# CURRENT

# GASTROENTEROLOGY

## VOLUME 7



*Edited by*

**Gary Gitnick**

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**YEAR BOOK MEDICAL PUBLISHERS, INC.**
**Chicago • London • Boca Raton**

International Standard Serial Number: 0198-8085
International Standard Book Number: 0-8151-3508-4

Sponsoring Editor: Betsy Banks-Golub
Manager, Copyediting Services: Frances M. Perveiler
Production Project Manager: Carol A. Reynolds
Proofroom Supervisor: Shirley E. Taylor

This book is dedicated to the members of my family, my wife Cherna, my children, Neil, Kim, Jill, and Tracy; my mother Ann Hahn and her husband David Hahn; my brother Jerry Gitnick, his wife Saranne and their children, Nan and Andrea. In one way or another, they have each contributed to the development of this text and the others for which I have been responsible and it is to them that I continue to have the deepest gratitude.

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# Preface

The practice of gastroenterology has evolved so rapidly that its literature overwhelms even the most dedicated reader. The goal of this book is to distill from this vast body of information the material most pertinent to the modern gastroenterologist. This book is practical. It is not encyclopedic, nor does it dwell on minutiae. Rather, it provides the reader with current, essential information derived from the world's literature published during the past year. Discussions of diseases of the liver, biliary tract, and gallbladder have been omitted and are reported in the companion text, *Current Hepatology*.

Any text in which expert authors review the work of their peers can suffer from the prejudices of the authors. Any author will have expertise in certain areas and shortcomings in others. To ensure that this text represents a broad consensus, experts in each field reviewed the final chapters and suggested areas inappropriately emphasized or works unnecessarily omitted.

This volume of *Current Gastroenterology* includes a unique section on inflammatory bowel disease. In celebration of the opening of the Joseph B. Kirsner Digestive Disease Center at the University of Chicago, a symposium was held to summarize recent progress in our understanding of inflammatory bowel disease. This was a unique opportunity not only to honor the lifelong work of Dr. Joseph B. Kirsner, but also to bring together a body of knowledge comprised of our remarkable achievements in the understanding of these diseases.

The authors who contributed to this book were carefully selected, not only because of their expertise, but also because of their demonstrated ability to write clearly and to differentiate significant accomplishments from less important undertakings. They were instructed to avoid discussing every article reviewed but rather to provide the reader with a summary of those concepts that have developed dur-

ing the past year and are thought to be of greatest significance. Unlike other texts, this book does not provide a series of abstracts, but instead summarizes in narrative form a summation of a large number of recorded works. It shows the interrelationships of research developing in many laboratories and points the reader toward the direction in which the most significant advances are taking.

I am indebted to my colleagues who served as reviewers for the chapters of this book They are Drs. Peter Banks, Bernard Levin, Thomas Kovacs, Andrew Ippoliti, Paul Guth, and Jerry Trier. I am greatly indebted to Mrs. Susan Dashe, whose remarkable skills efficiently brought this text to fruition. I am indebted to my friends at Year Book Medical Publishers, Inc., Nancy Chorpenning and Elizabeth Sugg Both have worked tirelessly to ensure that these books were well-written and that they are indeed current. I also am indebted to my colleagues in gastroenterology whose work is reported in these pages.

GARY GITNICK, M.D.

# Contents

# CHAPTER 1

# The Esophagus

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The Physiology and management of diseases of the esophagus and its sphincters is updated in this chapter. We have also attempted to apply this knowledge to understand the pathophysiology of the disorders afflicting the human esophagus. Since the last review of this topic, a large amount of literature has been published on the subject of this organ. While it was not possible to review each and every article, every effort was made to cover most of the new and interesting information. In keeping with the tradition of the last two volumes, we will begin with the physiology and proceed to pathophysiology of the diseased state.

## ESOPHAGEAL PERISTALSIS

Swallow-induced, esophageal peristalsis continues to fascinate a number of investigators. Both central and peripheral mechanisms are involved in the genesis of peristalsis. The role of the central nervous system (CNS) in the smooth-muscle portion of the esophagus has been further investigated. It has been previously

*Curr Gastroenterol* 7:1-30, 1987

0198-8085/87/07-001-030-$04.00

shown that secondary peristalsis in the smooth-muscle portion of the esophagus does not require CNS connection: it is mediated by a peripheral mechanism. However, using a vagal cooling technique, Reynolds et al. have shown that both primary as well as secondary peristalsis in the skeletal as well as the smooth-muscle portion of the cat esophagus required an intact vagus nerve.[1] Further investigating the role of the CNS in esophageal peristalsis, Gidda and Goyal looked at the swallow-evoked action potentials in vagal preganglionic efferents.[2] Long and short latency efferent fibers were recognized in the vagus. Short latency fibers were distinguishable from the long latency fibers by virtue of their low threshold of excitation and sensitivity to the changes in frequency of electrical current. The authors proposed a dual pathway for esophageal peristalsis, suggesting that short latency fibers mediate initial inhibition, and long latency fibers mediate the peristaltic contraction. The electrical equivalent of the inhibition phenomenon at the cellular level, known as inhibitory junction potential (IJP), was studied by Kannon et al.[3] The IJP seems to be the result of an increased permeability of the cell membrane to potassium ions. Also, the inhibitory response observed by stimulation of noncholinergic nonadrenergic nerves in the esophagus is essentially similar to that described for the smooth muscles of the other regions of the gastrointestinal (GI) tract. However, the potassium channels responsible for the extracellular shift of potassium in the opossum esophagus are distinct in that they are resistant to several of the known potassium channel-blocking agents.[4]

Multiple swallows during a short interval can affect each other. The effect of the second swallow on the first is the result of initial inhibition, whereas the effect of the first swallow on the second is due to the esophageal smooth-muscle refractory period. Gidda et al. found gradients of the duration and degree of initial inhibition and refractoriness along the length of the esophagus.[5] Since distal esophageal sites have more inhibitory innervation, the inhibition is stronger in the distal esophagus. Also, the refractory period following a swallow is of longer duration in the distal than the proximal esophagus. These gradients of initial inhibition and refractoriness are probably responsible for the esophageal response to multiple successive swallows and the peristaltic nature of the esophageal contraction.

Interstitial cells of Cajal (ICC), previously described in animal species, have been found in the human esophagus as well.[6] Based on their location and interrelationship to the smooth muscle bundles, three different kinds of ICC have been found in the human esophagus and lower esophageal sphincter. They differ from each other in the extent of smooth endoplasmic reticulum, number of cytoplasmic reticula, and presence of cytoplasmic crystalline inclusions. Interstitial cells of Cajal are closely related to the nerve terminals and are in abundance wherever there is inhibitory innervation. Because of the close relationship between nerve terminal and muscle, an intermediary role of these cells in neuromuscular transmission is possible.

Despite extensive studies, the physiologic role of neuropeptides in the control of esophageal motility and lower esophageal sphincter (LES) pressure modulation

remains far from clear. Contrary to previous reports, Dowlatshahi et al. found that morphine in pharmacological doses increased LES pressure and impaired relaxation.[7] Based on these observations, the authors concluded that excessive autonomic secretion of endogenous enkephalins could result in the esophageal motility disorders. Contrary to this study, we found that a 5-mg intravenous (IV) bolus of morphine reduces sphincter pressure significantly.[8] The data on the effect of various pharmacological agents on LES pressure should be analyzed carefully, since the resting sphincter pressures in awake subjects vary from minute to minute.

## LOWER ESOPHAGEAL SPHINCTER

The advent of the sleeve device has provided considerable insight into the physiology of the LES. This device works as a Starling resistor.[9] The rate of fluid flow in the range of 0.1 to 2 ml/minute does not affect the pressure measurements, and if the sleeve is faced with two pressures along its axial length, it will record the higher of the two pressures rather than sum them up. However, there are some limitations to its use. Since, when in position, part of the sleeve straddles the esophagus and stomach, the pressure changes in these organs may be transmitted and reflected in the sphincter pressure tracing.

Lower esophageal sphincter pressure monitored over a period of time shows significant phasic variation. Studies in human subjects have revealed that these phasic variations are related to the gastric migrating motor complexes (MMC). Similarly, studies in fasted unanesthetized opossums show large phasic variations in the LES pressure. These phasic variations, occurring at a rate of three to four/minute, are closely coupled with the gastric contraction and proceed to phases II and III of the gastric MMC.[10] It is remarkable that pressures as high as 150 mm Hg can be recorded in the LES.[10] Migrating motor complexes in the GI tract can be abolished by pentobarbital anesthesia, while phasic variations in LES pressure are inhibited by pentobarbital. Atropine also prevents the occurrence of both LES and gastric MMC activity.[10] Close coupling of LES and gastric phasic activity is vital for the prevention of fasting gastroesophageal reflux. Hollaway et al. found the occurrence and magnitude of phasic variations paralleled the spontaneous cyclic level of plasma motilin.[11] Pulse doses of exogenous motilin elicit a contractile LES response that mimics the phasic LES variation during MMC; motilin acts on the LES by stimulation of the preganglionic cholinergic nerves. However, the physiologic role of motilin in the induction of spontaneous activity is controversial. Other investigators have found that the rise in the plasma motilin level occurs after the onset of gastric and duodenal MMC activity, suggesting that this could be an epiphenomenon. Motilin is present in the bowel wall, and contractions of the stomach and intestine may squeeze motilin out into the peripheral circulation, thereby causing plasma motilin levels to rise.

Gastroesophageal reflux and regurgitation are common in infancy. One reason

for this is that the LES may not be well developed in infants. Lower esophageal sphincter pressure in the three-day-old kitten is lower than in the six-week-old. Force-length curve studies showed that the maximum active force generated was lowest in the three-day-old kitten and increased with age. Lower esophageal sphincter pressure is determined by the product of stress and the muscle-thickness-to-radius ratio. Stress in the three-day-old kitten muscle is high, but as a result of diminished muscle-thickness-to-radius ratio, the LES in the younger kitten generates low LES pressures.[12]

McCallum studied the effects of a therapeutic dose and a large dose of alkali on the LES pressure in normal subjects and postantrectomy patients.[13] Neither the LES pressure nor serum gastrin concentration was different after a therapeutic dose of antacid compared with a placebo. However, the LES pressure increased after the large dose of alkali in normal subjects and in postantrectomy patients who had gastroduodenostomy, whereas the LES pressure was unchanged in patients who had gastrojejunostomy. The author suggested that the excitatory effect of a large dose of alkali is not mediated through gastrin; but rather, the effect is attributed to the presence of an intact duodenum and is probably related to the volume and osmolarity of the alkali load. The physiologic role of gastrin in sphincter tone modulation was further de-emphasized by Smout et al.[14] The authors studied the effect of cimetidine and ranitidine on LES pressure and serum gastrin during the interdigestive and postprandial state. Even though both cimetidine and ranitidine increased serum gastrin concentrations, the LES pressure decreased during the interdigestive period and no postprandial effect was seen.

Contrary to earlier beliefs, cyclic changes in the estrogen and progesterone during the menstrual cycle were not found to affect the LES pressure and esophageal contraction amplitudes.[15] The physiologic role of most of the hormones and gut peptides is controversial except for vasoactive intestinal peptide (VIP), which is considered to be the most likely candidate for the inhibitory neurotransmitter at the postsynaptic site. There is a possibility that the VIP concentration in the LES may explain the LES dysfunction in patients with reflux esophagitis and achalasia. In accord with this hypothesis, Aggestrup et al., using techniques of immunochemistry and immunocytochemistry, found high levels of VIP in the LES muscle strips in patients with reflux esophagitis and low levels in achalasics compared with control subjects.[16]

There is general consensus that the intrinsic LES accounts for the end expiratory pressure measured at the gastroesophageal junction. Whether the diaphragm contributes to the LES pressure is not clear. Using a cat model, Boyle et al. showed that LES pressure was higher at end inspiration compared with expiration. Peak LES pressure at end inspiration corresponded with the peak diaphragmatic electromyogram. Blockade of diaphragmatic contraction by a skeletal muscle paralyzing agent (pancuronium) abolished the inspiration-induced increase in sphincter pressure.[17] Therefore, pinchcock action of the diaphragm, by enhancing the LES pressure, may act as an antireflux barrier at the time of inspiration when the abdominothoracic gradient is high. Further studies show that the right crus of the

diaphragm, which is responsible for the pinchcock action of the diaphragm, remains electrically silent or, in other words, relaxed at the time of intrinsic LES relaxation induced by swallowing or esophageal balloon distension.[18] The afferent pathway for the crural inhibition seems to be in the vagus nerve, and there is central inhibition of the phrenic nerve fibers that innervate the right crus of the diaphragm. Whether impaired facilitatory action of the diaphragm or lack of inhibition would respectively result in gastroesophageal reflux and dysphagia needs investigation.

## GASTROESOPHAGEAL REFLUX DISEASE (GERD)

### Pathophysiology

At one time considered synonymous with hiatal hernia, GERD is presently thought to be multifactorial in etiology. Factors such as impaired esophageal peristalsis, defective acid clearance, LES dysfunction, hiatal hernia, delayed gastric emptying, and duodenogastric reflux all probably play an important role in the pathogenesis of this disease.

Considerable interest has been aroused in the mechanism of GERD in recent years. The significance of resting LES pressure has been seriously challenged. Transient LES relaxation unrelated to swallowing is presently thought to be the major mechanism of GERD in both normal subjects and patients with GERD. Baldi et al. showed that the frequency of transient LES relaxation is similar in normal subjects and patients with GERD.[19] Also, they observed that about one third of the acid reflux episodes occurred during swallow-induced LES relaxation in both normal subjects and patients with GERD. However, the frequency of swallow-induced peristaltic activity was reduced in GERD patients and acid exposure time was high in this group. The differences between this and earlier studies are difficult to reconcile, except that Baldi studied patients who were in both sitting and supine postures, whereas the earlier studies were performed with subjects in the supine position only.

Even though the precise mechanisms of reflux in patients with GERD may be controversial, transient LES relaxations (TLESR) unrelated to swallowing have been observed by a number of investigators. Holloway et al. showed that gastric distension is a stimulus for TLESR.[20] These investigators distended the stomach with a balloon by injecting 0, 250, 500, and 750 ml of air in a randomized order in normal subjects and patients with GERD. The frequency of TLESR increased in a dose-dependent fashion with an increase of three- to fourfold recorded with the largest volume. The frequency of TLESR increased to an equal extent in normal subjects and GERD patients. However, the latter group had a slightly higher incidence of complete relaxations. These authors suggest that afferents from the mechanoreceptors in the stomach travel along the vagus nerve to the dorsomotor