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SERIES EDITOR
Lawrence M. Roth, M.D.

PATHOLOGY OF THE ESOPHAGUS, STOMACH, AND DUODENUM

Edited by
Henry D. Appelman, M.D.

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Preface

This book is a companion to the tome on the midgut and hindgut edited by H. Thomas Norris, which appears as Volume 2 of this series in Contemporary Issues in Surgical Pathology. It is clear that over the past decade the practice of gastrointestinal surgical pathology has been altered considerably by a change in the practice of clinical gastroenterology. Highly sophisticated, superbly trained gastroenterologists and gastrointestinal surgeons have been leaving the major teaching centers in ever-increasing numbers and establishing practices throughout the country, even in relatively small communities. They have brought with them a whole armamentarium of endoscopic and manometric technology, and a broad knowledge of the physiology and biochemistry of the gut. They depend to a great extent on the correlation of endoscopic appearances with biopsy findings and cytologic analyses for accurate diagnosis. Thus, surgical gastrointestinal pathology has rather rapidly changed from a resection-oriented activity to a biopsy-directed endeavor. As a result of these factors, gastrointestinal pathology is certainly one of the contemporary issues in surgical pathology. In fact, the past few years have seen an explosion in gut pathology texts, papers, and seminars. A subspecialty society, The Gastrointestinal Pathology Club, was organized in 1980 to bring together all pathologists interested in the gut in order to foster greater educational efforts in the field, promote cooperative studies, and develop a forum for the exchange of ideas. Almost all the contributors to this volume and Volume 2 are members of that society.

In this text, we cover surgical pathology of the foregut and its components—the esophagus, stomach, and duodenum, all sites which are now readily accessible by direct endoscopic visualization and biopsy. Emphasis is placed on endoscopic microscopic correlation and the problems inherent in evaluation of the type of tiny biopsy samples we are receiving in ever-increasing numbers. It is not the purpose of this book to be encyclopedic. Instead, selected diseases, especially the most common ones, are discussed in great depth with detailed analyses of current information. When supposedly up-to-date data are clearly unsatisfactory, we let the reader know. Uncommon diseases are occasionally evaluated at length when they are currently controversial or even unusually interesting or provocative, but most of the rare problems are either mentioned only briefly or omitted entirely. Thus, we have concentrated on reflux esophagitis, gastritis of many types, what is currently known about gastric polyps and giant folds, recent changes in patterns of gastric carcinoma, the whole gamut of stromal tumors of the upper gut, duodenitis, and duodenal-ampullary neoplasia. The very trendy subjects of lymphoid and endocrine pathology have been included, since no current book on surgical pathology could hope to live without them.

I wish to express my gratitude for the outstanding assistance I received from a group of tireless workers. Thanks go to my secretary, Zoann Biddle, for handling all the correspondence and some of the drafts, for her constant reminders to me to keep plugging, and for distributing an endless series of nags to my contributors; to Pamela

Chlebek and Cassandra Richardson for errorlessly processing all those words, deciphering my handwriting, and still maintaining their sense of humor; to photographers Craig Biddle and Eddie Burkes for keeping everything in focus and adding contrast even when none existed; and to John Caldwell for assuming much of the editorial drudgery. Finally, the six contributors, all overworked academic surgical pathologists, deserve a standing ovation from the editor, and, hopefully, from the readers as well.

Henry D. Appelman, M.D.

Contents

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Inflammatory and Neoplastic Diseases of the Esophagus

Frank A. Mitros

THE NORMAL ESOPHAGUS

The structure of the esophagus is deceptively simple. This squamous cell-lined muscular tube stretches about 25 cm from pharynx to stomach. In terms of the endoscopist, and consequently the surgical pathologist, it begins 15 cm from the incisors of an adult and ends about 40 cm from this landmark. While there have been attempts at defining this length in children of varying sizes,[1] no such figures are available to correct for differences in adults due to body habitus or other variables. The most commonly used landmark for the gastroesophageal junction, the appearance of a gastric type mucosa, can be misleading in the case of a Barrett's esophagus. Determination of the location of the lower esophageal sphincter (LES) manometrically is cumbersome and also fraught with difficulties likely to introduce error. The manometrically defined lower esophageal sphincter was shown to be located 38.7 ± 3.1 cm from the incisors in reflux patients, and 38.6 cm ± 2.2 cm from the incisors in control subjects in one study,[2] numbers which are virtually identical. However, it has been shown that the transition from gastric to squamous epithelium may lie above (0.7 ± 0.5 cm) the manometrically determined lower esophageal sphincter.[3] Clearly, the widely accepted value of 40 cm for the gastroesophageal junction must be used with some caution.

The muscularis propria is covered with an adventitia rather than a serosa, except for the most distal 1 – 2 cm. The well-defined circular and longitudinal muscle layers are much thicker than they are elsewhere in the gastrointestinal tract. The proximal two thirds also contain significant amounts of skeletal muscle. The much-discussed lower esophageal sphincter does not have a clearly defined anatomic structure, although functional differences in the smooth muscle of the distal esophagus have been documented. The myenteric plexus is similar to that seen more distally, but there are no submucosal ganglion cells.

The submucosa is thick and well vascularized, which accounts for the great propensity for microscopic spread of esophageal carcinomas in this area. It is rarely present in biopsies, even of the suction type.

The mucosa is limited by a very thick muscularis mucosae. A good suction biopsy often includes this entire structure, which can present a startling appearance if one is not aware of how thick it can be normally.

The squamous epithelium of the esophagus has been separated into basal, prickle, and functional layers by ultrastructural studies,[4] although practically only a separation into a basal and a superficial layer is necessary. This has been done by taking advantage of the absence of glycogen in the basal layer,[4] utilizing periodic acid-Schiff (PAS) staining techniques to demonstrate the glycogen in

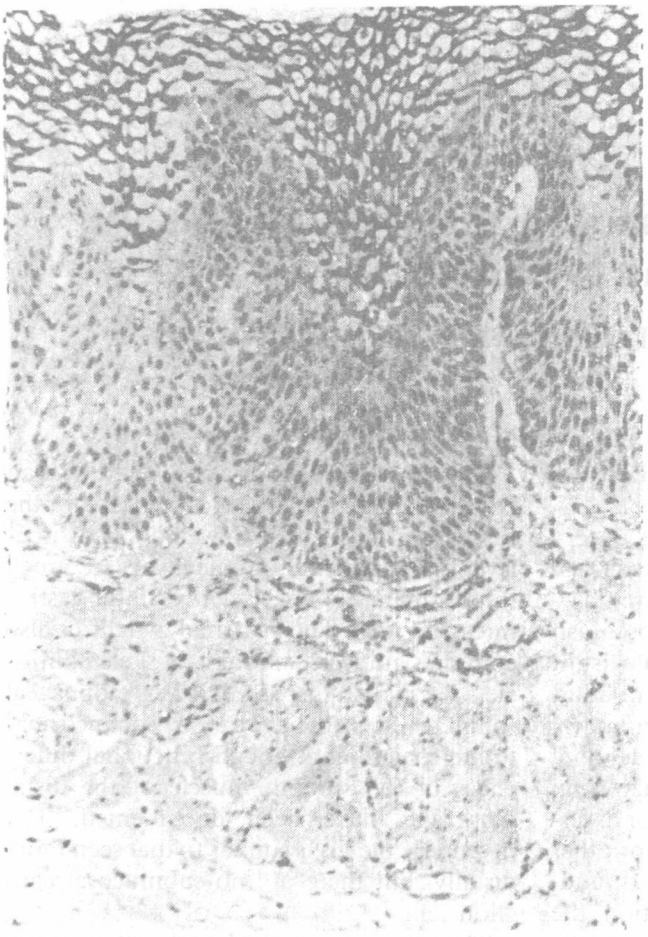

Fig. 1-1. Basal layer of increased thickness clearly revealed by PAS stain. ×40.

the superficial layer (Fig. 1-1). This step can be avoided by noting the increased cellularity, nuclear crowding, and basophilic cytoplasm in the cells of the basal layer, visible in standard hematoxylin and eosin sections (Fig. 1-2). However, the demarcation between basal and superficial layers is difficult to delineate. Probably the most reproducible guideline is defining the upper limit of the basal layer as that point at which the nuclei are separated from each other by a distance equal to their diameter.[5] The normal basal layer has been described as being one cell thick,[4] and, while a distinct single cell layer (Fig. 1-3) can sometimes be seen at the base of an apparently hyperplastic basal layer, those who have used hyperplasia of the basal layer as a criterion for esophagitis have included the several layers of cells with scant glycogen-free basophilic cytoplasm and prominent nuclei when quantitating basal hyperplasia.

The papillae, which consist of invaginations of lamina propria and blood vessels into the epithelial layer, are easier to quantitate. The height of a papilla is measured from basal lamina (of the surrounding squamous epithelium) to basal lamina (at the tip of the papilla). The papillae are ordinarily quite slender, containing only a capillary-size blood vessel and a scant amount of lamina propria.

The lamina propria is composed primarily of connective tissue. It can contain lymphocytes, plasma cells, and even lymphoid ag-

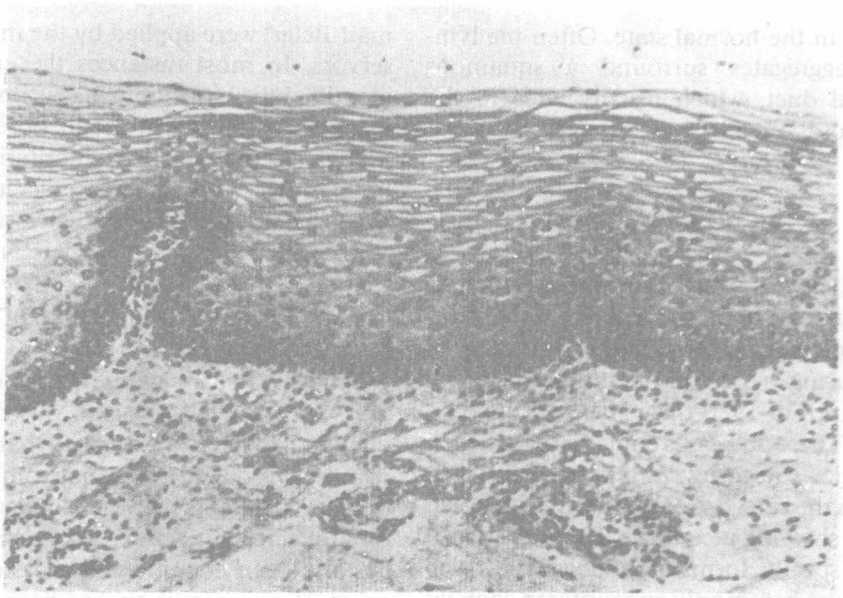

Fig. 1-2. Normal esophageal biopsy specimen with basal layer several cell layers thick, but occupying only 13% of the epithelial thickness. Scattered lymphocytes are present in the lamina propria. H & E. ×40.

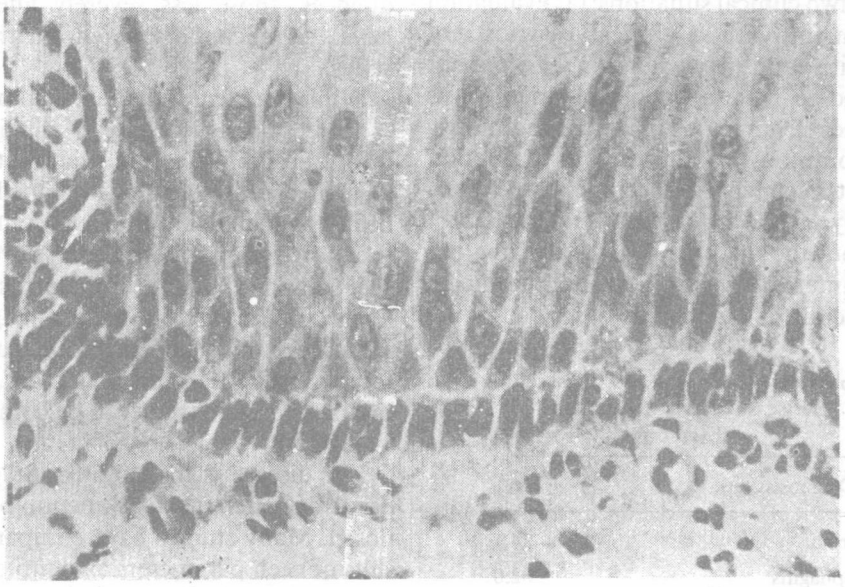

Fig. 1-3. An unusually distinct basal layer, consisting of a single cell layer. H & E. ×160.

gregates in the normal state. Often the lymphoid aggregates surround a squamous cell-lined duct, which usually ends in the submucosa.

OVERVIEW

In the process of preparing this chapter, all specimens of esophagus received in the surgical pathology laboratory at the University of Iowa during a period of approximately 2 years (April of 1980 through 1981) were reviewed. These 569 cases could be classified in four major categories, as seen in Table 1-1. Those in the category of esophagitis included biopsies showing ulceration, Barrett's esophagus, or specific forms of esophagitis, as well as the more commonly encountered changes of reflux esophagitis. The miscellaneous category included such entities as diverticula, glycogen acanthosis, and cysts. There were 18 surgical resection specimens; the remainder were endoscopic biopsies, the majority of which were obtained by suction rather than pinch biopsy. Essentially all the biopsies were done in two clinical situations: (1) evaluation of a patient with a clinical diagnosis of esophagitis, and (2) evaluation of a patient suspected to have a neoplasm. In patients suspected of having esophagitis, the biopsy most commonly obtained was a suction biopsy at 35 cm. These specimens were interpreted by several surgical pathologists, and I signed out the majority (56%), utilizing my specific interest in gastrointestinal pathology. The criteria for esophagitis described by Ismail-Beigi[6] were applied by the multiple observors. In most instances the endoscopist identified the biopsy site in centimeters from the incisors. Most, but not all, observers were aware that the Ismail-Beigi criteria may not be applicable in the distal esophagus, and utilized this information in their evaluation.

Table 1-1. Diagnoses of 569 Consecutive Surgical Pathology Specimens of Esophagus

Diagnosis	(%)
Normal	24.1
Esophagitis	62.0
Tumor	11.6
Miscellaneous	2.3

REFLUX ESOPHAGITIS

While there are many causes of esophagitis, the term, "esophagitis," used in an unqualified way, usually refers to that extremely common problem resulting from the reflux of gastric contents into the esophagus. This is usually acid, but reflux of alkaline material has also been documented occasionally as a cause of esophagitis. It has been estimated that 10% of the population in this country have had symptoms of reflux esophagitis[7]; since it is well known that esophagitis is not infrequently asymptomatic, the numbers of individuals affected is alarmingly large. Although only a small percentage of those affected develop life-threatening consequences, those less severely affected may have a significant interference with their lifestyles.

While it is clear that there is some defect in the forces opposing reflux of gastric contents into the esophagus, the exact pathophysiologic mechanism leading to reflux has not yet been elucidated. Interest has centered on a functional impairment of the lower esophageal sphincter, but other factors, such as the length of intraabdominal esophagus, clearance mechanisms of the esophagus, and the intrinsic defense mechanisms of the squamous mucosa, have yet to be completely investigated.

The disease is in search of a "gold standard" by which it can be unequivocally diagnosed. Many studies have compared the results of such parameters as symptomatology as judged by detailed questionnaires, endoscopic appearance, histologic appearance, lower esophageal sphincter pressure (at rest

and during various maneuvers), the response to acid instilled in the esophagus, and 24-hour intraluminal pH monitoring. None of these has proven uniformly satisfactory, and when a number of such tests are performed, there are frequently one or more that do not agree with the data derived from the others. Still a great deal of reliance is placed on them in evaluating patients thought to have esophagitis.

The only one of these parameters considered in the scope of this chapter is the histologic alteration resulting from gastroesophageal reflux. This has been a controversial area for some time, reflecting the problems discussed in the previous paragraph. Much of the problem stems from the fact that patients with well-defined esophagitis in the clinical sense may be lacking the parameters pathologists would expect to be associated with inflammation, namely, cellular infiltration and epithelial destruction (ulceration or erosion). If one waits for the appearance of these features, the esophageal biopsy remains a very accurate but insensitive measure of esophagitis.

Papillary and Basal Layer Height

It was not until 1970, with the description by Ismail-Beigi[6] of architectural alterations in papillary and basal layer (Fig. 1-4) in response to reflux, that the biopsy became more useful in diagnosing reflux esophagitis. This description was based on analogous changes previously described in skin as a response to injury.

The proposed mechanism is that damage to the superficial epithelium results in a stimulation of the basal layer, and consequent hyperplasia. The overall epithelial thickness remains normal, resulting in a relative increase in the percentage of the epithelium occupied by both the basal layer and the papillae. Some evidence confirmatory of this response was observed in studies of the incorporation of tritiated thymidine in the basal layer of clinically obtained esophageal biopsies.[8] Also, increased papillary and basal layer height have been observed to develop in sequential biopsies in experimental animals following surgery to produce reflux.[9]

Many significant problems still remain. Since it has been very difficult to define esophagitis in the less florid cases, and since the process is so common, the determination of what is normal has been quite difficult. Thus several groups have utilized different values of papillary and basal height as upper limits of normal. It has been noted that these values differ depending on the location within the esophagus, both values increasing more distally.[3] Whether this is a result of "physiologic reflux" or is completely "normal" is not clear. It is also evident that changes secondary to esophagitis tend to have a patchy distribution. Further compounding the problem is the difficulty in making these measurements. For accurate measurements, the biopsy specimens must be well oriented. This is best accomplished with the larger suction biopsy, which has been placed, cut surface down, on Millipore filter paper or some other appropriate medium for mounting immediately after having been obtained. It is difficult to orient pinch biopsies, and multiple-step sections may be necessary to obtain a well-oriented area (Fig. 1-5). Once such a well-oriented area is available, one still has to decide which and how many papillae and areas of basal layer to measure. Some studies have not specified such details, which may account for some of the disagreement still extant. Still, most observors agree that an increase in papillary and basal height correlates with the presence of esophagitis measured by other parameters.

Table 1-2 summarizes the most commonly cited studies providing critera for basal and papillary height in esophagitis. Of these, only the study by Seefeld[11] does not show a clear increase in these two measurements in esophagitis. One possibility for the discrepancy is a difference in the population studied

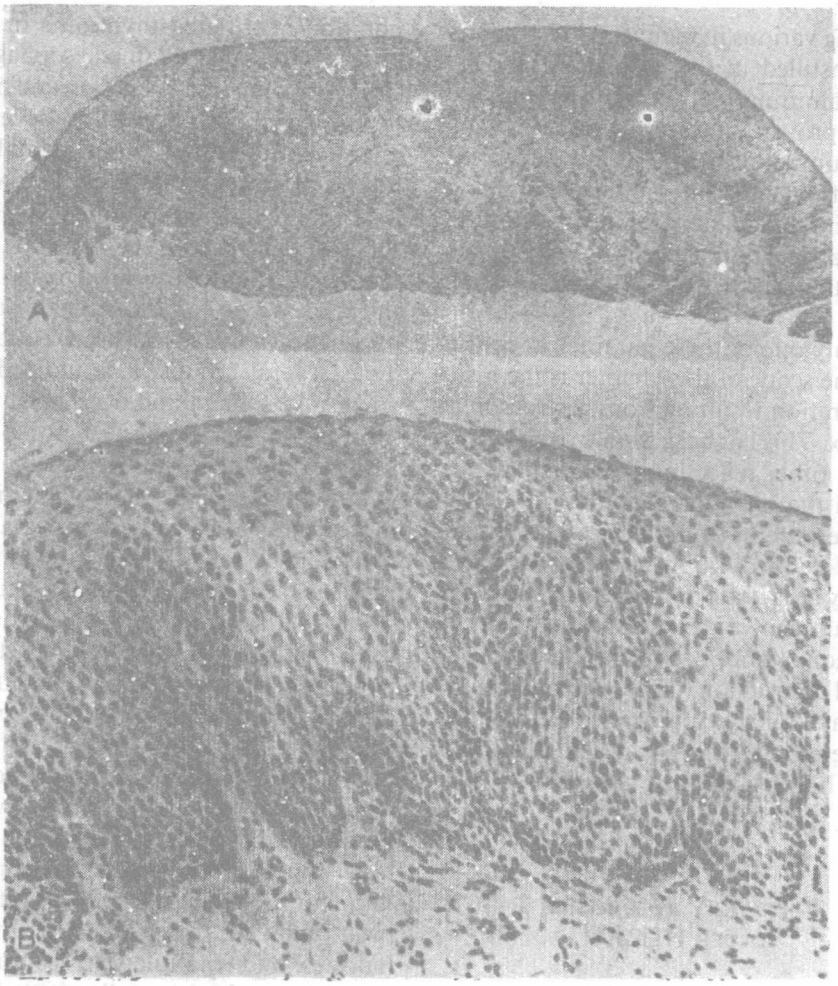

Fig. 1-4. **A:** Well-oriented suction biopsy specimen of reflux esophagitis with increased papillary and basal layer height throughout. H & E. ×10. **B:** Higher magnification of reflux esophagitis with increased papillary height (83%), basal layer height (57%), and numerous intraepithelial polymorphonuclear and eosinophilic leukocytes. H & E. ×40.

by Seefeld. The Ismail-Beigi and Behar studies were conducted in Veterans Administration Hospitals, and the patients in the esophagitis groups showed a strong male predominance (89% combined). The Johnson study did not specify the sex or age of the patients; it was conducted in a military setting (Tripler Army Medical Center). Only 58% of the proven reflux patients in the Seefeld study were male; also the extent of alcohol intake and smoking was quantified and relatively moderate in this study. The other studies did not quantify such parameters. There was some variability in the number of specimens, which may be of some significance, since esophagitis appears to be a patchy process. The site of biopsy also varies, with the Seefeld study coming from a site relatively more proximal than the other three, and the Behar study apparently including specimens from near the gastroesophageal junction. Another major difference is the method of obtaining the measurements. While visual estimation can

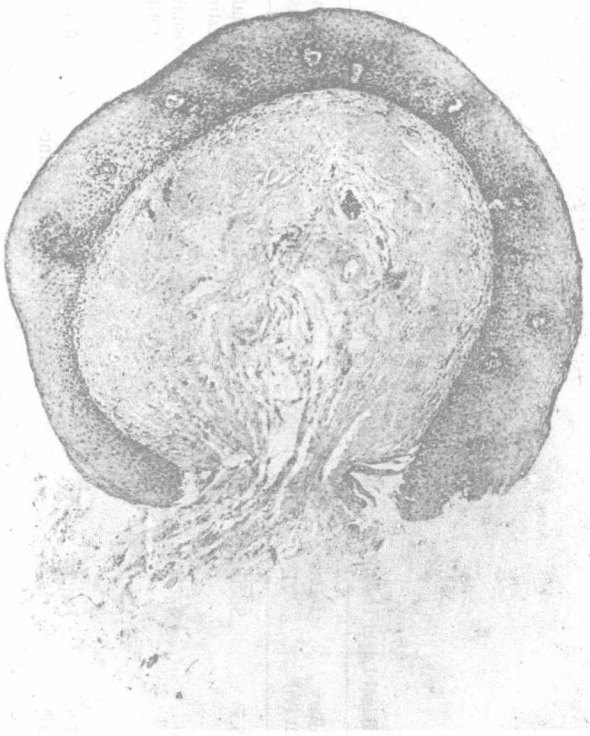

Fig. 1-5. Well-oriented central area of a pinch biopsy specimen of normal esophagus obtained by step sectioning. H & E. ×10.

be surprisingly accurate, there are obvious problems when many of the control subjects have values very near the cutoff value, as is often true in these two measurements. The Ismail-Beigi and Behar studies applied empirically derived criteria to multiple specimens, which were then classified as normal or abnormal with no more precise quantification. It is not clear what the precise definition of basal layer or papillary height is in the Ismail-Beigi study (and consequently the Behar study, which utilized the same criteria), nor is it stated whether the highest papilla, or all papillae, or only certain types of papillae were used to calculate the value for papillary height. The basal layer is described as a mean determined by visual estimation of a well-oriented central core. The other two studies, of necessity, take great pains to define how papillae and basal layer are defined, since they are directed toward a more exact quantitation. However, in doing so, other difficulties may arise. The criteria for the measurements were quite rigorous, but differed slightly. Johnson required a papilla to have a clearly defined central core of lamina propria, with at least two such papillae per section. All such papillae were measured, and a mean height obtained. The basal layer was defined on the basis of the internuclear distances, as described earlier. Seefeld required that three adjacent papillae have central cores of lamina propria along their entire length, with only papillae flanked on both sides by intact papillae being measured. The height of the papillae was not measured directly, but calculated from the mean of the thickness of the epithelium on either side of the papillae minus the height of the epithelium above the papilla. The mean of papillary height of all papillae meeting these criteria was then calculated. The basal layer was defined as the average of two values, the point of transition between densely and loosely packed basal cells, and the point of transition between loosely packed basal cells and the

Table 1-2. Papillary and Basal Layer Height in Esophagitis

Study	Definition of Abnormal	Basal Layer (%)[a]	Papillary Height (%)[a]	Biopsy Type	Specimens per Subject	Location	Method of Measuring
Ismail-Beigi[2]	Heartburn plus reflux (by intraluminal pH)	16 (10)[b]	66.7	Suction	2	2 cm proximal to LES[c]	Visual estimate
Behar[10]	Heartburn plus abnormalities in 1 of 3 tests (endoscopy, Bernstein, intaluminal pH)	16	50	Suction	4	Multiple, over distal 10 cm	Visual estimate
Johnson[5]	Score from 24-h intraluminal pH monitoring	19 ± 2 (15 ± 1)[b]	67 ± 1.5 (56 ± 3)[b]	Pinch	1.6	2–3 cm proximal to gastroesophageal junction	Quantitative
Seefeld[12]	Heartburn plus score from provocative tests	16.6 ± 6.9 (15.7 ± 7.0)[b]	56.0 ± 12.5 (49.7 ± 10.5)[b]	Suction	2.7	5 cm proximal to LES[c]	Quantitative

[a] ± 1 standard deviation.
[b] Normal values derived from control subjects.
[c] LES = lower esophageal sphincter.

Table 1-3. Quantification of Esophageal Biopsies (University of Iowa Data)

Diagnosis	Patients	Basal Layer (%)[a]	Papillary Height (%)[a]
Normal × 2	5	17.9 (7.6)	53.2 (14.0)
Disagreement	20	13.1 (9.5)	61.6 (6.9)
Esophagitis × 2	6	41.7 (17.0)	74.4 (4.1)

[a] 1 SD percent in parentheses.

stratified squamous layers. In both studies, the basal layer was measured only in the areas where papillae met the described requirements for mensuration, and mean values were calculated. It is quite possible that with such stringent criteria, areas of significant increase in papillary height and basal layer might be excluded from consideration.

Another potential source of error is inter- and intraobserver variation, particularly when a visual estimate of the basal layer and papillae is made. I reviewed the histology of all 569 cases from the University of Iowa series in a blind fashion, and the "blind" diagnoses were compared to the original diagnosis. Of those originally diagnosed as normal, there was intraobserver agreement in 72 of 88 cases (81.8%) and interobserver agreement in 38 of 48 cases (79.2%). This was increased to 78 of 88 (88.6%) and 39 of 48 (81.3%) after looking at the clinical data, since seven specimens with tall papillae and increased basal layer had come from the immediate vicinity of the gastroesophageal junction. For those originally interpreted as showing changes of esophagitis, intraobserver agreement was seen in 153 of 193 (79.3%) of cases and interobserver agreement in 126 of 152 (82.9%) of cases. It is interesting that these figures are comparable to the 80% interobserver difference reported in the Ismail-Beigi[6] study after their initial independent histologic evaluation. Cases were randomly chosen from three groups: (1) the original and blinded diagnosis were both normal, (2) both were esophagitis, or (3) there was disagreement between the two diagnoses. The basal layer and papillae were quantified as described by Johnson et al.,[5] and the results are given in Tables 1-3 and 1-4. Cases where the biopsies had been taken from the distal 2 cm of the esophagus were not considered in this analysis. It appears that the situation most likely to lead to a questionable interpretation of basal layer and papillary height is the combination of a borderline papillary height in the presence of an increased basal layer.

One further warning is in order concerning the basal layer. Because it is not clearly demarcated, it is very difficult to measure acurately, and measurements are dependent on how the basal layer is defined. While the use of PAS staining accentuates the line of demarcation making more accurate measurement possible, there is no evidence that the values so obtained correspond to the values in the major studies in Table 1-1, which were obtained on hematoxylin and eosin stained (H & E) sections. In fact, it has previously been noted that the values for the basal layer in normals were lower when obtained in PAS sections.[13] In the 11 cases described in Table 1-3 as either normal or showing esophagitis, the basal layer value obtained on PAS sections was $24.5 \pm 15.2\%$ compared to a value of $30.9 \pm 18.0\%$ when the techniques of Johnson et al.[5] were used. It appears that using glycogen content to determine the basal layer thickness may result in slightly lower values than the more commonly employed estimates from standard sections.