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GARY GITNICK

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This book is dedicated to my family: My wife, Cherna; my children, Neil, Kim, Jill, and Tracy; my mother, Ann; and my brother Jerry and his wife, Saranne, and their children, Nan and Andrea. They make it all worthwhile.

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Preface

This book series was developed to provide clinicians with an overview of the research progress in the clinical and basic sciences pertaining to gastroenterology. Each chapter's author is an expert in the area covered. Each was asked to read the world's literature published during the preceding year and to evaluate the year's most significant developments. The intention of each chapter is to place new concepts, treatments, and trends in the proper perspective rather than to provide a simple compilation of abstracts.

The authors were asked to organize the literature in an understandable manner, to be critical when appropriate, and to provide the reader with a comprehensive assessment of the work produced during the past year. Since this book represents the most significant research performed, it may not cover all areas of gastroenterology. To avoid individual bias and ensure a balanced view, authors are rotated from volume to volume. In addition, each chapter undergoes review by a second physician considered an expert in the field.

The editor and chapter authors have become convinced that the wealth of literature in gastroenterology is too great for any clinician to be expected to adequately review all pertinent research. It is our hope that this review will help clinicians keep up to date and adequately evaluate the major contributions to clinical and basic research.

I am indebted to those peer reviewers who have reviewed this volume's chapters: Paul Guth, M.D., Sidney Phillips, M.D., and Ronald Koretz, M.D. I also wish to express my gratitude to Susan Dashe for her dedicated efforts in bringing the chapters together in a timely fashion and preparing them in a manner suitable for publication.

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The Esophagus

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Disorders of the esophagus are among the most common reasons for patients to see internists or gastroenterologists. Disorders of the esophagus are not only common but may be life-threatening, as in the case of Boerhaaves syndrome and esophageal cancer. Symptoms from the esophagus may be the first sign of a systemic disorder, such as esophageal moniliasis in acquired immunodeficiency syndrome (AIDS), dysphagia in chronic idiopathic intestinal pseudoobstruction or amyloidosis, and reflux symptoms in scleroderma. In this chapter, we will review the latest basic and clinical information about the esophagus.

PHYSIOLOGY OF THE ESOPHAGUS

Many have thought that since the repertoire of functions of the esophagus are limited, it should be a realistic goal to be fully acquainted with the mechanisms involved in producing normal activities of swallowing, establishing a barrier to acid reflux, and clearance of esophageal secretions or refluxed acid. Regrettably, our understanding of the mechanisms of these functions remains very incomplete.

Peristalsis

Peristalsis, the predominant function of the esophagus, results from stimulation of local smooth muscles by a migrating neural reflex that has been initiated by intraluminal stimuli or vagal stimulation. Thus, the study of peristalsis can be separated into the study of vagal stimuli, local neural reflexes, and the smooth muscle component.

One can readily demonstrate the importance of the vagus nerve to the swallowing reflex. Peristalsis can be initiated by stimulation of the efferent vagal nerve. It is becoming increasingly clear, however, that most vagal fibers are not involved with stimulating contractions but are in fact afferent nerves carrying information back to the central nervous system. Gastrointestinal physiologists have recently taken a page from the neurology laboratory to record electrical signals generated from the cerebral cortex in response to stimulation of the esophagus. Researchers in Germany have recently used this technique to record cortical signals in response to electrical stimulation of the proximal, middle, and distal esophagus.[1] Signals were recorded with the greatest amplitude and shortest latency from the proximal esophagus. Bolus viscosity, temperature, volume, and pH (but not osmolality) can influence the frequency of peristalsis and the amplitude of contractions.[2] It is hoped that our understanding of the central nervous system processing of esophageal functions will expand as experience grows with this technique to evaluate the cortical responses to these more physiologic intraluminal stimuli.

Direct activation of intramural nerves by electrical stimulation of muscle strips results in relaxation if the muscle is first activated by bethanechol, a cholinergic agonist.[3] This inhibitory effect can be mimicked by the application of exogenous vasoactive intestinal polypeptide (VIP). Furthermore, both responses were inhibited by the application of a specific antiserum to VIP. This same antiserum had no effect in the presence of excess VIP, suggesting that the effect was being mediated by antibody neutralization of VIP. Dopamine inhibited both responses. When the electrical stimulus was terminated, the muscle contracted in a so-called "off-response," which could be blocked completely by atropine. Thus, this elegant work by Behar and colleagues has demonstrated that two transmitters involved in the

neural reflexes that are responsible for peristalsis in the cat esophagus include VIP and acetylcholine. Neuropeptides other than VIP that are present in abundance in the human esophagus include substance P, bombesin, and somatostatin.[4]

The electrical correlates of the smooth muscle during these responses were studied by Paterson in the opossum esophagus.[5] Electrical stimulation of esophageal smooth muscle causes an initial hyperpolarization followed by a rapid depolarization that leads to contraction. By varying the nature of the electrical stimulus or the duration of balloon distension, one can create either simultaneous or peristaltic contraction. By correlating the electrical signals associated with peristalsis induced by balloon distension, it was shown that the factor most important in determining whether a contraction is peristaltic or not is the timing of the depolarization. These recordings of electrical signals from esophageal smooth muscle are leading to a better understanding of the smooth muscle components of esophageal peristalsis. The findings in an opossum differ from Behar's findings in the cat in that cholinergic antagonism by atropine had no effect on peristalsis in the distal esophagus.[6]

The Gastroesophageal Barrier

The second major physiologic function of the esophagus is to establish a tonic functional barrier between the acid contents of the stomach, which is under increased pressure induced by abdominal contents and abdominal wall contractions, and the esophagus, which lies within the negative pressure of the intrathoracic cavity. The characteristics of lower esophageal sphincter (LES) function have been quantified with computer analysis.[7] Relaxation is induced by a non-adrenergic non-cholinergic transmitter. This signal is transmitted across the LES by electrical signals carried by a dense meshwork of gap junctions with an unclear contribution by the cells of Cajal.[8]

While initial studies suggested that this relaxation was induced by VIP, more recent studies have brought serious question to this hypothesis. While both VIP and electrical field stimulation cause relaxation of muscle strips, the inhibition of chloride channels blocked the response to VIP but not to electrical stimulation. Thus it was apparent that chloride conductance may be present in the sphincter muscle and influences cellular depolarization. The importance of VIP in mediating LES relaxation has also been studied by evaluating the changes in cyclic nucleotides associated with relaxation of the LES induced by field stimulation and in response to VIP. The data from two very reliable groups are in conflict and will not be resolved until further studies are completed.

In addition to extrinsic neural innervation from the v gus, recent studies suggest that nerve fibers innervate the LES from the stomach.[9] Electrical stimulation of the stomach was shown to profoundly inhibit LES tone. It is possible that this reflex may contribute to intermittent LES relaxation.

Contractions of the LES may be tonic or may occur in response to esophageal acid reflux. Basal LES tone is composed of myogenic tone and stimulation from both cholinergic (presumably parasympathetic nerves)[7, 10] and adrenergic transmitters (presumably sympathetic nerves). This rather simplistic model is complicated by the observation that both cholinergic and adrenergic nerves innervating the LES often contain more than one transmitter.

Parkman et al. have recently shown that the peptide neurotransmitter neuropeptide Y (NPY) is colocalized with sympathetic amines in the cat LES.[11] The role for multiple transmitters in a single nerve is unknown. In this study of the cat LES, it was shown that very small amounts of NPY can markedly augment the contractile effect of a threshold dose of norepinephrine on the LES. This has led to the concept that peptidergic transmitters serve as modulators of other primary signals.

The gastroesophageal barrier may also receive a contribution from contraction by the crural diaphragm, although this observation remains controversial. In the dog, surgical removal of the diaphragm reduced the pressure measured across the gastroesophageal junction by less than 20%, despite the associated trauma and extrinsic denervation that would be unavoidable with such a procedure.[12] A contribution to the gastroesophageal barrier by the crural diaphragm in man was recently suggested by the demonstration of electrical activity suggestive of crural electromyography (EMG) signals that showed changes that paralleled the relaxation or contraction of the LES.[13]

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is a frequent disorder encountered by gastroenterologists and nongastroenterologists. Symptomatic GERD is one of the most common disorders of the gastrointestinal tract. Heartburn has been reported to occur in anywhere from 10% to 20% of the general population.[14]

The term GERD includes a variety of clinical conditions and histologic changes of the esophagus that occur secondary to gastroesophageal reflux. This includes the inflammatory changes of esophagitis leading to erosions, ulcerations, or pseudomembranes, as well as the noninflammatory state of gastroesophageal reflux. Typically, only a small proportion of all patients who have gastroesophageal reflux will exhibit esophagitis endoscopically or histologically; however, gastroesophageal reflux is a necessary component for the development of reflux esophagitis. When esophagitis is present, there is a microscopic inflammatory infiltrate, whereas patients who simply have heartburn commonly have noninflammatory reflux changes of the esophagus consisting of epithelial basal hyperplasia without an inflammatory infiltrate.

This past year many articles have been published that address the pathogenesis, symptoms, treatment, and complications of GERD.

Pathogenesis

The pathogenesis of GERD is multifactorial. It may result from disorders of normal gastric and esophageal physiology including: (1) competence of the antireflux mechanism—primarily the LES pressure; (2) alteration of the esophageal clearance capacity; (3) delayed gastric emptying—leading to alterations in the volume of gastric contents; (4) perturbation of esophageal mucosal resistance and its ability to repair; and (5) increased quantity of the caustic nature of the refluxate, including ingested materials, gastric acid, or bilous alkaline duodenal contents.

The Importance of Ingested Substances

Many different foods and substances have been shown to produce heartburn or influence basal LES pressure including caffeine-containing products, chocolate, fatty foods, ethanol, cigarette smoking, and onions.

Fatty foods have been shown to lower the basal LES pressure; however, they have not been studied as to whether they increase total esophageal acid exposure with a prolonged esophageal pH monitor. Ten healthy subjects and ten patients with known gastroesophageal reflux underwent ambulatory 24-hour pH monitoring to assess esophageal acid exposure following low- and high-fat meals eaten in two body positions (supine and upright).[15] The meals ingested were similar in caloric content, volume, and protein content. The patients ingested one of the meals twice each day and subsequently ingested the other meal on the following day, followed by a random assignment to a 3-hour upright or a 3-hour recumbent position. Acid exposure was determined hourly, for a period of 3 hours postprandially, by calculating the percentage of time that the esophageal pH 5 cm above the LES was less than 4. In the upright position, healthy subjects had more reflux with the high-fat meals as compared with the low-fat meals ($6.2 \pm 2.1\%$ vs. $1.5 \pm 0.5\%$; $P < .05$). Patients with gastroesophageal reflux had increased acid exposure compared with that in healthy subjects in all study periods; however, there was no difference between low- and high-fat meals in either position of study. Of interest, acid exposure in healthy subjects during recumbency was not prolonged by the high-fat meal. This study suggests that high-fat meals increase upright gastroesophageal reflux in healthy subjects and not in patients with preexisting abnormal reflux.

Caffeine, a methylxanthine, is thought to have similar effects on gastroesophageal reflux as theophylline. Theophylline is commonly used in the treatment of patients with asthma. Patients with asthma have an increased incidence of gastroesophageal reflux. Aminophylline has been reported to increase gastric acid secretion in patients with chronic obstructive pulmonary disease[16] and to decrease the LES pressure in healthy patients as well as in patients with asthma.[17] When performing prolonged intraesophageal pH monitoring in healthy subjects and in children with asthma on a conventional theophylline regimen, it has been demon-

strated that there was no change in gastroesophageal reflux.[18] It is not known, however, if by using prolonged intraesophageal pH monitoring one can detect an abnormal increase in gastroesophageal reflux in adult patients with asthma on a conventional theophylline regimen. It has been postulated that theophylline is a major contributor to the high incidence of gastroesophageal reflux in patients with asthma. A randomized, double-blind crossover design was used to compare the effects of a 1-week conventional theophylline treatment and a 1-week placebo treatment in 16 adult patients with asthma.[19] Oral and parenteral steroids were not used; however, 7 patients were taking inhaled steroids, and all patients were using adrenergic drugs. Of significance in this study is that theophylline levels of less than 10 mg/L were documented in 4 of 16 patients studied. As in the previous study, no significant difference was found when theophylline was compared to placebo, suggesting that theophylline does not contribute to the increased incidence of gastroesophageal reflux in adults with asthma.

The Importance of LES Competence

Since the LES was first identified with manometry in 1956,[20] this physiologic zone of increased pressure has been thought to be one of the most important factors involved in the pathogenesis of GERD. It is currently believed that transient relaxation of the LES is the major mechanism of gastroesophageal reflux in healthy subjects.

It should be noted, however, that there are three mechanisms by which gastroesophageal reflux of free gastric juice may occur[21]: (1) spontaneous reflux, which occurs during transient relaxation of the LES and is often not associated with swallowing; (2) stress reflux, which occurs secondary to transient increases in intraabdominal pressure; and (3) free reflux.

The site and stimulus necessary for stimulating transient relaxation of the LES is currently unknown; however, it is most likely due to a physiologic reflex since it occurs in normal asymptomatic patients and is involved in belching. There is increasing evidence that transient relaxations of the LES are increased in patients with GERD compared to healthy subjects and that transient relaxations of the LES are the major cause of reflux in healthy patients. The characteristics and frequency of transient relaxation of the LES in healthy subjects when compared to patients with known GERD has not been critically assessed.

Recently, a study was performed to evaluate the characteristics and frequency of transient relaxations of the LES in patients with reflux esophagitis and to compare them with those in healthy patients.[22] In this study, 12 patients with symptomatic GERD confirmed by pH monitoring were compared to 10 healthy control patients to determine the mechanisms of GERD and the frequency with which transient relaxation of the LES occurs. The frequency of transient LES relaxation was identical in both groups; however, in healthy patients, 36% of the LES relaxations were associated with pH evidence of reflux whereas in patients with GERD, 65% of the transient LES relaxations were associated with a reflux event. The au-

thors conclude that other factors must contribute to the pathogenesis of GERD other than transient relaxation of the LES.

There are several factors that can be altered leading to gastroesophageal reflux; however, the gastroesophageal antireflux barrier still remains a primary determinant. There has been a suggestion that the physiologic LES is composed of both the crural diaphragm surrounding the esophageal hiatus and the LES itself.[12] Together, they are thought to act as a functional unit to maintain the high pressure zone between the esophagus and stomach to prevent acid reflux. To further investigate this concept, anesthetized dogs were studied and pressures in the gastroesophageal junction were recorded with a station pull through technique. The pressures in the gastroesophageal junction were decreased from a basal mean pressure of 20 mm Hg to a value of 15 mm Hg when the hemidiaphragm was excised. A mechanical barrier persisted even after excision of the left half of the dogs' diaphragms, suggesting that the greatest portion of the barrier is contributed by the intrinsic sphincter, the LES.

The mechanisms responsible for transient LES relaxations are not known. They may be mediated by efferent inhibitory vagal nerves that cause LES relaxation when the esophagus is distended or when swallowing occurs. Gastric distension is a stimulus for relaxation of the LES. If these inhibitory pathways (which are thought to be operative in achalasia) also mediate LES relaxation induced by gastric distension, then this response (transient relaxation of the LES in response to gastric distension) would be expected to be absent in such patients. To evaluate this, 10 healthy subjects were compared to 16 patients with achalasia.[23] In healthy subjects, gastric distension induced a fourfold increase in the rate of LES relaxations and gas reflux episodes, whereas this response was absent in patients with achalasia. The findings were suggestive that transient LES relaxations induced by gastric distension are neurally mediated, probably by the same inhibitory nerves that regulate swallow-mediated LES relaxation.

Acid reflux caused by abdominal muscle contraction with associated transient increases in intraabdominal pressure has been described as stress reflux. To determine the effects of different types of exercise on gastroesophageal reflux, a controlled study was performed.[24] It was found that vigorous exercise can induce gastroesophageal reflux in healthy subjects. Of the exercises studied, running induced the most reflux whereas aerobic exercise with less body movement (bicycling) induced less reflux. A weight routine (nonaerobic exercises) consisting of five different exercises (sit-ups, bench press, sitting arm press, prone leg curls, and sitting leg curls) induced gastroesophageal reflux in some patients. None of these specific exercises was associated with more reflux. The authors thus suggest that patients who have GERD might choose exercises that are less likely to increase gastroesophageal reflux.

Patients with chronic respiratory failure have been using negative pressure body ventilators with increasing frequency in recent years. Regurgitation occurs frequently in these patients, as may gastric aspiration. The mechanisms whereby negative pressure ventilation induces reflux were studied by measuring pressures in