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Esophageal Motor Disorders

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Introduction

This review summarizes important recent advances in the areas of esophageal motility and motility disorders. Several studies in 1996 have examined the central and enteric neural control of swallowing. The technique of transcranial magnetic stimulation has increased the understanding of the cortical control of swallowing in conscious human subjects. Studies of the chemical coding of the enteric nerves that regulate esophageal motility continued to focus on the important role of nitric oxide. Achalasia and gastroesophageal reflux disease are the two motility disorders that received the most attention in the recent literature. Several studies on the treatment of achalasia evaluated the effectiveness of intrasphincteric botulinum toxin and laparoscopic myotomy. Other studies examined the mechanisms of the transient lower esophageal sphincter relaxations that are responsible for gastroesophageal reflux disease and the utility of manometric testing in the evaluation of this disorder.

Central Nervous System Control of Swallowing

It has been known for a long time that swallowing reflex is regulated by cortical neurons. However, details of the cortical areas controlling the swallowing muscles and the plasticity of the cortical neurons in controlling swallowing in cerebral lesions has not been clearly understood. Hamdy and Aziz utilized transcranial magnetic stimulation as a

noninvasive method to focally stimulate regions of the cerebral cortex to evoke activity in different swallowing muscles [1,2,3]. Twenty healthy subjects and two stroke patients were included in the study. The magnetic stimulation did not induce a complete swallowing sequence but permitted the mapping of populations of cortical neurons that evoked activity in swallowing muscles that included the right and left mylohyoid muscle, pharyngeal muscles and striated muscles of the esophagus. The results revealed bilateral but asymmetric representations of these muscles to different areas on the motor and premotor cortex. No relationship was found between right or left handedness and the lateralization of the cortical representations. Plasticity of the cortical neurons controlling swallowing was illustrated by one of the stroke patients who presented with severe pharyngeal dysphagia. This patient was found to have a doubling in the size of the pharyngeal representation on the unaffected hemisphere coinciding with the complete recovery of swallowing function. This finding suggest that improvement in dysphagia after a unilateral stroke is due to compensation by cortical neurons on the contralateral hemisphere.

Enteric Nervous System Control of Swallowing

The chemical nature of enteric nerves that are involved in esophageal peristalsis and lower esophageal sphincter tone, relaxation and contraction remain incompletely understood. Two animal studies examined the chemical coding of the enteric nerves innervating the esophageal muscle. The first study by Christensen et al. [4] looked at the density of various nerve fibers along the length of the opossum esophageal body and

compared the distributions in the circular and longitudinal muscles and muscularis mucosa. Nerve fibers were stained for NADPH diaphorase and for immunoreactivity to vasoactive intestinal polypeptide, calcitonin gene-related peptide, galanin and substance P and constitutive nitric oxide synthase (cNOS). As expected, cNOS immunoreactivity colocalized with NADPH-diaphorase activity. The peptide containing nerves displayed similar densities at different levels of the esophagus. The density of NADPH-diaphorase fibers in the circular muscle layer, however, decreased from the proximal esophagus to the region of the lower esophageal sphincter (LES). In both the longitudinal muscle and muscularis mucosa, the opposite density gradient was found with the highest concentration of NADPH-diaphorase fibers localized in the region of the distal esophagus and LES. These studies show regional differences in the nitrergic innervation in the esophagus. However, the physiological relevance of these observations remains unclear.

The second study by Brookes et al [5] utilized a technique for retrograde labeling of intramural motor neuronal cell bodies innervating the LES of the guinea pig with subsequent identification of their chemical nature. The region of the LES appeared to have majority of neurons that were choline acetyltransferase immunoreactive with some NOS immunoreactive neurons. In contrast, inhibitory, NO synthase immunoreactive neurons localized primarily in the esophageal body. A different population of motor neurons located in the gastric body innervated the oblique muscle layer of the lower esophageal sphincter. Again, the physiological implications of the distinct distributions of inhibitory and excitatory enteric neurons that innervate the different muscle regions remain to be elucidated.

Developmental Disorders of Esophageal Motility

Recently a number of motility disorders have been linked to developmental disorders of the enteric nervous system [6]. Congenital esophageal stenosis is a rare disorder characterized by a concentric narrowing and aperistalsis of the entire esophagus. The pathogenesis of this disorder is not been clear. Recently, a study of 2 young adults with congenital esophageal stenosis showed a significant reduction in the NADPH-diaphorase and NOS immunoreactivity with preservation of other peptidergic neurons within the myenteric plexus and circular muscle nerve fibers in the esophagi of these patients [7]. Enteric innervation of the LES was unaffected. These findings suggest that congenital diminution of inhibitory innervation may be important in the pathogenesis of this disorder. Another recent study examined the esophageal motility patterns in healthy premature infants [8]. Non peristaltic motor patterns that included synchronous and incomplete esophageal body contractions were found to be almost three times more common than peristaltic motor patterns. Further studies are needed to establish that such abnormalities are related to immaturity of the either the central or enteric neural control of esophageal peristalsis.

Pathology of Achalasia

The neuropathology of achalasia and differences in the neural lesions in classical achalasia and vigorous achalasia has been investigated in esophagi from patients undergoing surgical myotomies. Wattchow and Costa [9] examined the

immunoreactivity to substance P, neuropeptide Y, vasoactive intestinal peptide, enkephalin and neuron specific enolase. Similar to the findings of earlier histopathological studies, very few nerve fibers were seen in the circular and longitudinal muscle layers and the majority of specimens demonstrated aganglionosis of the myenteric plexus. Within the myenteric plexus, however, a number of neuropeptide Y-reactive perivascular nerve fibers were found. This finding shows that the extrinsic nerve supply is preserved in patients with achalasia. In another study, Goldblum et. al. [10] examined the histopathological features in patients with classical achalasia and vigorous achalasia. These authors observed that 3 patients with vigorous achalasia had normal numbers of ganglion cells and absent fibrosis of the myenteric plexus whereas in 8 patients with classic achalasia had diminished to absent ganglia with neural fibrosis of the myenteric plexus. These observations are consistent with the view that vigorous achalasia is an earlier stage of disease from classic achalasia.

Treatment of Achalasia

Several studies in 1996 focused on the treatment of achalasia. Pneumatic dilation remains the most commonly used treatment for this disorder. Wong et. al. [11] performed a prospective evaluation of a variety of postpneumatic dilation parameters to assess which of these parameters might predict long-term outcome. 29 patients were included and treated with graduated pneumatic dilation with Hurst-Tucker dilators. None of the parameters studied, which included severity of pain during dilation, amount of blood on the dilator, insufflation pressures and esophageal emptying of gastrografffin or

barium, were predictive of long-term outcome. A second study retrospectively examined the results of 50 pneumatic dilations [12]. Two cases (4%) of transmural perforation occurred as well as 4 cases (8%) of mucosal tears. The latter complications were managed conservatively with intravenous antibiotics and observation. A perforation rate of 12 % is higher than generally reported in the literature. A third study retrospectively reviewed 60 patients treated with transthoracic myotomy and found that preoperative pneumatic dilation with or without perforation had no adverse effect on the postoperative outcome [13].

As reviewed by Oddsdottir [14], the surgical treatment for achalasia continues to move toward the laparoscopic approach to myotomy. Raiser et. al. reported on 39 patients with achalasia treated successfully with either thoracoscopic or laparoscopic Heller myotomy [15]. 10 patients underwent a Heller-Dor and 29 a Heller-Toupet operation. At a mean follow up of 26 months, dysphagia was present in 33 % of patients after the Heller-Toupet and 71% after the Heller-Dor operation. Heartburn was present in 27 % of patients after the Heller-Toupet and 57 % of patients after the Heller-Dor operation. These figures are substantially higher than those reported from other centers and could reflect earlier experience with the laparoscopic approach or inclusion of milder degrees of symptoms.

Meshkinpour [16] examined the issue of quality of life in patients treated for achalasia. Prior studies have noted success rates of over 90 % for both treatments with mean follow up periods of 4-5 years. In the present study, 52 patients treated with either pneumatic dilation or cardiomyotomy were studied by questionnaire. 52 % of the patients experienced dysphagia at least once a week with 34 % having dysphagia daily.

56% of patients reported modifying their diet and the residual symptoms were noted to have an impact on patients' lifestyles. This study suggests that there is a significant underreporting of residual symptoms in many patients treated for achalasia. Another preliminary study reported similar findings. 36 % of patients treated with pneumatic dilation and 23 % of patients treated with surgical myotomy had symptomatic recurrences but did not seek medical attention [17]. Both aperistalsis of the esophageal body and an incomplete myotomy could account for the persistence of dysphagia following treatment.

Botulinum Toxin

The newest potential treatment option for patients with achalasia, botulinum toxin A, continues to generate interest. Botulinum toxin A is a neurotoxin that inhibits the release of acetylcholine from nerve endings. The toxin has been used to provide relief for a variety of skeletal muscle spastic disorders such as strabismus and hemifacial spasm. The use of the drug in such disorders has been limited by the need for repeated injections every few months and the declining effectiveness of repeated injections possibly due to the development of blocking antibodies. The group at Johns Hopkins was the first to apply botulinum toxin in the treatment of achalasia, a neural disorder affecting smooth muscle. This form of endoscopic therapy is certainly easier to perform and less invasive than conventional treatments. The long-term follow up data from the group at Johns Hopkins reported on the results in 31 patients with achalasia treated with 80 units of botulinum toxin [18]. 20 patients had an initial symptomatic response lasting more than 3 months. Patients over the age of 50 and patients with vigorous achalasia (defined by

the presence of esophageal body contractile waves with amplitudes greater than 40 mm Hg) had significantly greater initial response rates. 19 of the initial 20 responders, however, had a relapse after a mean of 468 days. Of these 19 patients, 15 were treated with additional botulinum toxin injections. 9 of the 15 had a second remission. Thus overall, only 9 out of the initial 31 patients were kept in symptomatic remission using botulinum toxin. In a second study, Fishman et al treated 60 patient with idiopathic achalasia with botulinum toxin [19]. At one month, 42 (70%) of patients had a clinical response defined as a greater than or equal to 50% decrease in a symptom score. The differences in age and esophageal body contractile amplitudes were not statistically significant when comparing the responders and non-responders. Of the 33 patients followed for greater than 1 year, 12 (36%) maintained a good to excellent response. 12 patients received repeat injections with responses in 7.

Several issues are raised by the use of botulinum toxin for the treatment of achalasia. As the above studies illustrate, the majority of patients do not have sustained responses. For the patients who do respond, therapy for achalasia utilizing botulinum toxin would therefore require repeated injections, the efficacy and safety of which are not well established. Furthermore, although the initial symptomatic responses to botulinum toxin have been impressive, the effects on physiologic parameters such as LES pressure and esophageal retention have not been similarly impressive. In preliminary reports of randomized trials, pneumatic dilation has been more effective than botulinum toxin [20,21].

Two studies examined the use of botulinum toxin for swallowing or motility disorders other than achalasia where treatment options are quite limited. In the first study, 15 patients with diffuse esophageal spasm with LES dysfunction, isolated LES dysfunction or non specific esophageal motor disorders with or without LES dysfunction underwent endoscopic injection of botulinum toxin into the LES [22]. At one month, 11 patients had good to excellent improvement in chest pain, dysphagia or regurgitation. At a mean follow up of 10.6 months, 33 % had sustained responses. In the second study, botulinum toxin was used in 5 patients with dysphagia and a narrowed pharyngoesophageal segment following total laryngectomy [23]. These patients had received either preoperative or postoperative radiation therapy as well. Patients were selected for treatment with botulinum toxin based on an initial symptomatic response to injection into the pharyngoesophageal segment with lidocaine as a means of differentiating a stricture from spasm. Four of the five patients injected who responded to lidocaine and went onto receive botulinum toxin had clinical improvement in swallowing.

Mechanisms of Gastroesophageal Reflux Disease

The majority of episodes of gastroesophageal reflux in both normal subjects and patients with reflux esophagitis occur during neurally mediated, transient lower esophageal sphincter relaxations or TLESRs. Gastric distension and pharyngeal stimulation have been proposed as possible afferent nerve sites that trigger the TLESR. Trifan et. al. examined the effects of pharyngeal stimulation with water using volumes

below the threshold for stimulation of a swallow [24]. Such stimuli were found to induce a long duration LES relaxation that mimicked the pattern seen with TLESRs. In addition, such stimuli inhibited the progression of primary esophageal peristalsis. However, in a second study, crural diaphragm inhibition and gastroesophageal reflux were found to be infrequent events following subthreshold pharyngeal stimulation [25]. These observations suggest that the pharynx may not be the major trigger site for TLESR.

TLESRs can be distinguished from swallow-induced LES relaxations by the absence of pharyngeal contractions during TLESRs and the long duration of TLESRs, usually greater than 10 seconds. Another important difference was found by Sifrim et. al. in their study of the effect of spontaneous TLESRs on the esophageal body [26]. During normal primary peristalsis, a wave a descending inhibition precedes the sequential contractions of the esophageal body and initiates the relaxation of the LES. This inhibition can be detected by creating an artificial high-pressure zone in the esophageal body. Utilizing this technique, these authors found that TLESRs were not associated with inhibition of the esophageal body. Thus TLESRs can be distinguished from swallow induced LES relaxations by the absence of inhibitory neural activity in the esophageal body. This finding suggests that distinct inhibitory neural pathways are activated by TLESRs and swallowing induced LES relaxations.

Esophageal Motility Testing and Gastroesophageal Reflux Disease

In 1996, two papers reviewed the clinical use of esophageal [27,28]. Esophageal manometry is thought to have a limited role in predicting the response of gastroesophageal reflux to medical treatment [28]. A recent study by Cucchiara et al. [29]

examined the predictive value of manometry for the clinical and endoscopic response to medical therapy in 42 children with varying degrees of GERD. Children who were found to be refractory to an 8 week treatment combining cisapride and ranitidine were found to have significantly reduced LES basal pressures and peristaltic contraction amplitudes and significantly increased rates of TLESRs compared with the children who responded to therapy. This study suggests that the severity of the underlying motility disorder may be predictive of response to medical therapy. At the present time, however, choice of therapy continues to be based upon symptomatic response and endoscopic findings.

Preoperative esophageal manometry is often used in the evaluation for reflux surgery to exclude the presence of achalasia or diffuse esophageal spasm that could be worsened by a fundoplication. Additionally, the degree of fundoplication is sometimes modified based on the presence of impaired esophageal peristalsis. Slim et al prospectively examined the utility of intraoperative manometry for assessing the response of 48 patients to fundoplication [30]. They found that two patients who developed dysphagia following fundoplication had significantly higher increases in intraoperative LES pressure. The one patient who developed recurrent GERD had the lowest intraoperative LES pressure. If confirmed by further studies, these findings would suggest that intraoperative manometric studies could help predict the occurrence of these important postfundoplication complications. Another study of 118 patients undergoing fundoplication for GERD examined the effect of the surgery on respiratory symptoms [31]. Respiratory symptoms were found in 53 % of patients and fundoplication relieved the symptoms in 76%. Abnormalities of esophageal motility that included diminished

contraction amplitudes, incomplete peristalsis and simultaneous esophageal contractions were found to be significantly more common in patients who had persistent post operative respiratory symptoms.

Other esophageal motor disorders

Achalasia may be secondary to a variety of disorders that include Chagas' disease, paraneoplastic syndromes, Parkinson's disease, Allgrove's syndrome and MEN-2B [6]. A case reported in 1996 noted the occurrence of achalasia in a 66 y.o. patient with post polio syndrome [32]. Another case reported on a 40 y.o. woman with sarcoidosis who presented with liquid and solid dysphagia and frequent simultaneous contractions and failed peristaltic sequences with incomplete LES relaxation [33]. In the latter case, the dysphagia and esophageal dysmotility normalized following treatment with prednisone.

Patients with Parkinson's disease can present with dysphagia due to more than one problem. Oropharyngeal dysphagia is the most common deficit but esophageal motor abnormalities resembling achalasia have been reported as well. In a study of 19 patients with Parkinson's disease, the majority of patients showed oral and pharyngeal dysfunction even in the absence of symptoms of dysphagia [34]. Impaired pharyngeal bolus transport was the primary factor associated with dysphagia although both decreased upper esophageal sphincter opening and incomplete UES relaxation were seen as well.

Several studies in 1996 reported on the results of manometric studies in a variety of miscellaneous esophageal disorders. A study patients with chronic alcoholism found elevated esophageal body peristaltic contraction amplitudes in the middle third of the esophagus as well as elevated lower esophageal sphincter pressures [35]. These motility abnormalities normalized in patients who abstained from alcohol. The clinical significance of these findings is unclear. Esophageal motility was studied in a series of patients at a mean of 13 years after sodium hydroxide ingestion [36]. Although none of the patients had dysphagia, the majority demonstrated non-specific motor abnormalities with non-peristaltic contractions being the most common pattern seen. Another study examined the radiographic, endoscopic and motility effects of mediastinal radiation in eight patients with non-esophageal malignancies [37]. No structural or motility abnormalities were found by these techniques to explain the patients' symptoms of dysphagia or odynophagia. To examine whether stress induced motility disturbances can explain the common perception that stress induces heartburn, Johnston et. al. performed motility studies in a series of patients subjected to psychological and physical stress (cold pressor test) [38]. Neither form of stress induced significant changes in esophageal motility. And finally, in a study of patients with non-cardiac chest pain, hyperventilation significantly decreased the mean distal esophageal peristaltic amplitude and duration and induced simultaneous and non-transmitted esophageal body contractions in some patients [39]. These motility abnormalities were not associated temporally with symptoms of chest pain.

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REFERENCES

1. **Aziz Q, Rothwell JC, Barlow J, Thompson DG: **Modulation of Esophageal Responses to Magnetic Stimulation of the Human Brain by Swallowing and by Vagal Stimulation.** *Gastroenterology* 1995, **109**:1437-1445.
2. **Aziz Q, Rothwell JC, Hamdy S, Barlow J, Thompson DG: **The Topographic Representation of Esophageal Motor Function on the Human Cerebral Cortex.** *Gastroenterology* 1996, **111**:855-862. Clinical investigation of 10 healthy subjects using transcranial magnetic stimulation of the cerebral cortex with recordings of electromyographic activity in the proximal esophagus. This technique allows non-invasive mapping regions of the cortex that innervate various striated muscles involved in swallowing.
3. **Hamdy S, Aziz Q, Rothwell JC, Singh KD, Barlow J, Hughes DG, Tallis RC, Thompson DG: **The cortical topography of human swallowing musculature in health and disease.** *Nature Med* 1996, **2**:1217-1224. Clinical investigation of 20 healthy subjects and 2 stroke patients using transcranial magnetic stimulation of the cerebral cortex with recordings of electromyographic activity in the pharynx and proximal esophagus.
4. *Christensen J, Fang S, Rick GA: **NADPH-diaphorase-positive nerve fibers in smooth muscle layers of opossum esophagus: gradients in density.** *J Auton Nerv Syst* 1995, **52**:99-105. Nitric oxide producing nerve fibers showed different patterns of distribution at different levels of the esophagus and among the different smooth muscle layers.
5. *Brookes SJH, Chen BN, Hodgson WM, Costa M: **Characterization of Excitatory and Inhibitory Motor Neurons to the Guinea Pig Lower Esophageal Sphincter.** *Gastroenterology* 1996, **111**:108-117. Immunohistochemical study demonstrating distinct patterns of excitatory and inhibitory innervation to the LES.
6. Goyal RK, Hirano I: **The Enteric Nervous System.** *New England Journal of Medicine* 1996, **334**: 1106-1115.
7. *Singaram C, Sweet MA, Gaumnitz EA, Cameron AJ, Camilleri M: **Peptidergic and Nitrinergic Denervation in Congenital Esophageal Stenosis.** *Gastroenterology* 1995, **109**:275-281. Immunohistochemical study of 2 patients with congenital esophageal stenosis showing reduction in the number of nitric oxide producing myenteric neurons. This finding has important implications for the pathogenesis of this disorder.
8. Omari TI, Miki K, Fraser R, Davidson G, Haslam R, Goldsworthy W, Bakewell M, Kawahara H, Dent J: **Esophageal Body and Lower Esophageal Sphincter Function in Healthy Premature Infants.** *Gastroenterology* 1995, **109**:1757-1764. Micromanometric studies in 27 premature infants showing a predominance of nonperistaltic sequences.

9. Wattchow DA, Costa M: **Distribution of peptide containing nerve fibres in achalasia of the oesophagus.** *J Gastroenterol Hepatol* 1996, **11**:478-485. Evidence that extrinsic nerve fibers to the esophagus are preserved in achalasia.
10. Goldblum JR, Rice TW, Richter JE: **Histopathologic Features in Esophagomyotomy Specimens From Patients With Achalasia.** *Gastroenterology* 1996, **111**:648-654. Pathologic features differed between patients with classic achalasia and vigorous achalasia.
11. Wong RKH, Maydonovitch C: **Utility of Parameters Measured during Pneumatic Dilation as Predictors of Successful Dilation.** *Am J Gastroenterol* 1996, **91**:1126-1129. The degree of pain, amount of blood on the dilator and inflation pressure during pneumatic dilation did not predict long term treatment outcome in patients with achalasia.
12. Molina EG, Stollman N, Grauer L, Reiner DK, Barkin JS: **Conservative Management of Esophageal Nontransmural Tears After Pneumatic Dilation for Achalasia.** *Am J Gastroenterol* 1995, **91**:15-18. Retrospective review of 50 pneumatic dilations reporting transmural perforation in 2 patients and non-transmural mucosal tears in 4 patients.
13. Ferguson MK, Reeder LB, Olak J: **Results of Myotomy and Partial Fundoplication after Pneumatic Dilation for Achalasia.** *Ann Thorac Surg* 1996, **62**:327-330. Retrospective study of 60 patients who underwent transthoracic myotomy and fundoplication showing that outcome was unaffected by previous pneumatic dilation or perforation from dilation.
14. Oddsdottir M: **Laparoscopic Management of Achalasia.** *Surg Clin N America* 1996, **76**:451-459. Review of the use of laparoscopic myotomy for achalasia.
15. Raiser F, Perdikis G, Hinder RA, Swanstrom LL, Filipi CJ, McBride PJ, Katada N, Neary PJ: **Heller Myotomy via Minimal-Access Surgery.** *Arch Surg* 1996, **131**:593-598. Results of thoracoscopic or laparoscopic myotomy in 39 patients with achalasia.
16. Meshkinpour H, Haghighat P, Meshkinpour A: **Quality of Life among Patients Treated for Achalasia.** *Dig Dis Sci* 1996, **41**:352-356. Study showing that the majority of patients with achalasia treated with either pneumatic dilation or surgery continued to have varying degrees of dysphagia.
17. Torbey CF, Achkar E, Rice T, Baker M, Richter JE: **The Longterm Outcome of Achalasia Treatment: How Well are we Really Doing?**. *Gastroenterology* 1996, **110**: A279.
18. *Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN: **Botulinum Toxin for Achalasia: Long-term Outcome and Predictors of Response.** *Gastroenterology* 1996, **110**:1410-1415. Follow up results by the Hopkins' group on the use of botulinum toxin for the treatment of achalasia in 31 patients. 20 patients had a sustained response beyond 3 months but 19 of these patients relapsed after a median duration of 468 days. 9 patients of the original 31 were kept in symptomatic remission with repeated injections of toxin. Advanced age and vigorous achalasia were predictors of response to botulinum toxin.
19. Fishman VM, Parkman HP, Schiano TD, Hills C, Dabezies MA, Cohen S, Fisher RS, Miller LS: **Symptomatic Improvement in Achalasia After Botulinum Toxin**

Injection of the Lower Esophageal Sphincter. *Am J Gastroenterol* 1996, **91**:1724-1730. Results of botulinum toxin in 65 patients with achalasia.

20. Gaudric M, Guimbaud R, Chaussade S. Palazzo L, Quartier G, Samama J, Danel B, Couturier D: **Pneumatic Dilatation versus Intrasphincteric Botulinum Toxin in the Treatment of Achalasia: Preliminary Results of a Controlled Study**. *Gastroenterology* 1996, **110**: A667.
21. Bansal R, Koshy S, Scheiman JM, Barnett JL, Nostrant TT: Interim Analysis of a Randomized Trial of Witzel **Pneumatic Dilatation vs. Intrasphincteric Injection of Botulinum Toxin for Achalasia**. *Gastroenterology* 1996, **110**: A56.
22. Miller LS, Parkman HP, Shiano TD, Cassidy MJ, Ter RB, Dabezies MA, Cohen S, Fisher RS: **Treatment of Symptomatic Nonachalasia Esophageal Motor Disorders with Botulinum Toxin Injection at the Lower Esophageal Sphincter.** *Dig Dis Sci* 1996, **41**:2025-2031. Botulinum Toxin injection into the gastroesophageal junction in 15 patients with spastic esophageal motor disorders other than achalasia led to symptomatic improvement.
23. Crary MA, Glowasky AL: **Using Botulinum Toxin A to Improve Speech and Swallowing Function Following Total Laryngectomy.** *Arch Otolaryngol Head Neck Surg* 1996, **122**:760-763. Botulinum toxin injection into the pharyngoesophageal segment led to improvement in 4 of 5 patients with dysphagia following laryngectomy.
24. *Trifan A, Ren J, Arndorfer R, Hofmann C, Bardan E, Shaker R: **Inhibition of Progressing Primary Esophageal Peristalsis by Pharyngeal Water Stimulation in Humans.** *Gastroenterology* 1996, **110**:419-423. This study in healthy subjects showed that sensory stimulation of the pharynx induced by the injection of small volumes of water inhibited the progression of primary esophageal peristalsis. The authors propose this as a mechanism of failed esophageal peristalsis.
25. *Mittal RK, Chiareli C, Liu J, Shaker R: **Characteristics of Lower Esophageal Sphincter Relaxation Induced by Pharyngeal Stimulation with Minute Amounts of Water.** *Gastroenterology* 1996, **111**:378-384. Incomplete pharyngeal stimulation has been proposed as a stimulus for TLESRs. Previous work by the same group showed that pharyngeal stimulation using small volumes of water could induce long duration LES relaxation without triggering a swallow, thus mimicking a TLESR. This study, however, showed that the majority of such LES relaxations are not associated with either inhibition of the crural diaphragm or acid reflux.
26. *Sifrim D, Janssens J, Vantrappen G: **Transient Lower Esophageal Sphincter Relaxations and Esophageal Body Muscular Contractile Response in Normal Humans.** *Gastroenterology* 1996, **110**:659-668. A study in 10 healthy subjects showing that spontaneous TLESRs are not accompanied by inhibition of the esophageal body as detected by creation of an artificial high-pressure zone in the esophagus. This finding suggests important differences in the neural pathway mediating TLESRs and swallow induced LES relaxations.
27. Dent J, Holloway RH: **Esophageal Motility and Reflux Testing**. *Gastro Clin N America* 1996, **25**: 51-73.
28. Ergun GA, Kahrilas PJ: **Clinical Applications of Esophageal Manometry and pH Monitoring**. *Am J Gastroenterol* 1996, **91**:1077-1089.

29. Cucchiara S, Campanozzi A, Greco L, Franco MT, Emiliano M, Alfieri E, Calabrese F, Numeroso V: **Predictive Value of Esophageal Manometry and Gastroesophageal pH Monitoring for Responsiveness of Reflux Disease to Medical Therapy in Children**. *Am J Gastro* 1996, **91**:680-685. Prospective study in 42 children that found that reduced basal sphincteric pressure, reduced esophageal peristalsis amplitude, higher rates of TLESRs and increased rates of LES pressure drifts were predictive of poor response to treatment with cisapride combined with ranitidine.
30. Slim K, Goulant J, Pezet D, Lechner C, Pelissier E, Delasalle P, Bommelaer G, Chipponi J: **Intraoperative Esophageal Manometry and Fundoplications: Prospective Study**. *World J Surg* 1996, **20**:55-59. Prospective study in 48 patients supporting the use of intraoperative esophageal manometry as predictive of postoperative dysphagia and recurrent gastroesophageal reflux.
31. Johnson WE, Hagen JA, DeMeester TR, Kauer WKH, Ritter MP, Peters JH, Bremner CG: **Outcome of Respiratory Symptoms After Antireflux Surgery on Patients with Gastroesophageal Reflux Disease**. *Arch Surg* 1996, **131**:489-492. Case series of 50 patients with GERD and respiratory symptoms who underwent by fundoplication. Abnormalities of esophageal peristalsis were more common in patients who did not experience relief of respiratory symptoms.
32. Benini L, Sembenini C, Bulighin GM, Polo A, Ederle A, Zambito A, Vantini I: **Achalasia: A Possible Late Cause of Postpolio Dysphagia.** *Dig Dis Sci* 1996, **41**:516-518.
33. Geissinger BW, Sharkey MF, Criss DG, Wu WC: **Reversible Esophageal Motility Disorder in a Patient with Sarcoidosis.** *Am J Gastroenterol* 1996, **91**:1423-1426.
34. Ali GN, Wallace KL, Schwartz R, DeCarle DJ, Zagami AS, Cook IJ: **Mechanisms of Oral-Pharyngeal Dysphagia in Patients with Parkinson's Disease.** *Gastroenterology* 1996, **110**:383-392. Clinical investigation using simultaneous videoradiography and pharyngeal manometry to study the mechanisms of oral-pharyngeal dysphagia in 19 patients with Parkinson's disease.
35. Grande L, Monforte R, Ros E, Toledo-Pimentel V, Estruch R, Lacima G, Urbano-Marquez A, Pera C: **High amplitude contractions in the middle third of the oesophagus: a manometric marker of chronic alcoholism?** *Gut* 1996, **38**:655-662.
36. Dantas RO, Mamede RCM: **Esophageal Motility in Patients with Esophageal Caustic Injury.** *Am J Gastroenterol* 1996, **91**:1157-1161.
37. Yeoh E, Holloway RH, Russo A, Tippett M, Bermingham H, Chatterton B, Horowitz M: **Effects of mediastinal irradiation on oesophageal function.** *Gut* 1996, **38**:166-170.
38. Johnston BT, McFarland RJ, Collins JSA, Love AHG: **Effect of acute stress on oesophageal motility in patients with gastro-oesophageal reflux disease.** *Gut* 1996, **38**:492-497.
39. Cooke RA, Anggiansah A, Wang J, Chambers JB, Owen W: **Hyperventilation and Esophageal Dysmotility in Patients with Noncardiac Chest Pain**. *Am J Gastroenterol* 1996, **91**:480-484.