Secretory function of Barrett's epithelium

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EDITORIAL SYNOPSIS A detailed study is recorded of a patient with the oesophagus lined with gastric type epithelium associated with a hiatus hernia, and a benign stricture and peptic ulceration at the level of the aortic arch. Investigations showed that ectopic epithelium was present in biopsies taken along the whole length of the oesophagus and that the motor function of the body of the oesophagus was disordered and the gastro-oesophageal sphincter feeble and incompetent. Biopsies of the mucosa had the typical histological appearance of gastric mucosa, containing both chief cells with pepsinogen granules and parietal cells which responded to histamine stimulation by the secretion of hydrochloric acid. Over a year following these investigations the patient was readmitted and died with a carcinoma of the mid oesophagus. Post-mortem examination showed that the gastric-like mucosa was distributed in islands throughout the entire oesophagus.

The occurrence of columnar epithelium lining the lower two-thirds of the oesophagus was described by Barrett (1950) who considered that in his material the oesophagus was congenitally short and associated with a thoracic stomach. However, Allison and Johnstone (1953) considered that the abnormal epithelium lined the oesophagus and was a result of metaplasia secondary to reflux oesophagitis in association with hiatal hernia. Cohen, Wolfe, Som, and Janowitz (1963) reported a case studied radiologically and by manometry. The motor function of the abnormally lined segment was reported to be similar to that of a normal oesophagus although their records show features which suggested disordered motor function. Therefore when the present case came to our attention we were interested to examine the motor function of the oesophagus and also to determine whether the abnormal epithelium was in fact functioning gastric secretory mucosa.

CASE REPORT

HISTORY A 71-year-old male retired labourer was first seen by us in July 1963. He first attended the Winnipeg General Hospital in 1954 complaining of dysphagia for six months associated with a loss of weight of 31 lb. X-ray examination (Fig. 1) showed a hiatus hernia extending 4 cm. above the diaphragm and a narrowing of the oesophageal lumen at the level of the aortic arch suggestive of a carcinoma at this site. The radiologist also reported the presence of gastro-oesophageal reflux. Oesophagoscopy examination revealed an ulcerated stricture in this area which was biopsied and then dilated.

Reflux of gastric contents was observed below the stricture. The biopsy showed columnar epithelium con-

FIG. 1. Barium swallow examination of oesophagus showing a stricture (upper arrow) at the level of the aortic arch, the gastro-oesophageal junction (lower arrow), and with a hiatus hernia below.

taining numerous mucus cells but there was no evidence of neoplasm.

The patient remained relatively well with only occasional dysphagia until 1960 when he began to have 'heartburn' related to lying down, bending over, or straining. In addition he had lower retrosternal pain unrelated to effort which occurred after meals and was relieved by milk and antacids. Radiographic and endoscopic examinations were carried out again and a similar bleeding ulcerated stricture was found at the level of the aortic arch, which was dilated. Biopsy again showed columnar epithelium. He was re-admitted in 1961 and in 1962 for dilatation of the stricture.

In July 1963 he still complained of heartburn and dysphagia. On this occasion further investigations were carried out to study the motor function of the oesophagus and the secretory function of the epithelium.

RADIOGRAPHY The stricture at the level of the aortic arch and the large hiatus hernia were again shown.

STUDY OF OESOPHAGEAL MOTILITY This was assessed using open-tipped tubes according to the methods described by Code, Kelley, Schlegel, and Olsen (1962) and used routinely in our laboratory for the investigation of cases of hiatus hernia as reported by Wankling, Warrian, and Lind (1965). The study involved the use of both the pull-through technique and the simultaneous recording of pressure from three sites at 5 cm. intervals during and immediately after a swallow. By the pull-through technique the criteria of Code *et al.* (1962) for hiatus hernia were fulfilled: the gastro-oesophageal junctional zone was well above the level of the diaphragm and the pressure in this zone was feeble; the typical double respiratory reversal was present; the hernial sac was estimated to be 4 cm. long.

Figure 2 shows the tracing obtained during a swallow, while the tubes were maintained in one position. From below upwards the four tracings shown are from: (a) the tubular pneumograph about the lower ribs with upward inspiratory deflection; (b) the orifice of the distal pressure sensing unit in the stomach below the level of the diaphragm, since the respiratory deflections are in phase with the pneumograph; (c) the orifice of the middle pressure sensing unit located in the gastro-oesophageal sphincter zone; (d) the proximal unit in the body of the oesophagus. The latter two units were in the thorax since the respiratory waves were out of phase with the pneumograph. There was evidence of disordered motor activity in this segment of the lower oesophagus as indicated by the double wave in the body of the oesophagus, the absence of a phase of relaxation in the gastro-oesophageal sphincter, and the feeble contraction of the sphincter simultaneously with the second peak of the contraction wave in the oesophagus 5 cm. above the sphincteric zone.

This combination of findings is, in our experience, frequently found in patients with hiatus hernia, who show gastro-oesophageal reflux.

STUDIES OF THE MUCOSA The possibility that the mucosal lining of the oesophagus contained functioning parietal

FIG. 2. Oesophageal motility record showing disordered motor function of the oesophagus and the gastro-oesophageal sphincter.

cells was investigated by a modified maximal histamine test. Since reflux of gastric contents into the oesophagus was known to occur in this patient special precautions were required. A three-lumen tube was passed into the stomach, one for aspirating gastric contents, one to inflate a balloon fixed to the tube to block the cardia mechanically, and the third to inject an indicator dye, phenol red, into the stomach to detect any reflux from the stomach into the oesophagus. To prevent reflux the inflated balloon was positioned in the herniated part of the stomach and pulled snugly against the cardia. A radio-opaque Levine tube was then positioned in the mid oesophagus.

The contents of the oesophagus and of the stomach were separately aspirated during a one-hour initial control period; for 30 minutes after the subcutaneous injection of antihistamine; and finally for one hour after the injection of histamine. During all this time saliva was continuously aspirated from the mouth. The results are shown in Table 1. The pH, estimated in a Beckman pH meter, of the oesophageal juice was below the normal range in the first two samples, and fell to 3.88 in response to histamine, indicating a further secretion of acid. The gastric juice also showed an acid secretory response to histamine although the extent of this response was below the normal range for this age group ($8.1 \pm \text{S.E. } 1.15$).

No phenol red was aspirated from the oesophagus indicating that no reflux occurred. The volume of gastric

TABLE I

AUGMENTED HISTAMINE TEST WITH PHENOL RED

	Oesophageal Secretion			Gastric Secretion		
	Volume (ml.)	pH	Acid (mEq./hr.)	Volume (ml.)	pH	Acid (mEq./hr.)
Fasting (60 min.)	44	4.35	0.79	36	2.62	0.95
Post-antihistamine (30 min.)	5	4.32	0.08	34	2.55	1.00
Post-histamine (60 min.)	15	3.88	0.51	141	1.62	5.62

contents of pH 1.62 required to change the pH of 15 ml. of oesophageal secretion from 4.3 to 3.9 was estimated to be approximately 1 ml. The amount of phenol red in this volume of reflux would have been readily detected in the oesophageal aspirate. Therefore the acid aspirated from the oesophagus was presumed to have been secreted by the mucosa lining this organ.

BIOPSIES A Rubin's biopsy capsule was repeatedly positioned in the oesophagus under fluoroscopic control and biopsies taken from above (Fig. 3), below (Fig. 4), and at the level of the stricture. All these biopsies, including one taken at least 5 cm. above the stricture, showed columnar epithelium, mucus cells, and convoluted glands, identical in appearance to gastric mucosa from the body of the stomach.

In addition to the usual staining the biopsy taken from the body of the oesophagus below the stricture was also stained for pepsinogen granules as described by Bowie (1936). The tubular glands were lined with secretory cells filled with pepsinogen granules, and against the basement

membrane of the acini pink-staining parietal cells were also seen.

SUBSEQUENT COURSE In December 1964 the patient presented with severe dysphagia, weight loss, and hoarseness. On this occasion he was found to have an inoperable carcinoma of the mid oesophagus. His course was rapidly downhill and he died within a few weeks. Post-mortem examination revealed a large necrotic ulcerating tumour. Histologically this was classified as a poorly differentiated adenocarcinoma, and mucicarmine stains confirmed the presence of mucus-staining cells. Numerous blocks for histological study were taken from the length of the oesophagus, and showed islands of gastric mucosa with intervening squamous epithelium (Fig. 5) both above and below the tumour.

COMMENT

This patient had the features described by Barrett

FIG. 3. Biopsy of the oesophagus from above the stricture confirming the presence of gastric mucosa.

FIG. 4. Biopsy of the oesophagus from below the stricture confirming the presence of gastric mucosa.

FIG. 5. Post-mortem specimen showing the junction of squamous and columnar epithelium in a section taken from below the carcinoma. The gastric type glands are well shown. Similar pictures were seen in other areas, including those above the tumour.

(1950) and by Allison and Johnstone (1953), that is, high oesophageal ulceration with stricture, associated with columnar epithelium in the oesophagus, and hiatus hernia. There was also evidence of disordered motor function of the oesophagus and a feeble cardiac sphincter.

The major apparent differences between this and previously reported cases are: the demonstration that the columnar epithelium was functional gastric mucosa, and that contrary to our impression during life the necropsy showed the columnar epithelium to be scattered in islands throughout the length of the oesophagus, whereas other authors have described a continuous sheet.

The question arises whether our case is unusual in these two respects, or whether many cases of this syndrome have these same features. To our knowledge, the function of the glandular elements of the mucosa have not been previously studied. It may be a common feature in this syndrome, thus affording an explanation as to why ulceration is high in such cases since it need not depend on the reflux of gastric contents usually associated with ulceration and stricture in the lower oesophagus.

With regard to the distribution of the gastric-type mucosa, either as islands or as a sheet, in the present case the true picture was only apparent at necropsy. Some cases described in the literature, without resection or necropsy, which were presumed to

have a continuous sheet of columnar epithelium may be similar to our own.

With regard to the terminal carcinoma, from the numerous endoscopic examinations and biopsies it is considered that the neoplasm developed some time between the special investigations described here and the patient's final hospital admission.

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