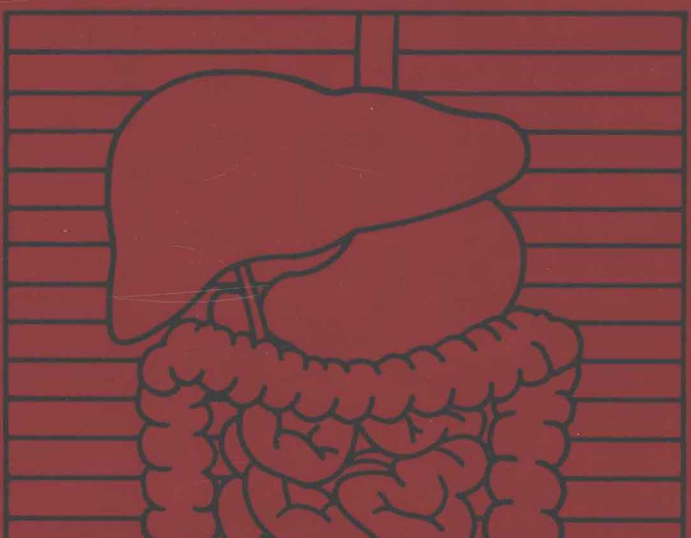
TEXTBOOK OF PEDIATRIC GASTROENTEROLOGY

Mervin Silverberg and Fredric Daum



Second Edition

Textbook of Pediatric Gastroenterology
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To the fond memory of my father, whose support and encouragement early in my career made this textbook possible.

MERVIN SILVERBERG, M.D.

To my wife Michelle, who makes things happen.

FREDRIC DAUM, M.D.

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Preface to the First Edition

In the spring of 1973, I attended the second National Digestive Disease Conference in Airlie House, Virginia, sponsored by the National Institute of Health, Arthritis, Metabolism, and Digestive Diseases. The most outstanding deficiency among the vast array of gastroenterological talent and presentations was the virtual absence of any reference to the problems and diseases in patients under the age of 18. This neglect epitomized the myopic view of many adult gastroenterologists, even at that late date.

The previous year, Dr. Lawrence Gartner and I had organized the first society dedicated to pediatric gastroenterology, The Pediatric Gut Club. The organization is now called the North American Society for Pediatric Gastroenterology and has over 150 active members. From these apparently humble beginnings, the field of pediatric gastroenterology has now become a potent force in the clinical and research activities of societies and funding agencies throughout North America. The volume of scientific articles and papers in this specialty during the past decade is very impressive and testifies to the tremendous progress we have made.

These rapid developments and the myriad of unanswered questions they raise leave room for new and fresh approaches to the field. The present textbook emerges from the numerous discussions and often heated arguments generated in one of the largest pediatric gastroenterological centers in the country at North Shore University Hospital. It is a team effort, with contributions by clinicians, biochemists, physiologists, and morphologists, both inside and outside our department. Diversification and variety is subtly introduced by the many different teachers and colleagues each of us has previously encountered. The emphasis in most chapters is true to the basic goals of the book; i.e., the elucidation of etiology, pathogenesis, diagnosis, differential diagnosis, and management. Overlap between chapters is inevitable, but it is hoped that this heterogeneity will add to both completeness and controversy.

The contributors have tried to be as clear and concise as possible. However, a good deal more information is left to motivated readers through the use of the exhaustive bibliography and a good local library.

My apologies go to the few readers who are more involved with and are desirous of new and updated writings in hepatology. We excluded the liver in the interests of keeping the volume modest in size and to qualify as a text exclusively on the gastrointestinal tract and pancreas. The three recently published excellent textbooks on liver disease in children also played a role in our decision.

The book is designed for prospective readers among pediatricians, surgeons, general practitioners, allied medical specialists, and medical students. Hopefully, gastroenterologists will also find new concepts in diagnosis and management, as well as recent research developments, to make this book of value to them. Additionally, the lucid organization of the text is basic enough to be of value to paramedical personnel, such as nurses and basic scientists, from many related biological fields.

I am especially indebted to the department secretarial staff who bore the burden of repeated revisions, modifications, and literature searches in addition to carrying on their extensive daily duties. Particular thanks are due to Evelyn McDonald, who was responsible for the major part of the work on the manuscript, as well as her associates, Louise Gabriel and Linda Thomas.

MERVIN SILVERBERG, M.D.
JANUARY 1983

Preface to the Second Edition

It is now more than 7 years since the first edition of *Pediatric Gastroenterology* was written and 5 years since it appeared in print. The rapid proliferation of information during the intervening time now dictates another edition: new disorders have been described and others have been clarified or placed in better clinical focus. As before, the thrust of the book is to provide basic and practical information of interest to all clinicians caring for children with gastrointestinal disorders. The comprehensive approach to each chapter also makes the book valuable to medical students, academic faculty, and basic scientists. Allied health personnel and surgeons should also find the textbook very helpful.

Without exception, every chapter has been extensively reviewed, many involving new authorship. We have moved beyond the boundaries of our large Gastroenterology Center at North Shore University Hospital, in order to recruit new contributors. These authors are not only recognized nationally as experts in their respective areas, but they also bring a diversity of opinion, which adds immensely to the depth and revitalization of the textbook.

A chapter on bile acid metabolism was added to provide the latest information on this complex subject for clinical application. The old chapter on *Protein Losing Enteropathy* was deleted and it is now appropriately covered in the chapter, "Malabsorption in the Pediatric Patient," as well as in other relevant areas.

The explosive literary contributions in pediatric gastroenterology has necessitated a total revision and updating of individual bibliographies. This is also a reflection of the popularity and importance of the field, as evidenced by the increasing number of specialists and general pediatricians interested in gastroenterology.

For both of us, the experience of contributing to, collating, and editing this textbook has been challenging and intriguing. We fully realize that the exponential growth of a young specialty in its early years signifies the rapidity of growth of new information and advancing obsolescence of old. We hope to fill the current void and promise to return with new revelations in the future.

MERVIN SILVERBERG, M.D.
FREDRIC DAUM, M.D.
JANUARY 1988

Acknowledgments

We wish to acknowledge the skills and support of our office staff who spent long hours in the preparation and revision of the manuscripts. In particular, we wish to thank Rose Mattei, Louise Gabriel, Theresa Battaglia, Lori X. Iadevia, and Carol O'Brien.

To all these people and other unnamed supporters, we are grateful.

MERVIN SILVERBERG, M.D.
FREDRIC DAUM, M.D.

Contents

Chapter 1

Morphology of the Gastrointestinal Tract

Ellen Kahn, M.D.

GENERAL CHARACTERISTICS

The pharynx, esophagus, stomach, and small and large intestines share a certain number of histological characteristics that will be described together. Special attention will be given to identifying patterns characteristic for each of the segments.[1–6]

The wall of the gastrointestinal tract is composed of four layers: the mucosa or mucous membrane, submucosa, muscularis or muscularis externa, and adventitia or serosa (Fig 1–1).

The *mucosa* is the innermost layer formed by epithelial elements, lamina propria, and muscularis mucosa.

The epithelium varies in different segments of the digestive tract. It assumes a squamous stratified or glandular pattern depending on its function—protective or secretory. Admixed with and supporting the epithelium is a layer of reticular connective tissue, the lamina propria, containing elastic, reticulin, and collagen fibers, lymphocytes, plasma cells, and eosinophilic granulocytes, as well as lymphatic and blood capillaries. Separating the lamina propria from the submucosa is the muscularis mucosa. It is made up of two thin layers of smooth muscle, an inner circular and an outer longitudinal, connected by elastic fibers and extending to the basement membrane of the epithelium.

The *submucosa*, between the muscularis mucosa and the muscularis externa, is a fibrous connective tissue layer containing blood and lymphatic vessels and a nerve fiber plexus, the submucosal or Meissner plexus, with non-myelinated, postganglionic sympathetic fibers, and parasympathetic ganglion cells.

The *muscularis externa*, mainly responsible for contractility, is made up of two large layers of smooth muscle—an inner circular coat and an outer longitudinal one; a helicoidal pattern has been noted in both. A prominent nerve fiber plexus called the myenteric or Auerbach plexus, is found between these layers, with preganglionic parasympathetic and post-ganglionic sympathetic fibers terminating in parasympathetic ganglion cells, and post-ganglionic parasympathetic fibers terminating in smooth muscle.

The *adventitia* is the outermost layer of connective tissue which, when covered by a single layer of mesothelial cells, is called *serosa*.

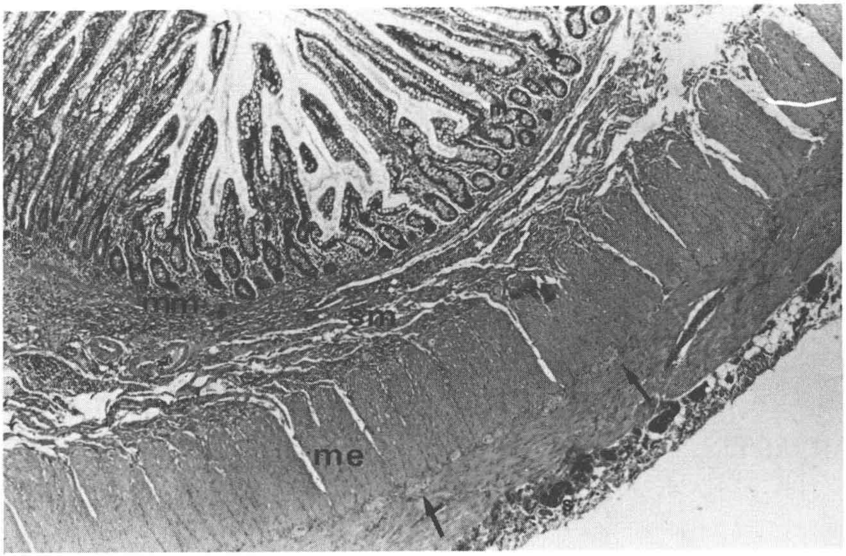

FIG 1–1.
General architecture of the gastrointestinal tract: *m* indicates mucosa; *mm*, muscularis mucosa; *sm*, submucosa; *me*, muscularis externa; and *s*, serosa; Arrow shows myenteric plexus (hematoxylin-eosin, ×39).

Enteroendocrine Cells

These specialized cells are found throughout the gastrointestinal tract. Due to their association with specific endocrine functions, they are called *enteroendocrine* or *neuroendocrine* cells.

Initially, these were divided into groups depending on their ability to reduce silver nitrate: *argentaffin cells*, containing granules able to reduce silver nitrate, and *argyrophilic cells* with granules that reduce silver nitrate only in the presence of a chemical reducer. Argentaffin cells may be stained by bichromate salts as well, and also are called enterochromaffin cells. These cells, also known as halo cells, have a basal position in relation to the remaining epithelial cells, are oval or triangular, pale with dark-stained granules, or agranular[7] in conventionally stained hematoxylin-eosin slides. Immunoperoxidase staining has uncovered a wider range in shape and size of the enteroendocrine cells, from small and oval to tall and flask shaped.[8]

With the development of different methods of study, specifically cytochemistry, electron microscopy, immunofluorescence, and, lately, immunoperoxidase staining, new cell types have been defined and their function and distribution characterized.

Seven types were initially defined following the Wiesbaden 1969 nomenclature, based on electron microscopic characteristics: A, D, EC, ECL, G, S, and L cells.[9] With the creation of the unifying APUD concept,[10] common characteristics of these specialized cells became apparent. APUD stands for *a*mine (amino acids) *p*recursor, *u*ptake, and *d*ecarboxylation, and encompasses a group of cells with common cytochemical and electron microscopic features, thought to have a common embryonic neural crest origin. The cytochemical properties are quite specific for the APUD cells, and consist of the content or uptake of fluorogenic amines (catecholamine, 5-hydroxytryptamine, etc.), the capability to take up amino acid precursors, such as 5-hydroxytryptophan and dihydrophenylalanine, and the presence of amino acid decarboxylase. Other cytochemical features, such as metachromasia, content of nonspecific esterase and/or cholinesterase, and alphaglycerophosphate dehydrogenase, are less specific.

Ultrastructurally, the enteroendocrine cells share the general morphology of peptide-secreting cells (Fig 1–2). More important for their characterization are the membrane-bound granules with variable electrodense cores, surrounded by a pale halo, averaging 100–250 nm. These can be demonstrated by light microscopy with the Grimelius stain, as dark granules, or more specifically by immunofluorescence, and with the immunoperoxidase method.[11]

Electron microscopy and immunocytochemistry have led to the identification of additional cell types and better characterization of others. Sixteen different cell types were defined up to 1981[12] and additional types added more recently.[8] Table 1–1 lists the most common designations used for the enteroendocrine cells and their products of secretion. These cells are better characterized by the nature of the stored peptide until a more uniform classification is agreed upon. In this fashion, the confusing terminology, predicated by assigning the same cell two different letters (i.e., K and D_1 cells producing gastrin inhibitory polypeptide [GIP]) can be avoided. It is also now generally accepted that enteroendocrine cells may store more than one biogenic amine.

New techniques have been developed to visualize enteroendocrine cells in paraffin embedded material. Instead of using specific monoclonal antibodies that are not always readily available, other methods have been tried such as using neuron-specific enolase NES[19] and chromogranin.[20] NES produces only faint staining, whereas chromogranin clearly demonstrates all mucosal gastrointestinal endocrine cells.

There is also new insight concerning the mode of action and origin of these specialized cells. Secretory granules are released through the basal and lateral surface of the enteroendocrine cells. These granules act on neighboring cells by direct contact or diffusion through intercellular spaces. Neurosecretory granules also reach the lamina propria acting on nerve endings, blood vessels, and smooth muscle, or

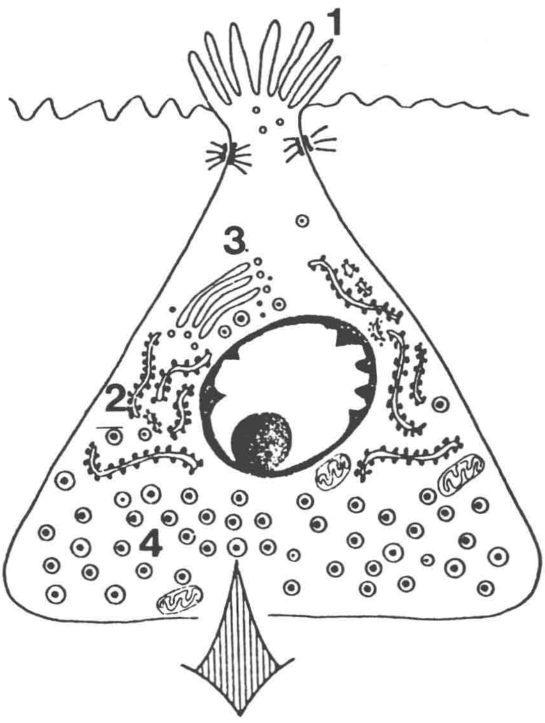

FIG 1–2.
Schematic drawing of the principal features of a neuroendocrine cell: (*1*), microvilli; (*2*), rough endoplasmic reticulum; (*3*), Golgi complex; and (*4*) secretory granules. (From Larsson LI: Pathology of gastrointestinal cells. *Scand J Gastroenterol* 1979; 53(suppl 14):1. Used by permission.)

TABLE 1–1.
Human Enteroendocrine Cells of the Gastrointestinal Tract and Pancreas*

CELL TYPE	OTHER DESIGNATION	STORES/SECRETORY PRODUCT
A		Glucagon
B		Insulin
D		Somatostatin (growth hormone release inhibiting hormone)[18]
D_1		? peptide
EC_1[†13]		5 HT
		Substance P
		Leu–encephalin
EC_2[†13]		5 HT
		Motilin–like
		Leu–encephalin
ECN[13]		5–HT[†]
		Unknown
ECL[†]		Unknown
		Histamine[7]
		Fundin[11]
G		Gastrin
		Encephalin/endorphin–related peptide[14]
GLI		Glucagon/glicentin[8]
H		VIP[†11]
I		CCK[†]
IG		Gastrin
K	D_1	GIP[†]
L	EG	GLI[†]
		PYY[†15]
M	EC_2	Motilin
N		Neurotensin
P		? peptide
		Bombesin[16,17]
PP	F	Pancreatic polypeptide
S		Secretin
SP	EC_1	P substance[†8]
TG		C–terminal gastrin[†]/CCK
X		Unknown
—		Pro–λ–MSH[†8]
—		β endorphin[8]
—		β lipotrophin[8]

*Modified from Solcia E, Capella C, Buffa R, et al: The diffuse endocrine–paracrine system of the gut in health and disease: Ultrastructural features. *Scand J Gastroenterol* 1981; (suppl 70) 16:25, unless otherwise specified.
†Somatostatin (GHRIH) indicates growth hormone release inhibiting hormone;[18] EC, enterochromaffin; ECL, enterochromaffin-like; 5-HT, 5-hydroxytryptamine (serotinin); VIP, vasoactive intestinal peptide; CCK, cholecystokinin (pancreozymin); GIP, gastrin inhibitory polypeptide; GLI, glucagon-like immunoreactivity; (glicentin-enteroglucagon); PYY, peptide YY; P, peptide-like; C-terminal gastrin, tetragastrin; and PRO-λ-MSH, PRO λ melanocyte-stimulating hormone.

enter the circulation and thus reach distant targets.[12]

The once controversial embryologic origin of the enteroendocrine cells is now well defined. For many years, Pearse's concept of an ectodermal origin for the enteroendocrine cells prevailed by assuming that neural crest cells migrated into the gastrointestinal tract.[10,21] Subsequent embryologic, tritiated (H^3)-thymidine, and morphologic data now support the endodermal origin of these cells.[22] Embryologic experiments[23,24] have shown that the mi-

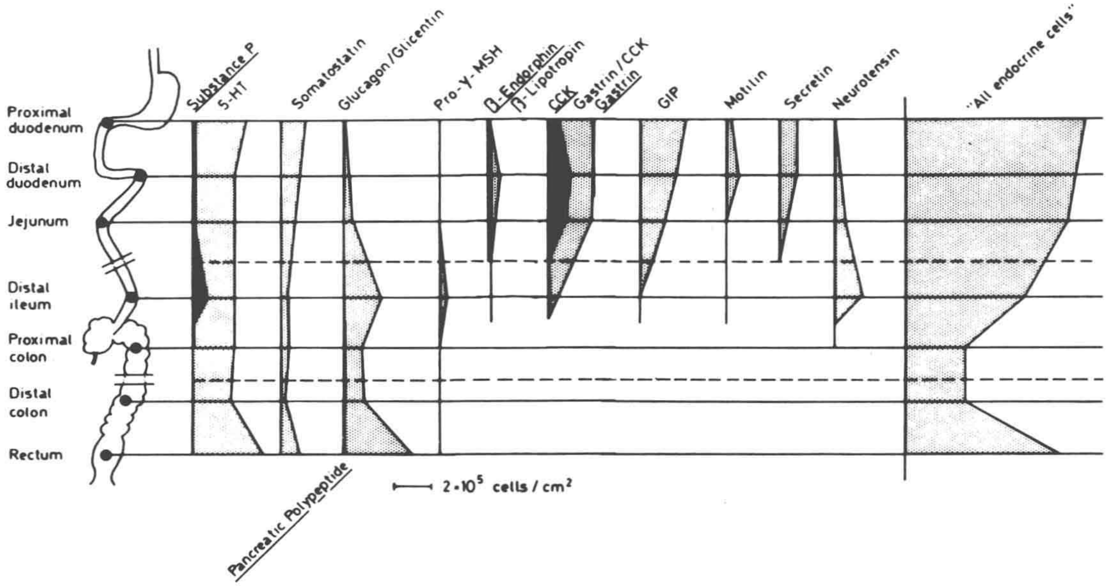

FIG 1–3.
Regional and quantitative distribution of the enteroendocrine cells of the gastrointestinal tract. (From Sjolund K, Sanden G, Hakanson R, et al: Endocrine cells in human intestine: An immuno-cytochemical study. *Gastroenterology* 1983; 85:1120. Used by permission.)

grating neural crest cells give rise to ganglia in the gastrointestinal tract and not to endocrine cells, and that enteroendocrine cells are still present when migration of neural crest cells is disturbed. In the mouse, H^3-thymidine labeling[25] has demonstrated that all epithelial cells of the small bowel develop from undifferentiated cells at the base of the crypt. Electron microscopic studies finally have revealed the simultaneous occurrence of neurosecretory granules and mucin in the same cell of the gastrointestinal tract mucosa, amphicrine cells,[26] and in tumors.[27,28]

The quantitative and qualitative distribution of the enteroendocrine cells of the gastrointestinal tract is illustrated in Figure 1–3. The small bowel contains the largest number of enteroendocrine cells, followed by the rectum. 5HT cells are the most frequently encountered type, present throughout the entire gastrointestinal tract; glucagon/glicentin- and somatostatin-producing cells are also seen throughout but in smaller numbers. The prevailing cell types in different sites of the gastrointestinal tract mucosa will be described in more detail.

PHARYNX

The general structure was mentioned previously (see Fig 1–1). The epithelium of the mucosa is of a nonkeratinizing, stratified, squamous type, except in the nasopharynx where it is a pseudostratified, columnar, ciliated epithelium. It is associated with few glands, and with lymphoid subepithelial nodules corresponding to the pharyngeal tonsil.

Striated muscle forms the muscularis. The adventitial outer layer is fibrous.

ESOPHAGUS

The layers of the esophagus are similar to those of the rest of the gastrointestinal tract.

The esophageal mucosa is covered by thick nonkeratinizing squamous stratified epithelium (Fig 1–4) with a few melanoblasts. This epithelium terminates abruptly 1.5 cm above the distal end of the esophagus in adults, appearing grossly as a gray-pink irregular line. Fingerlike projections of the lamina propria, the papillae, extend halfway up into the surface epithelium and are responsible for the corrugated appearance of the distal esophagus.

Two types of glands are encountered in the esophagus: cardiac and esophageal. The cardiac glands are found in the lamina propria, in the distal and proximal portion of the esophagus, with characteristics, as the name indicates, of those of the cardia (see Stomach). The esophageal glands are situated in the submucosa and predominate in the upper half of the organ. Cardiac and esophageal glands are both mucus secreting.

The muscularis is made up of striated muscle only in the upper third. These are mixed with smooth muscle in the middle third of the esophagus, whereas in the lower third, smooth muscle fibers are the only elements. Only the myenteric plexus is present.

The outer layer is the adventitia with two types of nerves: argyrophilic (controlling coordination of swallowing), and nonargyrophilic (with motor functions).

STOMACH

In addition to the previously noted general architecture, the stomach has the following characteristics:

The *mucous membrane* varies in the different segments of the stomach, i.e., the cardia, fundus (the portion of the stomach above a horizonal line that passes through the cardia), body, pyloric antrum, and canal. The body occupies most of the proximal two-thirds and the antrum the distal third (Fig 1–5). Transitional mucosa between cardia and fundus on the one hand, and body and pyloric mucosa on the other, have a mixed pattern,[4] i.e., the mucosa contains both cardiac and fundic glands in the former (transition between cardia and fundus) and body and pyloric glands in the latter (transition between body and pylorus).

The folds or rugae of the gastric mucosa are more prominent in the body than in the antrum and disappear with gastric distention.

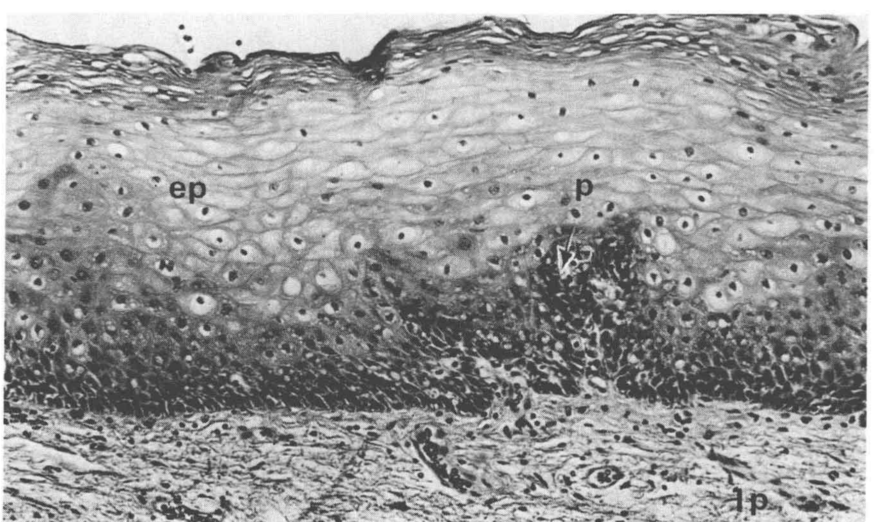

FIG 1–4.
Esophageal mucosa. Note the nonkeratinizing squamous stratified epithelium (*ep*) in the upper half: *lp* indicates lamina propria: *p,* papilla (hematoxylin-eosin, ×150).