BARRETT SYNDROME

Case Report with Discussion about Concepts of Pathogenesis

MARVIN C. GOLDMAN, M.D., AND ROBERT C. BECKMAN, M.D.

From the Veterans Administration Hospital and the University of Oregon Medical School, Portland, Oregon

In 1950 Barrett[1] described a developmental anomaly in which the distal esophagus was lined with a cylindric type of epithelium instead of the normal squamous type. This has been termed Barrett-type epithelium. The glands do not contain parietal cells or peptic cells. Esophageal mucous glands are present in the submucosa. This condition of heterotopic gastric epithelium in the esophagus, or "gastric-lined esophagus," is distinct from the rarer instance in which a discrete island of gastric mucosa lies in the distal esophagus; *i.e.*, ectopic gastric epithelium. An ectopic island consists of normal gastric epithelium which grossly resembles stomach and microscopically shows parietal cells, but is dislocated proximally and is separated from the gastric epithelium of the stomach by squamous epithelium of the esophagus. In heterotopia, the atypical cylindric epithelium exists as a complete sheet, connecting distally with the normal gastric epithelium of the stomach. The heterotopic mucosa, as seen in gross specimens, or as visualized by esophagoscopy, resembles normal squamous esophageal mucosa.

Barrett thought that this heterotopic epithelium was susceptible to ulceration under the influence of acid gastric juice and that cases of "chronic peptic ulcer of the esophagus" showed the ulceration to be located in heterotopic epithelium. He therefore suggested that the term "chronic peptic ulcer of the esophagus" be retained for ulceration in heterotopic epithelium, and that the term "reflux esophagitis" be applied to inflammation and superficial erosion of a normally lined esophagus usually seen in association with hiatal hernia.

Received September 28, 1959. Accepted November 26, 1959.

Barrett[1, 2] viewed the pathogenesis of esophagitis and esophageal ulcer as follows: peptic esophagitis is characterized by multiple shallow ulcerations, hyperemia, edema, friability, and leukoplakia. Later this inflammation may spread beyond the submucosa, leading to formation of dense fibrous tissue in the musculature which may result in stricture. Fixation of the esophagus to adjacent structures in the mediastinum may occur owing to fibrosis and lymphadenitis. Rarely, this may lead to ascending fibrosis of the esophagus. Above the stricture the mucosa is usually normal, perhaps being protected from the acid peptic juices by the stricture. Thus, peptic esophagitis occurs in squamous epithelium, beginning at the junction with gastric or Barrett epithelium, and is characterized by inflammatory changes of a superficial nature which eventually lead to fibrosis and stricture. This process usually does not cause massive bleeding and does not perforate. Peptic ulcer of the esophagus, on the other hand, occurs in gastric type of epithelium and may be associated with massive bleeding or with perforation. Stricture formation has also occurred here but is uncommon.

Other authors[3, 4] have confirmed Barrett's findings and have accepted his terminology, but there has been confusion about what to call the part of the esophagus lined with Barrett epithelium. Originally, because of its mucosal pattern, Barrett considered this to be stomach associated with a congenitally short esophagus. Allison and Johnstone,[3] however, considered this to be esophagus

lined with gastric epithelium. They pointed out that it had no peritoneal covering, that there was an esophageal type of musculature, that islands of squamous epithelium may exist within it, that there were no parietal cells, and that esophageal mucus glands were present. Wolf *et al.*[4] have also regarded this as esophagus, and recently, Barrett[5] too has used the term "lower esophagus lined by columnar epithelium." All authors on this subject have regarded Barrett's epithelium as probably being present from birth and only later in life becoming symptomatic in association with an hiatal hernia. All of Allison's cases had symptoms and hiatal hernias. Wolf *et al.*[6] felt that Barrett epithelium represents a persistence of embryonic epithelium which ordinarily is replaced progressively from above downward by squamous epithelium. If this process is incomplete, a variable portion of distal esophagus remains lined by this unusual Barrett type of epithelium. Barrett,[5] quoting the findings of Johns,[7] pointed out that in the human embryo ciliated columnar epithelium is replaced by stratified squamous epithelium, with this change beginning in the middle esophagus and extending both upward and downward. Again, according to this view, Barrett epithelium represents a congenital condition. Barrett, however, questioned why the abnormality always occurs in the lower end of the esophagus and not in the upper end.

We recently have encountered a case of esophagitis with stricture formation and with Barrett type of epithelium which presented an unusual opportunity to re-examine some of the concepts about the pathogenesis and significance of Barrett epithelium.

Case Report

A. H., a 66-year-old white man, was readmitted to the Portland Veterans Administration Hospital for the fourth time on January 7, 1959, with the history of dysphagia, regurgitation, and substernal burning pain of approximately 11 years' duration. In 1950, at another hospital, two esophagrams performed for this complaint were reported as negative. Esophagoscopy was first performed in July 1950 at the Walla Walla Veterans Administration Hospital. A normal

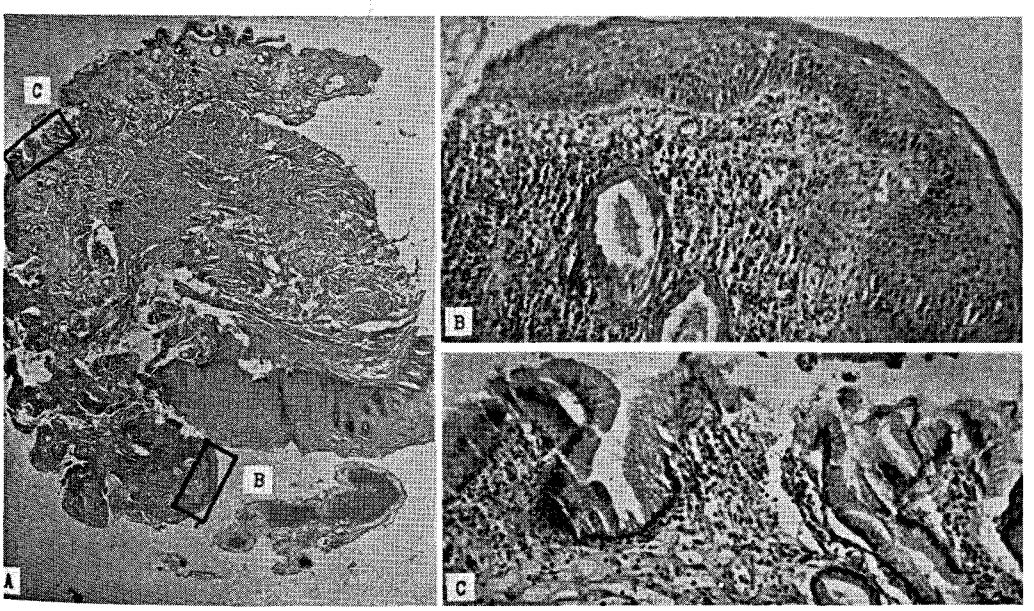

FIG. 1. *A*, Low power view of biopsy, taken in July 1951, at cardioesophageal junction, 33 cm. from the incisor teeth. This shows both squamous and cardiac type of epithelium. *B*, High power view of *A*, showing the presence of squamous epithelium and the presence of inflammatory reaction in the lamina propria. *C*, Another high power view of *A*, showing the cardiac type of epithelium.

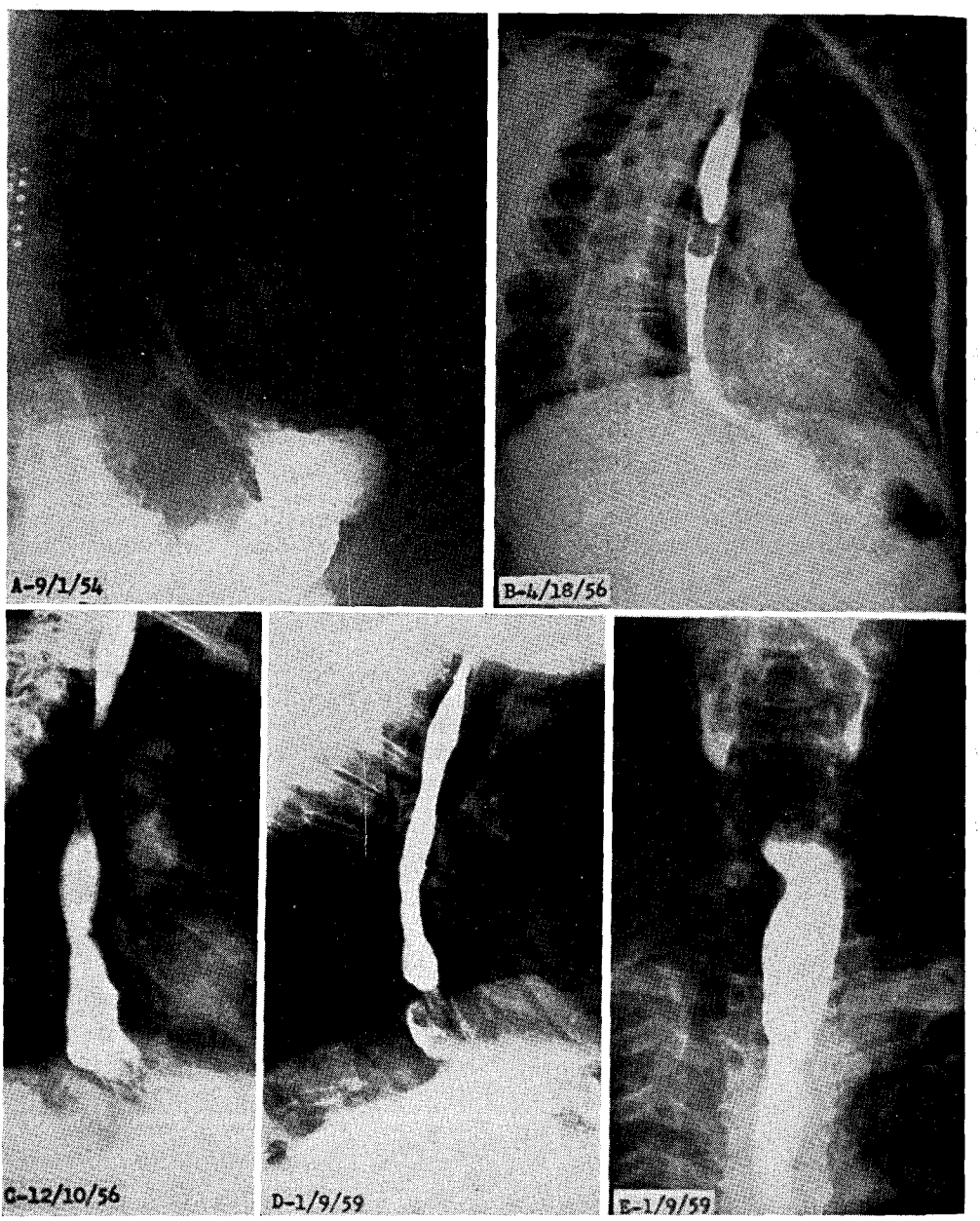

FIG. 2. *A*, Esophagram, taken September 1, 1954, depicting a stricture of the esophagus at the level of T 8-9. *B*, Esophagus, taken April 18, 1956, showing absence of stricture at this time. *C*, Esophagram, taken December 10, 1956, which shows a stricture at the level of T 6. A notch is seen lower in the esophagus overlying the 8th rib. This is thought to represent the esophagogastric junction. *D* and *E*, Esophagram, taken January 9, 1959, showing stricture formation at the level of T 2 with no evidence of stricture lower in the esophagus. The associated hiatal hernia is again demonstrated.

esophagus was noted to 33 cm. from the incisor teeth, but at this point a constriction was found. The mucosa in this area was described as granular and easily traumatized. A biopsy specimen was reported as showing esophagitis with squamous epithelium and inflammatory infiltrations in the lamina propria. Columnar epithelium was also seen in this specimen and it was felt that this

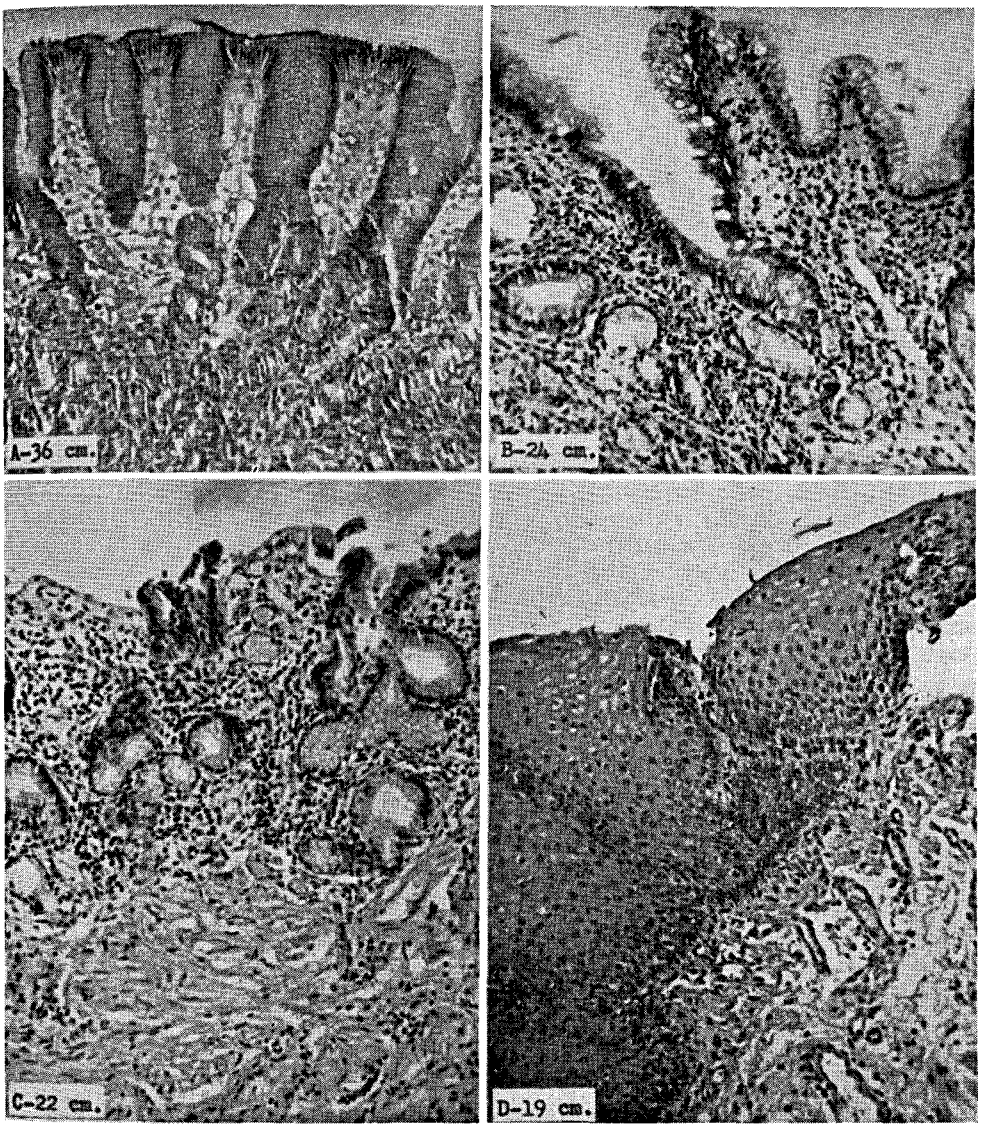

FIG. 3. *A*, High power photomicrograph, taken in 1959, of gastric epithelium at 36 cm. Parietal cells were identified in the specimen. *B*, High power photomicrograph (1959) showing Barrett type epithelium at 24 cm. Inflammatory exudate is present in the lamina propria and many goblet cells are evident. *C*, High power photomicrograph of the stricture at 22 cm. (1959). Note the erosion of the columnar epithelium and the inflammatory exudate and fibrosis in the subepithelial layers. *D*, High power photomicrograph of esophagus at 19 cm. (1959) showing squamous epithelium.

represented the esophagogastric junction (fig. 1*A* to *C*).

In January 1952, at the Seattle Veterans Administration Hospital, further esophageal studies were made. An esophagram was negative and esophagoscopy showed inflammation of the distal esophagus. A biopsy of the distal esophagus was reported as showing acute inflammatory changes, with no evidence of malignancy. While in the hospital on a soft diet the patient gained weight. He was discharged without more specific therapy.

In August 1954 the patient was first admitted to the Portland Veterans Administration Hospital with a history of a 20-pound weight loss during the preceding year, frequent regurgitation of food

and liquids, and burning retrosternal pain. Esophagoscopy revealed stricture formation 16 cm. below the cricopharyngeus muscle, with signs of marked esophagitis, including membrane formation and friability of the mucosa. X-ray studies (fig. 2*A*) confirmed a stricture at the level of T 8-9, at the junction of the middle and distal thirds of the esophagus. Bland feedings, antacids and, later, esophageal dilations, were instituted. The patient improved symptomatically and gained 15 pounds. Esophageal dilations with metal olives were done at monthly intervals until August 1955. In April 1956 the patient was having no trouble swallowing food and was free of pain. Esophagrams (fig. 2*B*) showed no stricture.

The patient was seen next at the Portland Veterans Administration Hospital in December 1956, with the complaints of food sticking in the esophagus and of burning retrosternal pain relieved by soda. Upper gastrointestinal series (fig. 2*C*) demonstrated a stricture of the esophagus at the level of T 6, and also a hiatal hernia. A string test was negative. The patient became asymptomatic on a bland diet and antacids and was advised to continue this program. In April 1958 the patient entered the Vancouver, Washington, Veterans Administration Hospital for evaluation of his chronic respiratory complaints. No dysphagia was noted at that time. An upper gastrointestinal series showed only a small hiatal hernia.

At the time of the current admission to the Portland Veterans Administration Hospital, the patient had noted a tendency for food to stick in the esophagus but at a point more proximal than previously, that is, under the upper sternal region, whereas formerly food would stick under the lower sternal area. Burning pain was again present and was also noted to be located at a higher level than previously. He had been following no therapeutic program at home. There was no history of melena, hematemesis, or recent weight loss. Physical examination revealed a well developed, well nourished, ambulatory white man who was in no distress. Physical findings were essentially normal except for chest findings compatible with moderate pulmonary emphysema. Pertinent laboratory data included a normal hemogram, stools negative for occult blood, and a normal electrocardiogram. Gastric aspiration studies showed no free acid before histamine stimulation, but 7.2 mEq. per hour of free hydrochloric acid after histamine. On the esophagram (fig. 2*D* and *E*) was a localized narrowing at the level of T 2 to T 3. The distal esophagus appeared to have a normal caliber on this study. The stricture of the esophagus at 22 cm. from the incisor teeth was noted at esophagoscopy. A bougie larger than 6 mm. could not be passed through the strictured area. The mucosa at this area appeared granular and friable Biopsies at the level of the stricture (fig. 3*C*) revealed papillary projections covered with well developed columnar epithelium which, however, was eroded in areas. Underlying this epithelium there was an inflammatory infiltrate with fibrosis. Progressive esophageal dilations were then performed during the next month until a no. 44 olive could be passed without resistance. On February 25, 1959, esophagoscopy was repeated, and at this time the instrument could easily be passed through the previously narrowed segment. The mucosa at this time still appeared granular and had an adherent white exudate. The distal esophagus appeared normal. Multiple biopsies were taken at 17, 19, 22, 24, 30, 32½, and 36 cm. Normal gastric mucosa was microscopically present at 36 cm. (fig. 3*A*). Specimens from 24, 30, and 32½ cm. (fig. 3*B*) revealed columnar epithelium with interspersed goblet cells (Barrett epithelium). Normal squamous epithelium was present at 19 cm. (fig. 3*D*). The patient was continued on a medical program for his esophagitis and when last seen on April 14, 1959, was free of symptoms.

Discussion

This case of Barrett syndrome is unusual in two ways. First, we had clear evidence of a stricture formerly being present in the terminal esophagus and now occurring at a much higher level. Indeed, it even appears on repeated x-ray examinations (fig. 2*A* to *E*) that the ascent of the stricture can be followed. This has been reported in association with Barrett epithelium on only one other occasion. In that case, reported by Som and Wolf,[8] the interpretation given was that originally the stricture may have occurred between Barrett epithelium and stomach. With evidence of ascent of the stricture, it was felt that there was first shortening of the esophagus and later occurrence of the stricture at a higher new location in the esophagus between Barrett epithelium and squamous epithelium. We place a different interpretation on the sequence of events in our patient.

The second unusual aspect of the present case is the demonstration by biopsy of squamous epithelium formerly occurring at

a much lower level in the esophagus, but now present only in the upper esophagus. This finding has not been reported in the previously published cases.

These two features suggest the possibility that Barrett epithelium represents an acquired condition in our patient. The following points are in favor of this thesis: First, and most pointedly, there is evidence that 7 years previously squamous epithelium was present at 33 cm. in the esophagus, and we see in the biopsy taken at that time what appears to be the cardioesophageal junction. (fig. 1*A*, *B*, and *C*) Although islands of squamous epithelium may exist in Barrett epithelium, it appears that in this case an active esophagitis is taking place in the squamous lined esophagus. From previous considerations this would favor the assumption that the squamous epithelium does in fact represent the site of connection of two different types of epithelium, *i.e.*, squamous and gastric. From Barrett's findings it is likely that there was a broad sheet of squamous epithelium above the site of biopsy and that the squamous epithelium in this earlier biopsy does not represent an isolated island of squamous epithelium within Barrett epithelium.

Second, the ascent of the stricture over the years as followed by repeated x-ray examinations (fig. 2*A* to *E*) would seem to indicate a process of destruction of squamous epithelium with replacement by Barrett epithelium. We postulate that as more and more squamous epithelium was destroyed the site of stricture formation occurred at a progressively higher level in the esophagus.

Thus, Barrett epithelium may well be an acquired condition in which esophageal squamous epithelium that is eroded and destroyed by peptic esophagitis is replaced by the special cylindric type of epithelial lining.

Between the squamous epithelium of the esophagus and the proper gastric glands of the stomach lies a narrow zone, usually only a few millimeters in width, containing cardiac glands.[9] These are composed of cylindric surface epithelial cells and mucous cells in the gastric pits. They contain neither parietal nor peptic cells. It is evident that the histology of the cardiac glands of the stomach is similar to that of the so-called Barrett epithelium, and Barrett epithelium might represent a simple extension of the normal cardiac glands of the stomach upward into the esophagus. Another possibility is that the Barrett columnar epithelium arises from the esophageal glands scattered throughout the lamina propria of the esophagus. Metaplasia of squamous epithelium into columnar Barrett epithelium would be another less likely possibility. Because of the continuous nature of the extension we favor the first explanation and speculate that the occurrence of this heterotopia is a response to injury of the esophagus (esophagitis), and is not a predisposing cause of the esophagitis. In this respect it is of interest that the recent papers by Oi and his associates[10-12] point out that esophageal, gastric, and duodenal ulcers tend to occur exactly at the junction between two kinds of epithelium. He shows that almost all gastric ulcers lie in the pyloric gland mucosa at the junction of pyloric glands and the fundic glands. When there is a high lying gastric ulcer, this is associated with a high lying junction between pyloric and fundic glands. He does not suggest that this junction line has moved up in response to the disease, but this is a possibility to be considered.

These considerations suggest that Barrett epithelium may represent an acquired condition which appears in response to esophagitis. It is suggested that a careful histologic study of all cases of hiatal hernia would be rewarding and might well reveal Barrett epithelium extending into the esophagus for a short distance in many such cases. Perhaps only the very extensive ones are called by his name.

Summary and Conclusions

A case of long standing esophagitis with stricture formation and with Barrett epithelium (columnar epithelium lining the lower esophagus) is presented. Over a 7-year span the stricture was shown to ascend from low esophagus to higher levels. In early biopsy sections squamous epithelium was

present low in the esophagus but in later ones only at high levels, with Barrett epithelium shown continuously below the stricture by biopsies at multiple levels.

The thesis is presented that Barrett epithelium may be an acquired condition and may represent a healing response of the esophagus to injury.

Acknowledgments. The authors gratefully acknowledge their appreciation to Dr. Morton I. Grossman of the Veterans Administration Hospital, Los Angeles, California, and Dr. Leonard W. Ritzmann of the Veterans Administration Hospital, Portland, Oregon, for helpful advice in preparation of the manuscript, and to Dean Altman for the illustrations.

Dr. Marvin C. Goldman
Veterans Administration Hospital
Portland 7, Oregon

REFERENCES

1. Barrett, N. R. Chronic peptic ulcer of the oesophagus and "oesophagitis." Brit. J. Surg., **38:** 175, 1950.
2. Barrett, N. R. Hiatus hernia; a review of some controversial points. Brit. J. Surg., **42:** 231, 1954.
3. Allison, P. R., and Johnstone, A. S. The oesophagus lined with gastric mucous membrane. Thorax, **8:** 87, 1953.
4. Wolf, B. S., Marshak, R. H., Som, M. L., and Winkelstein, A. Peptic esophagitis, peptic ulcer of the esophagus and marginal esophagogastric ulceration. Gastroenterology, **29:** 744, 1955.
5. Barrett, N. R. The lower esophagus lined by columnar epithelium. In *Modern Trends in Gastroenterology, Second Series*, edited by F. A. Jones, p. 147. Paul B. Hoeber, Inc., New York, 1958.
6. Wolf, B. S., Marshak, R. H., and Som, M. L. Peptic esophagitis and peptic ulceration of the esophagus. Amer J. Roentgenol., **79:** 741, 1958.
7. Johns, B. A. E. Developmental changes in the oesophageal epithelium in man. J. Anat., **86:** 431, 1952.
8. Som, M. L., and Wolf, B. S. Peptic ulcer of the esophagus and esophagitis in gastri-lined esophagus. J. A. M. A., **162:** 64, 1956.
9. Bensley, R. R., The gastric glands. In *E. V. Cowdry's Special Cytology*, Ed. 2, edited by E. V. Cowdry, p. 197. Paul B. Hoeber, Inc., New York, 1932.
10. Oi, M., Oshida, K., and Sugimura, S. The location of gastric ulcer. Gastroenterology, **36:** 45, 1959.
11. Oi, M., and Oshida, K. The association of esophageal, gastric and duodenal ulcers. Gastroenterology, **36:** 57, 1959.
12. Oi, M., and Sakurai, Y. The location of duodenal ulcer. Gastroenterology, **36:** 60, 1959.