Pathophysiology of Gastrointestinal Diseases

Edited by Sanjiv Chopra, M.D., and Roger J. May, M.D.

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This book is dedicated to Amita, Ratika, Kanika, and Bharat, and to Louise and Channing for their encouragement and understanding

Preface

There are many exhilarating moments in medicine. They can be a new observation of an old disease, the discovery of an entirely new syndrome, or the development of a successful treatment of a disabling illness. Understanding pathophysiology is the key to each of these insights and discoveries. With this understanding, one is able to translate the inexplicable into the comprehensible with the potential for preventing, treating, or curing disease. This understanding is also the foundation for the intelligent practice of clinical medicine. With comprehension of pathophysiology, one is able to transform symptoms, physical findings, and diagnostic results into a coherent model of disease and thus treat an illness rationally and specifically.

This book provides a scientific foundation for understanding the natural history, clinical features, and management of disorders of the gastrointestinal system. We also hope that this book communicates the joy of knowledge that we and our co-authors have derived from this study of pathophysiology. By understanding the diseases we treat, we find the practice of medicine truly exciting and fulfilling. We hope this zeal and excitement will also be shared by the reader and that the book will provide a framework through which medicine can be thoughtfully approached and patients can be intelligently managed.

In editing this book, we learned immeasurably from our contributors and each other. Our greatest source of learning, however, continues to be our patients and students, to whom we owe our sincere gratitude. In enlivening the readers' interest in our subspecialty, we hope to repay in some measure this debt of gratitude.

S. C.
R. J. M.

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Notice

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

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1 : Motor Disorders of the Esophagus

Jeffrey R. Crist

The human esophagus is a hollow, tubular organ consisting of three major structural components — the upper esophageal sphincter, the esophageal body, and the lower esophageal sphincter (Fig. 1-1). These structures serve two primary functions: (1) during swallowing, they provide a mechanism by which a food bolus received from the pharynx is propelled into the stomach, and (2) between swallows, they prevent the retrograde flow of esophageal and gastric contents.

Abnormalities in the function of the esophagus are not uncommon and range from the very common entity of gastroesophageal reflux to such uncommon entities as achalasia. To properly diagnose and treat motor disorders of the esophagus, one must first understand the anatomy and physiology of the esophagus and the pathophysiology of esophageal disorders.

Anatomy and Physiology

Upper Esophageal Sphincter

Anatomy

The upper esophageal sphincter (UES) refers to an intraluminal high-pressure zone that exists between the pharynx and upper esophageal body (Figs. 1-1 and 1-2). In humans, the length of this high-pressure zone ranges between 2 and 4 cm and does not correlate with any distinct anatomically defined sphincter. Although there has been controversy as to which anatomic structures actually constitute the UES, most investigators now agree that this high-pressure zone is due to contraction of the cricopharyngeus and the most caudal (lowermost) portions of the inferior pharyngeal constrictor muscles. The cricopharyngeal muscle is only 1 cm in width and is believed to make up the most caudal portion of the UES. The inferior pharyngeal constrictor is believed to make up the remaining 1- to 3-cm segment. Both of these muscle groups are composed of striated muscle and are innervated by somatic nerves emanating from cranial nuclei (the nucleus ambiguus) located in the medulla oblongata of the brainstem.

Composition of muscularis externa

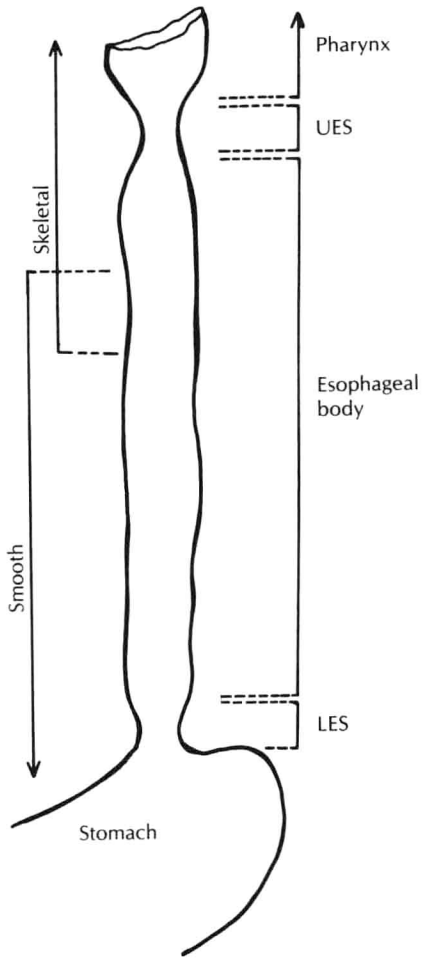

Fig. 1-1
Schematic diagram of the esophagus consisting of an upper esophageal sphincter (UES), esophageal body, and lower esophageal sphincter (LES). The muscularis externa of the UES is composed entirely of skeletal muscle, the LES of smooth muscle, and the esophageal body of both skeletal (uppermost portion) and smooth muscle (lowermost portion).

Physiology

In the intervals between swallows, the somatic nerves innervating the UES tonically stimulate the UES musculature. This continuous neural stimulation maintains muscle contraction and closure of the UES. This prevents esophageal contents from refluxing into the pharynx and respiratory tree, as well as entry of

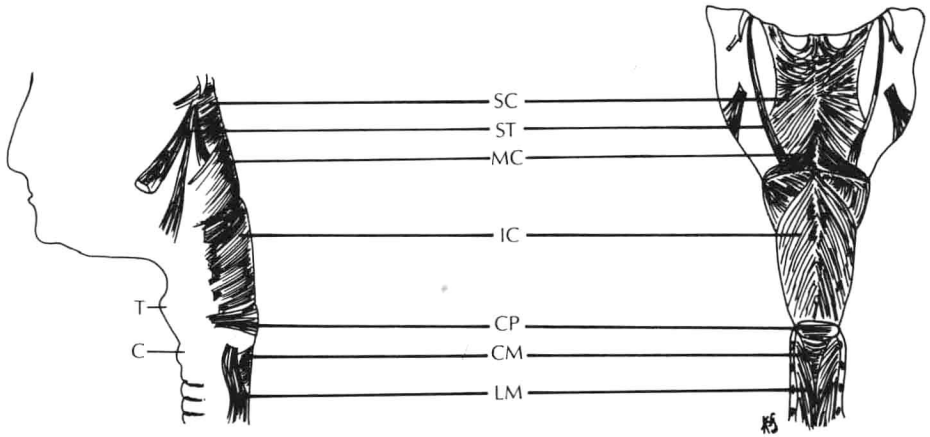

Fig. 1-2
Schematic diagram of the musculature of the oropharynx. The high-pressure zone comprising the upper esophageal sphincter is attributed to contraction of the cricopharyngeus (CP) and caudal portions of the inferior pharyngeal constrictor (IC) muscles. (SC = superior pharyngeal constrictor; ST = suprathyroid; MC = middle pharyngeal constrictor; CM = circular muscle layer of esophageal body; LM = longitudinal muscle layer of esophageal body; T = thyroid cartilage; C = cricoid cartilage)

air into the esophagus during inspiration. During swallows, this tonic nerve stimulation ceases and the muscles that constitute the UES abruptly relax. However, relaxation of the cricopharyngeus and inferior pharyngeal constrictor muscles alone is not capable of opening the UES. Opening of the sphincter requires associated contraction of the suprahyoid muscles. The UES remains open only long enough to allow the food bolus to pass rapidly from the pharynx into the upper esophagus before returning to its tonically contracted, closed state.

Esophageal Body

Anatomy

The esophageal body extends from the lower border of the UES to the upper border of the lower esophageal sphincter (LES). The length of the esophageal body varies among individuals; it may be between 18 and 24 cm, generally being greater in men than in women. The wall of the esophageal body, like most other regions of the gastrointestinal tract, consists of layers (extending from inner to outer) of mucosa, muscularis mucosa, submucosa, and muscularis propria (Fig. 1-3). The muscularis propria in turn is made up of an inner circular muscle layer and an outer longitudinal muscle layer.

The mucosa throughout the esophageal body consists of stratified squamous epithelium. Only in the pathologic entity of Barrett's esophagus does columnar mucosa extend cephalad from the stomach into the esophageal body. Just external to the

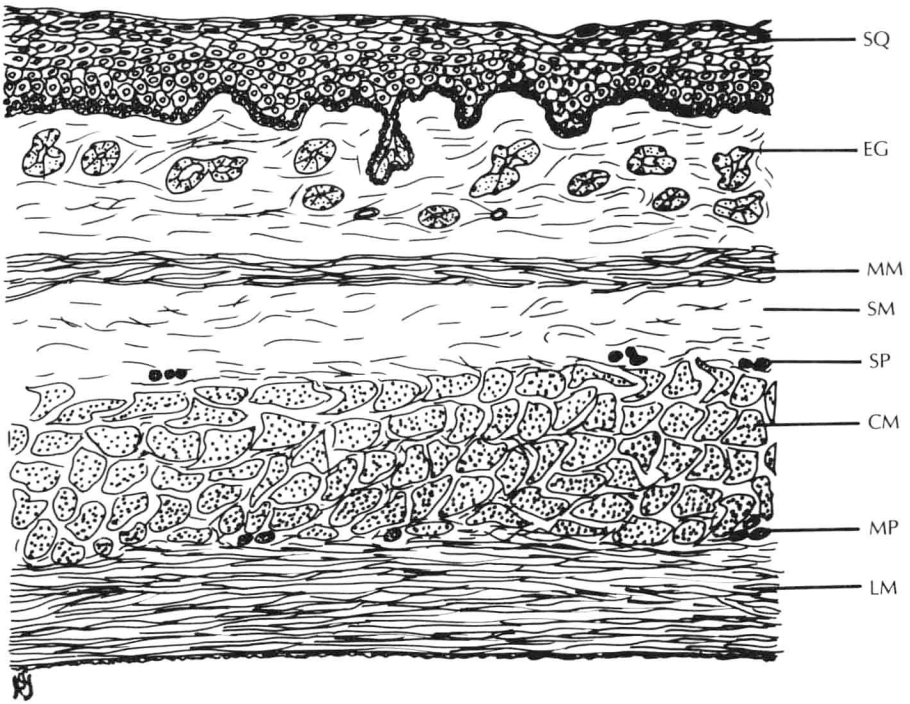

Fig. 1-3
Cross-sectional diagram of the esophageal wall. Note that the submucous plexus (SP, or Meissner's plexus) is located in the submucosa (SM) between the muscularis mucosa (MM) and the circular muscle layer (CM), whereas the myenteric plexus (MP, or Auerbach's plexus) is located between the CM and longitudinal muscle layers (LM). (SQ = squamous epithelium; EG = esophageal glands)

mucosa is a longitudinally oriented muscle layer known as the muscularis mucosa. This muscle layer is composed of smooth muscle throughout the length of the esophageal body.

Proximally, the esophagus is composed of striated muscle in both the inner circular and outer longitudinal muscle layers. Smooth muscle first begins to replace striated muscle in both layers at 4 to 5 cm from the most cephalad aspect of the esophageal body. A mixture of striated and smooth muscle exists from 4 to 5 cm to 11 to 12 cm from the most cephalad portion of the esophageal body. Caudal to this point, the circular and longitudinal muscle layers are composed entirely of smooth muscle. Hence, despite some minor variations among individuals, the most caudal half of the circular and longitudinal muscle layers of the human esophagus are composed entirely of smooth muscle (see Fig. 1-1).

The intrinsic nerves of the esophagus have their cell bodies in the submucosal (Meissner's) and myenteric (Auerbach's) plex-

uses. The submucous plexus is located between the muscularis mucosa and the circular muscle layer of the muscularis externa. Nerves of this plexus are believed to be primarily involved in the sensory innervation of the esophagus, as well as in the control of mucous secretion and vascular blood flow. The myenteric plexus is located between the circular and longitudinal muscle layers of the muscularis externa. Nerves of this plexus are believed to be primarily involved in the control of circular and longitudinal muscle contractions along the esophagus and play a key role in esophageal peristalsis.

The extrinsic nerves that serve to connect the central nervous system with the intrinsic nerves of the esophageal body run primarily within the vagus nerve. The cell bodies of vagal fibers that innervate the striated muscle of the esophagus are located in the nucleus ambiguus, whereas those vagal fibers that innervate the more caudal smooth muscle portion of the esophagus have their cell bodies located in the dorsal motor nucleus of the vagus. Both the nucleus ambiguus and the dorsal motor nucleus are located in the medulla oblongata of the brainstem (Fig. 1-4). The lower motor neurons whose cell bodies are located in the nucleus ambiguus project via the vagus nerve, directly to the striated musculature of the esophagus where they release acetylcholine at the neuromuscular junction. The vagal preganglionic fibers whose cell bodies are located in the dorsal motor nucleus do not directly innervate the smooth muscle of the esophagus but instead synapse with intrinsic neurons located in both the submucosal and myenteric plexuses of the esophagus. These intrinsic neurons send fibers that directly innervate the smooth muscle layers of the esophagus. Essentially all extrinsic motor fibers to the esophageal body run within the vagus nerve as it passes rostrally from the cranium. However, these fibers all leave the vagus trunk high in the neck to form an esophageal plexus at the level of the mid-esophageal body. This explains why a thoracic vagotomy performed for peptic ulcer disease has no effect on esophageal function.

Physiology

Primary and Secondary Peristalsis

The act of swallowing is associated with an orderly, progressive series of contractions throughout both the striated and smooth muscle portions of the esophageal body (Fig. 1-5). Peristalsis initiated by the conscious act of swallowing is termed *primary peristalsis,* whereas peristalsis initiated by intraluminal distention of the esophagus is known as *secondary peristalsis*. Secondary peristalsis is not accompanied by pharyngeal contractions or relaxation of the UES. Secondary peristalsis plays an important