CURRENT GASTROENTEROLOGY

GARY GITNICK

VOLUME 6

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CURRENT GASTOENTEROLOGY
Volume 6

This book is dedicated to my wife Cherna and to my children Neil, Kim, Jill, and Tracy. They continue to support me as well as to inspire and amaze this husband and father.

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Preface

Like its predecessors, this volume of *Current Gastroenterology* covers a wide range of developments that we, the editor and authors, think are most important to the practice of gastroenterologists. This volume extracts from the published literature those concepts currently considered the most significant.

Experts from each of the major areas of gastroenterology were asked to prepare chapters and to assess scientific trends in their areas of expertise. They reviewed the most important articles published during the past year; in all over 2,000 articles.

These experts were instructed to avoid discussing every article reviewed, but rather to provide the reader with a summation of those concepts that developed during the past year and that were thought to be of greatest significance.

As in previous volumes, we undertook to avoid the unnecessary bias that can occur when authors review their own work. To ensure that bias was not a factor, the editor and one or two peer reviewers reviewed chapters in addition to the chapter authors. These experts were asked to ensure that important work was not deleted and that reported works were not inappropriately described or emphasized.

In a further effort to mitigate bias and to bring new ideas to this volume, 30% of the authors are new each year. This constant infusion of "new blood" brings new thinking and new approaches. As editor I am indebted to my colleagues who served as peer reviewers for this edition. They are Andrew Ippoliti, M.D., and Jon Isenberg, M.D.

I am also indebted to Mrs. Susan Dashe whose administrative skills resulted in the efficient compilation of this volume. Finally, I am indebted to those many scientists whose work is reviewed in these pages. They have taught us much. I am especially indebted to our younger colleagues who not only continue to teach us, but also inspire us.

GARY GITNICK, M.D.

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Contents

CHAPTER 1

The Esophagus

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THE ESOPHAGUS continues to be a dynamic structure both in its function and in the year's recent literature. Extensive papers have been published concerning its physiology and disease states. As in previous editions, this chapter is designed to point out the highlights of new information and to direct the reader into the areas of current treatment modalities and future investigation.

PHYSIOLOGY

The Upper Esophageal Sphincter

The upper esophageal sphincter (UES) prevents the reflux of esophageal contents into the pharynx and tracheobronchial tree, and it has been proposed that the patient with reflux-related respiratory complaints may have an abnormality of UES function. An increase in UES tone after gastroesophageal reflux might be precipitated by distension of the esophageal body by either the volume of the refluxed

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material or its chemical (i.e., acid or alkaline) content. Accordingly, Madsen et al.[1] infused fluid volumes of 2.5, 5, 10, and 15 ml (pH 1.0, 4.0, or 7.0) into the distal esophagus in eight healthy persons. Pharynx-mediated peristalsis was found to be specifically related to the acidity of the infused fluid. Despite this presumed protective effect, extensive pulmonary complications have been associated with and purported to be secondary to gastroesophageal reflux.[2] Tuchman et al.[3] have shown that as little as 0.05 ml of 0.2N HCl infused into the trachea can evoke an average 4.65-fold increase in the total lung resistance from baseline values.

Sondheimer[4] studied the upper esophageal sphincter and pharyngoesophageal motor function in infants with and without gastroesophageal reflux. Overall, the resting UES pressure and pharyngeal contraction amplitude, duration, and velocity were the same in both groups. Perfusion of the esophagus with distilled water resulted in no significant increase in the mean UES pressure of controls or reflux patients. During acid perfusion, both groups showed significant increases.

Overall, the role of the UES in patients with respiratory complaints with or without gastroesophageal reflux is still poorly characterized. Further careful manometric evaluation, under provocative and/or inhibitory stimulation, is needed.

Esophageal Body

The development of the esophageal peristaltic wave continues to receive much attention. The determination of its pathophysiologic basis will obviously result in a greater understanding of both the broad range of motor dysfunction continually being elucidated and the mechanisms of esophageal injury secondary to gastroesophageal reflux.

The act of swallowing is associated with a peristaltic wave of esophageal contraction. While the peristaltic activity of the skeletal muscle portion of the esophagus is secondary to the sequential activation of the lower motor neurons of the vagal nuclei, the smooth muscle portion seems to be controlled by peripheral intramural mechanisms.[5] A stimulus applied to esophageal circular muscle, in vitro, evokes a contraction after a certain latent period. This latency increases gradually in muscle strips taken from more distal regions of the esophagus, and the gradient produced may represent the physiologic equivalent of peristalsis.[6]

Crist et al.[6] demonstrated that transmural stimulation of esophageal circular muscle produced contractions that occurred either during or after the period of stimulation. The most prevalent contractions were those that occurred after the termination of the stimulus (''off'' contractions), followed in frequency by those that occurred at the onset of the stimulus (''on'' contractions). Both of the contractile patterns were neurogenic in origin. The ''on'' contraction was antagonized by atropine, while the ''off'' contraction was not. This suggested that cholinergic pathways were involved in the ''on'' contraction only.

Additional work by Crist et al.[5] continued to show that both cholinergic and

noncholinergic nerves were involved in peristalsis. Proceeding distally along the esophagus, there was a gradient of decreasing cholinergic influence and increasing noncholinergic influence. Noncholinergic nerves appeared to be responsible for a period of inhibition followed by rebound contraction. Overall, the cholinergic nerves were thought to modulate the speed, amplitude, and duration of the peristaltic contractions associated with the noncholinergic inhibitory nerves.

From a more mechanical aspect, Sugarbaker et al.[7] used miniature strain gauges to selectively monitor the mechanical forces and suction electrodes to record the electrical activity of the longitudinal and circular muscle layers. During peristalsis and in response to swallows and vagal stimulation, longitudinal muscle contraction occurred prior to circular muscle contraction and was of longer duration. The longitudinal muscle contracted while the circular muscle was inhibited, showing no hyperpolarization prior to depolarization and thus no latency. It was suggested that the longitudinal muscle aided aboral transport of the intraluminal bolus by providing advancing rigidity of the esophageal conduit.

The correlation between the motor activity of the esophageal body and gastroesophageal reflux has continued to draw extensive attention. Helm et al.[8] evaluated the factors that affected esophageal acid clearance in normal subjects by infusing acid boluses into the esophagus and having the patient swallow every 30 seconds. The authors correlated manometry with pH monitoring and showed that esophageal acid clearance occurred by a series of stepwise increases in pH, each with a swallow-induced peristaltic sequence. The specific amplitude of normal peristaltic contractions was not a critical factor in acid clearance. Helm et al.,[9] in a later work, injected 15-ml boluses of 0.1N HCl (pH 1.2) into the esophagus with radiolabeled (technetium [Tc 99m]) sulfur colloid. Concurrent radionuclide imaging and manometry showed nearly complete emptying of acid from the esophagus by an immediate secondary peristaltic wave. Esophageal pH again returned to normal, with stepwise increases again initiated by swallow-induced peristaltic waves. A key point to be made is that saliva, and its neutralizing capability, was the major component of esophageal pH neutralization, with the swallow-induced elevations in pH being blocked by oral suction. Nonetheless, the authors did feel that an abnormality in esophageal peristalsis could result in a large residual acid volume that physiologic amounts of saliva were incapable of neutralizing.

Along these lines, Orr and colleagues[10] suggested that impaired esophageal acid clearance of refluxed material during sleep played a major role in the pathogenesis of esophagitis. The esophageal contraction measures of amplitude, velocity, and duration were found to be similar in both asleep and aroused subjects. This led to the suggestion that episodes of prolonged acid clearance in patients with nocturnal reflux were more directly attributable to a poor arousal response leading to a markedly diminished initial swallowing rate and a diminished deliverance of saliva.

Calcium is essential for esophageal smooth-muscle contraction. The calcium channel blockers inhibit membrane fluxes of calcium and thus have an important role in the evaluation, study, and treatment of esophageal body function and dysfunction. Hongo et al.[11] noted that both intracellular calcium ions and cholinergic

neural input played important roles in esophageal contraction. These researchers tested normal subjects with 20 mg of sublingual nifedipine and/or 15 mg of oral propantheline bromide (an anticholinergic) vs. placebo and compared the subsequent effects on esophageal motor function. Contraction amplitude in the body of the esophagus diminished significantly after propantheline (25%), but only by 11% (not significant) after nifedipine administration. In combination, contraction amplitude diminished significantly by 37%.

More extensive and detailed studies by Hongo et al.[12] addressed the effects of sublingual nifedipine on esophageal contraction amplitude, peristalsis, velocity, and duration after wet swallows. In this report, plasma nifedipine concentrations were carefully monitored. Contraction amplitudes diminished significantly with 30- and 40-mg sublingual doses of nifedipine, with the effect lasting up to 60 minutes. There were no changes in esophageal peristalsis, velocity, or duration of contraction at any dose. Clearly, the role of calcium channel blockers in the treatment of motility disorders of the esophagus is being extended. Prospective, placebo-controlled clinical trials still are needed to determine whether these agents can be effective in tolerable doses.

Overall, it is evident that the neural and chemical aspects of esophageal body motor function are being defined. When coupled with a pathophysiologic understanding of disease states and the ability of pharmacologic manipulation, the control of esophageal body dysfunction is rapidly approaching.

Lower Esophageal Sphincter

Despite intensive study of both esophageal and gastric emptying and their relation to gastroesophageal reflux, the lower esophageal sphincter (LES) and its competence seems to be of paramount importance in reflux esophagitis. Significant mechanical, neuronal, and hormonal factors all seem to contribute to LES competence and tone.

It seems reasonable that the bulk of gastroesophageal reflux would occur either in patients with diminished LES pressure or at least during episodes of LES pressure drops. In support of this, Corazziari et al.[13] recorded 131 episodes of reflux in 13 patients with complaints of heartburn and regurgitation. Of these 131 episodes, 118 were preceded by a swallow, while 13 were not. Their results tended to show that low basal LES pressure was not specifically related to gastroesophageal reflux, but that swallow-induced LES inhibition was. Once esophageal inflammation is present, an associated marked decrease in LES pressure has been shown to occur, suggesting that acid-induced mucosal injury affects the ability of the LES muscle to develop wall tension and produce intraluminal pressure. Biancani et al.[14] isolated LES muscle rings from acid-perfused cats and demonstrated a general reduction in basal resting pressure and induced wall tension. The injury was specific for the LES, as the mechanical properties of muscle rings isolated from the esophageal body were not affected. The induced esophagitis may have

impaired the cholinergic excitatory innervation of the LES or may have directly affected the calcium-handling mechanisms of the LES smooth muscle.

An important mechanism protecting against gastroesophageal reflux is the rise in LES pressure induced by a rise in intra-abdominal pressure. Ogilvie et al.[15] studied 24 normal subjects, measuring LES pressure with graded increments in intra-abdominal pressure. The observed LES pressure rise was blocked by atropine and was absent in nine of 11 patients who had undergone previous truncal vagotomies for peptic ulcer disease. The results indicated that the response of the LES to increases in intra-abdominal pressure was dependent on both intact afferent and intact efferent vagal fibers.

Recent studies have centered on the neurotransmitters that may be directly involved in LES function. Reynolds et al.[16] noted that the LES responded to a wide variety of neurohormonal agents, suggesting the presence of specific sphincteric neural or muscle receptors. In their study, an attempt was made to find the neurohormonal mechanism of acidification-induced LES pressure increases in anesthetized cats. Substance P exerts a dose-dependent increase in LES pressure and spike activity. Using manometric catheters and serosal bipolar silver-silver chloride electrodes, it was determined that intravenous (IV) tetrodotoxin partially antagonized the LES pressure increase to substance P and that large doses of a substance P antagonist significantly inhibited the LES pressure response to infused acids. Overall, the studies suggested that the increase in LES pressure and the spike activity following distal esophageal acidification occurred through a spike-associated enteroneural reflex that involved substance P as a neurotransmitter. Because tetrodotoxin gave only partial antagonism of the LES response to substance P, a direct action of this hormone on LES muscle was thought to be possible.

Along similar lines, Biancani et al.[17] noted that vasoactive intestinal polypeptide (VIP) was hypothesized to be an inhibitory neurotransmitter responsible for LES relaxation. LES muscle strips were removed from cats and placed in three solutions, one containing VIP antiserum, the second containing normal rabbit serum, and the third simply Tyrode's solution. Using electrical stimulation and treatment with varying doses of VIP, it was found that VIP relaxed the LES by direct action and mimicked the action of neural stimulation. Further, VIP antiserum inhibited the relaxation induced by exogenous VIP or by electrical stimulation of nonadrenergic, noncholinergic inhibitory nerves at the level that was known to cause the release of VIP from the nerve terminals. Overall, it seems that VIP, in the cat LES, in vitro, fits the bill as the inhibitory neurotransmitter.

ESOPHAGEAL FUNCTION TESTS

Potential Difference/Electrical Resistance

Esophageal injury causes disruption of the mucosal barrier. In most experimental models, this disruption included an increased permeability of the mucosa to

luminal hydrogen and other ions. Electrophysiologic studies have shown that the normal electrical potential difference (-15 ± 5 mV) changes with tissue injury, usually falling in patients with esophagitis (-5 mV) and rising in patients with Barrett's epithelium (-25 mV).[18] While the change in esophagitis results from increased epithelial permeability and inhibited active sodium transport, the mechanisms for the high PD seen in Barrett's esophagus may simply reflect an intrinsically higher PD for columnar epithelium.

Herlihy et al.[19] evaluated the PD profiles in normal patients and 20 individuals with Barrett's esophagus. In healthy subjects, the PD profile obtained by pulling the PD probe from the stomach through the LES into the esophagus was characterized by a fall in PD to less than -25 mV. In contrast, patients with Barrett's esophagus showed an increase in PD to greater than -25 mV as the probe entered the esophagus or showed a normal decline in PD over the LES, followed by an abrupt increase to values greater than 25 mV in the lower esophagus. The study demonstrated that a high PD was fairly specific (92%) for the diagnosis of Barrett's esophagus, but was only moderately sensitive.

Kidder et al.[20] used an experimental model of rabbit esophageal injury and attempted to use transesophageal electrical resistance measurements to assess the degree of injury. Tissue resistance, which falls with injury, was compared with standard indices of mucosal injury such as acid flux, PD, and morphological change. Tissue resistance was found to be more sensitive in detecting early injury. While these results were encouraging, the actual measurement of tissue resistance was crude and could not be entirely attributed to esophageal sources.

Despite mild optimism for these two methods, neither the measurement of PD nor tissue resistance is being widely used to screen for gastroesophageal reflux or Barrett's esophagus.

Manometry

Although manometric evaluation has been shown to change the clinical diagnosis in only about 6% of all those tested,[21] esophageal motor evaluation and pressure measurement still remains the major tool of experimental and clinical investigation. Blackwell and Castell[22] suggested that appropriate patient selection, achieved by excluding those with cardiac disease, gastroesophageal reflux, or cholelithiasis, coupled with provocative challenge, would enhance the usefulness of manometric evaluation in diagnosis of esophageal dysmotility as a cause of chest pain. In fact, when patients with reflux alone were excluded, esophageal dysmotility could be demonstrated in up to 45% of patients tested.

Unfortunately, the elimination of cardiac disease and the use of provocative challenge is not so simple. Ergonovine maleate, an adrenergic agonist, is a nonspecific stimulator of smooth-muscle spasm and has been used to induce both esophageal and coronary artery contraction. To answer the obvious problem, Lie-