Current Gastroenterology

VOLUME 2

EDITED BY

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Preface

During the past several years, research in digestive diseases has flourished, leading to the acceptance of innumerable papers for publication. It soon became obvious that even the most dedicated physician could not read, assimilate, and integrate information contained in the available published literature. In order to provide an authoritative assessment of the manuscripts published annually, a book entitled *Current Gastroenterology and Hepatology* was developed with 12 well-known authorities assessing knowledge in their respective fields. The success of this book led to the development the following year of two separate volumes, *Current Gastroenterology*, volume 1 and *Current Hepatology*, volume 1. The formula used for the first volumes has further been improved for the publication of the second volumes. To avoid bias and to ensure a balanced view of the literature, many different authors have been recruited for volume 2. In addition, peer reviewers have evaluated the information presented in the book.

Each author has been asked to read the world's literature in his or her field during the preceding year and to prepare a chapter describing the development of new concepts, being careful to avoid presenting a series of abstracts. The goal is to ensure that each chapter accurately represents the medical literature in a particular field for a year and that each author strives to place new concepts, treatments, and trends in proper perspective. Writers have been asked to be critical if they think it appropriate. However, most importantly, they have been requested to organize the literature in an understandable manner and to review it so that the reader may benefit from the comprehensive assessment of the work produced during the year. This book is intended for the clinician as well as for the basic scientist. From year to year there may be a heavier concentration on clinical or basic papers and, if so, the review chapter for that year will reflect this tendency.

I am indebted to chapter authors, who diligently and successfully produced this book. I also wish to thank the peer reviewers, Charles Pope II, M.D., Jon Isenberg, M.D., Sidney F. Phillips, M.D., Lawrence Way, M.D. and I. Michael Samloff, M.D., who helped me in the development of this volume. A well-known baseball manager has often said that "coming close only counts in horseshoes, hand grenades, and dancing." I hope that this book does more than come close, that it actually reaches its goals and fulfills an important need.

Gary L. Gitnick

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Esophagus

Charles S. Winans

This review of the published progress in investigative esophagology from 1979 to 1980 must begin on a sad note, for it was within this review period that Franz Joseph Ingelfinger died. Dr. Ingelfinger's accomplishments as teacher, physician, investigator, journalist, and ethicist were extraordinary (1,2). Although gastroenterology as a whole benefited from his ability to ask critical questions about digestive disease pathophysiology and his insistence upon answers based on scientific methods, it was the gullet, among all the organs of the gut, that interested him most. He was a master clinician at the bedside of the patient with dysphagia, usually arriving at the correct diagnosis from a series of discerning questions to the patient long before his junior colleagues could position the x-ray films on the view box or report the results of manometric studies and endoscopy. In the laboratory he put many questions to his students. Is hiatus hernia really important? Is there a lower esophageal sphincter? How do laryngectomees learn esophageal speech? What controls the peristaltic wave in the normal esophagus, and what has gone wrong in patients with achalasia and diffuse esophageal spasm? The bountiful harvest of this year's research publications testifies to the advanced state of scientific investigation of esophageal physiology and disease, much of which was stimulated by the penetrating queries of Franz Ingelfinger. His wisdom, critical thought, and stimulating questions were a vital stimulus to esophageal investigation and will be sorely missed.

NORMAL ANATOMY AND PHYSIOLOGY

As in previous years, many investigations of the mechanisms and control of the motor function of the esophagus and its sphincters have been reported. For studies requiring invasive techniques not feasible in humans, the opossum, endowed with an esophagus with easily elicited peristalsis and a distribution of striated and smooth muscle like that of humans, continues to be the species of choice. Indeed, the esophageal physiologist must be public enemy number one in the opossum world. One might envision the species being placed on the endangered list if the riddle of esophageal motor function is not soon solved!

Upper Esophageal Sphincter

Previous manometric studies in humans and opossums have shown that there is both radial and axial asymmetry to the upper esophageal high-pressure zone. The radial asymmetry has been presumed due to the vicelike nature of the cricopharyngeus muscle, which exerts a strong compressing force in the anteroposterior plane but little squeeze in the transverse, whereas the origin of the axial asymmetry has been uncertain. Welch et al. (3) used sophisticated computer analysis of radial pressure measurements from an eight-orificed motility probe to map the three–dimensional topography of the human upper esophageal high-pressure zone. Radial asymmetry was confirmed in normal subjects but found absent in laryngectomees with resection of the larynx and cricoid cartilage, confirming that these structures are responsible for the radially asymmetric peaks. Axial asymmetry in normals was such that the anterior pressure peak occurred about 8 mm more orad than the posterior peak. A possible explanation for this axial asymmetry was offered by Gates (4) who studied the anatomy of the pharyngoesophageal junction of cadaver specimens distended with a plaster-formalin mixture. The inferior border of the cricopharyngeus was as much as 5 mm below that of the cricoid lamina, suggesting that the former was responsible for the posterior pressure peak and the latter for the anterior. Intraoperative manometry in patients undergoing laryngectomy also confirmed the loss of the orad, the radially asymmetric portion of the upper-esophageal high-pressure zone, when the cricopharyngeus was cut. The distal, radially symmetric portion of this high-pressure zone remained intact, however, adding further support to the claim that an intrinsic circular muscle sphincter exists in the most proximal esophagus. The physiologic significance of this latter mechanism, however, remains uncertain and, thus, a prime candidate for further investigation.

Esophageal Body

Those who perform manometric studies of human esophageal function have long recognized that isolated nonpropulsive (tertiary) esophageal contractions are frequently recorded even in healthy subjects. Ingelfinger speculated in 1958 that such contraction might result from various distant stimuli. Stacher et al. (5) have examined the possibility that sound might be one such stimulus. Intraesophageal pressure was, therefore, monitored in healthy subjects exposed through headphones to a sequence of 1000 Hz tones of 1.5 seconds duration, and varying from 70 to 125 dBA in intensity. All 22 subjects responded with tertiary contractions to a mean threshold intensity of 86.8 dBA. No peristaltic waves were elicited by the sound stimuli. The mean latency from stimulus to tertiary contraction was 0.95 seconds compared to the 0.05-second latency period for the response of the mylohyoid muscles (determined electromyographically) to the same stimulus. Tertiary contractions after the sound stimuli were not more common in older than younger subjects. The tertiary contractile response might be interpreted as part of the defense reaction. Its relevance to normal or disordered patterns of esophageal motor activity cannot be determined from the data of Stacher et al. (5), but the phenomenon is interesting in view of the paucity of information concerning the mechanisms of tertiary esophageal contractions.

Forty opossums were studied by Dodds et al. (6), who investigated the pharmacology of peristaltic control in the striated and smooth muscle segments of the esophagus in vivo. Under pentobarbital anesthesia the esophageal peristaltic response to pharyngeal stimulation was measured with the aid of an 8-lumen, minimally compliant, high-fidelity recording system, equipped with a probe with orifices at 2-cm intervals. Peristalsis in both types of muscle was not affected by α-adrenergic and β-adrenergic agonists or antagonists, by histamine or H_1- and H_2-receptor antagonists, by a tryptamine antagonist, or by glucagon. Succinylcholine, a nicotinic antagonist for striated muscle, was the only drug to abolish peristalsis in the proximal, striated muscle esophagus. Cholinergic drugs enhanced the amplitude and duration of peristaltic waves in the smooth muscle esophagus, whereas atropine depressed smooth muscle peristalsis significantly without abolishing it. The nicotinic ganglionic antagonist hexamethonium caused small decreases in peristaltic amplitude only at the transition zone between the two types of muscle. However, hexamethonium plus atropine, as well as nicotine alone, completely abolished smooth muscle peristalsis. The experiments confirm that ganglionic synapses are not important in the pathways controlling peristalsis in the striated muscle esophagus, although they suggest that cholinergic nerves acting on previously demonstrated muscarinic receptors of esophageal circular smooth muscle influence peristalsis. The failure of atropine to block completely smooth muscle peristalsis is consistent with the authors' hypothesis that a class of noncholinergic, nonadrenergic postganglionic nerves exists that is capable of eliciting peristalsis in the smooth muscle esophagus after muscarinic blockade. Previous vagal stimulation studies have also indicated the existence of such nerves. Species differences, however, suggest caution in the extrapolation of these conclusions to human physiology.

The distribution and function of enkephalin immunoreactive nerves in the esophagus was studied by Uddman et al. (7). Immunohistochemical study of guinea pig, opossum, cat, pig, monkey, and human esophageal tissue demonstrated in all species enkephalin immunoreactivity associated with the muscularis mucosae, smooth muscularis propria, and myenteric plexus. No conspicuous accumulation of such nerves was found in the region of the lower esophageal sphincter (LES) as had been previously reported for vasoactive intestinal polypeptide (VIP). Enkephalin immunoreactivity was not depleted in reserpinized cats. Strips of feline esophageal circular smooth muscle were studied in vitro. Short-pulse-duration electrical stimulation, which activates nerve tissue but does not directly stimulate muscle, caused contraction of muscle strips that was blocked by tetrodotoxin (TTX), reserpinization, α-adrenergic antagonists, and both met- and leu-enkephalin, but not by atropine or hexamethonium. The enkephalins had no effect on contractions induced by choline esters or norepinephrine, excluding the possibility that they have a direct relaxing action on esophageal smooth muscle. These observations suggest that the inhibitory action of enkephalin is exerted by presynaptic blockade of adrenergic transmission, possibly by modulating the release of an adrenergic neurotransmitter.

Lower Esophageal Sphincter

Intense investigation of the properties of the LES continues with particular emphasis on the mechanisms of muscular contraction, the pathways of hormonal

modulation of sphincter strength, and the nature of the inhibitory neurotransmitter involved in sphincter relaxation. The muscarinic cholinergic receptors in the LES were characterized by a study (8) of the kinetics of binding of [^{3}H] quinuclidinyl benzilate to tissue homogenates of the muscular layer of the distal feline esophagus. The muscarinic receptors of the cat LES appear to be present as a single population of saturable sites. Binding capacity of circular LES muscle was similar to that of longitudinal muscle in the LES region, smooth muscle in the proximal esophagus and muscle from small intestine, but only one-fourth that of muscle from the adjacent gastric fundus. Although muscarinic receptor density determined by such binding techniques apparently cannot distinguish LES from non-LES esophageal muscle, it is possible that similar studies of diseased or functionally abnormal tissue will provide insight into the pathophysiology of esophageal motor disorders.

Contraction of smooth muscle is believed to involve two distinct calcium activation systems, one important for maintenance of resting tone and the other for mediation of phasic contractions. In uterine muscle the phasic system is antagonized by verapamil that blocks influx of extracellular calcium, whereas nitroprusside antagonizes the tonic system by causing either sequestration or efflux of intracellular calcium. Goyal and Rattan (9) studied the effect of these two drugs on the resting LES of the opossum in vivo. Manometrically monitored LES pressure in this animal displays a variable profile, often including both tonic and phasic components. Both verapamil and nitroprusside administered intravenously reduced both components. Nitroprusside produced an abrupt fall in basal LES pressure, completely abolishing it at higher dose rates. Verapamil produced a more gradual but also nearly complete abolition of LES pressure. At doses causing similar falls in blood pressure, nitroprusside produced a greater fall in LES pressure than did verapamil. When doses causing similar reductions in LES pressure were infused, verapamil was slightly more effective in reducing the amplitude of peristaltic contractions in the body of the esophagus following electrical stimulation of the vagus nerve. These experiments indicate that, at least in the opossum LES, phasic and tonic contractions are not selectively dependent upon specific calcium activation systems and that blockade of either system is capable of nearly abolishing resting sphincter pressure by itself. The sites of action of verapamil and nitroprusside were not disclosed by these studies, but they probably act directly on the smooth muscle.

That various polypeptide hormones have at least a pharmacologic effect on gastrointestinal sphincter muscle is well established. For the LES, the observation that gastrin has a direct agonist effect initiated a still unresolved controversy regarding the physiologic importance of gastrin in controlling sphincter strength. Jensen et al. (10) studied the effect of intravenous injections of synthetic human gastrin G-34 and G-17 on human LES pressure. The threshold increase in serum gastrin needed to produce any increase in LES pressure was 30–50 fmol/ml for both hormones, whereas a half maximal LES response required an increase in serum gastrin of about 140 fmol/ml. As a 10% peptone meal increased peak total gastrin by only 58 fmol/ml, it was concluded that neither hormone is likely to be a physiologic regulator of the human LES.

The mechanism of action of various polypeptide hormones on the lower esophageal sphincter was investigated in opossums, cats, and baboons by pharmacologic analysis of hormone effect on the LES and its modification by various

agonists and antagonists in intact animals. VIP and secretin relaxed the LES in cats (11) by what appears to be a direct action on smooth muscle not antagonized by a variety of receptor blockers or TTX. In contrast, glucagon (11) appeared to stimulate contraction of the feline LES indirectly by activating preganglionic sympathetic nerves in the adrenal. This glucagon effect was abolished by TTX reserpinization, phentolamine, and adrenalectomy. In the baboon (12), intravenous VIP, secretin, and glucagon all caused a fall in basal or pentagastrin stimulated LES pressure. The action of VIP was most profound and occurred at a dose only one-sixteenth to one-sixty-fourth that of secretin or glucagon needed to produce the same effect.

Fifty opossums participated in studies that clarified the mechanisms by which bombesin (13) and bovine pancreatic polypeptide (BPP) (14) stimulate contraction of the LES. This action of both hormones is partially antagonized by TTX, suggesting that hormone effect may be twofold: A direct effect on sphincter muscle and an indirect neurally mediated effect. For bombesin the latter may have involved postganglionic adrenergic neurons as bombesin-induced sphincter contraction was abolished by phentolamine. In contrast, atropine partially antagonized the effect of BPP on the LES, suggesting that this hormone acts partially by stimulation of cholinergic neurons.

Techniques of pharmacologic analysis have proved fruitful in studying the complex action of humoral agents and neurotransmitters on the LES. Conclusions must remain tentative, however, because of methodologic difficulties. For instance, the effect of TTX blockade of the sodium channel-dependent neural conduction system on drug or hormone action is critical to the decision regarding neural mediation of a substance's effect. Yet completeness of TTX neural blockade is difficult to prove: there may be TTX-insensitive nerves, and TTX may not block release of neurotransmitters by agents acting on nerve terminals. The importance of species differences is exemplified by the opposite effects of glucagon on the resting LES of the baboon and the cat (11,12).

The physiologic significance of hormone effect on the LES is also difficult to ascertain. Bombesin (13), a tetradecapeptide obtained from frog skin, has the most dubious relevance, yet immunofluorescence studies have revealed the presence of a bombesinlike material in the gastrointestinal mucosa of humans. The doses of BPP used in the study cited (14) are probably supraphysiologic compared with the postprandial rise in human serum pancreatic polypeptide and the dose needed to exert the hormone's inhibitory action on pancreatic secretion in dogs. Yet the possibility of regional differences in tissue hormone concentration makes it impossible to exclude entirely a physiologic role. In truth, the action of no hormone on the human LES has been proved physiologic beyond reasonable doubt. The determination of physiologic relevance of polypeptide hormone action remains an exciting challenge to the investigator.

Electrical stimulation of the vagus nerve causes relaxation of the LES, an effect not altered by adrenergic or cholinergic antagonists. The neurotransmitters released by these noncholinergic, nonadrenergic postganglionic inhibitory neurons remain in doubt, although some believe that ATP or related purines are responsible. Rattan and Goyal (15) investigated the possibility that ATP or adenosine may be the elusive inhibitory neurotransmitter in a study of 37 opossums. Both substances caused a marked fall in LES pressure following bolus injection into the left gastric artery, a response not antagonized by atropine, propranolol,

or phentolamine. TTX, however, caused only minimal reduction of the inhibitory effect of ATP and adenosine. Furthermore, tachyphylaxis with a large dose of either ATP or adenosine did not modify the vagal-stimulated LES relaxation. Hence, neither ATP nor adenosine seems likely to be the inhibitory neurotransmitter of the noncholinergic, nonadrenergic neurons.

Further studies of the mechanism of vagally induced LES relaxation were performed by Fournet, Snape, and Cohen (16) who investigated whether specific agents that increase LES pressure might inhibit stimulated LES relaxation. Neither histamine nor gastrin infused intravenously in a dose that approximately doubled resting LES pressure significantly modified LES relaxation after vagal stimulation, esophageal-balloon distention, or swallowing. On the other hand, both bethanechol and phenylephrine reduced the fall in LES pressure subsequently produced by vagal stimulation or esophageal-balloon distention. Bethanechol decreased the sphincteric inhibitory response to swallowing. Thus, some specific agonists that increase LES pressure seem to inhibit LES relaxation. The mechanism involved is not clear, but presumably is not merely a nonspecific consequence of LES contraction, for gastrin and histamine did not reduce stimulated LES relaxation. Instead, a modulation of the inhibitory mechanism may involve α-adrenergic and muscarinic effects at the level of the myenteric ganglia.

ESOPHAGEAL FUNCTION TESTS

As much as we might wish it otherwise, symptoms of esophageal disease, particularly chest discomfort, are nonspecific, and accurate, sensitive, and specific tests of esophageal function would be highly desirable in the differential diagnosis of disease of the gullet. The multiplicity of currently available tests testifies to the fact that none has been found completely satisfactory and suggests the need for critical evaluation of the usefulness and accuracy of individual tests.

Such critical inspection of the methodology for measurement of LES pressure has been continued by Hay, Goodall, and Temple (17,18) and by Welch and Drake (19). The former group investigated the reproducibility (17) of LES pressures measured by triple-lumen, fluid-perfused, lateral-orifice catheters and by a commercially available motility probe equipped with three miniature-strain-gauge transducers. Asymptomatic volunteers were studied on three occasions by the station pullthrough (SPT) technique. Best correlation ($r = 0.88$; $P < 0.01$) was obtained between two studies with the perfused catheter 8 hours apart on the same day. A significant correlation ($r = 0.74$; $P < 0.05$) was still found between LES pressure measured on two occasions separated by a week. Poorer correlations were found using the strain-gauge probe in a separate group of volunteers. The study design contained too many variables to allow identification of the causes for the difference in reproducibility between the two pressure-measuring systems. In a separate study (18) the reproducibility of LES pressure determined by the rapid pullthrough (RPT) technique was assessed. Poor correlation was found between test results on the same day ($r = 0.44$) or 1 week apart ($r = 0.43$). The study of Welch and Drake (19) compared RPT and SPT techniques in normal subjects using a perfused multilumen tube, the eight recording orifices of which were at the same axial level. Six RPTs and six SPTs

were performed over 45 minutes in each of 18 subjects. The SPTs were scored in four different fashions (peak, mean, and minimum gradients between high-pressure zone and expiratory gastric pressure, and maximal pressure gradient at the point of respiratory reversal). Smallest coefficients of variation were found for the SPTs scored for maximum or mean gradients. RPTs had significantly higher coefficients of variation. Greatest interobserver variation in scoring was found when LES pressure was measured at the respiratory reversal point. The results of these studies seem to support Welch's suggestion that LES pressure be measured by SPT technique and scored by tabulating the gradient between the peak of the greatest respiratory pressure oscillation and end-expiratory gastric pressure. Although these studies have addressed the reproducibility of LES-pressure measurement and scoring, they leave unanswered an important question: Which measuring technique and scoring method yields a pressure that correlates meaningfully with clinical function of the LES? There seem to be so many variables in LES-pressure measurement, such as catheter compliance, catheter diameter, orifice radial orientation, withdrawal technique, and scoring method, that it is virtually certain that LES pressures measured by different laboratories are not comparable. Certainly for individual patients in a clinical setting measurement of LES pressure is of limited usefulness as a diagnostic tool. This latter point is underscored by another study of Welch and colleagues (20). They used radial manometry to compare the LES pressures of asymptomatic volunteers with those recorded from heartburn patients with positive standard acid reflux tests. The latter subjects were divided into two groups according to the presence or absence of polymorphonuclear leukocytes in suction biopsy specimens of the distal esophageal mucosa. Manometry could not distinguish normal from reflux patients without mucosal inflammatory cells. On the other hand, the reflux patients with inflammatory cells in their biopsy specimens had significantly lower LES pressures at all radial orientations. As three-fourths of the latter group had gross exudative esophagitis apparent at endoscopy, LES manometry added little to their diagnosis and was too insensitive and nonspecific to help where help was needed, that is, in the symptom group where inflammatory cells were absent on biopsy and endoscopy revealed a normal mucosa or mere erythema. This study and others like it do not answer the important questions of physiology as to whether the LES is a major antireflux mechanism and whether a weak LES might be a consequence rather than a cause of reflux. They do, however, warn the clinician that important diagnostic and therapeutic decisions cannot reliably be made on the basis of LES pressures.

Tests of esophageal function that do not require intubation are more acceptable to patients and research subjects and are usually more physiologic. Hence, scintiscan techniques for the quantitation of reflux have gained in popularity, and radioisotopes are being applied by investigators to study esophageal transit and emptying. Gross, Johnson, and Kaminski (21) used a technetium-labeled meal of corn flakes and milk to quantitate esophageal emptying in achalasia patients. Serial gamma camera counts over the stomach and esophagus allowed construction of an emptying curve showing the percent of the isotope meal remaining in the esophagus. Not entirely unexpectedly, the achalasis patients retained a far greater portion of the meal than did normal subjects. Though details differ, the study is similar in principle to that of Tolin et al. (22) who

previously have used esophageal scintigraphy to study esophageal transit in the spectrum of esophageal motor disorders. Such methods hold great promise for investigating the role played by motor disorders of the esophagus in patients with reflux injury, where they seem capable of quantitating esophageal clearance in a reproducible, safe fashion. Their utility in everyday clinical practice is uncertain, and they should not be indiscriminately used in a fashion that increases the cost of esophageal care without providing added benefit to the patient.

GASTROESOPHAGEAL REFLUX DISEASE

The last few years of research in the field of gastroesophageal reflux have seen the questioning of the supremacy of LES as an antireflux mechanism, and a renewed, open-minded search for other important pathophysiologic factors. This trend continues.

Pathophysiology

The role of hiatus hernia in the genesis of gastroesophageal reflux continues to create controversy. Last year Wright and Hurwitz (23) presented data showing that 84% of patients with endoscopically detected hiatus hernias also had endoscopically evident peptic esophagitis, whereas only 12% of those without hernia had esophagitis. The difference was highly significant statistically. They argued with some logic that if the two phenomena were unrelated, one would expect a similar incidence of hernia among those with and without esophagitis. As this was not the case, an association between the two is likely. Achord (24) subsequently questioned the methodology of the study, however, emphasizing the subjective aspect of the endoscopic diagnosis of esophagitis and the possibility of bias when the same observer decides on the presence or absence of both hernia and esophagitis. Clinical research is certainly not as simple as it appears at first glance! In addition, some might be surprised that only 22% of the total group endoscoped had hiatus hernias, since radiologic studies have shown an incidence closer to 50%. The published discussion and comments also fail to raise another possibility: hiatus hernia could be the consequence of esophagitis, perhaps the result of spasm or inflammatory shortening of the esophagus. All agree that the relationship between hiatus hernia and reflux esophagitis is complex and remains uncertain.

Wernly et al. (25) discovered a new nonsphincteric factor that is a potential cause of reflux. They observed by prolonged monitoring that frequent episodes of increased intra-abdominal pressure (IAP) occur spontaneously during which intra-abdominal pressure rises transiently by more than three times the respiratory pressure excursion. Intraesophageal pH was monitored for 24 hours in 19 patients with excessive reflux while IAP episodes were detected by a tocodynamometer compressed against the anterior abdominal wall. Reflux was assumed to result from IAP if the latter occurred within a 30-second period before the former. On the average, patients experienced 12.2 IAP and 2.7 reflux episodes per hour. Eight percent of IAP episodes were followed within 30 seconds by reflux, and 39% of reflux episodes were preceded by less than 30 seconds by