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Mixed crypt cell carcinoma

A clinicopathological study of the so-called 'Goblet cell carcinoid'

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Summary. The clinicopathological features of six appendix and five bowel tumours with features of the so-called 'goblet cell carcinoid' are described. By light microscopy, these tumours were composed predominantly of mucous cells, together with variable proportions of endocrine and Paneth cells. Immunohistochemical and ultrastructural study confirmed this impression and no amphicrine cells were seen. The clinical course of all cases arising in the bowel, and three out of six appendix tumours was characterised by an aggressive behaviour with the development of widespread lymphatic and often intraperitoneal metastasis, but liver metastasis occurred in only one instance. We conclude, both from this study and from a review of the literature, that the 'mixed crypt cell carcinoma' forms a distinct clinicopathological entity justifying separate classification from adenocarcinoma and carcinoid tumour.

Key words: Appendix – Colorectal neoplasm – Carcinoid – Ultrastructure

Introduction

Over the past decade there have been several reported studies of an unusual tumour of the appendix (Subbuswamy et al. 1974; Warkel et al. 1978; Isaacson 1981; Edmonds et al. 1984; Hofler et al. 1984), and occasional isolated reports of similar tumours in the bowel (Lyss et al. 1981; Hofler et al. 1984; Kochevar 1984). The origin, composition, and biological behaviour of this tumour, perhaps best known as the 'goblet cell carcinoid', have been the subject of controversy. Although it was originally considered to be a variant of a carcinoid tumour, with a generally benign behaviour (Subbuswamy et al. 1974), this concept has recently been challenged by the findings of immunohistochemical and ultrastructural study of a few appendix tumours. The terms 'adenocarcinoid' (Warkel et al. 1978) and 'crypt cell carcinoma' (Isaacson 1981; Wolff 1982) have been proposed to reflect a sometimes more aggressive behaviour, and a possible origin from lysozyme producing mucous cells of the intestinal crypt.

The purpose of this report is to study a broader series of these tumours in both appendix and bowel, from all aspects – clinical, histological, ultrastructural and immunohistochemical. Our findings together with a review of the literature suggest that these tumours form a distinct clinicopathological entity and justify separate classification from both carcinoid tumours and adenocarcinomas.

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Materials and methods

We have reviewed all 36 carcinomas and carcinoid tumours of the appendix, and 44 carcinoid tumours of the bowel from the files of the Health Sciences Center, Winnipeg, diagnosed over the 20 year period 1966 to 1986. All mucinous adenocarcinomas diagnosed in the small and large bowel over a 5 year period from 1975 to 1980, were also reviewed. From among these tumours four appendiceal and three bowel tumours showing the features of the goblet cell carcinoid (Subbuswamy et al. 1974) were identified. Following the addition of one recent case and three cases from St Boniface Hospital, Winnipeg, a total of six appendix tumours and five bowel tumours formed the basis of this study.

All slides and blocks from each case were available for conventional light microscopic examination. Additional stains included Grimelius and/or

Cherukian Schenk argyrophil stains, PAS, and Alcian blue pH 0.5 and 2.5. All cases were also studied by immunohistochemistry, using the peroxidase-antiperoxidase (PAP) technique, for the following antigens; CEA, secretory component, IgA, lysozyme, and neuron specific enolase. Three additional cases of carcinoid tumours of the appendix and rectum, and a colorectal adenocarcinoma were also stained as controls. Initial treatment with trypsin digestion was carried out on all sections stained for lysozyme. The primary antisera used were all commercially available polyclonal antisera from Dimension Lab. Mississauga, Ontario.

Electron microscopy was performed on three appendix tumours. Material from one case was obtained fresh at the time of frozen section, and fixed in glutaraldehyde for electron microscopy. In the other two cases tissue was reclaimed from the formalin fixed specimen and was processed routinely. Multiple 1 micron thick sections were examined, and thin sections were selected from three blocks in each case for further study. One rectal tumour was also studied using material reclaimed from the paraffin block.

Results

The clinical features of tumours arising both in the appendix and outside the appendix are summarised in Table 1.

Among six patients with appendix tumours, five were male and one female, and the average age was sixty-two. Local invasion to the serosal surface of the appendix was present in all cases, nodal metastases in four, and distant intraperitoneal metastasis in two cases. All patients were treated by right hemicolectomy. While three patients died of their disease, in no case was there evidence of liver metastasis either at the time of initial surgery, or in two of these cases at second laparotomy for intestinal obstruction one and two and a half years later.

Outside the appendix, five similar tumours were located in the ileum (1), colon (2), and rectum (2). No lesion in the region of the appendix was noted in any of these cases, and this was confirmed by histology in three instances. Among these patients the average age was fifty-nine, three were male and two female, and two were Cree indians. All patients presented with advanced lesions (with nodal or small bowel metastasis) and four subsequently died with widespread intraperitoneal metastasis. In three of the latter cases, second laparotomies for intestinal obstruction within one month of death found no evidence of liver metastasis. In one case, presenting with intraabdominal metastasis, bone and liver metastasis developed within one year of diagnosis.

Table 1. Clinicopathological features

Case	Age/sex	Location	Stage[a]	Survival (months)[b]
1	51/M	Appendix	B	a&w (14)
2	76/M	Appendix	B	a&w (21)
3	69/M	Appendix	C	a&w (18)
4	76/F	Appendix	C	d (21)
5	39/M	Appendix	D	d (19)
6	62/M	Appendix	D	d (27)
7	56/M	Ileum	C	d (20)
8	42/F	Asc. colon	C	a&w (2)
9	68/M	Asc. colon	C	d (18)
10	57/M	Rectum	C	d (6)
11	70/F	Rectum	D	d (18)

[a] Modified Dukes Stage [D = distant peritoneal or bowel metastasis].
[b] a&w = alive and well, d = died of disease

The gross features of the tumours arising in the appendix were similar to previously described 'goblet cell carcinoids'. They ranged from small lesions not visible on initial inspection, to tumours measuring up to 5 cm in diameter, with a firm and fibrous appearance. Mucin was not evident. By light microscopy all were composed predominantly of mucous producing cells, many of which resembled normal goblet cells, with prominent intracytoplasmic mucin vacuoles causing distension of the cytoplasm, and variable compression of the nucleus (Fig. 1). In other cells in which cytoplasmic vacuoles were smaller or undetectable, there was abundant amphophilic cytoplasm. Although single cells were seen, most were arranged in characteristic nests with occasional lumen formation (Fig. 1 a) or trabecular cords with peripherally located nuclei, and central cytoplasm (Fig. 1 b). Pools of extracellular mucin were present in four cases in the deeper layers of the wall of the appendix. Mitoses were infrequent in all cases.

Argyrophil stains showed endocrine cells in four out of six tumours. These cells were only common in two cases, and in all instances argyrophil cells were far outnumbered by mucous producing cells (Fig. 1 a). In three of the six cases, cells with bright eosinophilic granular cytoplasm resembling normal Paneth cells were present (Fig. 1 b). They were only seen in cases with endocrine cells, and were most often present within nests of mucous producing cells in close proximity to the muscularis mucosa. However, both argyrophil positive cells and Paneth cells were seen together in lymph node and small bowel metastases in three cases.

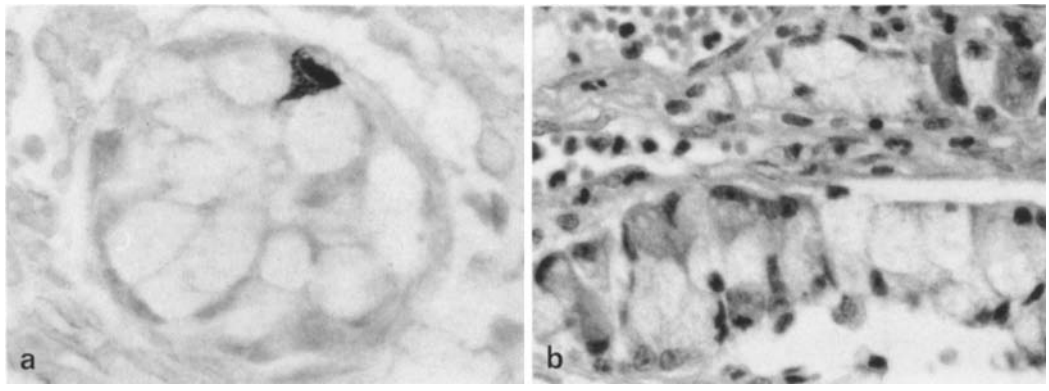

Fig. 1. Appendix tumours showing (**a**) nest of goblet cells with a single argyrophil positive cell (*case 2*), and (**b**) trabeculae of goblet cells and Paneth cells within a small bowel metastasis (*case 6*)

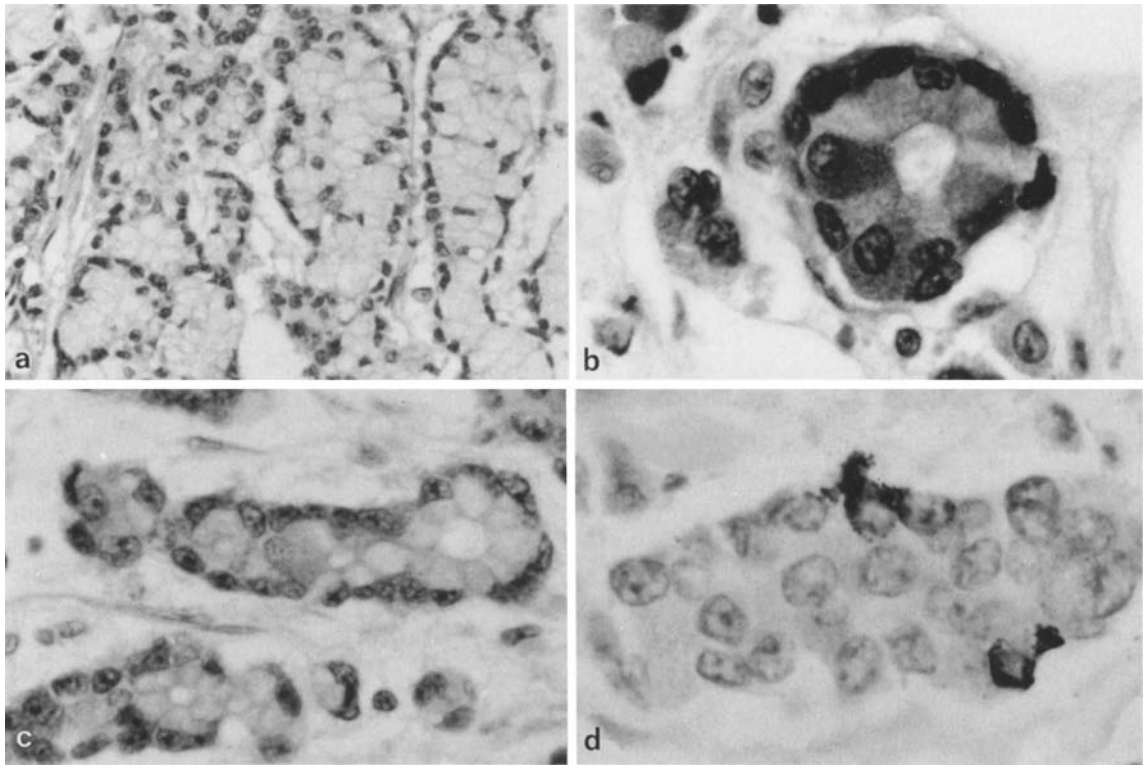

Fig. 2. Large bowel tumours showing (**a**) trabeculae and nests of goblet cells (*case 8*), (**b, c, d**) nests of goblet cells, Paneth cells with granular cytoplasm, and argyrophil cells (*case 10*)

The five tumours arising outside the appendix were fungating or ulcerating lesions, ranging in size from 5 to 20 cm in maximum diameter. All possessed a firm consistency with no mucin visible grossly. The histological pattern, in both the primary lesions and nodal metastases was similar to the appendix tumours, with cells producing abundant intracellular mucin arranged in nests and trabecular cords (Fig. 2). In contrast, single cells and mitoses were more common, and in all cases extracellular mucin was also prominent. Focal argyrophil positive cells were seen in only one tumour (case 10) while Paneth cells were present in two (cases 9&10) both in the primary neoplasms and their nodal metastases (Fig. 2). In both rectal tumours small tubules and infiltrating clusters and cords of less differentiated cells were also present at the deep margins of the primary tumour. In

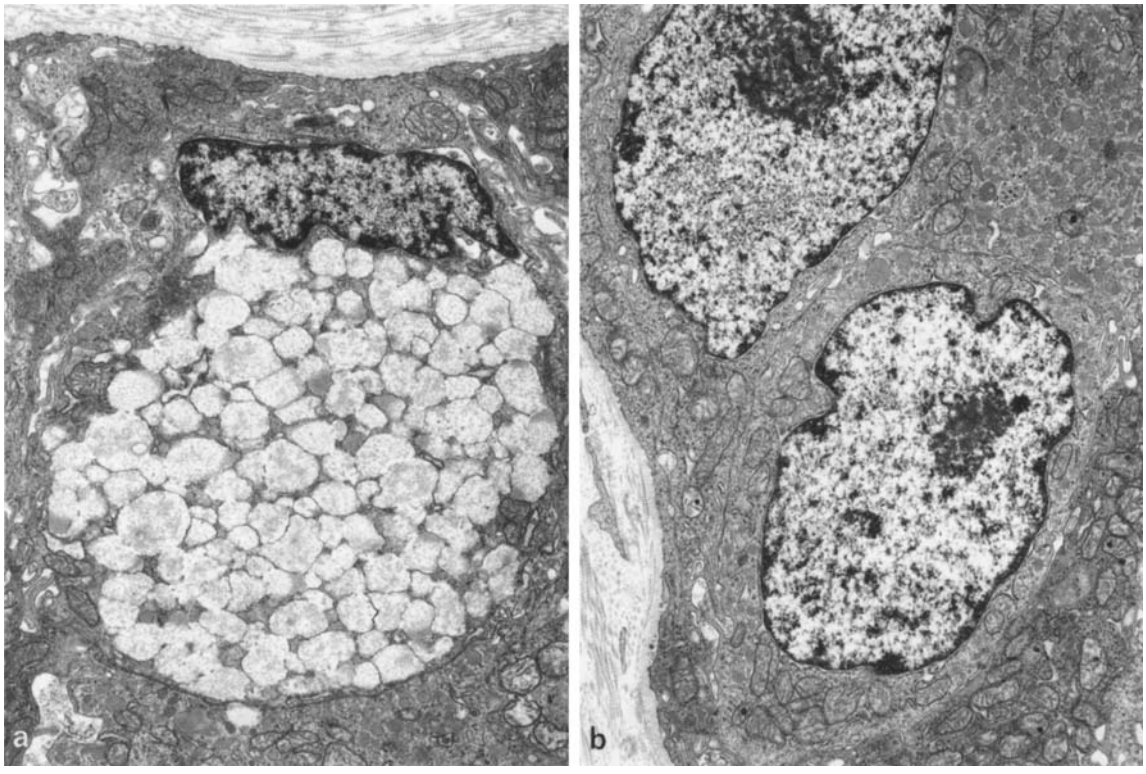

Fig. 3. Electron micrographs of cells showing a range of mucin production; (**a**) tumour cell resembling the normal goblet cell type with coalescent mucin granules distending the cytoplasm and compressing the nucleus. The cell borders show complex interdigitation. (**b**) Cells with smaller and dense mucin granules (*case 1*, mag 8000).

one of these (case 11) a metastasis to the mandible one year later showed similar cells and glandular differentiation.

The ultrastructure of two primary appendix tumours, and a small bowel metastasis from a third tumour were studied in detail. In all three cases the tumours were almost entirely composed of mucous producing cells. The degree of mucin production ranged from cells distended by coalesent mucin granules (Fig. 3a) to cells with variable numbers of smaller, dark granules (Fig. 3b). Features associated with columnar cell differentiation such as a well developed apical region and microvilli at the luminal surface were absent.

In two cases endocrine cells were seen very rarely within nests of mucous cells (Fig. 4a). In all cases, occasional cells showed evidence of early differentiation towards mucous, or endocrine cells, while other cells showed no such differentiation. No hybrid cells were identified.

In one rectal tumour studied (case 10), mucous cells were seen together with many cells which contained very large, round, uniformly electron dense cytoplasmic granules (Fig. 4b). These were similar to the granules of normal Paneth cells studied in glutaraldehyde fixed tissue, and formalin fixed material reclaimed from the paraffin block.

Table 2. Immunohistochemistry results

Case	CEA	IgA	SC	Lys	NSE
1	+	−	−	(+)	−
2	+	+	+	−	−
3	+	−	−	(+)	−
4	+	+	+	(+)	−
5	+	+	+	−	−
6	+	+	+	(+)	−
7	+	−	−	−	−
8	+	(+)	(+)	−	−
9	+	+	(+)	−	(+)
10	+	−	−	(+)	−
11	+	+	+	+	−
12[a]	−	−	−	−	+
13[b]	−	−	−	−	+
14[c]	+	(+)	−	−	−

+ = many cells positive, (+) = few cells positive; − = negative

[a] appendix carcinoid (control)
[b] rectal carcinoid (control)
[c] colorectal adenocarcinoma (control)

The results of immunohistochemistry are shown in Table 2. All goblet cell tumours were pos-

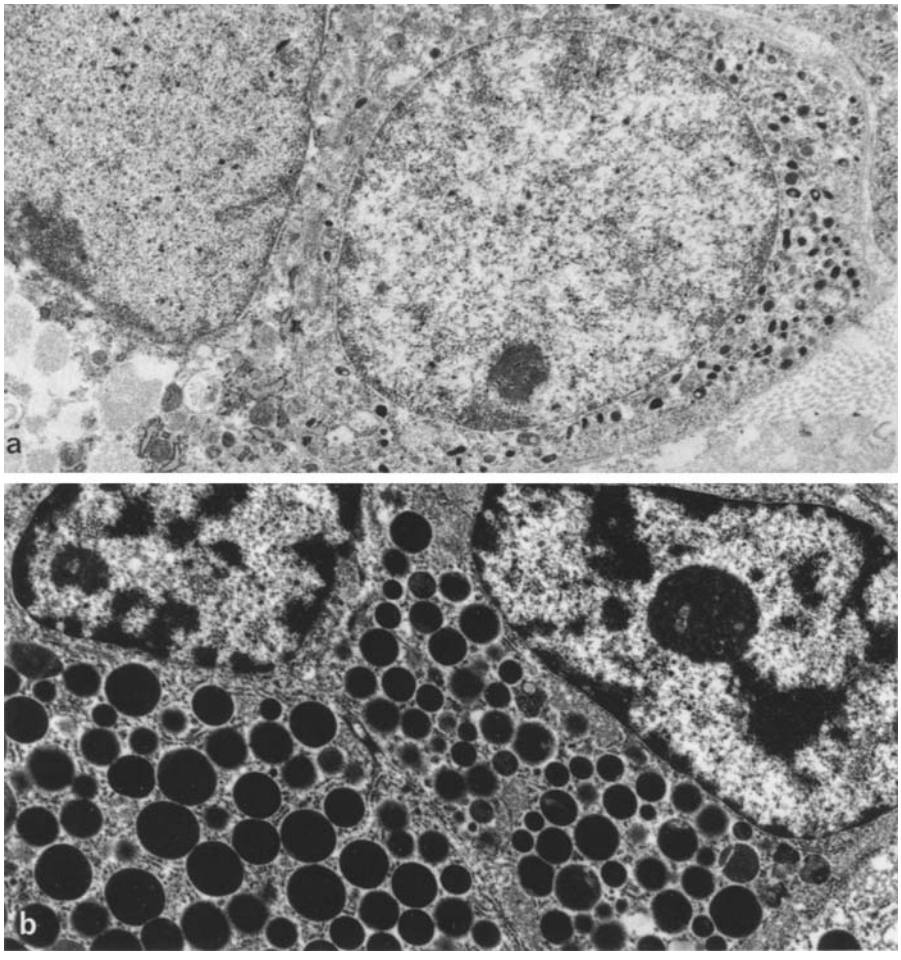

Fig. 4. (**a**) Adjacent cells showing mucin granules in part of the cytoplasm of one cell (*left*), and electron dense membrane bound endocrine type granules in the other (*right*). (*case 6*, mag 8800). (**b**) Partial view of two cells showing large round Paneth type cytoplasmic granules (*case 10*, mag 8800)

itive for CEA, and seven out of eleven were positive for IgA and Secretory Component. Only in one case were most of the cells positive for lysozyme, while six cases were also focally positive; usually within areas showing Paneth cell differentiation. Neuron specific enolase was positive focally in one tumour while in all other cases this was negative. However, the propensity of these tumours to invade perineural lymphatics occasionally lead to false focal positivity from neural elements within clusters of tumour cells. In contrast, both carcinoid controls were negative for CEA and positive for neuron specific enolase.

Discussion

In 1974 Subbuswamy et al. reported the first large series of cases of a peculiar appendiceal tumour composed predominantly of nests of goblet cells. The generally benign behaviour and the presence of argyrophil positive cells by light microscopy in most of their cases lead these authors to conclude that this tumour is a mucinous variant of the carcinoid tumour.

Subsequent reports of these tumours showed that the cell composition could be variable, including goblet, endocrine, Paneth, and hybrid or amphicrine cell components. Argyrophil cells may be seen, in both the primary tumours and their nodal metastases (Warkel et al. 1978). However, they are not often present in large numbers and rarely, if ever, as the dominant cell population (Klein 1974; Wolff and Ahmed 1976; Warkel et al. 1978; Chen and Quizilbash 1979; Isaacson 1981; Heisterberg et al. 1982; Hofler et al. 1984). Similarly, ultrastructural studies on a handful of these tumours have found endocrine cells present in unspecified numbers (Edmonds et al. 1984; Hofler et al. 1984), frequently (Hernandez and Fernandez 1974; Cooper and Warkell 1978; Warner and In Sook Seo 1979), infrequently (Rodriguez et al. 1982), or not at all (Hirshfield et al. 1985). Paneth cells are reported in between one third and one half of cases

(Haqqani and Williams 1977; Warkel et al. 1978), and in this series were also seen in metastases. In addition to these cell types, there is immunohistochemical and ultrastructural evidence to suggest that some of these tumours contain amphicrine cells. That is to say, cells showing both endocrine and mucous, or Paneth and mucous differentiation. As with the endocrine and Paneth cell types, these hybrid cells may vary in their relative frequency from inconspicuous (Cooper and Warkel 1978; Rodriguez et al. 1982; Hirshfield et al. 1985) to frequent (Abt and Carter 1976; Edmonds et al. 1984; Hofler et al. 1984; Chejfec et al. 1985).

Our study confirms the histological and cytological features that define this tumour. These include a predominance of goblet type cells both histologically and ultrastructurally, a variable but often minor component of endocrine, Paneth and hybrid cells, and an architectural arrangement of these cells within nests and trabeculae that is somewhat reminiscent of the intestinal crypt (Cheng and Leblond 1974; Cheng et al. 1984).

Small numbers of goblet cells and endocrine cells can be present within adenocarcinomas of the bowel (Kubo and Watanabe 1971; Lundquist and Wilander 1983; Smith and Haggitt 1984), and mucin production which may be seen in both the columnar cell of adenocarcinomas and the endocrine cell of carcinoid tumours (Soga and Tazawa 1971; Whitehead and Cosgrove 1979), is not restricted to the goblet cell. However adenocarcinomas, carcinoid tumours, and rare 'mixed' tumours (Hernandez and Reid 1969; Toker 1969; Klappenbach et al. 1985) differ from the well defined cellular composition and crypt-like architectural pattern of the tumour described above.

The clinical behaviour of these tumours was initially thought to be benign (Subbuswamy et al. 1974; Chen and Quizilbash 1979). It is now apparent that this is not always the case. Review of the literature shows that out of 93 patients with appendix tumours reported with some degree of clinical follow-up, at least 20 patients (22%) have developed recurrence or died of their disease.

Attention has only recently been drawn to the pattern of metastasis seen in these tumours (Bak and Jorgensen 1987). In most cases in which the outcome is reported, the patients succumbed to intra-abdominal disease (Warkel et al. 1978) and ovarian metastasis in females is common (Olssen and Ljungberg 1980; Hirshfield et al. 1985). However vascular metastasis to the liver and other distant organs is rarely mentioned. In our own series, liver metastasis was only seen in one case, and in this instance the tumour included a less differentiated cell component. By comparison, liver metastasis is reported to be present in some 10 to 30% of colorectal adenocarcinomas at the time of initial surgery (Russell et al. 1984; August et al. 1985), developing in many more as the disease progresses (Russel et al. 1985). A similar incidence of liver metastasis is also seen in carcinoid tumours of the bowel (Welch and Malt 1977; Dilawari and Douglass 1979; Kirkegaard et al. 1981; Martensson et al. 1983).

Several case reports of 'goblet cell carcinoid' or 'adenocarcinoid' tumours arising in the stomach (Ali et al. 1984), small bowel (Hofler et al. 1984; Kochevar 1984) and large bowel (Hernandez and Reid 1969; Lyss et al. 1981), gallbladder (Muto et al. 1984) and ovary (Alenghat et al. 1986) have appeared in the literature. In addition, some authors have drawn attention to the morphological similarities between the 'goblet cell carcinoid' and signet-ring cell carcinomas of the GI tract (Shousha 1982; Tahara et al. 1982; Arends and Bosman 1983). As signet-ring cell carcinomas also show a similar tendency to intra-abdominal metastasis without liver involvement (Bonello et al. 1980; Almagro 1983; Nadel et al. 1983; Giacchero et al. 1985; Lui et al. 1985) these might be regarded as poorly differentiated variants of the well and moderately differentiated tumours of the appendix and large bowel described above.

In conclusion, from our own study and a review of the literature, it seems that these tumours form a distinct clinicopathological entity. Occurring predominantly in the appendix, but also in many other sites within the GI tract and the ovary, they are composed of goblet cells and variable proportions of other crypt cells – endocrine, Paneth and hybrid cells. Those tumours which metastasise show a tendency towards lymphatic and direct intraperitoneal spread. However, haematogenous metastasis to the liver, or other distant organs is uncommon.

In regard to terminology, it now seems inappropriate to use terms such as 'goblet cell carcinoid' or 'adenocarcinoid' for a tumour that frequently includes only a small component of endocrine cells and often shows an aggressive behaviour bearing similarities to poorly differentiated signet-ring carcinomas. 'Crypt cell carcinoma' is a better name, recognising the crypt-like composition and architecture. However there is a lack of uniformity in immunohistochemical results (Isaacson 1981; Hofler et al. 1984) and absence of definite proof of an origin from a distinctive crypt cell type. We therefore suggest that 'mixed crypt cell carcinoma' may be a better and more descriptive term.

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