GASTROINTESTINAL DISORDERS

A PATHOPHYSIOLOGIC APPROACH

NORTON J. GREENBERGER

THIRD EDITION

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A Pathophysiologic Approach

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Preface to the First Edition

During the past decade there have been widespread and rapid advances in the field of gastrointestinal disorders. Indeed, there has been, literally speaking, an explosion of new information. This has resulted in revised concepts of our understanding of normal gastrointestinal physiology as well as the pathophysiologic alterations that occur in several disorders. To illustrate, the medical student, house officer and practitioner have had to assimilate new information about gastroesophageal reflux, peptic esophagitis, disorders of esophageal motility, the gastric mucosal barrier, erosive gastritis, acid peptic disease, gastrointestinal hormones such as gastrin, secretin, cholecystokinin-pancreozymin and vasoactive intestinal peptide, pancreatitis, exocrine pancreatic insufficiency, cholesterol gallstone disease, malabsorptive disorders, inflammatory bowel diseases, viral hepatitis, drug-induced liver disease, cirrhosis of the liver and gastrointestinal neoplasms. The above is a partial listing and is by no means exhaustive. Such rapid and widespread advances in the field of gastroenterology have required that medical educators continuously distill and reorganize vast amounts of information from the investigative and clinical literature for presentation and publication. During the past few years, we have prepared hundreds of slides of original data, tables, line diagrams and printed handouts for students and house officers. On many occasions, we were asked where such information was available for further in-depth study. Such requests led to the development of this book.

We have written a textbook which emphasizes applied pathophysiology and clinical interpretation. To accomplish this and at the same time write a relatively short textbook, we have included a large number of line diagrams, tables and graphs. Whenever possible, original data and diagrams from the relevant literature have been included. The book is not a comprehensive treatise of gastrointestinal disorders. Rather, emphasis has been placed on disorders in which there is new and important information on pathophysiologic alterations that occur. It is anticipated that the book will prove to be most useful to medical students and house officers, as well as practitioners seeking a concise work on new concepts of gastrointestinal disorders.

Several individuals have contributed greatly to this book. Of immeasurable help have been the efforts of our secretaries. We are indebted to Alice Algie, Alice Dworzack, Patty DeCelles, Linda Hucker, Shirley Sears and Judy Wilson for their help in the preparation of the manuscript. Dr. Giomar Gonzales and Dr. Harold Henstorf kindly provided several gastrointestinal roentgenograms, Dr. Donald Svoboda, liver and histopathology slides, and Dr. Frank Mantz, slides of gross and microscopic pathology of gastrointestinal disorders. We also wish to thank Mr. Fred Rogers of Year Book Medical Publishers for his advice and encouragement.

NORTON J. GREENBERGER

DANIEL H. WINSHIP

Preface to the Third Edition

THE CONTINUED extensive use of the second edition of this book in pathophysiology courses in medical schools throughout the United States has been quite gratifying. For this reason, the basic format of presenting important material in figures, tables, and diagrams has been retained and, indeed, expanded. During the four years that have elapsed between the second and third editions, several important advances in gastroenterology and liver disease have occurred. These advances have resulted in extensive revisions in all chapters but this is especially so in the chapters dealing with the stomach, pancreas, liver, and biliary tract. To cite just a few examples of these changes, new information is presented on gastroesophageal reflux, role of muscarinic receptors and Na^+-K^+ ATPase on gastric acid secretion, pharmacology of substituted benzimidazoles in inhibiting gastric secretion, pathophysiology of diarrhea, mechanism of effect of antidiarrheal drugs such as codeine, and pathophysiology of malabsorption in pancreatic exocrine inefficiency. The liver section has undergone considerable revision with addition of new information on bilirubin metabolism, hepatitis B e antigen, Delta agent, immunology of B viral, and non-A, non-B hepatitis, chronic active hepatitis, hepatic encephalopathy, ascites, and gallstone disease. New sections on Budd-Chiari syndrome, sclerosing cholangitis, and motility disorders of the biliary tree have been added. The references have been updated to include several key articles published between 1981 and 1985.

I wish to reiterate comments made in the preface to the second edition. Specifically, the changes described above have made the third edition "reasonably current." However, it should be emphasized that the rapid changes occurring in our understanding of digestive diseases will mandate that students, residents, fellows, and practicing physicians using this textbook supplement their reading with appropriate journal articles.

I thank Shirley Sears and Juanita Stika of my staff for their superb work in the preparation of the manuscript and Dr. K. R. Lee for his help in the preparation of various x-rays. Richard Lampert of Year Book Medical Publishers was particularly helpful in the final preparation of the manuscript.

NORTON J. GREENBERGER, M.D.

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1

Esophagus

I. NORMAL ANATOMY AND PHYSIOLOGY

A. NORMAL ANATOMY

1. General Considerations

A reasonably comprehensive understanding of the normal anatomy of the human esophagus is important because esophageal function, normal and abnormal, is related in large part to the structure of the organ.

The esophagus is a hollow cylindrical organ which extends from the pharynx to the stomach and merges with those structures—the pharynx proximally and the stomach distally. In its course from pharynx to stomach, it lies successively in the neck, posterior mediastinum, diaphragm, and, for a short distance, in the abdomen. The organ is pliable and quite distensible, and is easily displaced by adjacent organs. Thus, in its course through the mediastinum, it characteristically demonstrates three indentations: the first and most proximal is produced by the aortic arch, the second is due to the left main-stem bronchus, and finally, a gentle posterior curve is effected by the left atrium of the heart (Fig 1–1). Exaggerations of the natural indentations occur with enlargements or abnormalities of these structures.

The wall of the esophagus from inside out consists of three major layers: the mucosa, the submucosa, and the muscularis propria (Fig 1–2).

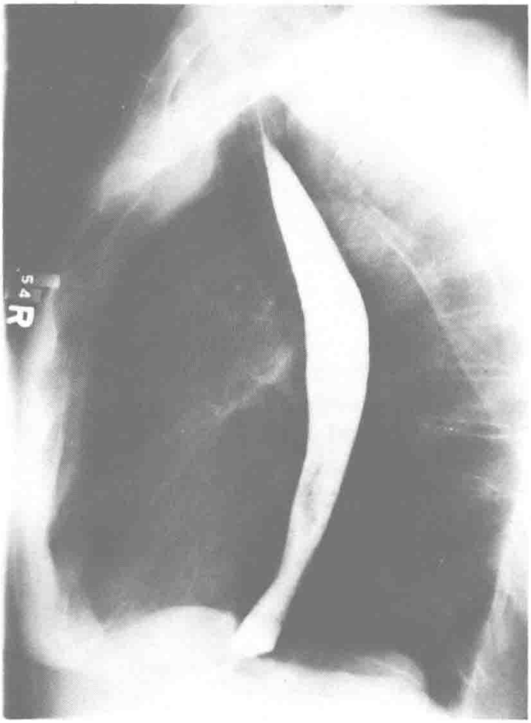

Fig 1–1.—X-ray film of the entire barium-filled esophagus, showing the course of this organ through the mediastinum from hypopharynx to stomach. Note the three indentations produced by the aorta, left main-stem bronchus, and left atrium.

2. Mucosa

The normal esophageal mucosa is composed of three layers: the squamous epithelium, lamina propria, and muscularis mucosae. The epithelium can be divided into two portions: a basal zone consisting of several layers of basophilic cells with dark nuclei, and a stratified zone containing many layers of squamous cells with flattened nuclei. The thickness of the basal zone is less than 15% of the total thickness of the epithelium. Infrequently, mitotic figures are seen. The papillae extend less than two thirds of the distance to the surface of the epithelium. A few round cells, such as lymphocytes and plasma cells, are present in the lamina propria. The muscularis mucosae is relatively prominent, especially in the distal esophagus. It consists of both longitudinal and circular smooth muscle fibers.

3. Submucosa

The submucosa of the esophagus consists of loose connective tissue containing many blood vessels and nerve trunks traversing to the mucosa. It contains few cells of any type and a small amount of fat.

Esophageal glands may be present. Those characteristic of the esophagus itself are tubular in form and are sparsely distributed throughout the submucosa. Their secretory cells are partly serous but chiefly produce mucus.

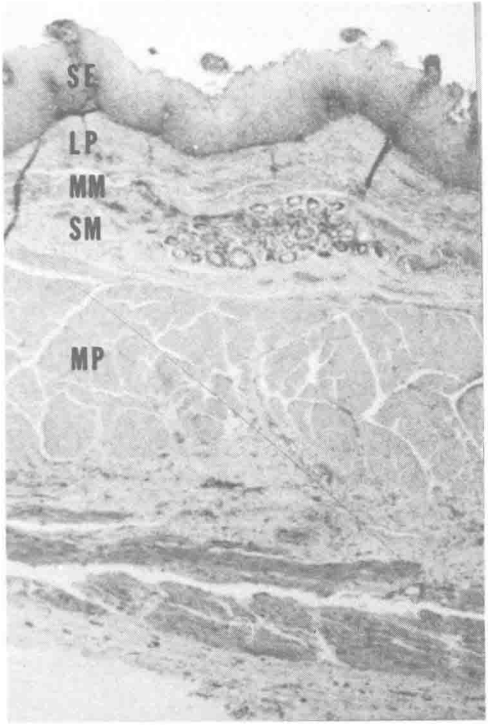

Fig 1–2.—Photomicrograph of the normal esophagus showing histologic features of the squamous epithelium *(SE)*, lamina propria *(LP)*, muscularis mucosae *(MM)*, submucosa *(SM)*, and muscularis propria *(MP)*. (Courtesy of M. Beck.)

4. Muscularis Propria (Fig 1–3)

The inferior pharyngeal constrictor, although not actually a part of the esophagus, must be considered in connection with the most proximal portion of the esophagus, since it overlaps the proximal end of the organ and because the upper esophageal sphincteric structure, the cricopharyngeus, is a clearly definable segment of the inferior pharyngeal constrictor. This is a striated muscle, as is the upper fourth of the muscularis propria of the esophagus. The inferior pharyngeal constrictor arises laterally from the lateral aspects of the cricoid and thyroid cartilages and inserts posteriorly in a fibrous raphe. The cricopharyngeus arises from the posterolateral aspect of the cricoid cartilage and wraps around the esophagus posteriorly in a continuous fashion, without a raphe. This structure is identified as the upper esophageal sphincter and, by convention, marks the most proximal portion of the esophagus.

Distal to these muscles and merging with them are inner circular and outer longitudinal muscle coats enveloping the esophagus all the way to the stomach; they are actually continuous with the muscular coats of the stomach. Both muscle layers consist of striated fibers in the

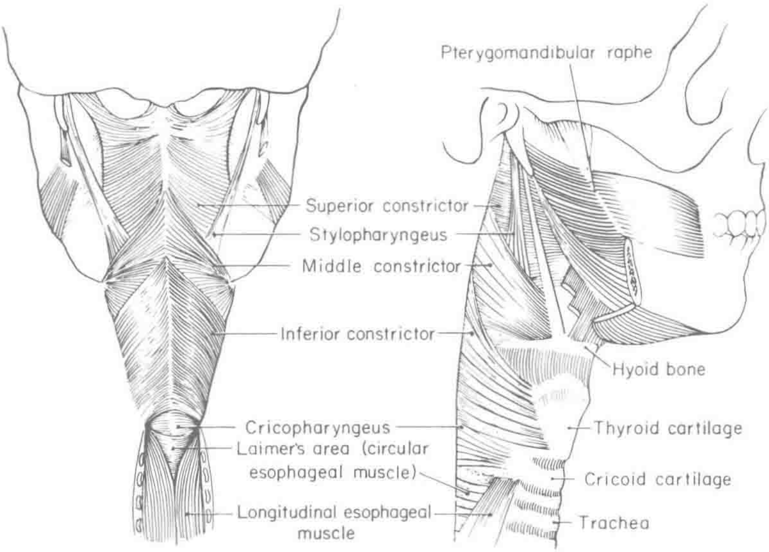

Fig 1–3.—The muscular anatomy of the esophagus and distal pharynx: posterior and lateral views. (From Payne W.S., Olsen A.M.: *The Esophagus.* Philadelphia: Lea & Febiger, 1974. Reprinted by permission.)

proximal portion of the esophagus. The muscle coats of the distal one third of the esophagus are all smooth muscle; the intervening region is mixed smooth and striated muscle, with more striated muscle proximally and more smooth distally.

No identifiable anatomical modification in muscle coats at the lower end of the esophagus can be recognized to account for any specialized sphincteric function.

5. Adventitia

The esophagus has no serosa. Rather, there is loose areolar and elastic tissue surrounding and attaching to the outer wall of the esophagus. It simply merges with loose mediastinal tissue.

6. Diaphragmatic Hiatus and Distal Esophageal Segment (Fig 1–4)

Since the distal esophagus penetrates the diaphragm through the diaphragmatic hiatus, the relationship between those structures is of considerable importance. It is generally considered that the inferior esophageal sphincter straddles the esophageal hiatus. The right crus of the diaphragm, forming the hiatus, surrounds this portion of the esophagus. The phrenoesophageal ligament, a direct continuation of the transversalis fascia which lines the abdominal cavity outside the peritoneum, arises from the undersurface of the diaphragm and inserts into the esophagus about 3 cm above the cardia, there merging with the longitudinal and circular muscles of the esophagus. It is variously described as fragile or tough.

7. Nerve Supply

Although the upper esophageal sphincter is innervated by the glossopharyngeal nuclei, the remainder of the esophagus is innervated by the autonomic system.

a. PARASYMPATHETIC.—Both of the vagus nerves are intimately associated anatomically and functionally with the esophagus (Fig 1–5). The vagus is considered to be the motor nerve of the esophagus.

b. SYMPATHETIC.—Although the esophagus is richly supplied with sympathetic fibers, their function is poorly understood. The sympathetic

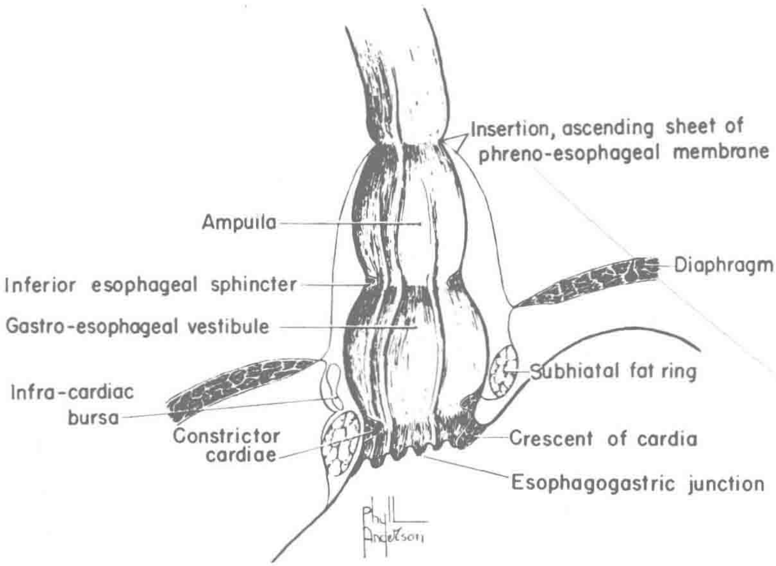

Fig 1–4.—Diagrammatic representation of the physiologic divisions of the distal esophageal segment. This region is called by Lerche the "gastroesophageal segment of expulsion," and the terminology used is his. (From Palmer E.D.: *The Esophagus and Its Diseases*. New York: Paul B. Hoeber, 1952. Reprinted by permission.)

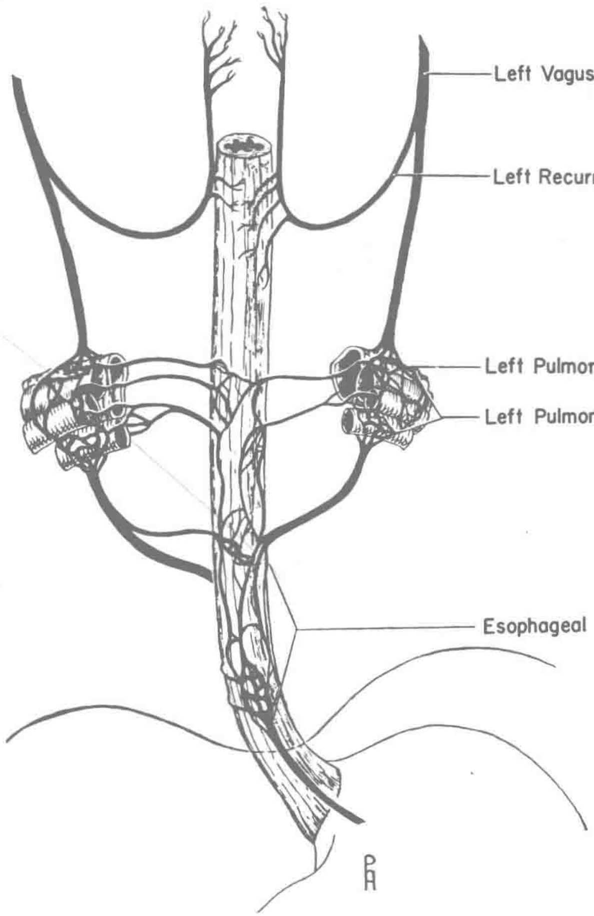

Fig 1–5.—Diagrammatic representation of the parasympathetic nerve supply of the esophagus. Note that the left vagus is located on the anterior surface of the distal esophagus, and the right vagus, posteriorly. (From Palmer E.D.: *The Esophagus and Its Diseases.* New York: Paul B. Hoeber, 1952. Reprinted by permission.)

fibers arise from superior and inferior cervical sympathetic ganglia to innervate the proximal portion of the esophagus, from the greater splanchnic nerve to innervate the midbody, and from the lesser splanchnic nerve and the celiac plexus to innervate the distal portion of the esophagus.

c. INTRINSIC NERVES.—Auerbach's (myenteric) plexus, located between outer longitudinal and inner circular muscle coats, extends throughout the esophagus. The fibers are largely unmyelinated. The ganglia of Meissner's plexus, located in the submucosa, are very sparse and are not easily identified.

8. Blood Supply

a. ARTERIAL SUPPLY.—Basically four groups of arteries supply the esophagus in a regional fashion. These are (1) the thyrocervical trunks, inferior thyroid arteries, and branches from the subclavian arteries supplying the upper esophagus, (2) bronchial arteries and esophageal arteries arising from the upper descending aorta supplying the upper esophageal body, (3) intercostal arteries and paired esophageal arteries from the lower thoracic aorta, which supply the distal esophageal body, and (4) branches from the inferior phrenic, left gastric, and short gastric arteries supplying the diaphragmatic region of the esophagus.

b. VENOUS DRAINAGE.—Venous blood from the esophagus also flows regionally. The proximal esophagus is drained by the anterior and posterior hypopharyngeal plexuses and the superior laryngeal and internal jugular veins. The inferior thyroid vein and intercostal veins drain the upper body, while the azygos system and other intercostals drain the distal body. Distally, potential collaterals with the portal system are present. The anatomy of venous drainage of the esophagus, especially in the distal portion and the region of the cardia, is particularly important because of the potential collateral circulation relieving congested portal vessels in cases of portal hypertension.

c. LYMPHATIC DRAINAGE.—Seven lymph node groups forming the major portion of the lymphatic system of the esophagus are particularly important in consideration of the oncology of the esophagus. Since the esophagus has no serosa and is supplied with a rich lymphatic drainage in the submucosa, early spread of esophageal cancer into the regional lymph nodes is extremely common; in fact, this spread has usually occurred by the time the patient becomes symptomatic. The five groups of nodes adjacent to the esophagus that drain the esophageal lymphatics and thus are commonly involved in metastatic cancer are the paratracheal, parabronchial, paraesophageal, paracardial, and posterior mediastinal nodes. The remaining two groups, at some distance, are the superior and inferior deep cervical nodes.

B. NORMAL PHYSIOLOGY

1. Mechanism of Swallowing

> Nor is this for any other reason than it is in a piece of machinery which, though one wheel gives motion to another, yet all the wheels seem to move simultaneously, or in that mechanical contrivance which is adapted to firearms, where the trigger being touched, down comes the flint, strikes against the steel, elicits a spark, which falling among the powder, it is ignited, upon which the flame extends, enters the barrel, causes the explosion, propels the ball, and the mark is attained—all of which incidents, by reason of the celerity with which they happen, seem to take place in the twinkling of an eye. So also in deglutition: by the elevation of the root of the tongue and the compression of the mouth the food or drink is pushed into the fauces, the larynx is closed by its own muscles and the epiglottis, whilst the pharynx, raised and opened by its muscles no otherwise than is a sack that is to be filled, is lifted up, and its mouth dilated; upon which, the mouthfull being received, it is forced downward by the transverse muscles, and then carried farther by the longitudinal ones. Yet all these motions, though executed by different and distinct organs, perform harmoniously, and in such order, that they seem to constitute but a single motion and act, which we call deglutition. (William Harvey, 1628)

Harvey's accurate description of the swallowing complex is concerned with the initiation of swallowing, or the oral and pharyngeal components of swallowing. It is worthwhile to consider swallowing mechanics in three phases: (1) the oral and pharyngeal, (2) transport through the body of the esophagus, and (3) delivery to the stomach through the lower esophageal sphincter.

a. ORAL AND PHARYNGEAL COMPONENTS.—This portion of the swallowing complex is a rigidly controlled sequence. It consists of closure of the buccal cavity and the forcing of food into the esophagus by generation of pressure differential and the establishment of a corridor within the mouth and pharynx through which the bolus may pass.

Initially, the mouth is closed by approximation of the lips. The tongue is pushed up, the fauces are approximated, and the soft palate rises to occlude the nasopharynx by the simultaneous contraction of levator veli palatini and palatopharyngeal muscles. Next, the respiratory pathway is closed by elevation of the larynx and by closure of the glottis. Respiration therefore is temporarily inhibited. Retroversion of the epiglottis over the laryngeal orifice further protects the respiratory pathway. The esophagus opens by a brief relaxation of the tonically contracted cricopharyngeus muscle (pharyngoesophageal or upper esophageal sphincter). The bolus is forced into the esophagus by sequential contractions of the muscles of tongue and pharynx, then of the cricopharyngeus (closure of the sphincter behind the bolus).

The pharyngoesophageal sphincter, or upper esophageal sphincter, is composed of the transverse fibers of the cricopharyngeus muscle posteriorly, but its anterior margin is the rigid cricoid cartilage (Fig 1–3). Intraluminal pressure measurements in this region reveal a short (2–3 cm) zone on increased resting pressure (Fig 1–6). The highest pressure is in the center of this zone, falling off somewhat proximally and distally. Spatial orientation of the pressure measuring device is important in determining the pressure generated in this sphincter; the greatest pressures (average, 100 mm Hg) are recorded in the anterior-posterior axis, while least pressures (average, 33 mm Hg) are detected in the lateral orientation (Fig 1–7). This peculiarity of pressure orientation is explainable by the fact that the cricopharyngeus does not contract circumferentially; rather, the posterior belly of the muscle contracts against the rigid anterior cricoid cartilage.

On swallowing, the sphincter relaxes and then contracts (Fig 1–8). This is a rapid sequence, the sphincter opening briefly (less than 1 second) before the arrival of the pharyngeal peristaltic contraction and permitting the bolus to enter the esophagus. Following rapid passage of the bolus, the sphincter contracts, participating in the peristaltic wave coming from the pharynx. The contraction lasts 2–4 seconds, then the pressure returns to its baseline.

Relaxation of the cricopharyngeus occurs as a result of powerful neural inhibition of the otherwise rather constant level of motor impulses to the muscle and action potentials in the muscle.

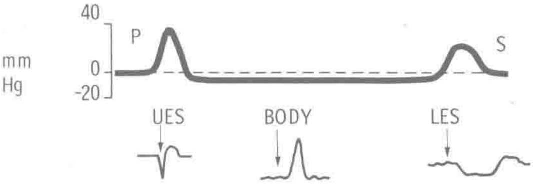

Fig 1–6.—Diagram of the intraluminal esophageal pressure profile. *S,* stomach; *P,* pharynx. Pressures in pharynx and stomach are virtually the same and similar to ambient pressure. Pressure in the body of the esophagus is negative, reflecting intrathoracic pressure. High-pressure zones separate the pharynx from the esophagus and the stomach from the esophagus. Below each esophageal pressure region is diagrammed the characteristic wave which occurs following a swallow.

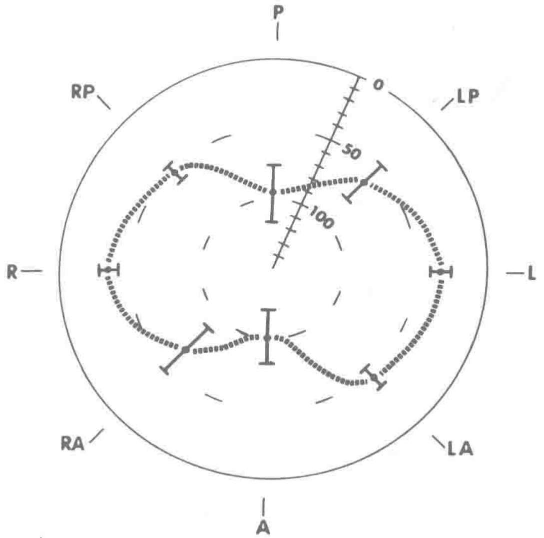

Fig 1–7.—Spatial pressure orientation in the upper esophageal sphincter. Pressures were measured in each of eight directions in 18 subjects. Each pressure designation represents the mean maximal pressure within the pharyngoesophageal high-pressure zone for each of the eight orifices. Note the greatest pressures are observed in the anterior *(A)*-posterior *(P)* axis. *LP* = left posterior; *L* = left; *LA* = left anterior; *RA* = right anterior; *R* = right; *RP* = right posterior. (From Winans C.: *Gastroenterology* 63:768, 1972. Reprinted by permission.)

Closure of the sphincter is associated with a burst of impulses in the nerve and by action potentials in the fibers of the cricopharyngeus muscle. The degree of neural integration required for the act of swallowing is obviously enormous. A summary of the neural interrelations participating in the deglutition is diagramed in Figure 1–9.

b. BODY OF THE ESOPHAGUS.—The peristaltic wave which began in the pharynx, or perhaps even in the tongue, continues after closure of the upper sphincter through the esophageal body. The peristaltic wave has been described as the "caudad migration of a band of contracting circular muscle fibers," or "a lumen-obliterating contraction, about 4–8 cm in length, moving aborally at 2–4 cm per sec." By convention, when the peristaltic wave is excited by a swallow it is termed primary and when by distention it is termed secondary.

The peristaltic wave is reflected by a mono-

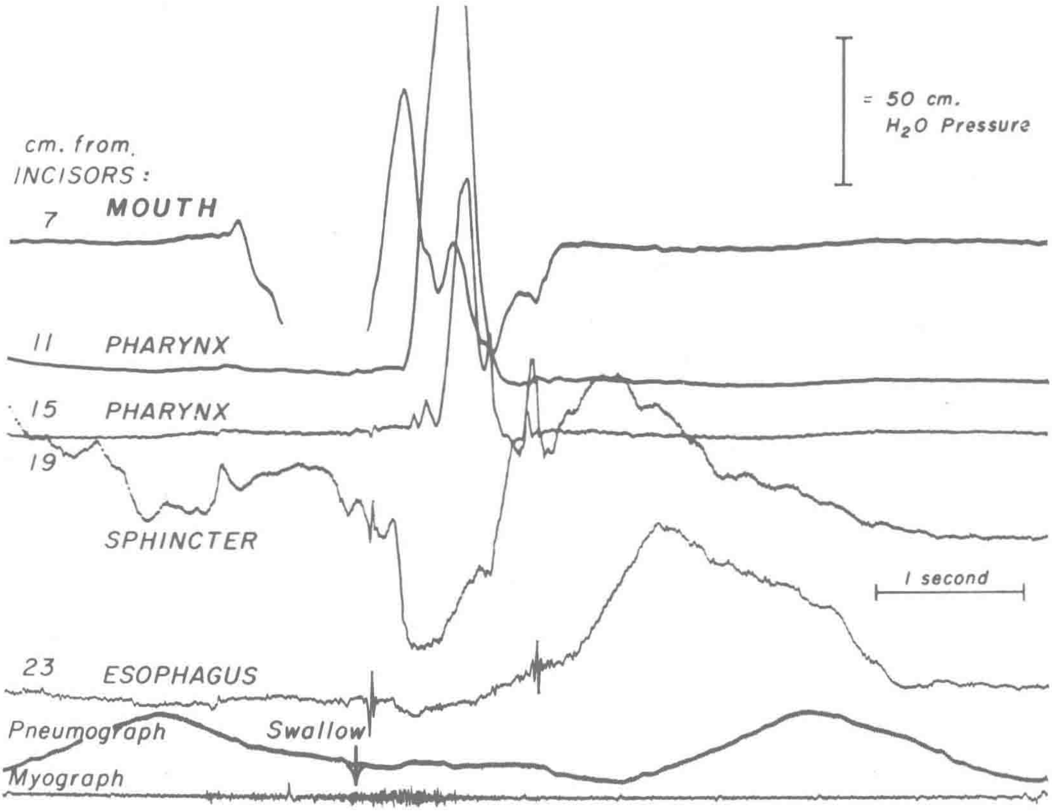

Fig 1–8.—Simultaneous recording of pressure in the pharynx, pharyngoesophageal sphincter, and esophagus during a swallow in a healthy person. The pressure spike due to muscular contraction swept in a peristaltic wave through the pharynx and the sphincter into the esophagus. (From Code C.F., et al.: *An Atlas of Esophageal Motility in Health and Disease.* Springfield, Ill.: Charles C Thomas, Publisher, 1958. Reprinted by permission.)

phasic pressure wave within the lumen of the esophagus (Fig 1–10). Closely associated with the pressure wave at any given point in the body of the esophagus is a burst of fast action potentials, which may be recorded from the muscular wall.

The mechanism by which the monophasic wave progresses down the esophagus is not completely understood. Christensen et al., however, have demonstrated an intrinsic time gradient of contractility of esophageal circular muscle, i.e., the time from stimulation to contraction of muscles increases distally (Fig 1–11).

It seems reasonable that such a pressure wave would simply push the bolus before it. Axial motion of the esophagus, brought about by contraction of the longitudinal muscle, is also of importance in the peristaltic sequence, however. Radiopaque tantalum markers implanted in the esophageal wall in cats have been studied cineradiographically. Movement of the markers during swallow of a bolus demonstrates a motion of the esophagus which tends to engulf the bolus. First, the markers move orad to meet the bolus, then laterally to accept the bolus into the lumen, and then aborally trailing the bolus, finally arriving at the resting position.

c. GASTROESOPHAGEAL SPHINCTER.—At the distal end of the esophagus, separating the esophagus from the stomach, is the lower esophageal or gastroesophageal sphincter. This sphincteric mechanism consists of functionally but not anatomically specialized smooth muscle,