Histological and histochemical changes in the columnar lined (Barrett's) oesophagus

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SUMMARY Multiple endoscopic specimens were obtained from 58 patients with a columnar lined oesophagus to study the histological and histochemical features of this metaplastic epithelium. Five patients (8.6%) had presented with a primary oesophageal adenocarcinoma. Three different epithelial types, junctional, atrophic fundic and intestinal were identified. Twenty two (38%) patients had just one type of epithelium present, the other 36 (62%) having a combination of two or three different types. Intestinal type of epithelium, either alone or in combination with gastric type epithelium was present in 48 (83%) patients. In every case this intestinal type epithelium took the form of an incompletely differentiated variant of intestinal metaplasia, although complete intestinal metaplasia as a focal change was also present in 14 of these patients. Histochemically, sulphomucins were present in the biopsies of 43 (74%) of the patients studied. They were seen in both goblet and columnar mucous cells with almost equal frequency. Incomplete intestinal metaplasia with sulphomucin production was present in four of the five patients with an oesophageal adenocarcinoma. In the columnar lined oesophagus sulphomucin production is common and its presence does not help to identify those individuals at particular risk of developing an adenocarcinoma.

In 1950 Barrett described the syndrome of peptic ulceration of the oesophagus arising in gastric type epithelium associated with an oesophageal stricture which he considered, incorrectly, to be because of a congenitally short oesophagus. Subsequent studies have shown that these patients do not have a congenitally short oesophagus but that the lower oesophagus itself becomes lined by metaplastic columnar epithelium. In the majority of patients this is the result of prolonged gastro-oesophageal reflux. It is well recognised now that this is a premalignant disorder, predisposing to the development of an oesophageal adenocarcinoma. The epithelium lining the oesophagus is characterised by its marked heterogeneity being composed of a variety of cell types which include columnar mucous cells, mucous gland cells, goblet cells, chief and parietal cells, Paneth cells and neuroendocrine cells. From this histological mosaic two main types of columnar epithelium can be identified; firstly, a gastric type including both atrophic fundic type epithelium with parietal and chief cells and junctional type epithelium with cardiac mucous glands only, and secondly, an intestinal type in which there is intestinal metaplasia with goblet cells and variably differentiated columnar cells. In the stomach an incompletely differentiated variant of intestinal metaplasia secreting sulphomucins has been shown in several studies to be associated with the presence of gastric carcinoma of intestinal type. Jass has reported a similar association between this variant of intestinal metaplasia and well differentiated adenocarcinoma arising in the columnar lined oesophagus and he suggested that the presence of this type of intestinal metaplasia in oesophageal biopsies may serve as an important marker for identification of a subgroup of patients at particular risk of developing oesophageal adenocarcinoma.

The aim of this investigation was to study the histochemical characteristics of oesophageal columnar epithelium and to assess the prevalence and significance of sulphomucins in endoscopic biopsies of patients with a columnar lined (Barrett's) oesophagus.
Methods

Patients
During a 42 month period between September 1981 and February 1985, a total of 5534 upper gastrointestinal endoscopies were carried out on 4443 patients in the Gastroenterology Unit at the Royal Liverpool Hospital. Olympus GIFQ or GIFP2 endoscopes were used for these examinations. The endoscopy records of all patients were reviewed. Macroscopic oesophagitis was observed and recorded by the endoscopist in 776 patients (17.5% of the total) of whom 58 (7.5% of those with oesophagitis) had a columnar lined lower oesophagus.

With respect to the oesophagus a careful assessment was made at endoscopy of the distance of the squamocolumnar junction and gastro-oesophageal junction from the incisor teeth, the presence and size of any sliding hiatus hernia, the presence and proximal limit of oesophagitis in the squamous lined portion of the oesophagus, and the presence of any oesophageal ulcer or stricture. The diagnosis of a columnar lined oesophagus was defined as the presence of columnar epithelium, confirmed by biopsy and histological examination, for a distance of greater than 5 cm above the endoscopically determined gastro-oesophageal junction.

The 58 patients with a columnar lined oesophagus underwent a total of 135 endoscopies during the course of this study. Endoscopic biopsies were taken with spiked biopsy forceps 5 cm above the gastro-oesophageal junction, just below the squamocolumnar junction and midway between these two points. There were 492 biopsy specimens of oesophageal columnar mucosa available for histological and histochemical evaluation. After formalin fixation all specimens were processed routinely and embedded in paraffin, and haematoxylin and eosin stained sections, cut at three levels, were examined together with alcian blue (pH2.5)/periodic acid Schiff (AB/PAS) and high iron diamine/alcian blue (pH2.5) (HID/AB) stained sections of the middle level. The AB/PAS method distinguishes between neutral and acidic mucins, which are stained red and blue respectively, while the HID/AB technique differentiates between brown-black sulphated acidic mucins (sulphomucins) and blue non-sulphated acidic mucins (sialomucins). In biopsy specimens from each endoscopy the following features were assessed: type of columnar epithelium and, when present, type and extent of intestinal metaplasia (complete or incomplete), degree of inflammation, presence and distribution of sulphomucin secretion, and presence of dysplasia or carcinoma.

Results

Clinical Features
The 58 patients who fulfilled the criteria for diag-

Fig. 1 Complete intestinal metaplasia. The epithelium is composed of goblet cells and absorptive cells which have a well developed brush border (arrow). H & E.
nosis of a columnar lined oesophagus comprised 38 men and 20 women (male to female ratio of 1.9:1) ranging in age from 27 to 92 years (mean 63±15 years). The mean age of female patients (74±11 years) was significantly higher than that of the male group (58±15 years). All patients had symptoms of gastro-oesophageal reflux, the duration of which ranged from six weeks to 28 years (mean 6±5 years). Heartburn was present in 79%, dysphagia in 63% and regurgitation in 47%. Five patients were found to have a primary oesophageal adenocarcinoma of whom four underwent oesophagogastrectomy. Twelve other patients had transabdominal antireflux surgery (eight partial fundoplication, the Lind operation, and four a total fundoplication, the Nissen procedure). The remaining patients were all treated medically.

ENDOSCOPIC FEATURES
The length of the distal oesophagus above the gastro-oesophageal junction which was lined by columnar epithelium ranged from 5–18 cm (mean 8.2±4.1 cm). A sliding hiatus hernia was present in 54 patients (93%). An oesophageal stricture and/or ulcer was present in 72% of patients. Three patients also had a benign gastric ulcer and a duodenal ulcer was present in six.

HISTOLOGICAL FEATURES
The different types of columnar epithelium found in the 58 patients in this study are shown in Table 1. The results reflect the heterogenous nature of metaplastic oesophageal columnar mucosa: one type of epithelium alone was only found in 22 (38%) patients and in these, intestinal type epithelium was the most common. The other 36 patients all had a mixture of epithelial types, predominantly intestinal and junctional type epithelium. Atrophic fundic epithelium was the least common finding and was present as the sole type of epithelium in only one patient. Intestinal type epithelium, either alone or in combination with other epithelial types, was present in 48 (83%) of the patients: this was a focal change in 12 (25%), moderate in 19 (40%) and extensive in 17 (35%). Scattered Paneth cells were observed in 21 (44%) of these patients.

Intestinal metaplasia was classified into two main types according to whether the surface columnar cells resembled normal enterocyes with well developed brush borders, so called complete intestinal metaplasia (Fig. 1), or showed 'intermediate' features with apical cytoplasmic mucin and incompletely developed or absent brush borders, and referred to as incomplete intestinal metaplasia (Fig. 2). Incomplete metaplasia was present in all 48 patients with intestinal type columnar epithelium. Complete intestinal metaplasia was only observed in 14 patients in whom it was generally present as a focal change only, not exceeding the extent of

![Image](http://gut.bmj.com/)

**Fig. 2** Incomplete intestinal metaplasia. Mucus secreting columnar cells (arrowhead) with no brush border line the glands, together with goblet cells (arrows) which are often less prominent than in complete IM. H & E.

<table>
<thead>
<tr>
<th>Type of columnar mucosa*</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>One type of mucosa only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td>J</td>
<td>7</td>
<td>12</td>
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<td>AF</td>
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<td>2</td>
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<td>I</td>
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<td>24</td>
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<td>More than one type of mucosa</td>
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<tr>
<td>J+AF</td>
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</tr>
<tr>
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<td>2</td>
</tr>
<tr>
<td>J+I</td>
<td>29</td>
<td>50</td>
</tr>
<tr>
<td>J+AF+I</td>
<td>4</td>
<td>7</td>
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*J=junctional; AF=atrophic fundic; I=intestinal
incomplete metaplasia to which it was usually more deeply situated. The type and extent of intestinal metaplasia present in patients with a columnar lined oesophagus did not appear to be related to the degree of inflammation present within the mucosa; complete intestinal metaplasia, however, was most often seen in mucosa in which there was extensive intestinal metaplasia.

Mucin histochemistry demonstrated that the columnar mucous cells, of both gastric and intestinal type epithelium, contained predominantly neutral mucins, whilst the goblet cells of intestinal type epithelium contained acidic mucins almost exclusively. Sulphomucin secretion (Fig. 3) was present in biopsies from 43 (74%) patients and, although there was some variation in the distribution and staining intensity between different biopsies from the same patient, a similar pattern of secretion and metaplasia was usually discernible overall. The prevalence and site of sulphomucin secretion in all the patients in this series and in selected subgroups are shown in Table 2. In 16 patients, staining for sulphomucins was weak (trace only) and in 27 it was strong (corresponding to that of a colonic control). Neither the site nor the intensity of the staining reaction appeared to be related to the degree of inflammation present within the mucosa or to the sex or age of the patient. Sulphomucins were detected in columnar mucous cells of both the surface and glandular epithelium in 36 (62%) patients and, in this site, were associated with areas of intestinal type epithelium in all but two cases. These showed only weak, focal staining of surface and pit columnar cells. Sulphomucins were also present in some of the goblet cells in 35 (73%) of the 48 patients with intestinal type epithelium but sialomucin was the predominant mucin in goblet cells in all but three patients. In 23 (40%) patients sialomucins were also

![Image](http://gut.bmj.com/)

**Table 2** Distribution of sulphomucins

<table>
<thead>
<tr>
<th>Staining for sulphomucins</th>
<th>Site of sulphomucin secretion</th>
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<tbody>
<tr>
<td></td>
<td>Goblet cell</td>
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<tr>
<td>N</td>
<td>– ve</td>
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<tr>
<td>All patients</td>
<td>58</td>
</tr>
<tr>
<td>All patients with intestinal-type epithelium</td>
<td>48</td>
</tr>
<tr>
<td>Patients with no intestinal-type epithelium</td>
<td>10</td>
</tr>
<tr>
<td>Patients with dysplasia/adenocarcinoma</td>
<td>5</td>
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</tbody>
</table>

*Fig. 3* Incomplete intestinal metaplasia. Sulphomucins, appearing black, are present within both goblet cells and columnar mucous cells (arrows). The paler, grey mucin is sialomucin which is present in an occasional goblet cell (arrowhead). HID/AB.
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Fig. 4 Severely dysplastic epithelium (above) adjacent to an area of metaplastic columnar mucosa (below). H & E.

present in columnar mucous cells, mainly of the surface epithelium.

Five (8-6%) patients in this series had biopsy diagnosed adenocarcinoma arising in a columnar lined oesophagus at the time of their initial presentation. Three were women and two were men with a mean age of 66±11 years. Two of the tumours were poorly differentiated while three showed a moderate degree of differentiation. Biopsies from all five patients included non-neoplastic columnar mucosa with areas of intestinal metaplasia, staining positively for sulphomucins in all but 1 case (Table 2). Severely dysplastic epithelium was also present in each case (Fig. 4) but in these areas there was neither intestinal metaplasia nor sulphomucin secretion. Carcinomatous tissue was also negative for sulphomucins in all five patients. Dysplastic epithelium was not found in this study other than in the presence of adenocarcinoma as described in the above five cases.

Discussion

The columnar lined (Barrett’s) oesophagus is characterised by the heterogeneity of epithelial types which comprise its mucosa. These have been described as resembling either gastric or intestinal epithelium and, in this study, both types were present in 59% of patients. Although several authors have reported that these different epithelial types show ‘zonation’ within the oesophagus, with intestinal type occurring proximally to gastric type, and we, in common with others, have found no evidence of this. Moreover, as previously reported by Paull, we found no correlation between either the type of columnar epithelium or the length of involved oesophagus and the degree of inflammation present within the mucosa.

The pathogenesis of oesophageal columnar mucosa has long been a subject for debate and while it is now accepted that the majority of cases are acquired lesions, secondary to reflux oesophagitis, the origin of this mucosa remains uncertain. Derivation from the superficial oesophageal glands and from proximal growth of cardiac epithelium have both been proposed. It has also been suggested that the columnar mucosa is a metaplastic epithelium derived from a primordial stem cell, in the oesophagus or stomach, which has the capacity for multipotential differentiation. The metaplastic nature of the column lined oesophagus is supported by ultrastructural and enzyme histochemical studies which have shown that oesophageal columnar
mucosa is distinct from that of either the stomach or small intestine and that even though some cells such as chief, parietal and Paneth cells, appear mature and fully differentiated, others such as the columnar mucous cells, show only partial differentiation. These cells have been described by Trier as 'principal cells' and by Jass as 'intermediate cells' and they show features intermediate between gastric mucous cells and small intestinal absorptive cells in that they have apical cytoplasmic mucin granules, partially developed microvillus borders and terminal webs, and absent disaccharidase activity. They also differ from gastric mucous cells in that they frequently secrete a mixture of neutral and acidic mucins, both sulphated and non-sulphated. Although not all authors are in agreement on this point, in this study we have found oesophageal columnar mucous cells containing sialomucins and sulphomucins in 40% and 62% of patients respectively.

Cells resembling these oesophageal columnar mucous cells have been described in the incompletely differentiated type of intestinal metaplasia of the stomach and, in the presence of sulphomucin secretion, this variant of metaplasia has been shown to have a closer association with gastric carcinoma, particularly of 'intestinal' differentiation, than have other types of intestinal metaplasia. In a histochmical study of 22 malignant and 10 benign oesophageal specimens, Jass has reported that a similar sulphomucin secreting variant of intestinal metaplasia in oesophageal mucosa was significantly associated with well differentiated adenocarcinoma but occurred only focally in benign specimens. From these observations, he suggested that detection of this variant of intestinal type epithelium in patients with a columnar lined oesophagus may enable identifcation of those at greater risk of developing adenocarcinoma. We have found, however, that both incomplete intestinal metaplasia and sulphomucin secretion are common features of the columnar lined oesophagus (in 83% and 74% of the patients respectively), and similar results have been reported by others. The lower prevalence of sulphomucins found by Jass in a small number of benign specimens is probably related to sampling as well as to the possibility that some of the retrospectively examined material was of gastric rather than oesophageal origin. In this study, secretion of sulphomucins appeared to be particularly characteristic of intestinal type epithelium and was found in the absence of intestinal metaplasia in only two patients. From our results it would appear that the presence of sulphomucins in oesophageal biopsies of columnar mucosa is not sufficiently discriminating to allow detection of a subgroup of patients at particular risk of malignant transformation. The neoplastic potential of the columnar lined oesophagus is well recognised, however, and the frequent finding of sulphomucins within this metaplastic epithelium supports the suggestion that production of these mucins may represent a marker of incompletely differentiated metaplastic epithelia in the upper gastrointestinal tract which have a propensity for malignant transformation. It has been suggested that sulphomucin secretion within the stomach may not so much be the product of early malignant change but rather represents an important cytoprotective mechanism to a carcinogenic microenvironment, and it is possible that its presence in the columnar lined oesophagus has the same significance.

In this series the prevalence of adenocarcinoma arising in a column lined oesophagus was 8-6% which is almost identical to that reported by Naef from a larger series of 140 cases of columnar lined oesophagus. Histochemically, biopsies of uninvolved columnar mucosa from these patients appeared similar to those from benign oesophageal lesions. In contrast with the findings of Jass and Sheahan, and probably as a result of the small amount of material available for examination, sulphomucins were not detected in any of the biopsies of carcinomatous tissue. Multifocal dysplasia and carcinoma in situ have frequently been found in association with adenocarcinoma of the columnar lined oesophagus and, in our series, severe dysplastic changes were seen in the biopsy specimens of all five cases of carcinoma. Observations that adenocarcinoma appears to develop directly from dysplastic mucosa provides evidence in support of the neoplastic nature of this epithelium and, in view of the lack of discrimination afforded by the detection of sulphomucins, dysplasia would appear to be the most valuable and specific indicator of potential malignant transformation.

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References
1 Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. Br J Surg 1950; 38: 175-82.