6I.

ESOPHAGEAL ACHALASIA SYNDROMES

INTERNAL MEDICINE GRAND ROUNDS

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INTRODUCTION

The esophagus is a muscular tube which transports ingested materials and secretions from the pharynx to the stomach. The esophagus is approximately 20-22 cm long in adults, extending from just below the upper esophageal sphincter (UES), which is technically a pharyngeal structure, to the caudal end of the lower esophageal sphincter (LES). While most of the esophagus is thoracic (in the posterior mediastinum), its last few centimeters are intra-abdominal just below the esophageal hiatus.

Like the rest of the gut, the esophagus has two muscle layers: an outer longitudinal layer and an inner circular layer. The upper esophagus consists of skeletal muscle in both muscle layers, while the lower esophagus and LES consists of smooth muscle in both layers. The middle third of the esophagus is a transition zone, containing both types of muscle. The mucosa of the esophagus is lined by stratified squamous epithelium. This epithelium is important clinically because it may become inflamed (esophagitis), undergo metaplasia to a columnar-type epithelium (Barrett's esophagus), and/or undergo malignant change (esophageal carcinoma). The irregular junction of the esophageal mucosa and the gastric mucosa (squamo-columnar junction) is usually located approximately 40 cm from the incisor teeth and can be recognized endoscopically ("Z-line").

In addition to the UES (at the junction of the pharynx and esophagus) and the LES (at the junction of the esophagus and stomach), the gastrointestinal tract has other recognized sphincters: the pylorus (at the junction of stomach and duodenum), the sphincter of Oddi (junction of common bile duct and duodenum), the ileocecal sphincter or valve (junction of small intestine and colon) and the anal sphincters (internal and external). Failure of any sphincter to relax normally is referred to as achalasia. Achalasia of the LES is fairly common and will be referred to in this Grand Rounds as *esophageal achalasia* or simply *achalasia*. Esophageal achalasia is also sometimes referred to as *cardiospasm*. Achalasia of the UES (cricopharyngeal achalasia) and achalasia of the internal anal sphincter (Hirschsprung's disease) are well-recognized clinical entities. It is possible that achalasia syndromes involving the pylorus, the sphincter of Oddi, and the ileocecal sphincter will be added to this list as endoscopy-facilitated manometric studies of these sphincters become more and more feasible. There is no apparent relationship between esophageal achalasia and other achalasia syndromes of the gut, such as cricopharyngeal achalasia or Hirschsprung's disease (1). However, one patient with esophageal achalasia and apparent achalasia of the pylorus has been reported (2).

The first case of achalasia was described over 300 years ago by Thomas Willis, an English clinician who first described the network of arteries at the base of the brain (circle of Willis) and the eleventh cranial nerve (spinal accessory nerve or nerve of Willis). Willis also first noted the sweetish taste of diabetic urine and gave the first written accounts of typhoid fever and puerperal fever. In his description of a patient with achalasia, he stated "the mouth of the stomach (i.e., the cardia) being always closed either by a tumour or palsie, nothing could be admitted into the ventricle (i.e., the stomach) unless it were violently opened." Consequently, he devised a dilator of sorts, made of whalebone with a little sponge at the end, with which the patient forced his food into the stomach after eating. This patient was alive and well 15 years later, continuing postprandial dilatation therapy (3). While Willis correctly

suggested that there may be a palsy of the cardia (now recognized as the LES), von Mikulicz in 1881 suggested that spasm of the cardia was present (hence the term cardiospasm). Hurst and Rake in 1929, aware of the ease with which bougies could be passed into the stomach in patients with achalasia questioned the spasm concept and coined the term achalasia, believing that the sphincter was unable to relax normally (3).

To understand the pathophysiology of esophageal achalasia, it is first important to review normal esophageal physiology, both under resting conditions and during peristalsis.

NORMAL ESOPHAGEAL PHYSIOLOGY (4-6)

Resting Conditions. When the normal esophagus is at rest (i.e., not being used for swallowing), there is no motor activity in the body of the esophagus and the LES is closed, occluding the esophageal lumen (Figure 1, left), thus preventing gastroesophageal reflux. There is no histologically identifiable region of the esophageal smooth muscle corresponding to the LES; instead, this 3-4 cm long high pressure zone is defined physiologically (i.e., manometrically). On the average, normal LES pressure is 10-25 mmHg above gastric pressure.

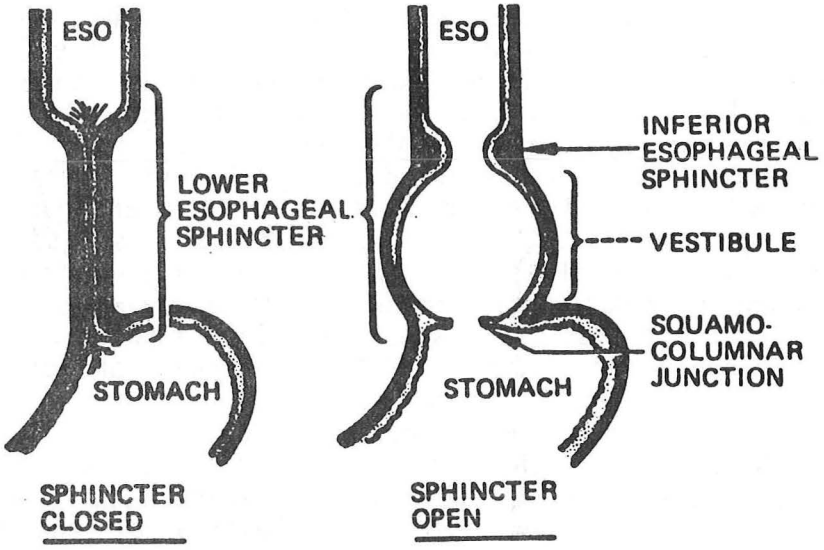

Figure 1. Anatomy of the LES region at rest (sphincter closed) and during swallowing (sphincter open). From ref. 5.

Mechanisms responsible for resting or basal LES pressure have been the subject of considerable investigation and controversy (5). At one time it was believed that hormones (gastrin, e.g.) and/or nerves (vagal or enteric) played a major role in determining resting LES pressure. Although GI hormones and neurotransmitters can alter resting LES pressure, many of these effects are probably pharmacologic and not physiologic. With respect to gastrin, Goyal and

McGuigan showed that a quantity of gastrin antiserum sufficient to bind 85-90% of circulating gastrin had no effect on resting LES pressure in anesthetized opposums in vivo (7), disproving an earlier study by Lipshutz, Hughes, and Cohen (8). Furthermore, resting LES pressure in opposums is not altered by the nerve toxin, tetrodotoxin (9). These observations have gradually led to the concept that resting LES pressure results from the intrinsic myogenic tone of the sphincter smooth muscle. Thus, LES contraction at rest is a property of the muscle per se, although stimulatory and inhibitory nerves and hormones may affect the level of basal tone present. The cellular, biochemical mechanism responsible for contraction of LES smooth muscle cells when the remainder of the esophagus is at rest has yet to be clarified. Smooth myocytes from the LES region do differ from myocytes from the esophageal body ultrastructurally, having larger more centrally located mitochondria and a more developed endoplasmic reticulum (4).

Swallowing and Peristalsis. Under normal conditions, a swallow induces a peristaltic wave in the body of the esophagus (primary peristalsis), at a velocity of approximately 3 cm/second (Figure 2). Repetitive swallowing with short intervals between swallows (< 3 sec) inhibits primary peristaltic contractions until the end of the last swallow, a phenomenon referred to as deglutitive inhibition. Esophageal peristalsis in the smooth muscle portion of the esophagus can also be triggered by esophageal distention even in the absence of swallowing (secondary peristalsis); this mechanism may facilitate esophageal emptying when gastroesophageal reflux has occurred.

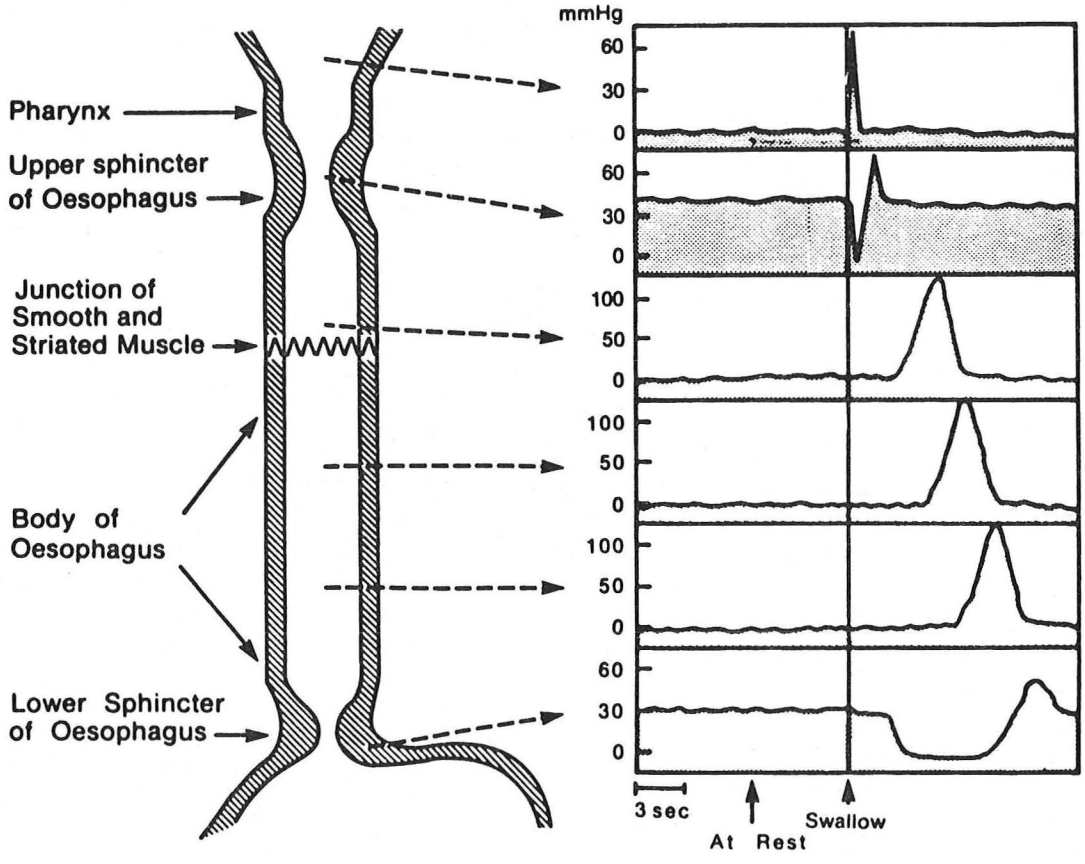

Figure 2. Diagram showing pharyngeal and esophageal intraluminal pressures at rest and after a swallow. From ref. 4.

Primary peristalsis involves both the skeletal and smooth muscle portions of the esophagus and results from coordinated, sequential contractions of the inner, circular muscle layer. Aborally-directed peristalsis in the upper (skeletal muscle) esophagus is accomplished by a sequential firing of lower motor neurons whose cell bodies are located in the nucleus ambiguous of the tenth cranial nerve (vagus nerve) and whose axons directly innervate skeletal muscle cells of the esophagus at the motor end plate. Neurons that innervate the most proximal esophagus are activated first and then activation spreads in turn to neurons that innervate more and more distal (aboral) regions of the esophageal skeletal muscle. Swallowing-induced peristalsis may be impaired by diseases of (a) supramedullary upper motor neurons that normally innervate the nucleus ambiguous (as in pseudobulbar palsy), (b) the brain stem (as in bulbar poliomyelitis), (c) the lower motor neuron-skeletal muscle junction (as in myasthenia gravis), or (d) the esophageal skeletal muscle itself (myotonic dystrophy, polymyositis). Symptoms that result include dysphagia, regurgitation, and aspiration of food and secretions into the airway, as well as difficulty in initiating swallowing (oropharyngeal dysphagia).

Control of peristalsis in the smooth muscle portion of the esophagus is complex and not understood completely (4,6). As in the skeletal muscle portion of the esophagus, the act of swallowing initiates peristalsis via a vagally-activated pathway. Thus, bilateral cervical vagotomy abolishes swallowing-induced peristalsis in the smooth muscle portion of the esophagus. Unlike in the skeletal muscle portion of the esophagus, where neurons from the nucleus ambiguus of the vagus directly innervate the muscle, the myocytes in the smooth muscle portion of the esophagus are not innervated directly by vagal fibers. Instead, neurons originate in the dorsal motor nucleus of the vagus and innervate ganglion cells of the myenteric plexus within the esophagus between the longitudinal and circular muscle layers (Figure 3). These ganglion cells,

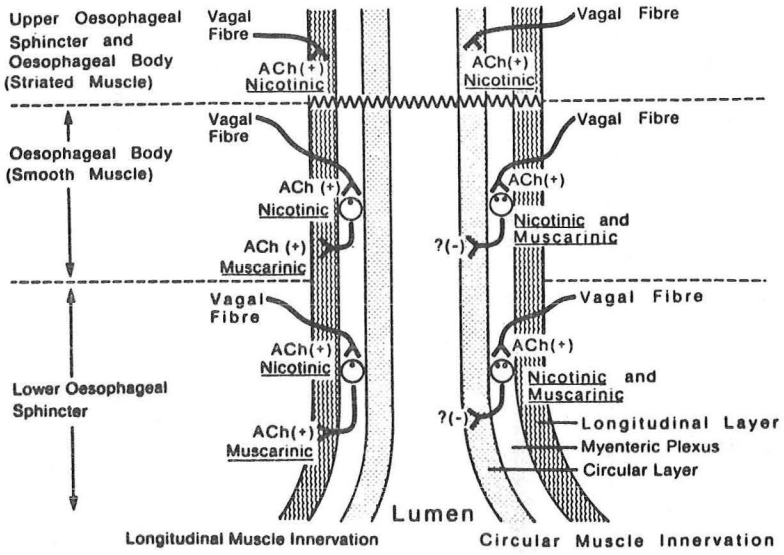

Figure 3. Innervation of the esophageal musculature. Acetylcholine (ACh) is indicated at appropriate loci and the known receptors (muscarinic and nicotinic) are indicated by dots. Unknown transmitters are indicated by a question mark. Actions are indicated by a (+) or a (-) to indicate excitation and inhibition, respectively. Innervation of the longitudinal muscle is indicated at the left; circular muscle at the right. From ref. 4.

once activated by preganglionic vagal neurons, then release an unknown noncholinergic, nonadrenergic transmitter which inhibits muscle contraction within the circular layer. It is currently believed that immediately after swallowing the entire circular smooth muscle portion of the esophagus is inhibited simultaneously by this unknown transmitter and that this inhibition occurs concomitant with relaxation of the LES. How then can orderly aboral peristalsis develop in the already inhibited smooth muscle portion of the esophagus? Most experimental evidence indicates that contraction of the circular smooth muscle occurs as a passive rebound contraction which follows the antecedent neurogenic inhibition. The period of time required for this post-inhibition rebound contraction (the so-called latency period) is shortest in the proximal smooth muscle portion of the esophagus and progressively lengthens as one proceeds caudally. This gradient of latencies explains the sequential peristaltic contraction of the smooth muscle portion of the esophagus (4,6).

It is remarkable that swallowing leads to a smooth coordinated contraction of the entire esophagus (skeletal, mixed skeletal-smooth, and smooth muscle) despite two markedly different mechanisms for inducing sequential contraction of the inner circular muscle layer. Presumably, the two mechanisms, as well as oropharyngeal events, are organized by the swallowing center in the brainstem.

Although the effects of swallowing on primary peristalsis are clearly centrally-mediated, secondary peristalsis can be induced by distention of or even pinching of the smooth muscle portion of esophagus and this occurs even after bilateral cervical vagotomy. Moreover, esophageal peristalsis can be induced in vitro, indicating a peripheral site of organization of peristalsis. In animals, electrical stimulation of the peripheral end of either vagus nerve or transmural stimulation of the smooth muscle portion of the esophagus can induce peristalsis, presumably as a result of the above-described latency gradient following recovery from an initial neurogenic inhibition of smooth muscle function.

In addition to peristaltic contraction of the inner circular smooth muscle portion of the esophagus, the esophagus shortens during swallowing as a result of contraction of the outer longitudinal muscle. This is mediated by direct vagal-cholinergic innervation of longitudinal skeletal muscle (nicotinic) and by vagally-activated postganglionic innervation of longitudinal smooth muscle (muscarinic) (see Figure 3).

LES Relaxation. When either primary or secondary peristalsis is induced, peristalsis is preceded by complete (100%) or nearly complete (> 90%) relaxation of the LES (Figure 2). With relaxation the diameter of the esophagus in the region of the LES may exceed the diameter the more proximal esophagus (Figure 1, right). Once the swallowed material enters the stomach (i.e., within seconds), the LES once again contracts, restoring a pressure barrier across it. The nature of the inhibition of LES function has been studied extensively (10-15). The current body of knowledge can be summarized as follows:

1. LES relaxation with swallowing is mediated by long preganglionic vagal neurons which originate in the dorsal motor nucleus of the vagus and which synapse with short, intramural postganglionic inhibitory neurons near the LES (Figure 3).

2. Activation of intramural postganglionic inhibitory neurons by preganglionic vagal neurons is cholinergic, using both nicotinic- and muscarinic-type cholinergic receptors (M_1 subtype of muscarinic receptors). These inhibitory neurons can also be activated locally by distending the esophagus which also induces secondary peristalsis.

3. Postganglionic neurons exert their inhibitory influence on sphincteric smooth muscle cells via a transmitter which is neither acetylcholine or norepinephrine (noncholinergic, nonadrenergic).

4. Relaxation of the smooth muscle of the LES is associated with increases in intracellular cyclic AMP and cyclic GMP, implying that these nucleotides may act as second intracellular mediators for the neurotransmitters which mediate LES relaxation (15).

5. In vitro electrical stimulation of muscle strips obtained the region of the LES in cats results in LES relaxation and release of vasoactive intestinal peptide (VIP). LES relaxation induced by electrical stimulation can be prevented by anti-VIP rabbit antiserum (14). Furthermore, VIP is known to relax the LES (13) and to increase cyclic AMP content in LES smooth muscle (15). Thus, VIP is a candidate for an inhibitory neurotransmitter in the LES (13-15).

6. As VIP does not increase cyclic GMP, it is possible that another as yet unidentified agent may be as important as VIP, or even more important, as an inhibitory neurotransmitter at the LES (15); this is shown below (Figure 4).

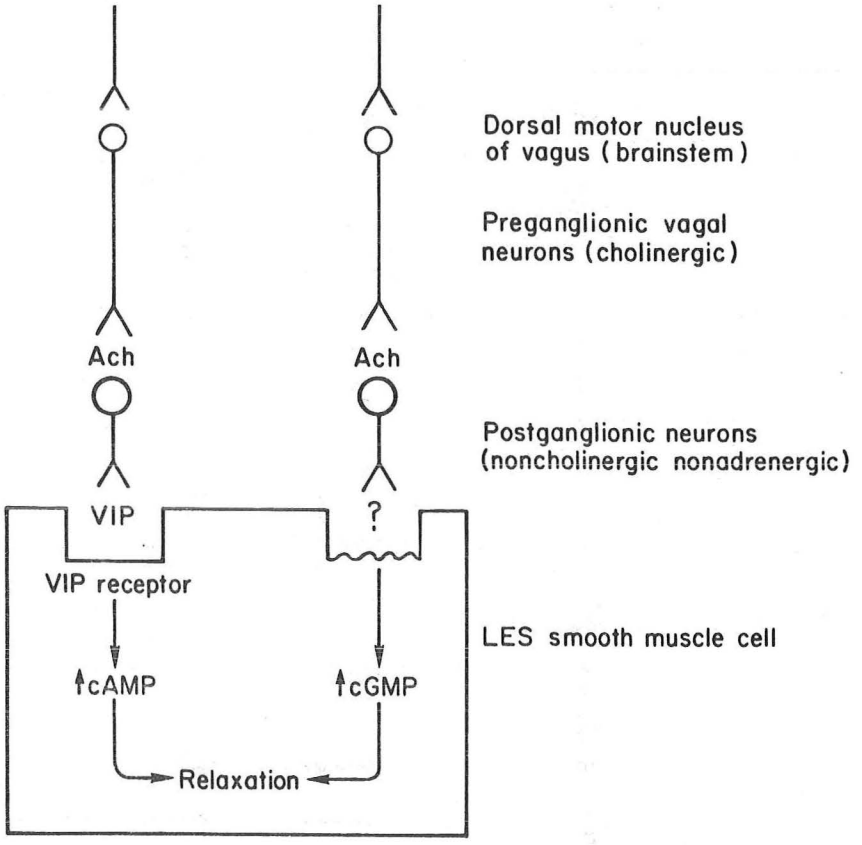

Figure 4. Model for relaxation of lower esophageal sphincter (LES) smooth muscle.

Recently, it has been recognized that the normal LES undergoes periodic relaxation which is not triggered by the act of swallowing or by secondary peristalsis, with LES pressure transiently decreasing to the level of gastric pressure (16). The mechanism responsible for this spontaneous "inappropriate" LES relaxation is uncertain. Patients with gastroesophageal reflux (reflux esophagitis) have a higher frequency of spontaneous "inappropriate" LES relaxations than individuals without reflux (16).

CLASSIFICATION OF ACHALASIA SYNDROMES

Esophageal achalasia is present when all 3 abnormalities listed in Table 1 are present (17).

Table 1.
Physiologic Abnormalities in Esophageal Achalasia

1. Increased resting (basal) LES pressure.
2. Incomplete relaxation of LES with swallowing.
3. Aperistalsis (often with tertiary contractions).

Aperistalsis in achalasia may be associated with low-amplitude nonperistaltic tertiary contractions in the body of the esophagus (classic achalasia) or less commonly with high-amplitude tertiary contractions (vigorous achalasia). High-amplitude contractions may cause angina-like chest pain, especially in younger patients, although these contractions may give way to low-amplitude contractions over time. Some patients may not manifest all 3 cardinal manifestations of achalasia listed in Table 1. Thus, some patients may have basal LES pressures within the normal range (10-25 mmHg). Others may have complete LES relaxation, especially early in the course of their disease; however, the duration of LES relaxation in such patients is usually much shorter than normal (18). Finally, peristalsis may be present in achalasia, but usually only after treatment by pneumatic dilatation or myotomy (see below).

As shown in Table 2 below, achalasia is part of a spectrum of motility disorders of the esophagus (17,19). When all 3 features listed in Table 1 are present, the disorder can be classified as achalasia. If LES function is normal but high-amplitude nonperistaltic tertiary contractions are present, then *diffuse esophageal spasm* (DES) is present. When classic features of achalasia or DES are absent, a nonspecific motility disorder is diagnosed and these are probably more common than achalasia or DES. Examples include individuals with a hypertensive LES that relaxes completely with swallowing and individuals with abnormally high-amplitude peristaltic contractions in the body of the esophagus with normal LES function ("nutcracker esophagus"). Transitions from DES or nonspecific motility disorders into typical achalasia over time have been documented (20,21), reinforcing the notion that these represent a group of overlapping syndromes that may have a common pathogenesis. Some individuals with these various esophageal motility disorders are asymptomatic, especially the elderly.

Table 2. Spectrum of Esophageal Motility Disorders[a]

(Modified from ref. 19)

DISORDER	RESTING CONDITIONS	SWALLOWING		
	LES PRESSURE	LES RELAXATION	PERISTALTIC CONTRACTIONS	TERTIARY CONTRACTIONS
Classic Achalasia	↑ or normal	incomplete	absent	present
Vigorous Achalasia	↑ or normal	incomplete	absent	present[b]
Diffuse spasm	Normal	complete	present intermittently	present[b]
Nutcracker	Normal	complete	present[b]	absent
Hypertensive LES	↑	complete	present	absent

a Nonspecific motility disorders that do not fit any of the above 5 categories are also common.

b Contractions are of increased amplitude and often of increased duration.

Achalasia may be idiopathic (primary achalasia) or secondary to another underlying disease, most often Chagas' disease in South America and cancer in this country. A classification of primary and secondary achalasia syndromes is proposed in Table 3.

Table 3. Classification of Achalasia Syndromes

I.	Primary (idiopathic) Achalasia
	A. classical achalasia
	B. vigorous achalasia
II.	Secondary Achalasia
	A. Trypanosoma cruzi infection (Chagas' disease)
	B. Cancer (pseudoachalasia)
	1. involving LES region
	2. remote from LES region
	C. Infiltrative Disorders of LES
	1. amyloidosis
	2. Fabry's disease
	3. eosinophilic infiltration
	4. sarcoidosis
	D. Association with Systemic Disorders
	1. diabetes mellitus
	2. familial adrenal insufficiency with alacrima
	3. sicca syndrome with gastric hyposecretion
	4. multiple endocrine neoplasia, type 2b
	5. multiple congenital defects with achalasia
	E. Association with Gut Motility Disorders
	1. idiopathic intestinal pseudo-obstruction
	2. achalasia with pylorospasm

Clinical differentiation of primary and secondary achalasia can be difficult, and will be discussed below.

CLINICAL FEATURES OF ACHALASIA SYNDROMES (3,17,19,22)

History and Physical Examination. Regardless of whether achalasia is primary or secondary to one of the disorders listed in Table 3, the clinical presentation is similar (23). Symptoms of achalasia are listed in Table 4. The most characteristic symptom is dysphagia for both liquids and solids. This contrasts with diseases which produce mechanical obstruction of the esophagus (e.g., carcinoma, stricture, rings) where dysphagia for solids but not liquids is frequently present.

Table 4. Symptoms of Achalasia

Dysphagia for liquids and solids
Odynophagia
Regurgitation of undigested food
Cough, often productive
Chest pain
Weight loss

Regurgitation of undigested food must be distinguished carefully from vomiting. Rare patients with achalasia may have no esophageal symptoms and have only cough with or without repeated episodes of bronchitis or bronchopneumonia. Chest pain is rare in classic achalasia but common in vigorous achalasia and in other esophageal motility disorders which may overlap with achalasia. Heartburn is notably absent, presumably due to the elevated basal LES pressure which prevents gastroesophageal reflux. However, achalasia may develop in patients with pre-existing gastroesophageal reflux and it has even been speculated that some patients with achalasia evolve through a stage where reflux is prominent at the onset of their disease (24). While physical examination in primary achalasia is usually unrewarding, a thorough examination is mandatory since an underlying disease associated with achalasia may be disclosed (Table 3).

Age at Onset. Achalasia of the primary type usually begins between the age of 25-60, but an onset in childhood is well documented (25). Achalasia in early childhood should raise suspicion of a systemic syndrome associated with achalasia (Table 3) or a congenital syndrome (26), while achalasia in older age should raise the suspicion of malignancy (pseudoachalasia). The relationship between achalasia and cancer will be discussed below.

Genetics. Achalasia has been reported in monozygotic twins (27), in siblings (28,29), and in a father and son (30). Co-existence of achalasia in these settings could be coincidental, due to some genetic predisposing factor, or to exposure of both affected individuals to a common environmental etiologic factor (e.g., a virus). A recent study of 159 patients with achalasia found no proven cases of achalasia in 1012 first degree relatives surveyed (31). Thus, the role of genetic factors in primary achalasia is uncertain.

Incidence and Prevalence. The annual incidence of achalasia (annual incidence = number of newly diagnosed cases per year/population at risk during that year) has been estimated in 5 studies (Table 5).

Table 5. Incidence of Achalasia

CITY (reference)	INCIDENCE PER 100,000 POPULATION
Rochester, Minnesota, USA (32)	0.6
Cardiff, Wales (33)	0.4
Nottingham, UK (34)	0.5
Richmond, Virginia, USA (35)	0.6
Harare, Zimbabwe (36)	0.003

Thus, the incidence of achalasia in the USA and Europe is 0.4-0.6/100,000 population at risk, while the incidence in Black Africans appears to be much lower. In the Dallas-Fort Worth metroplex with approximately two million people, approximately 10 new cases of achalasia will be diagnosed each year. Thus, even in the U.S.A., the condition is relatively uncommon. One study from England (34) suggested that the age-related incidence of achalasia increases in older age (Figure 5).

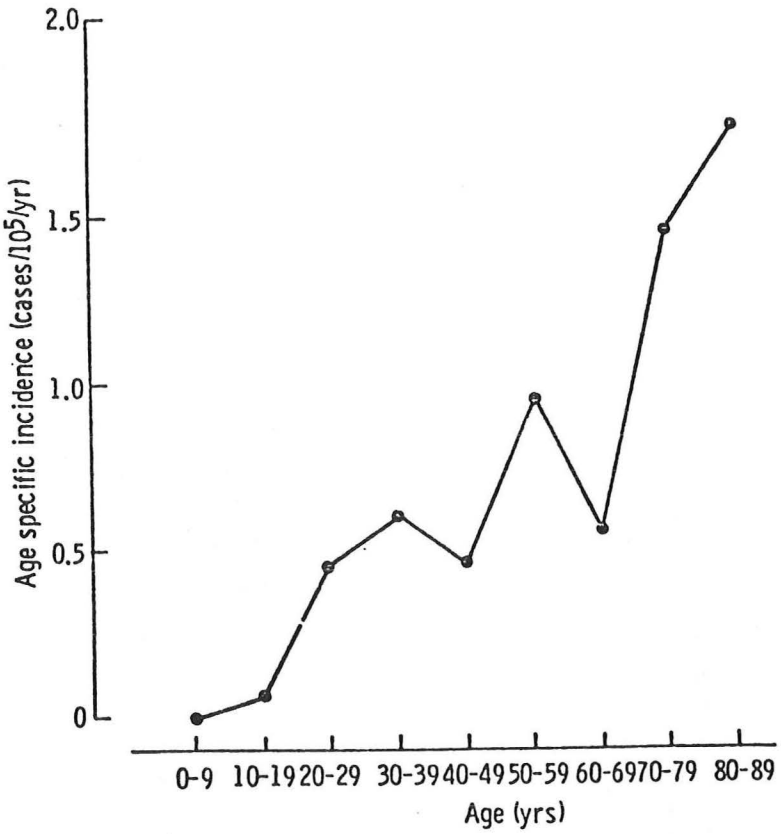

Figure 5. Age-specific incidence of achalasia in Nottingham, England. From ref. 34.

Since achalasia is a chronic disease, its prevalence exceeds incidence by a considerable amount. A study in England estimated a prevalence of achalasia of 8 per 100,000 population (34). Thus, at any one time in the Dallas-Fort Worth metroplex there may be 160 patients with achalasia.

Sex and Race. Most studies find that men and women are affected equally. As already alluded to in Table 5, Caucasians are affected more commonly than blacks. A recent case of achalasia in a young black man was seen at Parkland. His history is summarized below.

> Case 1. A 17 year old man had dysphagia for liquids and solids and postprandial regurgitation for 2 months, with weight loss from 169 to 145 pounds. He denied any heartburn. He was first diagnosed as having an anxiety disorder. Five months later he developed coughing episodes at night. A chest x-ray (Figure 6, left) was normal, but erythromycin was prescribed for possible M. pneumonia pneumonitis.

The patient was lost to follow-up until age 20 when he again complained of dysphagia for liquids and solids and a chronic cough productive of greenish sputum. Chest x-ray (Figure 6, right) showed massive dilatation of the esophagus. Barium, endoscopic, and motility studies of the esophagus were compatible with primary (idiopathic) achalasia.

Comment. This case points out the classic symptomatology, including pulmonary symptoms and the difficulty in accurate early diagnosis.

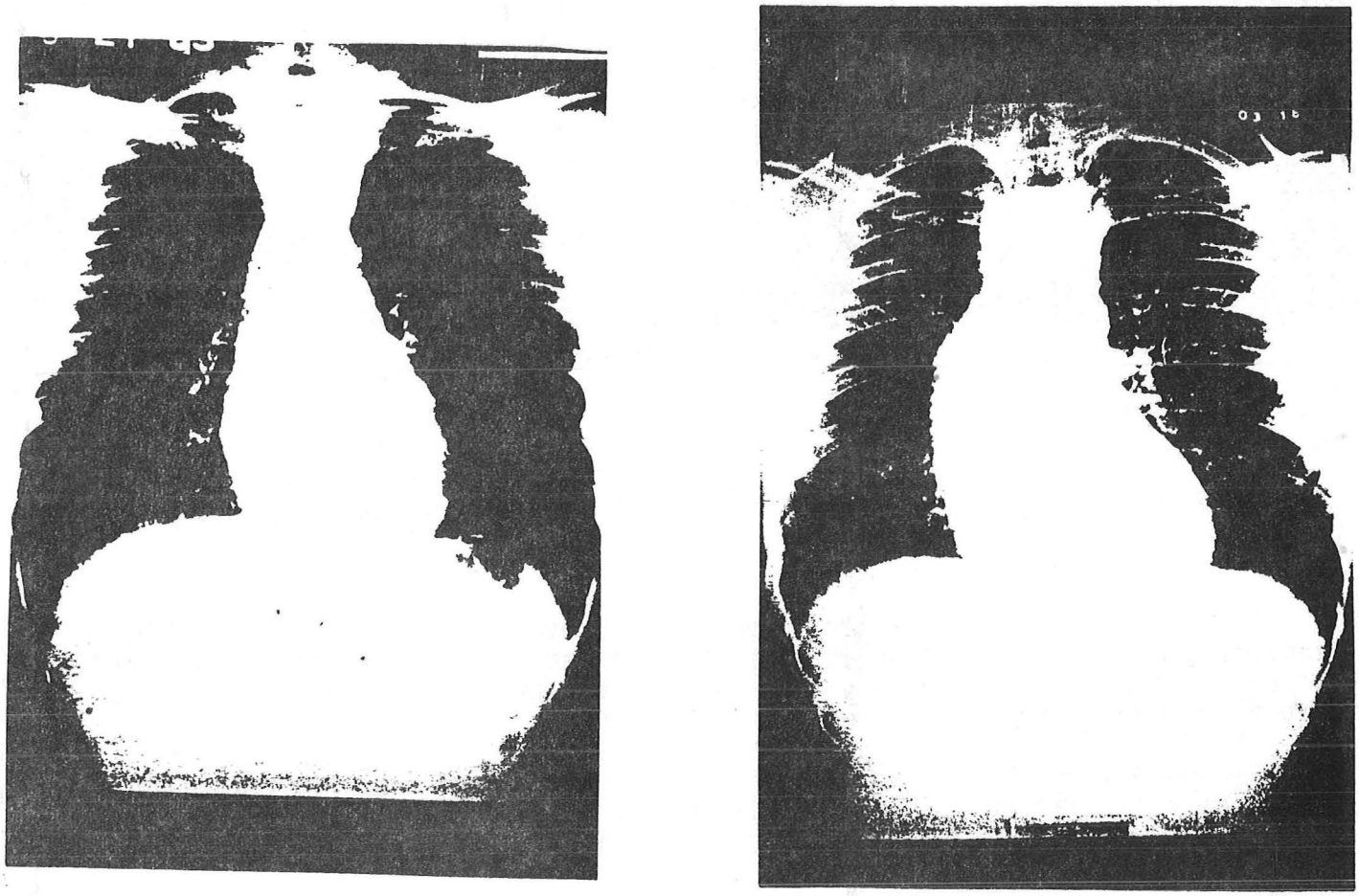

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Figure 6. Chest radiograph in Case 1 at age 17 (left) and age 20 (right).

PATHOGENESIS OF PRIMARY ACHALASIA

Theoretically, achalasia could either be a neuropathic or myopathic disorder (Figure 3).

Esophageal Muscle in Primary Achalasia. Degenerative, regenerative and fibrotic changes in esophageal smooth muscle and loss of contact between muscle cells have been reported in achalasia (37). Recently, Friesen et al carried out an ultrastructural study of small pieces of smooth muscle obtained at the time of surgery from the LES region and 5 cm above the LES in patients with primary achalasia, DES, and in control patients with other diseases (e.g., reflux esophagitis). Ultrastructural alterations in smooth muscle were not prominent. Nonspecific changes (filament disarray, mottling, nuclear and cytoplasmic inclusions) were sometimes present in the patients with achalasia but were thought to be secondary to impressive neuropathic alterations, specifically a marked loss of small nerve fibers and paucity of granules in remaining nerve fibers (38).

Another way to evaluate LES smooth muscle in achalasia is to assess its response to pharmacologic agents. These studies indicate that LES smooth muscle function is preserved. In fact, LES smooth muscle appears to be hyperresponsive to the hormone gastrin and to cholinergic stimulation (39-41). It has been suggested that LES hyperresponsiveness to gastrin or acetylcholine is not a property of the target organ per se but a result of denervation hypersensitivity (40). To test this hypothesis, Padovan et al studied LES sensitivity to the gastrin analog pentagastrin in patients with megaesophagus due to Chagas disease, a disorder in which loss of myenteric ganglion cells is prominent and in which denervation hypersensitivity of the LES could theoretically be present. However, these authors found reduced responsiveness to pentagastrin in chagasic patients (42). Thus, hyperresponsiveness to exogenous gastrin in primary, idiopathic achalasia is probably not due to denervation of the LES. Although it was once proposed by Cohen that basal LES hypertension in achalasia is due to LES hypersensitivity to normal circulating concentrations of endogenous gastrin (39), he now acknowledges lack of experimental support for this concept (17).

Neural Involvement in Primary Achalasia. There is extensive evidence, both anatomic and physiologic, for primary neuropathology in achalasia with changes in smooth muscle secondary to the neuropathology (38,43-53).

Neuroanatomic Studies. The most striking and consistent finding in histopathologic studies of achalasia is an absence of or a marked reduction in the number of ganglion cells within the myenteric (Auerbach's) plexus. (The submucosal Meissner's plexus in the normal esophagus is not prominent). Of interest, the degeneration of the myenteric plexus is more apparent in the dilated portion of the esophageal body than in the LES region per se. In some cases, inflammation is present within the myenteric plexus. Damaged ganglion cells may contain intracytoplasmic hyaline, spherical eosinophilic inclusions (Lewy bodies). Lewy bodies are also seen in the brain in Parkinson's disease and in degenerating ganglion cells of the esophagus in some Parkinsonian patients with dysphagia (50).

Besides loss or destruction of ganglion cells, there is a reduction in nerve fibers within the wall of the esophagus in achalasia, especially smaller diameter nerve fibers. It is reasonable to postulate that the postganglionic neurons which mediate LES relaxation are selectively damaged in achalasia. Recently, Aggestrup et al demonstrated a marked reduction of VIP-staining neurons in the lower esophagus of 5 patients with achalasia subjected to myotomy compared to the tumor-free portion of the lower esophagus of 11 patients with esophageal or gastric carcinoma (51). Furthermore, the concentration of VIP in the achalasic esophagus, measured by radioimmunoassay, averaged 8.5 pmol/g tissue, compared to 95.6 pmol/g in controls ($P < 0.001$). Thus, VIP-containing nerves appeared to be deficient in achalasia, and this could account for inability of the LES to relax. Since peristalsis in the smooth muscle portion of the esophagus is triggered by an initial phase of inhibition by noncholinergic, nonadrenergic postganglionic neurons, selective destruction of these inhibitory neurons in achalasia could conceivably explain aperistalsis as well.

In addition to changes in postganglionic neurons within the wall of the esophagus, changes in the extra-esophageal vagus nerves and in the dorsal motor nucleus of the vagus have also been described in achalasia (43,46). Furthermore, diseases of the dorsal motor nucleus region (e.g., polio) or surgical section of the cervical or thoracic vagi can induce an achalasia-like illness (3,46). It has been suggested that achalasia begins in the medulla and that the changes in vagal fibers, myenteric plexus ganglion cells and their associated postganglionic fibers, and smooth muscle cells are all secondary changes which occur later in the course of the disease. This would explain aperistalsis in the skeletal muscle part of the esophagus as well as in the myenteric plexus-containing smooth muscle portion.

Not only is the site of primary neuropathology in achalasia uncertain, but also the nature of the pathologic process. Two theories exist: (a) achalasia is primarily a degenerative disease of neurons whose cell bodies are either in the medulla or the myenteric plexus; (b) achalasia is primarily an infection of neurons by a virus or some other infectious agent. It has been suggested (46) that achalasia may be due to herpes zoster, a known neurotropic virus, although neither virologic nor serologic studies support this (54). A serologic study did find an association between measles virus and achalasia, but this has not been repeated (54). Another argument in favor of an infectious etiology is that infection with T. cruzi produces ganglion cell damage and an achalasia-like syndrome with megaesophagus (see below).

Neurophysiologic Studies. Physiologic studies using esophageal manometry also favor a neuropathic process in achalasia, with prominent involvement of postganglionic noncholinergic, nonadrenergic inhibitory neurons. For example, Dodds et al reported that cholecystokinin (CCK), a peptide hormone structurally related to gastrin, reduces LES pressure in normal individuals yet causes a paradoxical increase in LES pressure in many patients with achalasia (52). The normal inhibitory effect of CCK on the LES is almost certainly indirect and mediated by an effect on an inhibitory neuron, since the nerve toxin tetrodotoxin blocks CCK-induced LES relaxation in cats (55). After tetrodotoxin treatment, CCK paradoxically increases LES pressure in cats by a direct effect on sphincteric smooth muscle (probably acting via a stimulatory gastrin/CCK receptor). Dodds et al propose that CCK increases LES pressure in achalasia patients because the normal postganglionic noncholinergic inhibitory neurons are damaged or absent. In contrast to inhibitory fibers, studies have suggested

that postganglionic cholinergic stimulatory fibers to the LES may be spared in achalasia (41). Thus, the LES pressure in achalasia increases following administration of the acetycholinesterase inhibitor edrophonium (40,41) and decreases following administration of the muscarinic antagonist atropine (41).

Another physiologic observation favoring a neuropathic etiology of achalasia was reported by Dooley et al who utilized a sham feeding technique and measured two vagally-mediated responses: gastric acid secretion and release of pancreatic polypeptide (PP) into the circulation (53). In 7 of the 13 achalasia patients who were sham fed (using a chew-and-spit method), acid secretion and PP release were reduced to levels similar to those of surgically vagotomized patients. These studies suggested that vagal impairment is often present in achalasia and that it may extend to other vagally-mediated organs (i.e., the stomach and pancreas). However, sham feeding studies of this nature cannot localize the site of the neural abnormality (sensory, dorsal motor nucleus, peripheral vagus, postganglionic neurons, target cells).

Studies in animals (cats, dogs, rats) have attempted to clarify the role of nerves in the pathogenesis of megaesophagus and achalasia, but no major insights have resulted (56,57). A satisfactory animal model for achalasia does not exist. Dogs exposed to acrylamide develop megaesophagus and vagal neuropathy; however, these dogs also develop peripheral neuropathy (58,59).

In summary, the etiology of primary achalasia is unknown. The disease is either a degenerative or infectious disease of nerve cells located either in the dorsal motor nucleus of the vagus nerve (and perhaps the neighboring nucleus ambiguus), the myenteric plexus or both sites. Axonal degeneration and smooth muscle changes are probably secondary to neuronal damage. The noncholinergic, nonadrenergic inhibitory nerves to the LES and perhaps to the esophageal body are selectively impaired (including VIPergic nerves), while the cholinergic stimulatory nerves are largely spared.

PATHOGENESIS OF SECONDARY ACHALASIA

Chagas' Disease. This disease (also called American trypanosomiasis) is endemic in South and Central America, although cases in South Texas have been reported. The illness is due to infection with Trypanosoma cruzi and is transmitted by a bite from reduviid ("kissing") bugs (60). After the bug bites the affected person or animal (often domestic animals like cats or dogs), usually at a mucocutaneous junction near the lip or eye, the bug deposits into the bite site feces contaminated with T. cruzi (infection by posterior station). A lesion may develop at the bite site (chagoma). Then, an acute septicemic phase of the illness develops that can be very severe (even fatal) or can be so mild as to go unnoticed. A chronic phase of the disease develops many years later with destruction of parasympathetic ganglion cells throughout the body, including the heart and the gastrointestinal, urinary, and respiratory tracts. Chronic cardiomyopathy with prominent conduction system disturbances and arrhythmias is most frequent and is the commonest cause of death in these patients. Involvement of other visceral organs leads to their gradual dilatation: megaesophagus, megacolon, megagastria, megaduodenum, megagallbladder, megajejunum, megacystis, megaureter, bronchiectasis, and so on. Thus, the pathogenesis of esophageal Chagas' disease resembles to a striking degree

the proposed pathogenesis of primary achalasia already discussed. Aperistalsis is a cardinal feature of both disorders. Sphincter of Oddi dysfunction has recently been documented in Chagas' disease (61).

Diagnosis of Chagas' disease in the acute phase requires demonstration of the parasite in the blood (esophageal involvement is rare during this phase). During the chronic form of the disease, serologic tests (e.g., complement fixation tests) are generally required for diagnosis, as parasitemia is absent or minimal. There is no effective therapy for Chagas' disease.

Cancer-Induced Achalasia (Pseudoachalasia). Malignancies can produce an achalasia-like illness (62). At one time it was thought that certain clinical features could help distinguish pseudoachalasia due to cancer from primary achalasia, including duration of dysphagia for < 1 year, age > 50 years, and weight loss > 15 pounds (62). However, these criteria have been shown to have poor predictive value and are not especially helpful when facing an individual patient (23). Most series report 10-40 cases of primary achalasia for every case of pseudoachalasia (23,63).

How tumors that locally involve the LES region produce achalasia is not known for certain. Most evidence suggests that the infiltrating tumor interferes with the inhibitory innervation to the LES, preventing swallowing-induced relaxation. It is noteworthy that certain tumors remote from the LES may be associated with achalasia. Presumably, this represents an example of a neuromyopathic syndrome associated with malignant disease akin to carcinomatous myopathy and the myasthenic-like syndrome (Eaton-Lambert syndrome). Aperistalsis is common in pseudoachalasia.

The commonest tumor associated with achalasia is adenocarcinoma of the gastric cardia that infiltrates the LES region through the muscularis, often with no mucosal involvement. A comprehensive list of cancers that have been associated with secondary achalasia is provided in Table 6 (23,62-74).

Table 6. Malignancies Associated with Achalasia

Involving LES region
Gastric adenocarcinoma
Gastric or esophageal lymphoma
Esophageal squamous cell carcinoma
Esophageal lymphangioma
Prostatic adenocarcinoma
Pulmonary small cell carcinoma
Pulmonary adenocarcinoma
Apparently remote from LES region
Hodgkin's disease
Hepatocellular carcinoma
Pulmonary carcinoma, poorly differentiated

A patient with carcinoma-induced achalasia (pseudoachalasia) was recently seen at the Dallas VA Medical Center.

> Case 2. A 62 year old man complained a chronic cough productive of yellowish sputum for 4 months which was diagnosed as bronchitis and treated with antibiotics. Three weeks prior to admission he complained on dysphagia for solids more than for liquids and odynophagia without weight loss. Physical examination was unremarkable. Chest x-ray showed a new 1.5 cm noncalcified nodule in the apex of the right lung. CBC and SMA_{20} profile were normal. An upper GI series showed a long segment of concentric, persistent narrowing in the distal esophagus and irregular, thickened folds in the gastric fundus. Endoscopy showed narrowing or compression of the distal esophagus without mucosal changes and markedly enlarged nodular folds in the fundus of the stomach, with one area of gastric ulceration. Endoscopic mucosal biopsies of the stomach were negative for cancer, however.
>
> Motility study of the esophagus showed an elevated resting LES pressure of 40 mmHg (normal, 12-25 mmHg), no relaxation of the LES with swallowing, and occasional swallowing-induced tertiary contractions in the body of the esophagus. Some normal peristalsis was present.
>
> Abdominal CT scan showed mass-like thickening of the gastro-esophageal junction and posterior wall of the gastric fundus, a retropancreatic mass and a left adrenal mass. Fine needle aspiration cytology of the latter two masses each disclosed adenocarcinoma.
>
> Due to the multifocal metastatic disease, palliation of dysphagia was attempted by pneumatic dilatation of the LES region with a balloon dilator (Rigiflex Achalasia dilator). This was unsuccessful and thus the patient was then taken to surgery for a possible palliative resection of the tumor at the gastroesophageal junction. However, the tumor was too extensive to be resected. The patient died 2 weeks later. No autopsy was performed.
>
> Comment. This patient had achalasia secondary to metastatic adenocarcinoma involving the LES region, probably from a gastric primary. While older age at onset of disease and short history of dysphagia may have suggested the possibility of pseudoachalasia, the absence of weight loss is notable. As in Case 1, pulmonary symptoms (productive cough) were prominent features of the illness.

If the underlying tumor can be treated successfully, for example by radiotherapy or chemotherapy, the clinical, radiographic and manometric abnormalities sometimes (65,69,74), but not always (71), disappear and

esophageal peristalsis may even return. In one case, a gastric adenocarcinoma involving the LES region and producing achalasia was removed surgically, after which esophageal peristalsis returned (73). These observations, and similar ones in primary achalasia, suggest that aperistalsis may occur secondary to achalasia of the LES and that once functional obstruction of the distal esophagus is relieved, peristalsis may sometimes return.

Infiltrative Disorders. Reports of achalasia secondary to esophageal infiltration by amyloid (75), sphingolipids (76), eosinophils (77), or sarcoidosis (78) probably occur by a mechanism similar to cancerous invasion of the LES region.

Diabetes Mellitus. Diabetes results in an autonomic neuropathy that may involve the vagus nerves and intramural esophageal nerves, leading to various esophageal motility disturbances (79). Most diabetic patients with esophagopathy are asymptomatic, but some develop dysphagia and/or chest pain. DES, nonspecific motility disorders, and, less commonly, achalasia-like disorders have been reported in diabetes (80).

Familial Adrenal Insufficiency with Alacrima. In the last decade, a new syndrome has been described in several centers throughout the world. Allgrove et al in England were the first to call attention to the association between achalasia, isolated glucocorticoid deficiency, and deficient tear production in two pairs of siblings in separate families (81). In these cases, onset of disease was in childhood (ages 2-6 years) and histologic examination of esophageal smooth muscle showed abnormalities of ganglion cells and nerve fibers similar to those seen in achalasia. Adrenal function of affected patients is normal at birth but falters in early childhood. Adrenal insufficiency is characterized by markedly elevated plasma ACTH levels, skin hyperpigmentation, absence of antiadrenal antibodies, and preservation of mineralocorticoid function. Alacrima is often present from birth and can be confirmed quantitatively by a Shirmer's test.

Subsequent reports from the United States, Spain, and Australia have led to an expansion of the clinical manifestations of this syndrome (82-87). While glucocorticoid secretion is most prominently impaired as a result of unresponsiveness to ACTH, leading to hypoglycemia, partial mineralocorticoid deficiency may also be present with resultant hyponatremia. As achalasia and alacrima could conceivably be due to disordered autonomic (parasympathetic) innervation of the LES and lacrimal glands, respectively, other autonomically-innervated organs have also been studied. By measuring electrocardiographic variations in R-R intervals at rest and during deep respiration, a patient was described with less than normal fluctuation in R-R intervals, implying abnormal vagal-parasympathetic innervation of the SA node (84). Another study confirmed abnormal cardiac-vagal responses in this syndrome and also documented abnormally pupillary responses to light and accommodation and delayed gastric emptying (87). Finally, disorders of the peripheral nervous system (both sensory and motor neuropathy) and the central nervous system (microcephaly, mental retardation, ataxia, optic atrophy) have been reported in some families with this syndrome (86,87).

The nature of this curious disorder is unknown. Limited family studies suggest an autosomal recessive inheritance. Autonomic nervous system dysfunction

may explain some of the clinical manifestations of the disease, but probably not the ACTH-resistant adrenal cortical dysfunction. The achalasia component of this syndrome can be radiographically, manometrically, and histologically similar to primary achalasia. Although the syndrome has its onset in childhood, the fully developed syndrome may not be apparent until early adulthood (87).

Sicca Syndrome. A patient with Sjogren's syndrome (keratoconjunctivitis sicca), gastric hyposecretion, and achalasia has been reported (88). Of interest, patients with Sjogren's syndrome have reduced tear production. Whether this syndrome is related in any way to the familial adrenal insufficiency/achalasia/alacrima syndrome is uncertain.

Multiple Endocrine Neoplasia, type 2b. A patient with medullary carcinoma of the thyroid, pheochromocytoma, mucosal neuromas and alimentary tract ganglioneuromatosis who had an achalasia-like illness was reported by our own Dr. Cuthbert and her associates (89). Esophageal gangioneuromas develop from myenteric plexus ganglion cells, possibly replacing normal ganglion cells that mediate LES relaxation and peristalsis.

Idiopathic Intestinal Pseudo-obstruction. This represents a heterogeneous group of inherited and acquired syndromes that primarily affect small intestinal motility. However, other portions of the gastrointestinal tract (colon, stomach, esophagus) may be involved and families have been reported with an esophageal motor disorder that resembles achalasia (90,91).

DIAGNOSIS OF ACHALASIA AND DIFFERENTIAL DIAGNOSIS

If a patient presents with one or more of the symptoms listed in Table 4, achalasia should be considered in the differential diagnosis. Additional tests are necessary to support or exclude a diagnosis of achalasia.

Chest Radiography. Megaesophagus may be seen on a routine chest x-ray, appearing as a vertical shadow running along the entire length of the mediastinum. This is a late finding in achalasia (see Case 1, Figure 6). Chest radiographs may also show (a) changes in the lung parenchyma as a result of aspiration or (b) tumors that may be involving the esophagus and/or producing secondary achalasia. Another clue pointing toward achalasia on an upright chest x-ray is the absence of a gastric air bubble. LES hypertension may prevent air that is swallowed from entering the stomach. In one study, a gastric air bubble was present in only 12 of 24 untreated patients with achalasia, but in 17 of 19 treated achalasics, 20 of 24 patients with an esophageal stricture, and all 25 asymptomatic controls (92). Thus, absence of a gastric air bubble can suggest achalasia, while the presence of a gastric air shadow by no means rules out this diagnosis.

Barium Study of the Esophagus and Stomach. In a new patient with dysphagia, one should request a complete upper GI series rather than just a barium swallow (esophagogram) for initial evaluation. This is because diseases of the stomach, most notably cancer, can cause dysphagia; therefore, barium examination of just the esophagus may be insufficient. The fluoroscopic component of the examination is extremely important, since the radiologist may be able to diagnose aperistalsis, diffuse esophageal spasm, or other motility disorders.

The most characteristic radiographic changes in achalasia are a persistent "bird's beak" type of narrowing in the distal esophagus, with a delay in emptying of liquid barium through this region. Dilatation of the proximal esophagus may be absent early in the disease, but as the disease progresses, megaesophagus may become more and more apparent and the dilated esophagus often contains food residue and retained secretions, with an air-fluid level. The esophagus may become as large as or even larger than the colon and assume a sigmoid configuration due to concomitant lengthening of the esophagus. A characteristic radiographic appearance of the lower esophagus in achalasia is shown below (Figure 7).

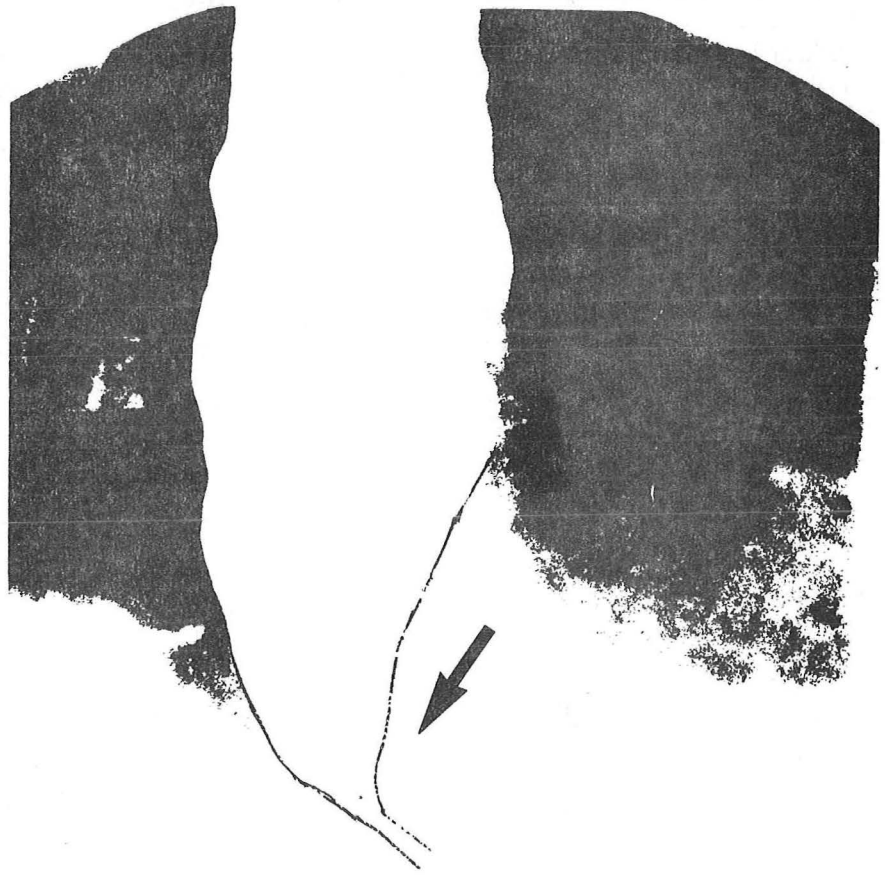


Figure 7. Radiographic "bird's beak" appearance of lower esophagus in achalasia.

Differentiation of primary from secondary achalasia on barium study can be difficult unless radiographic evidence of a malignant disease is found (see Case 2). Recently, Dodds et al suggested that inhalation of amyl nitrite during barium examination may help make this distinction (93). In patients with primary achalasia, four deep inhalations of amyl nitrate led to an increase in the sphincter diameter of $\geq$ 2 mm, often associated with free flow of barium into the esophagus, while the narrow LES of patients with pseudoachalasia due to tumor was unaffected by amyl nitrate. If these observations are confirmed by other groups, they would also suggest a different pathogenesis for primary achalasia and pseudoachalasia.

Endoscopy. In primary achalasia, the lower esophagus is tapered and there often is resistance to entry into the stomach. This resistance is often overcome with moderate pressure with a "pop" when the scope enters the stomach. The esophagogastric mucosa is normal in primary achalasia and often in secondary achalasia. However, cancer may be evident near the esophagogastric junction in secondary achalasia.

Esophageal Motility Studies. As already discussed, the hallmark in the diagnosis of achalasia (primary or secondary) is a manometric study. Manometric abnormalities in achalasia are listed in Table 1 and shown graphically in Figure 8 below. Motility studies are generally done in achalasia to confirm the diagnosis and to serve as a baseline prior to therapy (see below). A recent study suggested that wet swallows (i.e. with water) rather than dry swallows are preferred in evaluating esophageal dysfunction manometrically (94). Motility studies are not generally helpful in separating primary from secondary achalasia syndromes.

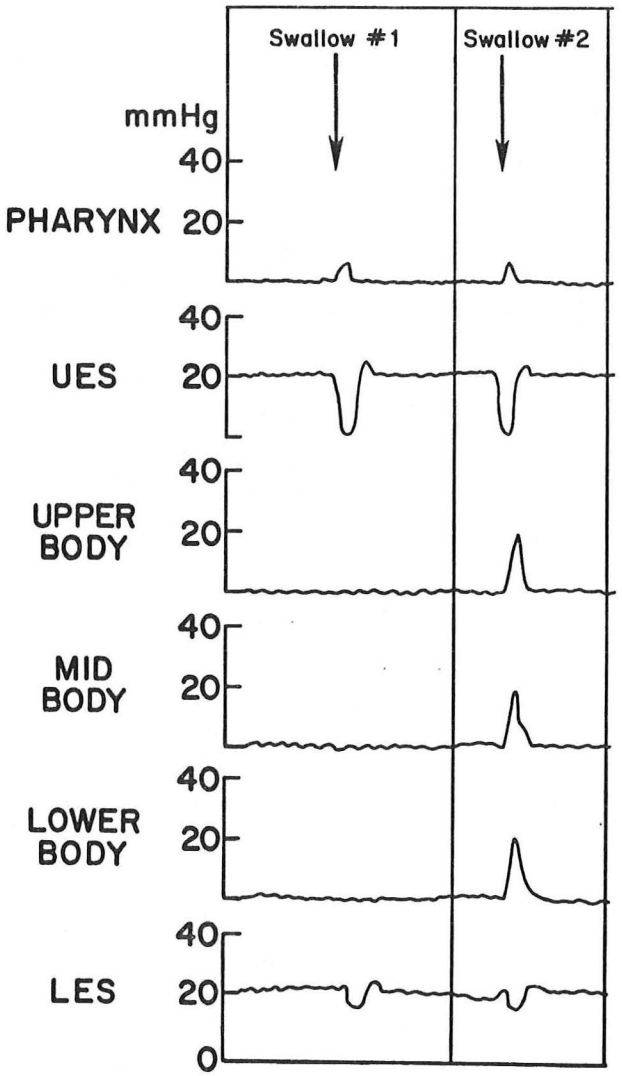


Figure 8. Manometric features of achalasia with aperistalsis, swallow-induced simultaneous tertiary (nonperistaltic) contractions (swallow #2) and incomplete relaxation of lower esophageal sphincter (LES).

Computed Tomography (CT). Chest CT in achalasia may demonstrate not only dilatation of the esophagus, but thickening of its wall (95). CT is too expensive for the routine diagnosis of achalasia. However, chest and/or abdominal CT is very useful when searching for a tumor in the region of the gastroesophageal junction in suspected pseudoachalasia (see Case 2).

Radionuclide Esophageal Transit Studies. These methods measure the rate at which radiolabelled liquid or solid test meals empty from the esophagus into the stomach. They will be abnormally slow if there is a disorder of esophageal peristalsis or if there is anatomical obstruction in the esophagus. Therefore, the test lacks specificity in terms of diagnosis (sensitivity is unknown). However, radionuclide transit studies are often used to assess adequacy of pneumatic dilation therapy or surgical therapy in achalasia (96-98).

Differential Diagnosis of Achalasia. The major differential diagnosis of achalasia is carcinoma involving the mucosa near the gastroesophageal junction (squamous cell carcinoma of the distal esophagus or adenocarcinoma of the gastric cardia) and benign stricture of the distal esophagus (99). Other diseases with which classic or vigorous achalasia may be confused include anorexia nervosa (100) and angina pectoris. On rare occasions, achalasia can present as a neck mass due to a markedly dilated cervical esophagus (101).

COMPLICATIONS

A number of complications of achalasia have been described (Table 7). A few of these complications will discussed in some detail; the others are primarily case reports, references to which are provided in Table 7. Complications of achalasia specifically related to therapy (e.g., reflux esophagitis) will be discussed later and are not listed in Table 7.

Table 7. Complications of Achalasia

Esophageal
Diverticulum
Bezoar (102)
Intramural hematoma (103)
Squamous cell carcinoma
Fistula
esophago-pericardial (104)
esophago-bronchial (105)
Tracheobronchial
Airway obstruction/compression
Aspiration with bronchopulmonary infection
Hypertrophic osteoarthropathy (106)

Lower Esophageal Diverticulum. A diverticulum is a sac-like bulging of the esophageal wall. A classification of the types of esophageal diverticula and their etio-pathogenesis is shown in Table 8.

Table 8. Classification of Esophageal Diverticula (modified from ref 107)

TYPE OF DIVERTICULUM	SYNONYMS	ETIOPATHOGENESIS			
		PULSION	TRACTION	CONGENITAL	TRAUMATIC
Upper	Zenker's, para-pharyngeal, hypo-pharyngeal, pharyngeal, cervical	+++	-	-	-
Middle	thoracic, epibronchial, parabronchial	+	+	-	-
Lower	epiphrenic, para-hiatal	++	-	++	+

As can be seen in the Table, an upper esophageal diverticulum (Zenker's type) is always a pulsion diverticulum (i.e., resulting from increased intraluminal pressure). Diverticula in the middle portion of the esophagus are relatively uncommon and result from pulsion (high local pressure) or traction, usually from adjacent peribronchial lymph node disease (e.g., tuberculous adenopathy). Lower esophageal diverticula are usually related to pulsion, associated with a motility problem, but may be congenital or traumatic.

Debas et al found that 50 of 65 patients with lower esophageal diverticula studied manometrically at the Mayo Clinic had an esophageal motor disorder, usually DES, achalasia, or vigorous achalasia (108). Thirteen of the remaining 15 patients had a lower esophageal peptic stricture, with increased intraesophageal pressure proximal to the stricture. Of interest, the LES pressure in patients with achalasia and lower esophageal diverticulum did not differ from the LES pressure in patients with achalasia without a diverticulum. Diverticula may develop in achalasia as a function of duration of disease, especially in these individuals with (? congenital) areas of weakness within the wall of the esophagus. The percentage of patients with achalasia who develop lower esophageal diverticula is not known, but it is probably <10%.

Diverticula, especially if large, may in and of themselves cause symptoms (dysphagia by compressing the normal esophagus or chest discomfort). If they are thought to be producing symptoms they should be resected. It is important to perform manometric studies first, since a satisfactory result requires both diverticulectomy and myotomy if achalasia is present. Simple diverticulectomy without myotomy may result in recurrence of diverticulum formation. If LES and esophageal body motor function are normal manometrically, a simple diverticulectomy can be performed. Presumably, most of these latter diverticula are congenital in origin.

Squamous Cell Carcinoma of the Esophagus. An association between achalasia and subsequent development of squamous cell carcinoma of the esophagus was first noted over 100 years ago (109). This association can be summarized as follows:

1. In various series, less than 1% to more than 20% of patients with primary achalasia will develop squamous cell carcinoma of the esophagus (3,17,19,22,110). An average figure is 5%.

2. The tumor develops years, often decades, after the diagnosis of achalasia has been made.

3. The tumor most often occurs in the dilated, mid-portion of the esophagus and not in the contracted lower segment. Because of this, dysphagia is not a prominent early symptom of the carcinoma.

4. There is no statistical evidence that Heller's myotomy, pneumatic dilatation, or any other form of therapy for achalasia reduces the risk of carcinoma.

5. Prognosis of squamous cell carcinoma associated with achalasia is poor, as in esophageal squamous cell carcinoma in general.

6. The pathogenesis of the carcinoma is obscure. Presumably, long-term retention of ingested materials in the esophagus (possibly containing carcinogens) leads first to inflammation ("retention esophagitis"), then to dysplasia and carcinoma in situ, and then finally to invasive cancer. However, the early stages of this sequential process have rarely been documented (111).

Since 1978, two patients with achalasia complicated by squamous cell carcinoma of the middle esophagus have been diagnosed at the Dallas VA Medical Center. One of these patients had been treated previously by Heller's myotomy. His case history is present below.

> Case 3. A 44 year old alcoholic man developed dysphagia and regurgitation and was found to have classic achalasia. At thoracotomy a modified Heller's myotomy plus a Belsey fundoplication (to prevent gastroesophageal reflux) was performed with resolution of his symptoms. He remained well for the next 6 years, except for one episode of alcoholic pancreatitis. At age 50, he presented with a 2-3 month history of intermittent, non-exertional, retrosternal chest pain and weight loss of 6 pounds. He denied dysphagia, odynophagia, heartburn, or other GI symptoms. Electrocardiogram was normal. A barium study of the esophagus was compatible with achalasia (narrowed distal segment, dilated esophagus) and also demonstrated a large, bulky intraluminal mass in the middle esophagus. Endoscopy confirmed a large, very friable mass extending from the mid- to the lower esophagus, biopsies of which showed squamous cell carcinoma.
>
> Comments. This case demonstrates that squamous cell carcinoma may develop even after a satisfactory clinical response to Heller's myotomy; this has been commented upon previously (112).

If achalasia is a risk factor for development of squamous cell carcinoma of the esophagus and if the mucosa goes through a dysplastic phase initially, it is natural to consider these patients for periodic endoscopic surveillance. Whether this approach will prove cost-effective is unknown and thus each physician will have to make his own decision regarding surveillance. However, there are some concerns about surveillance esophagoscopy in achalasia:

1. The actual incidence of cancer is not known and this will affect the yield per endoscopy. Chuong et al at Yale found no cases of cancer in 93 patients with achalasia. They concluded that the risk of cancer in achalasia may not be higher than in the general population and that other risk factors for cancer (tobacco, alcohol) need to be considered in future studies (113). However, follow-up of their patients after diagnosis of achalasia was relatively short, averaging only 6½ years (range, 0.5-23 years).

2. There is no evidence that "early" detection of cancer in achalasia will improve survival.

3. Endoscopy with multiple esophageal biopsies (with or without brush cytology) is expensive and may rarely cause complications.

4. If biopsies show pre-cancer (dysplasia) without invasive cancer, it is difficult to recommend with enthusiasm radical surgery (esophagectomy, possibly with colonic interposition), since the natural history of esophageal dysplasia in achalasia is not known and the mortality and morbidity after esophagectomy are considerable.

In my opinion, patients with achalasia are at increased risk for squamous cell carcinoma, but the relative risk is not known. Whether periodic surveillance of these patients with esophagoscopy and random esophageal biopsies would be cost-effective is unknown and deserving of study (a multi-center study would be ideal). At the present time, I do not insist on yearly (or every 6-monthly) esophagoscopy for patients with achalasia. Any new symptoms or a change in symptoms demands thorough evaluation, however.

Airway Obstruction. Several reports attest to the fact that the dilated, food- and fluid-filled esophagus in achalasia can lead to acute obstruction of the airway, usually the trachea (114-118). Such patients may be very difficult to intubate endotracheally, requiring decompression of the megaesophagus by a nasoesophageal tube (117) or rarely by pharyngotomy (118).

Pulmonary Infections. These are especially frequent, both in primary and secondary achalasia. As already mentioned, bronchopulmonary symptoms may be prominent early symptoms (see Cases 1 and 2) and may even be present in the absence of esophageal symptoms. Organisms involved are most commonly aerobic and anaerobic oropharyngeal flora which are aspirated, leading to bronchitis, bronchopneumonia or lung abscess. There is also an apparent increased incidence of pulmonary infection with mycobacteria in achalasia, including atypical mycobacteria (119,120).

TREATMENT OF ACHALASIA

Rationale. The rational for therapy of achalasia is based upon reducing LES pressure to as close to zero as possible when the individual swallows. The final LES pressure after swallowing is a function of two factors: (a) the initial, resting LES pressure and (b) the percent relaxation of the LES after swallowing. There is little evidence that the latter of these processes can be affected by therapy at present. Even after dilatation or myotomy, the percent relaxation with swallowing remains abnormal in achalasia. Therefore, the goal

of therapy is to reduce resting LES pressure. Thus, if resting LES pressure in achalasia is 50 mmHg and if relaxation is only 50% with swallowing, a residual LES pressure of 25 mmHg will be present during swallowing, impairing esophageal emptying. If therapy could reduce resting LES pressure to 10 mmHg, then 50% relaxation with swallowing would result in a residual pressure of only 5 mmHg, a reduction of 20 mmHg. This reduction may lead to a marked improvement in esophageal emptying and symptoms.

Approaches available for reducing resting LES pressure include: drug therapy, dilatation, bougienage and surgery. I will review each of these, comparing them whenever possible.

Pharmacotherapy. A number of drugs act on the LES smooth muscle directly or indirectly to reduce resting LES pressure both in normal individuals and in patients with achalasia.

Anticholinergics. Two subtypes of muscarinic receptors for acethycholine exist: M_1 and M_2. Atropine and related antimuscarinic agents block M_1 and M_2 receptors nonselectively. Since the muscarinic receptor on the LES is of the M_2 subtype (121), atropine and related agents reduce resting LES pressure by 30-70% both in normal people and patients with achalasia (40,41). One preliminary placebo-controlled study suggested that chronic oral therapy with the anticholinergic dicyclomine reduced LES pressure and improved symptoms in 10 patients with achalasia (122). The disadvantages of chronic oral anticholinergic therapy in achalasia are twofold: (1) these agents have side effects (dry mouth, tachycardia, visual difficulties, and bladder dysfunction) and (2) these agents reduce contraction amplitude in the body of the esophagus (123), potentially reducing already impaired esophageal smooth muscle function. At present conventional anticholinergics play little role in the therapy of achalasia. Recently, M_1-selective antimuscarinic agents have been developed. An example is pirenzepine, and this drug has fewer side effects than nonselective antimuscarinic agents (124). However, pirenzepine does not act on the M_2 receptor on the LES and has no effect on LES pressure (125).

Nitrites and Nitrates. The fact that amyl nitrite, when inhaled, transiently reduces LES pressure in primary achalasia (but not in pseudoachalasia) has already been discussed. This effect has been incorporated into a diagnostic radiologic test (see above). While short-acting nitrates and nitrites were tried in achalasia in the 1940s and 1950s, they were for the most discarded because of their side effects and only brief duration of action. The development of relatively long-acting nitrates, given sublingually or orally, has led to their re-evaluation.

In 1981, Gelfond et al reported on the sublingual use of the long-acting preparation, isosorbide dinitrate, in 24 patients with achalasia, 8 of whom had previously been treated unsuccessfully by pneumatic dilatation or myotomy (126). Resting LES pressure was 46 $\pm$ 3 mmHg and this decreased quickly after isosorbide (within 2-8 min) and to a minimum pressure of 15 $\pm$ 2 mmHg in around 15 min; the relaxation usually lasted for at least 90 minutes. Of 23 patients who received the drug chronically in a dose of 5 mg sublingually before meals (for 2-19 months), 19 experienced a marked (n=8) or complete (n=11) relief of dysphagia. A large drop in LES pressure in response to the drug predicted a good clinical response to chronic therapy, but this did not reach statistical significance

with the number of patients tested. Side effects (i.e. headache) were common, but were reduced when the route of administration was changed to per os (10 mg). Two patients who responded initially became refractory to the medication after 2-6 months. Gelfond et al subsequently carried out a randomized study comparing sublingual isosorbide dinitrate therapy (5 mg) with sublingual nifedipine therapy (20 mg) and found that isosorbide was superior (127). (Calcium channel blockers are discussed in more detail below.)

Long-acting nitrates have not yet been compared with more conventional forms of therapy in achalasia (pneumatic dilatation, myotomy). Thus, their role is still being defined. This therapy is certainly worth considering in elderly individuals who are "high-risk" patients for dilatation or surgery. A combination of a long-acting oral nitroglycerin and an anticholinergic (propantheline bromide) was used successfully to treat a patient with vigorous achalasia (128).

Calcium-channel Blockers. While better known for their effects on cardiac muscle, these agents also have inhibitory effects on smooth muscle contraction. In normal people, calcium-channel blockers such as nifedipine reduce resting LES pressure and reduce the amplitude of peristaltic contractions in the body of the esophagus (123). The effect of calcium-channel blockers on the LES and esophageal body is additive with the effect of anticholinergic agents (123). Nifedipine also reduces LES pressure in patients with achalasia. For example, in one study 20 mg nifedipine sublingually reduced LES pressure by 47%, compared to a 64% reduction after 5 mg sublingual isosorbide dinitrate in the same 15 patients (127). In another study of 20 patients, 20 mg sublingual nifedipine reduced LES pressure by 30% (129). In a third study, intravenous verapamil (0.15 mg/kg or approximately 10 mg) reduced resting LES pressure by 34% in 7 patients with achalasia (130).

A study in Italy confirmed the 30-40% decrease in resting LES pressure in achalasia patients given sublingual nifedipine. The investigators then carried our a placebo-controlled clinical study of chronic, sublingual nifedipine therapy. Nifedipine was found to be significantly superior to placebo. Unlike the isosorbide dinitrate trial by Gelfond et al (126), side effects of nifedipine were uncommon and clinical tachyphylaxis was not encountered (131).

Beta-Adrenergic Agonists. Alpha-adrenergic agonists increase LES pressure, while beta-adrenergic agonists reduce it. The selective beta-2 agonist, carbuterol, reduced LES pressure in normal people (132). The same study reported a substantial (40-50%) reduction in resting LES pressure in 10 patients with achalasia following oral administration of 4 mg carbuterol (132). Long-term clinical studies using beta-2 agonists have not been reported in achalasia.

Summary of Pharmacotherapy. Several classes of drugs reduce LES pressure in achalasia including anticholinergics, beta-adrenergic agonists, nitrates/nitrites, and calcium-channel blockers. Of these, the most attractive are long-acting nitrates, given sublingually or perhaps orally, and calcium-channel blockers given sublingually. The former are probably more effective but have more side effects. Furthermore, tachyphylaxis to nitrates may occur. It is probably prudent to consider pharmacotherapy as initial therapy for elderly "high-risk" patients with achalasia (133). The role of pharmacotherapy in

younger patients is still not clearly defined, although promising results in children have been reported (134). Controlled trials comparing pharmacotherapy with pneumatic dilatation or myotomy are needed.

Pneumatic Dilatation. The goal of dilatation therapy in achalasia is to permanently disrupt sphincteric smooth muscle fibers in the LES, reducing resting sphincter pressure to normal or even below normal levels. Most dilatation procedures are pneumatic (i.e., they use air pressure to disrupt the LES). It is beyond the scope of this Grand Rounds to review and compare all of the different types of dilators that have been used over the years. All of the devices have in common a bag or balloon that is attached to a long tube, bougie, wire, or catheter, the tip of which is positioned in the stomach. Many of these devices are named for their designers [e.g., Browne McHardy (or Hurst-Tucker), Mosher, Rider-Moeller, Witzel, Sippy, and so on]. Recently, dilators that are attached directly to an endoscope have been developed (135-137). The dilator we are currently using at the Dallas VA Medical Center is the Rigiflex Achalasia Dilator, which is similar in design to Grunzig angioplasty catheters (138). Once the tip of the device is in the stomach, the bag or balloon is positioned across the gastroesophageal junction and inflated to a high pressure (~ 300 mmHg) for anywhere from several seconds to 3 minutes, after which the dilator is deflated. Most physicians inflate the dilator a second time at the same session. It is not uncommon for blood to be present on the dilator when it is removed. Even under sedation, this procedure is quite painful; furthermore, the risk of esophageal perforation is substantial. Most physicians keep their patients n.p.o. for several hours and obtain a barium swallow as soon as possible after the procedure using a water-soluble contrast material such as Gastrografin to diagnose esophageal perforation. A patient recently dilated successfully at the Dallas VA Medical Center is presented below.

> Case 4. A 72 year old man complained of dysphagia for liquids and solids for 15 years, nocturnal coughing spells, and regurgitation of food at night. An upper GI series and endoscopy were compatible with achalasia. Manometry: LES pressure 40 mmHg; no LES relaxation with swallowing; aperistalsis after swallowing with low-amplitude tertiary contractions. After oropharngeal anesthesia with Pontacaine and 10 mg intravenous Valium, the Rigiflex Achalasia Dilator (120 french, 40 mm) was passed over a guide wire and then positioned fluoroscopically and inflated in the LES region (17 pounds per square inch for 2 min and then again for 1 min). A small amount of blood was present on the balloon when it was withdrawn. A Gastrograffin swallow immediately after the procedure showed no extravasation of contrast material. The patient noted almost immediate improvement in swallowing and his other symptoms. He is now completely asymptomatic nearly 2 years later without further therapy.

Early Outcomes After Pneumatic Dilatation. In 6 recent series which include a total of 188 patients (range, 16-63 patients per series), 9 perforations occurred (4.7%). Each of the 6 series had at least one perforation (139-144). The incidence of perforation is probably related to the experience of the physician performing the procedure. Vantrappen in Belgium treated over 250

patients with a perforation rate of only 1.1% (145,146). It is likely that the 4.7% incidence of perforation referred to above is more realistic and the figure is probably even higher in centers where few cases of achalasia are seen. A strong case can be made for referring all patients with achalasia within a given geographic region to a single physician or small group of physicians with the most experience with the procedure. Esophageal perforation often requires immediate thoracotomy and repair (147); however, some patients respond to close observation and conservative medical management (n.p.o., intravenous fluids, parenteral antibiotics).

Besides the 5% of patients who experience a perforation, a small number of patients cannot be dilated because the bag or balloon cannot be safely positioned across the gastroesophageal junction. Some of these patients have an enlongated and tortuous (sigmoid) esophagus. In others, it may be impossible to pass the deflated apparatus through the high pressure zone into the stomach. Finally, some physicians consider the presence of a lower esophageal diverticulum or a history of previous myotomy as a contraindication to pneumatic dilatation for fear of rupture of the diverticulum or esophagus, respectively.

In the remaining patients (~ 90%), most have a marked reduction in LES pressure and improvement in symptoms immediately after dilatation, although a few will require a second dilatation session prior to discharge from the hospital. Some physicians recommend that, prior to discharge from the hospital after an apparently successful dilatation, an esophageal motility study should be repeated to confirm reduction of resting LES pressure. In practice, this is often omitted, probably because it represents still another intubation session for the patient. Recently, noninvasive radionuclide esophageal transit studies have been popularized for evaluating esophageal emptying function after dilatation (96-98).

Late Outcomes After Pneumatic Dilatation. Approximately half of patients who receive pneumatic dilatation have good to excellent long-term outcomes and do not require additional therapy (see Case 4). A few of these individuals develop mild, moderate, or even severe reflux esophagitis as result of loss of sphincter function.

One-third to one-half of the patients, after an apparently successful initial dilatation, will have a gradual recurrence of their symptoms months to years later. These patients generally require either one or more additional dilatation procedures or surgery, although some have been managed successfully with pharmacologic agents (126). As already mentioned, a small percentage of patients post-dilatation will develop squamous cell carcinoma of the esophagus.

In summary, the overall outcome after pneumatic dilatation therapy is quite variable, with a spectrum of outcomes ranging from complete and permanent relief of all symptoms with no complications through failure of the procedure, with or without procedure-related complications.

Bougienage. This technique (also called passive dilatation) is widely used to treat strictures of the esophagus. Mercury-filled bougies of either the Maloney-type (pointed tip) or the Hurst-type (rounded tip) and of various diameters are swallowed by the patient and advanced by either the physician or the patient into the stomach across the LES. The procedure is simple and

inexpensive and can be taught to the patient for periodic use at home. Complications (perforation, bleeding) may occur but are uncommon.

Bougienage in achalasia has been unpopular because the improvement in symptoms is thought to be transient, at best. Thus, pneumatic dilatation or surgery are usually performed. However, Mandelstam and associates recently have reported in an uncontrolled study satisfactory results with bougienage in 4 of 5 patients with achalasia. At one sitting, a series of Hurst bougies was passed in sequence [i.e., starting at 36 French (12 mm) and ending at 58 French (19.3 mm)]. In 2 of the 4 patients who improved, additional sessions were not required (follow-up 14 months and 2 years), while in the other 2 patients repeat bougienage sessions were required at approximately 6 monthly to yearly intervals (148).

Rauzman et al recently carried out a comparison of bougienage and pneumatic dilatation (Brown-McHardy balloon) in 18 patients with achalasia secondary to Chagas' disease (149). More serious cases received pneumatic dilatation and so the study was not strictly randomized between the two modalities. Nevertheless, the study showed superiority of pneumatic dilatation over bougienage with respect to symptoms. Moreover, LES pressure decreased by 65% one year after pneumatic dilatation but only by 15% one year after bougienage. One patient had acute esophageal perforation following pneumatic dilatation, however.

In summary, bougienage may be effective in some patients with achalasia, but is not as effective as pneumatic dilatation or surgery. The technique is less dangerous and less expensive than these other modalities, however, and should be considered in high-risk patients.

Surgery. The surgical therapy of achalasia has been reviewed in detail by Shackelford (150). The most popular operative procedure is an esophagocardiomyotomy, first reported in 1913 by Heller and subsequently modified by several surgeons. In the original operation by Heller, an anterior and posterior myotomy were performed, either through an abdominal or thoracic approach. Most surgeons now only perform an anterior myotomy. The basic component of a myotomy is to make a vertical incision across the cardia and LES, first transecting the outer longitudinal smooth muscle layer and then carefully transecting the inner circular smooth muscle fibers down to the level of the submucosa, which has a white, smooth surface. Great care is taken to avoid cutting into the mucosa. In patients with the vigorous achalasia variant, which overlaps with DES, the myotomy is extended cephalad to include the spastic smooth muscle portion of the body of the esophagus.

There is no question that a modified Heller's myotomy is usually effective in reducing LES pressure and in relieving symptoms of achalasia (151-154), although in a few cases the operation is unsuccessful and further surgical, dilatation, or pharmacologic therapy may be required. Reasons for failure include incomplete division of the circular muscle fibers in the region of the LES and restenosis due to scar formation at the site of the myotomy. One surgeon from China has reported that the latter complication can be prevented by suturing a pedicle of diaphramatic skeletal muscle into the site of the myotomy defect (155).

The major drawback of myotomy, at least in several series, is that sphincter function is sometimes completely destroyed, leading to gastroesophageal reflux with esophagitis in 10-50% of patients, often with complications of esophagitis [stricture, Barrett's esophagus with or without adenocarcinoma (156,157)]. Post-myotomy gastroesophageal reflux is especially dangerous in patients with achalasia since esophageal clearance of acid by primary or secondary peristalsis is absent. This had led some surgeons to recommend intra-operative manometric studies to allow preservation of some sphincter function during myotomy (158). Another group has proposed that extensive mobilization of the esophagus and stomach prior to myotomy disturbs normal anatomic relationship between these organs and the diaphragm and is a major predisposing factor to post-operative reflux. They developed a myotomy method that does not require esophagogastric mobilization, the myotomy being done via a thoracotomy and through an incision in the peri-hiatal portion of the diaphragm. A low incidence of postoperative reflux esophagitis was reported in this uncontrolled study (159).

Some surgeons advocate an anti-reflux procedure (e.g., Nissen or Belsey fundoplication) at the time of myotomy (160). Fundoplication may be coupled with proximal gastric vagotomy (161), which reduces gastric acid secretion. However, some surgical experts still contend that an anti-reflux procedure is unnecessary when performing a modified Heller's myotomy (162).

Besides failure of the operation to relieve symptoms or the development of postoperative reflux esophagitis, other problems with myotomy are its high cost and its postoperative morbidity/mortality. Morbidity includes atelectasis, pneumonitis, mediastinal and/or pleural infection, intra-abdominal infection, paralytic ileus, and deep venous thrombosis. In 3 recent reports involving 156 patients, 5 died postoperatively (3.2%), with at least one death in each series (151-153).

Patients in whom esophageal peristalsis returned (at least partially) after Heller's myotomy have been reported (163,164). In one study from Italy (165), some esophageal peristalsis returned after myotomy in 3 of 22 patients (14%). The explanation for return of peristalsis is not certain, but a similar phenomenon has been described in approximately 20% of patients after pneumatic dilatation (166). Unfortunately, in the majority of patients, peristalsis does not return after an otherwise successful myotomy or pneumatic dilatation (167).

Surgery Versus Pneumatic Dilatation. It is difficult to compare these two modalities from literature reports since few comparative or controlled studies have been carried out. Six review articles, editorials, or audits on this topic have appeared since 1980 and five of these concluded that pneumatic dilatation should be employed as initial therapy, reserving surgery for dilatation failures (168-173). This recommendation was based upon considerations of efficacy, patient preference, cost, and complications.

Only one randomized controlled trial comparing pneumatic dilatation and esophagomyotomy has been performed. This was done by Csendes and his colleagues in Santiago, Chile, where 38 patients with previously untreated achalasia were studied between 1973 and 1979 (174). Five of the 38 patients (13%) had a positive serologic test for Chagas disease; in the other 33 patients achalasia was of the primary (idiopathic) type. Eighteen patients were randomized to receive pneumatic dilatation using a Mosher bag under fluoroscopic guidance, performed

by a single investigator. The other 20 patients were randomized to receive surgery, specifically anterior esophagomyotomy performed by a single investigator. Patients in the two groups were well-matched for age, sex, and duration of symptoms prior to treatment. The clinical outcomes for the two groups are shown in Table 9.

Table 9. Clinical Comparisons in Study by Csendes et al (174)

	Pneumatic Dilatation (n = 18)	Surgery (n = 20)
Mortality	0	0[a]
Ave. length of hospitalization	1 day	8 days
Ave. recovery period	1 week	4 weeks
Early post-treatment dysphagia	0	0
Late post-treatment dysphagia	10	7
Complications: infection	0	2[b]
heartburn	0	2
Mean follow-up (range)	42 months (15-73)	43 months (16-83)

a One patient died 6 months postoperatively; the cause of death was not stated.

b Intra-abdominal infection postoperatively in both patients; one required reoperation for subphrenic abscess.

Examination of Table 9 shows that the pneumatic dilatation procedure was cheaper than surgery (i.e. shorter hospitalization time), had a much shorter recovery period, and fewer complications. However, after initial relief of symptoms dysphagia recurred after pneumatic dilatation in 10 of the 18 patients and was often "moderate" (defined as patients who could only take minced foods) or "severe" (defined as patients who could only tolerate liquids). Three patients required one or two additional dilatation sessions, after which one became asymptomatic and the other two were left with only "mild" dysphagia. Three other patients with severe dysphagia were subsequently subjected to surgery.

The diameter of the gastroesophageal (GE) junction and the diameter of the middle third of the esophagus were measured radiologically before and after therapy in both groups (Table 10).

Table 10. Radiologic Comparisons in Study by Csendes et al (174)

	Pneumatic Dilatation (n = 18)	Surgery (n = 20)
Ave. diameter at GE junction		
Before treatment	2.6 mm	2.2 mm
After treatment	6.6 mm	8.5 mm
Ave. diameter of body of esophagus		
Before treatment	4.1 cm	5.1 cm
After treatment	3.0 cm	2.8 cm

Both therapies increased the diameter of the GE junction significantly, although surgery appeared to be somewhat more effective. The diameter of the mid-esophagus decreased after therapy in both groups, but to a somewhat greater extent after surgery. Manometric studies before and after therapy are summarized in Table 11.

Table 11. Manometric Comparisons in Study by Csendes et al (174)

	Pneumatic Dilatation (n = 18)	Surgery (n = 20)
Ave. LES pressure		
Before treatment	30.0 mmHg	30.3 mmHg
1 mo. after treatment	15.2 mmHg	7.6 mmHg
Peristalsis present		
Before treatment	none	none
After treatment	none	none
Intra-esophageal pressure		
Before treatment	5.6 mmHg	6.4 mmHg
After treatment	-1.7 mmHg	-3.6 mmHg

LES pressure 1 month after treatment decreased in both groups, but more after myotomy. The reduction in LES pressure was maintained after surgery (8.4 mmHg at a mean follow-up of 43 months). LES pressure in the 8 patients who became and remained asymptomatic after pneumatic dilatation remained reduced (14.5 mmHg) at late follow-up (mean, 42 months). However, in the 10 patients who developed late symptoms of dysphagia, LES pressure had returned to the baseline preoperative value (6 of these required redilatation or surgery; the other 4 refused additional therapy). In no case in either group did esophageal peristalsis return after treatment. Resting intra-esophageal pressure was elevated above fundic pressure in all patients before therapy and became negative (which is normal) after dilatation or surgery.

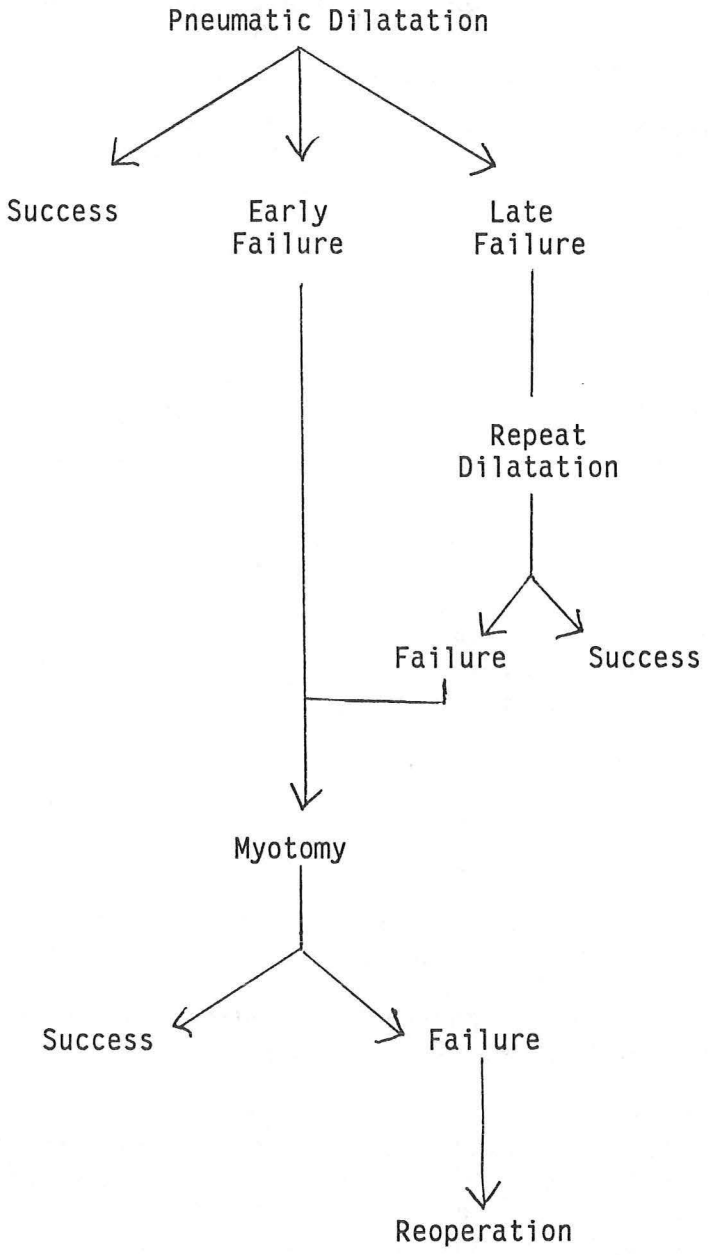
It appears from this small controlled study with a relatively short follow-up period that myotomy may be somewhat superior to pneumatic dilatation. However, it is more costly, more temporarily disabling, and associated with more complications. Additional controlled studies are desirable, especially those that address cost-effectiveness.

Reoperations. That several large series have appeared in the surgical literature describing various types of reoperation after myotomy attests to the fact that myotomy is not always as successful as reported by Csendes et al (see above) and by others. Indications for reoperation include but are not limited to inadequate myotomy, peptic stricture related to reflux esophagitis, and carcinoma of the esophagus (175).

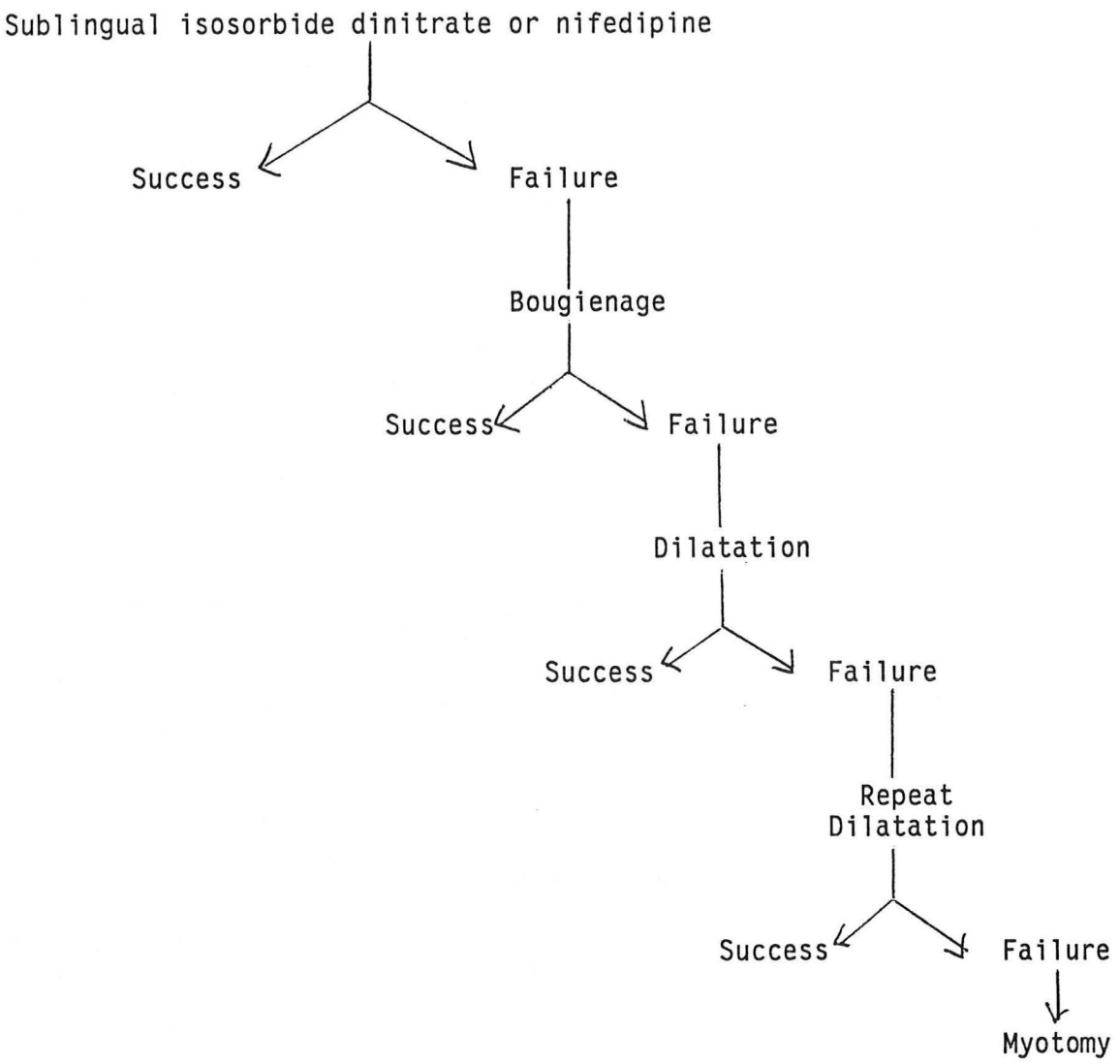
For inadequate myotomy, various operations have been proposed, including iterative myotomy (176,177), cardioplasty (178, side-to-side esophago-gastric anastomosis with fundoplication (179), and transhiatal esophagectomy with gastric interposition (180).

Summary of Therapy. Based upon the above review, I have presented below an approach to the therapy of primary, idiopathic achalasia. Two extremes are presented, a young, healthy adult (low risk patient) and an elderly person with multiple associated medical problems (high risk patient).

Low-Risk Patient



High-Risk Patient



Obviously, these schemata are provided only as guidelines and each case much be individualized. Many, perhaps most, patients with achalasia are "intermediate" risk patients rather than "low risk" or "high risk". The schema proposed for the high risk patient, beginning with non-invasive therapy and proceeding ultimately to more and more invasive therapy may be attractive in some younger, healthier patients as well, especially children. However, myotomy, and to a somewhat lesser extent, pneumatic dilatation have the potential to relieve all symptoms in one fell swoop, and thus these approaches will continue to be popular, despite their risks, until the cause of achalasia and specific therapy are discovered.

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