystrophies. Abnormal swallowing associated with these diseases is best revealed by cineradiography of the swallowing act. This study may reveal difficulty in initiating swallows, prolonged propulsion of the bolus because of muscle weakness, deviation of the barium column to one side, pharyngeal stasis or dilatation and outpouching, pooling of the barium in the pharynx, and nasal or tracheal aspiration of barium. Manometry, however, may

be more sensitive in the detection of UES dysfunction which may be found as an isolated abnormality such as UES achalasia or premature closure leading to cricopharyngeal incoordination and dysphagia.

Gastro-oesophageal reflux (GER)

The LES is one of the most important factors that prevent the reflux of gastric content into the oesophagus. Reduction in the resting LES pressure, transient LES relaxation and inappropriate response of the LES to increased intra-abdominal pressure are important in the genesis of reflux. Oesophageal peristalsis is one of the most important mechanisms in the prevention of peptic oesophagitis. Primary peristalsis associated with swallowing clears the oesophagus of any refluxed material. However, secondary peristalsis which may be induced by the refluxed material is an important mechanism of oesophageal clearance during sleep. Abnormal motility including defective secondary waves has been found in many patients with GER and oesophagitis. It is still unclear, however, whether these abnormalities are the cause or the effect of oesophagitis.

References

[1]Gates GA. Upper esophageal sphincters: Pre and post-laryngectomy, a normative study. *Laryngoscope* 1980; **90**: 454–464.

[2]Meyer GW, Austin RM, Brady CE, *et al.* Muscle anatomy of the human esophagus. *J Clin Gastroenterol* 1986; **8**: 131–134.

[3]Gryboski JD. The swallowing mechanism of the neonate, esophageal and gastric motility. *Pediatrics* 1965; **35**: 445–452.

[4]Goyal RK, Cobb BW. Motility of the pharynx, esophagus, and esophageal sphincters. In: Johnson LR, ed. *Physiology of the gastrointestinal tract*. New York: Raven Press, 1981.

[5]Weisbrodt NE. Neuromuscular organization of esophageal and pharyngeal motility. *Arch Intern Med* 1976; **136**: 524–531.

[6]Ott DJ, Wu WC, Gelfand DW. Efficacy of radiology of the esophagus for evaluation of dysphagia. *Gastrointest Radiol* 1981; **6**: 109–110.

[7]Decaestecker JS, Blackwell JN, Adam RD, *et al.* Clinical value of radionuclide esophageal transit measurement. *Gut* 1986; **27**: 659–666.

[8]Mughal MMM, Marples M, Bancewicz J. Scintigraphic assessment of esophageal transit measurement. *Gut* 1986; **27**: 946–953.

[9]Dodds WJ, Hogan WJ (Editorial). Measurement of LES pressure. *Gastroenterology* 1980; **79**: 588–591.

[10]Pope CE (Editorial). Is LES enough? *Gastroenterology* 1976; **71**: 328–329.

[11]Casella RR, Brown AL, Sayre GB, Ellis FH Jr. Achalasia of the esophagus: Pathologic and etiologic considerations. *Ann Surg* 1968; **160**: 474–487.

[12]Casella RR, Ellis FH Jr, Brown AL. Fine structure changes in achalasia of the esophagus: I. Vagus nerves. *Am J Pathol* 1965; **46**: 279–288.

[13]Csendes A, Smok G, Braghetto I, *et al.* Gastro-esophageal sphincter pressure and histological changes in the distal esophagus in patients with achalasia of the esophagus. *Dig Dis Sci* 1985; **30**: 941–945.

[14]Clouse RE, Eckert TC. Gastrointestinal symptoms of patients with esophageal contraction abnormalities. *Dig Dis Sci* 1986; **31**: 236–240.

[15]Clouse RE, Lustman PJ. Psychiatric illness and contraction abnormalities of the esophagus. *N Eng J Med* 1983; **309**: 1337–1342.

[16]Richter JE, Obrecht F, Bradley LA, *et al.* Psychological comparison of patients with nutcracker esophagus and irritable bowel syndrome. *Dig Dis Sci* 1986; **31**: 131–138.

[17]Dabich L, Sullivan DB, Cassidy JT. Scleroderma in the Child. *J Pediatr* 1974; **85**: 770–775.

[18]D'Angelo WA, Fries JF, Masi AT, *et al.* Pathologic observation in systemic sclerosis (scleroderma). *Am J Med* 1969; **46**: 428–440.