# Goblet Cell Carcinoids and Related Tumors of the Vermiform Appendix

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**Appendiceal carcinoids with glandular differentiation pose difficulties in classification and prediction of clinical behavior. Sixty-four such cases were divided into three histologic groups on the basis of routine and immunohistochemical stains: (1) Tubular carcinoids were small and confined to the appendix, had small amounts of intraluminal mucin with few or no goblet cells, were nonargentaffin, lacked serotonin, and were diffusely positive for glucagon. All ten with follow-up (mean, 17 months) were without metastasis. (2) Goblet cell carcinoids were confined to the appendix and mesoappendix, circumferentially surrounded the appendiceal lumen, and were often not suspected grossly. Histologically, they were often mixed with small crypt-like glands and were serotonin positive. All 22 with follow-up (mean, 19 months) were without metastasis whether or not right hemicolectomy was performed. (3) Mixed carcinoid–adenocarcinomas showed spread into the cecum or adjacent viscera at the time of diagnosis and had a large carcinomatous pattern with areas of mucinous, signet-ring, or single-file structure, in addition to goblet cell or insular carcinoid. All patients had right hemicolectomies, and all but two with follow-up died of the disease (mean, 16 months). Although a histologic spectrum exists among carcinoid tumors and certain adenocarcinomas of the appendix, it is possible to delineate three biologically distinct groups. Surgical margins should be taken of all appendices because these tumors often do not form discrete masses. (Key words: Carcinoid tumor; Appendix; Adenocarcinoid; Goblet cell carcinoid) Am J Clin Pathol 1990;94:27–35.**

THERE IS CONFUSION REGARDING the classification of appendiceal neoplasms having both endocrine and glandular differentiation. This is reflected in the variety of names used for these lesions, such as adenocarcinoid, goblet cell carcinoid, crypt cell carcinoma, and mucinous carcinoid.[1–4,6–18,20–25] Furthermore, the management and the need for additional surgery after appendectomy of patients who have such tumors is unclear.[3,4,7,8,22,24] We studied a number of these appendiceal tumors to clarify their histologic and immunohistochemical features and their clinical behavior.

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## Materials and Methods

All appendiceal carcinoid tumors with available paraffin blocks in the files of the Armed Forces Institute of Pathology (AFIP) accessioned between January 1985 and September 1988 were collected. Contributors included military, Veteran's Administration, and civilian sources. This constituted 133 cases; 64 had evidence of glandular differentiation by routine histology. These 64 cases were the subject of this study.

Argentaffinity was demonstrated by the Fontana-Masson stain, argyrophilia by the Churukian-Schenk method,[5] and mucin by periodic acid-Schiff (PAS) and Alcian blue. Immunostains were performed according to the method of Sternberger[19] using the peroxidase–antiperoxidase technique with diaminobenzidine as chromogen. Antisera and dilutions are in Table 1.

Follow-up questionnaires were in accordance with the AFIP Human Use Committee and the statutes of the Privacy Act.

Mitotic counts were performed on 5-$\mu$m sections with the use of a $\times$40 power objective (490 $\mu$m field diameter). The highest count in ten consecutive fields in up to 50 viewed (depending on the size of tumor) was recorded. The most cellular areas of the tumor were selected for mitotic count.

For 30 goblet cell carcinoids or mixed carcinoid–adenocarcinomas for which follow-up material was available, clinical outcome (dead of disease *vs.* no evidence of disease) was correlated by means of $2 \times 2$ contingency tables with pathologic features. The mean ages of the patients with tubular carcinoids were compared with those of the other groups by the Student's unpaired *t*-test.

Twenty-three of the original cases with follow-up data studied by Warkel and associates[22] were retrieved from the files. These were classified into the three diagnostic

*Table 1.* Antisera, Source, and Dilution

| Antiserum | Source | Dilution |
|---|---|---|
| Chromogranin | Hybritech, Inc., San Diego, CA | 1:200 |
| Serotonin | IncStar; Stillwater, MN | 1:20 (purified) |
| Glucagon | DAKO; Santa Barbara, CA | 1:400 |
| Cytokeratin AE1/3 | DAKO (with digestion) | 1:10 |
| HPP | DAKO | 1:400 |
| CEA | DAKO | 1:160 |

HPP = human pancreatic polypeptide; CEA = carcinoembryonic antigen.

categories described below, without the examiners' knowledge of follow-up data. The diagnoses were then compared with follow-up data to determine if there was a correlation between outcome and tumor type.

## Results

Of the 64 tumors constituting the current study, 17 were classified as tubular carcinoids, based on a typical histologic appearance of compressed tubules and trabeculae, rare or no goblet cells, and diffuse glucagon positivity. The remaining 47 tumors were more difficult to classify. For these, the following histologic features were tabulated without the examiners' knowledge of clinical outcome: mitotic rate, presence of extracellular mucin, presence of structures containing Paneth's cells and resembling crypts, immunohistochemical results, and percentage carcinomatous growth. The last was defined as fused or cribriform glands, single-file structures, diffusely infiltrating signet-ring cells, or sheets of solid cells. These findings were then correlated with clinical outcome, and the presence of more than 50% carcinomatous growth significantly correlated with death resulting from disease ($P < 0.0005$). The presence of greater than 2 mitoses/HPF correlated weakly with death resulting from disease ($P = 0.06$). Other parameters did not correlate with outcome. Tumors with more than 50% carcinomatous growth were therefore classified as mixed carcinoid–adenocarcinoma, and those composed predominantly (more than 75%) of separated nests of cells as goblet cell carcinoids (no tumor contained between 25% and 50% carcinomatous growth). This classification is similar to that used by the World Health Organization (WHO).[14,17] These groups are compared pathologically in Table 2.

*Table 2.* Tubular Carcinoid Goblet Cell Carcinoid Mixed Carcinoid-Adenocarcinoma

| | Histologic Features | | |
|---|---|---|---|
| | Tubular (n = 17) | Goblet Cell (n = 33) | Mixed (n = 14) |
| Tubules | 17 | 6 | 0 |
| Goblet cell nests | 2 | 32 | 12 |
| Crypt-like glands | 1 | 14 | 0 |
| Carcinomatous growth* | 0 | 11† | 14‡ |
| Immunostains | | | |
| Chromogranin | 6/12 | 26/28 | 10/14 |
| Serotonin | 0/12 | 27/30 | 10/14 |
| HPP | 1/12 | 10/32 | 3/13 |
| Glucagon | 17/17 | 3/27 | 0/13 |
| CEA | 17/17 | 30/30 | 14/14 |
| Cytokeratin | 8/8 | 14/14 | 8/8 |

CEA = carcinoembryonic antigen; HPP = human pancreatic polypeptide.

* Includes patterns seen in adenocarcinomas (*e.g.*, single file, signet ring, and poorly differentiated areas). (See Figs. 6–11.)

† In all cases an inconspicuous component.

‡ In all cases more than 50% of tumor.

### *Tubular Carcinoids (17 cases)*

*Histologic Features.* All tumors were made up primarily of compressed tubular structures and trabeculae composed of cuboidal cells, separated by stroma or smooth muscle. The tubular lumina contained small amounts of mucin positive for PAS and Alcian blue. The tumor cells were typically poorly defined among the relatively abundant stroma (Fig. 1). Two had small goblet cell areas, and one had glands containing Paneth's cells. The mitotic rate ranged from 0 to 2 mitoses per 10 HPF; all but two were amitotic. All tumors were diffusely positive for glucagon, carcinoembryonic antigen, and cytokeratin. In fact, the otherwise poorly defined extent of the tumor is best evaluated with any of these preparations. Staining for chromogranin was weak and variable; serotonin had negative results in all (Table 2). About half were focally argyrophil; none was argentaffin. Sixteen were located in the appendiceal tip; none grew circumferentially around the appendiceal lumen.

*Gross Features.* Five appendices were described as normal; 11 were described as inflamed (*i.e.*, surface exudate or opacified serosa). Tumors were suspected grossly in three cases; all were less than 5 mm.

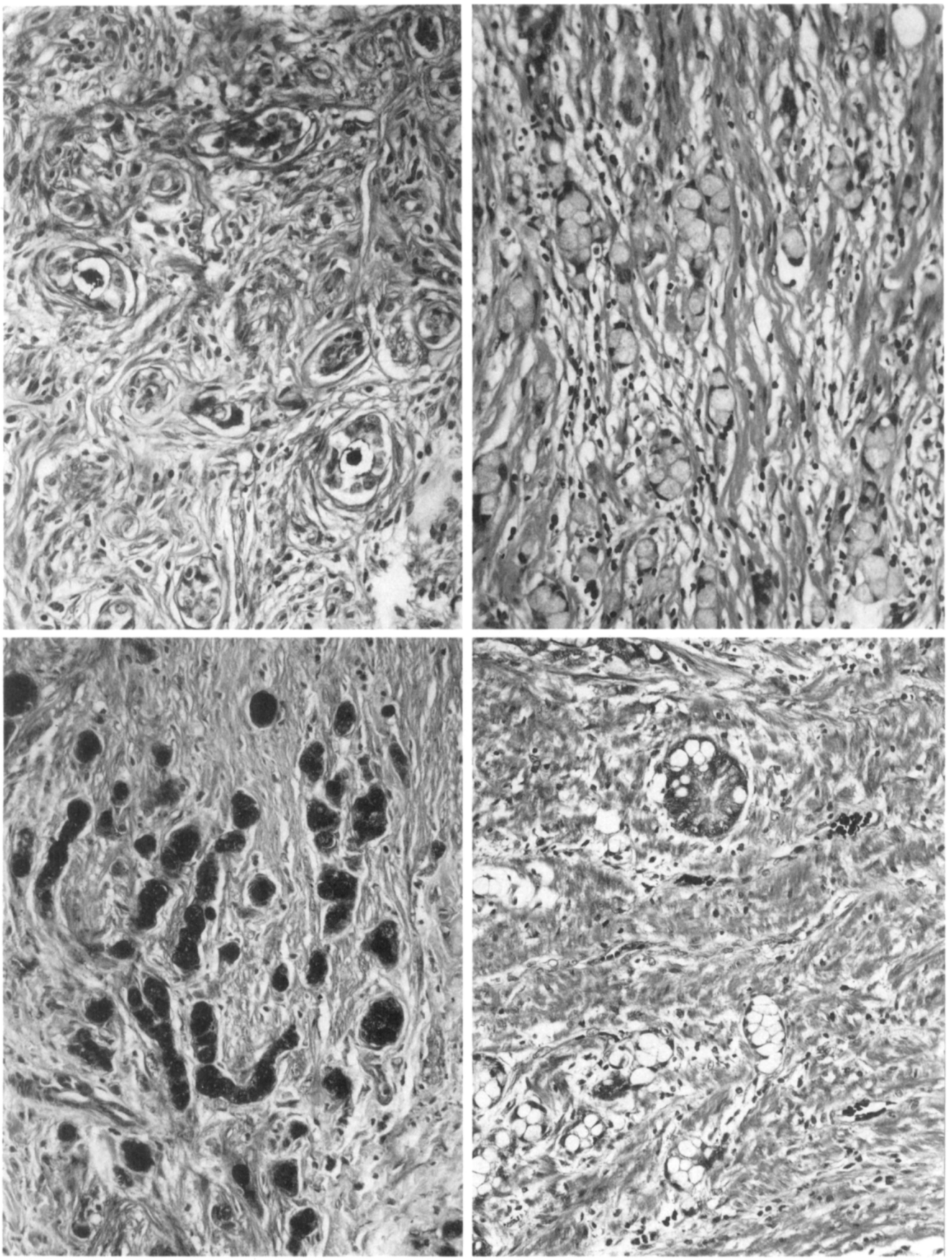
*Clinical Findings and Follow-Up Data.* Nine patients

FIG. 1 (*upper, left*). Tubular carcinoid. Typical poorly defined tubules obscured by abundant stroma. Intraluminal mucin. Periodic acid-Schiff (×250).

FIG. 2 (*upper, right*). Goblet cell carcinoid. Nests of goblet cells separated by stroma (×250).

FIG. 3 (*lower, left*). Goblet cell carcinoid. Goblet cells contain abundant mucin. Periodic acid-Schiff (×250).

FIG. 4 (*lower, right*). Goblet cell carcinoid. Crypt-like gland adjacent to goblet cell nests.



were male and eight female. The average age was 29 years and ranged from 16 to 60 years. This was significantly lower than the mean age for goblet cell carcinoids or mixed carcinoids–adenocarcinomas ($P < 0.0005$). Fourteen patients presented with acute appendicitis; in three the lesion was found incidentally. No tumor grossly extended beyond the appendix at the time of surgery. Follow-up was obtained on ten patients and averaged 17 months; clinical or radiologic evidence of metastatic disease did not develop in any of the patients; none had additional surgery beyond simple appendectomy.

*Goblet Cell Carcinoids (33 cases)*

*Histologic Features.* The hallmark of goblet cell carcinoid is the presence of individual glands separated by smooth muscle or stroma. Unlike tubular carcinoids, in which the mucin is usually restricted to the lumina, the lining cells in goblet cell carcinoids contain intracytoplasmic mucin. In 26 cases, these glands were predominantly compact clusters of mucin-filled, PAS- and Alcian blue–positive goblet cells without central lumina (Figs. 2 and 3). In the remaining seven tumors, most glands were lined by flattened mucin-filled cells and occasional Paneth's cells (Fig. 4). Most of these glands had central lumina, resembled normal crypts, and did not fuse into cribriform or solid structures. Fourteen goblet cell carcinoids had lakes of mucus in the stroma, usually in a small part of the tumor. Unlike mucinous carcinoma, the glands within the mucous lakes had central lumina resembling normal crypts and remained separate from one another (Fig. 5). A third of the tumors had foci in which goblet cell nests fused into structures with signet-ring cells (Fig. 6), but these foci constituted less than 25% of the tumor area. Cribriform glands or poorly differentiated solid sheets of cells, as seen in many mixed carcinoids–adenocarcinomas, were not present. The mitotic rate ranged from 0 to 7 per 10 HPFs; the average rate was 1 per 10 HPFs.

All tumors showed endocrine differentiation, but the number of such cells was uniformly low. Most tumors had scattered argentaffin and argyrophil cells and cells positive for chromogranin and serotonin; one-third had a few cells positive for human pancreatic polypeptide. Six tumors had small numbers of glucagon-positive cells; these were usually in areas resembling tubular carcinoid; none was diffusely glucagon positive. All were positive throughout for carcinoembryonic antigen and cytokeratin.

*Gross Features.* Sixteen appendices were described as thickened; in only 2 was a tumor suspected grossly. In 23 there was surface exudate and 8 appendices perforated. Only one was described as normal. Because of the infiltrating nature of these tumors and the lack of a well-defined lesion, size was not measured in any case. In fact, the location of the tumor in the appendix had to be ascertained histologically. Eleven involved the tip, and 22 were circumferential. Of the latter, 16 were near the tip, 4 involved the entire appendix, 1 was in the midportion, and 1 was near the base.

*Clinical Findings.* Nineteen patients were male and 14 female. Age at presentation ranged from 31 to 71 years and averaged 53 years. In 27 patients, the tumor produced symptoms. The preoperative diagnosis was acute appendicitis in 25, small bowel obstruction in 1, and abdominal mass in 1. The remaining six cases were incidental findings during surgery for other conditions. The cause for the obstruction in the case presenting as such was adhesions secondary to ruptured appendix; the tumor had not spread beyond the appendix. Likewise, the patient who presented with an abdominal mass had a large retrocecal abscess; the goblet cell carcinoid itself was small and did not grow outside the appendix. All tumors included in this group were confined to the appendix at surgery; in 32 of 33 patients the initial surgery was appendectomy alone.

*Follow-Up Data.* Follow-up data were available for 25 patients and averaged 19 months. Thirteen patients had subsequent hemicolectomies; in 4 there was a small focus of residual tumor and in 9 there was none. Of the four patients with residual tumor, two had positive margins at initial appendectomy, one was not evaluated, and one was obscured by abscess. Of the eight without residual tumor, the margin was described as free in five of the appendectomies, involved in one, and not evaluated in three. Of the nine patients who were followed without hemicolectomy, the appendiceal margins were described as free of tumor in four and were not evaluated in five; two of the latter tumors were distal and one proximal. No patient had metastasis develop or showed evidence of residual disease at last follow-up.

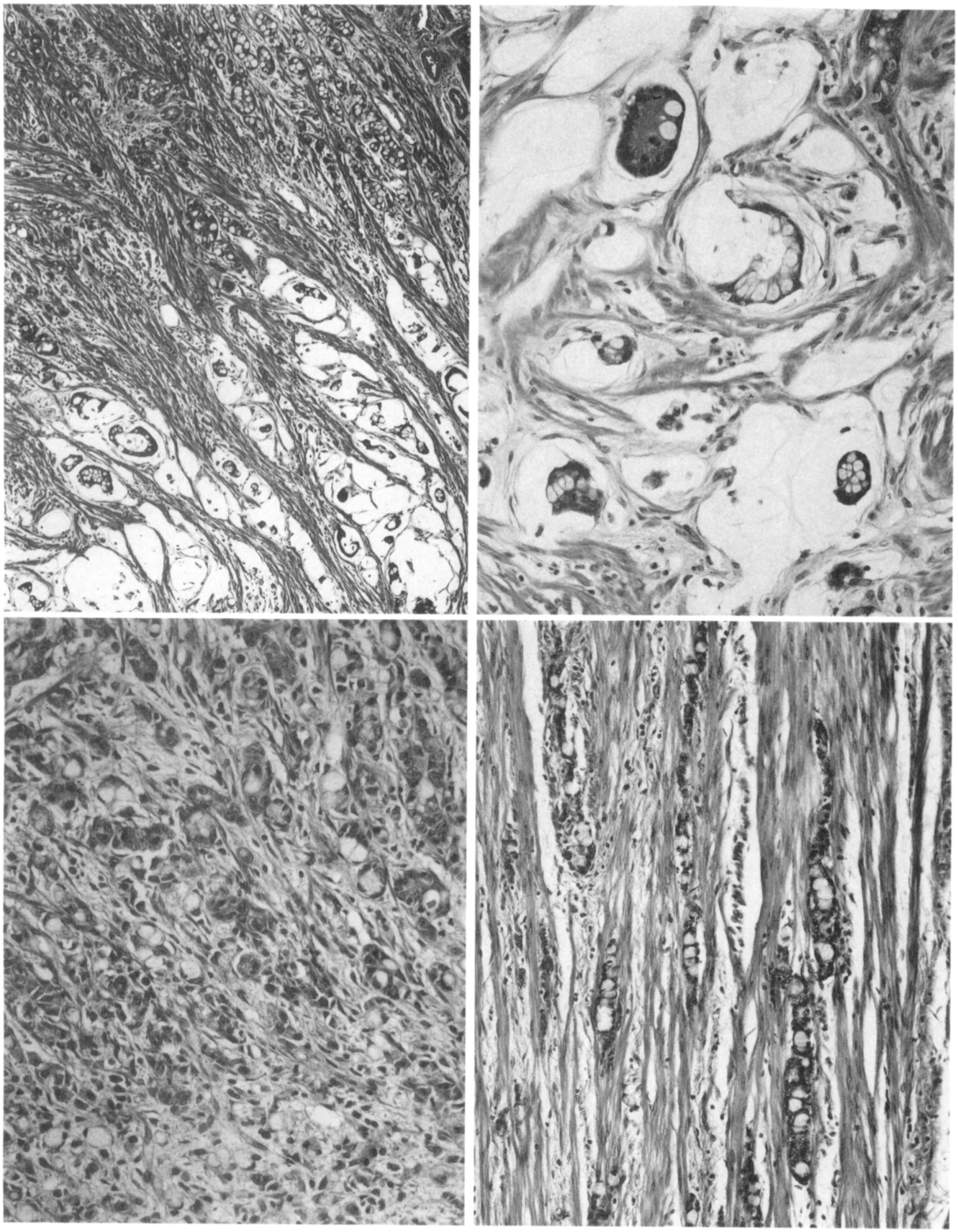
*Mixed Carcinoid–Adenocarcinomas (14 patients)*

*Histologic Findings.* In all cases the tumor primarily infiltrated the submucosa and muscular wall in a circumferential fashion, sparing the mucosa, typical of appen-

FIG. 5. Goblet cell carcinoid. *A* (*upper, left*). Focal extracellular mucin deposits. Glands remain separated, and resembled crypts (×125). *B* (*upper, right*). Higher power demonstrates distinct glands, one of which is extruding mucin.

FIG. 6 (*lower, left*). Mixed carcinoid-adenocarcinoma. Crowded growth pattern composed of signet ring cells, small glands, and compressed goblet cell nests. Although some goblet cell carcinoids show this pattern, it is only a small proportion of tumor (×250).

FIG. 7 (*lower, right*). Mixed carcinoid-adenocarcinoma. Single file pattern. Other areas of this tumor were typical goblet cell pattern. This tumor infiltrated into the cecum (×250).



diceal carcinoids. In none was there a sign of an adenoma or a luminal tumor, nor was the lumen dilated as with typical mucinous cystadenocarcinomas of the appendix. Mucin-containing cells resembling goblet cells were present in all. Scattered endocrine cells were also present in all, as demonstrated by at least one silver or endocrine stain. Ten showed areas typical of goblet cell carcinoid, and all had more than 50% growth, resembling carcinomas of one or more of the following patterns: compressed goblet cell nests with small glands and signet-ring cells with little or no intervening stroma (eight tumors, Fig. 6); linear single-file growth (ten tumors, Fig. 7); mucinous (six tumors, Fig. 8), glandular (nine tumors, Fig. 9), and poorly differentiated with signet-ring cells (three tumors, Fig. 10). The mucinous carcinomas differed from goblet cell carcinoids by the presence of glandular fusion and lack of glandular lumina within the mucin lakes (Figs. 5 and 8). The mitotic rate ranged from 0 to 25 per 10 HPFs and averaged 10 per 10 HPFs. Three tumors had small areas of typical insular carcinoid composed of diffusely serotonin-positive cells.

Staining for endocrine content was focal in all cases and was generally positive in both carcinomatous and goblet cell areas. Most were argentaffin and positive for chromogranin and serotonin; none showed glucagon reactivity (Table 2). The single-file pattern typically contained frequent argentaffin cells positive for chromogranin and serotonin. All were carcinoembryonic antigen positive.

*Gross Features.* In all cases tumor was grossly apparent as diffusely infiltrating indurated masses. In 13 the tumor grew into the adjacent cecum; in 1 the bowel was free but the tumor grew into the bladder. All appendices were described as scarred, fibrotic, or obliterated. Lymph nodes were involved in four cases and the ileal wall in six.

*Clinical Findings.* Nine patients were male and five female. Their ages ranged from 49 to 83 years and averaged 68 years. All patients had symptoms. Eight presented with small bowel obstruction: one with sepsis and pneumaturia (this tumor grew into the bladder), one with an abdominal mass, and two with acute appendicitis. Thirteen of 14 patients had hemicolectomy initially.

*Follow-Up Data.* Follow-up was obtained in ten patients and averaged 16 months. Eight patients are dead of disease. Organs involved by direct spread or metastasis included cecum (13 cases), serosal surfaces (8 cases), ileum (6 cases), lymph nodes (7 cases), bladder (1 case), lungs, adrenal, and liver (1 case of each). Six patients died of obstruction secondary to serosal metastases, one of widespread metastases. The eight died from causes attributable to metastatic carcinoma.

One patient was alive at 41 months; this tumor presented with extension into the bladder and four positive lymph nodes; growth into the cecum was absent. He was required to have subsequent surgery to remove tumor in the bladder and was reported to be free of urologic or gastrointestinal symptoms. One patient without spread beyond the bowel wall was treated with radiation therapy and was being followed for radiation colitis without evidence of tumor 48 months after surgery.

Histologic material from metastatic deposits was available in 12 cases. In eight the predominant pattern was moderately or poorly differentiated adenocarcinoma; three had goblet cell areas and five had mainly single-file or signet-ring cell growths. In three, the metastases resembled small cell carcinomas; one had psammoma bodies. In one tumor the metastasis resembled goblet cell carcinoid with extracellular mucin deposits; many of the goblet cell nests were fused into complex structures.

### *Review of Old Cases*

Twenty-three of the original cases described by Warkel and associates[22] were reclassified with above criteria either as goblet cell carcinoid (16 tumors) or mixed carcinoid–adenocarcinoma (7 tumors), without knowledge of follow-up data. Follow-up averaged 71.3 months; metastases developed in all 7 patients with carcinoid–adenocarcinoma and the patients died of disease; all 16 patients with goblet cell carcinoid were alive at last follow-up (mean, 97 months).

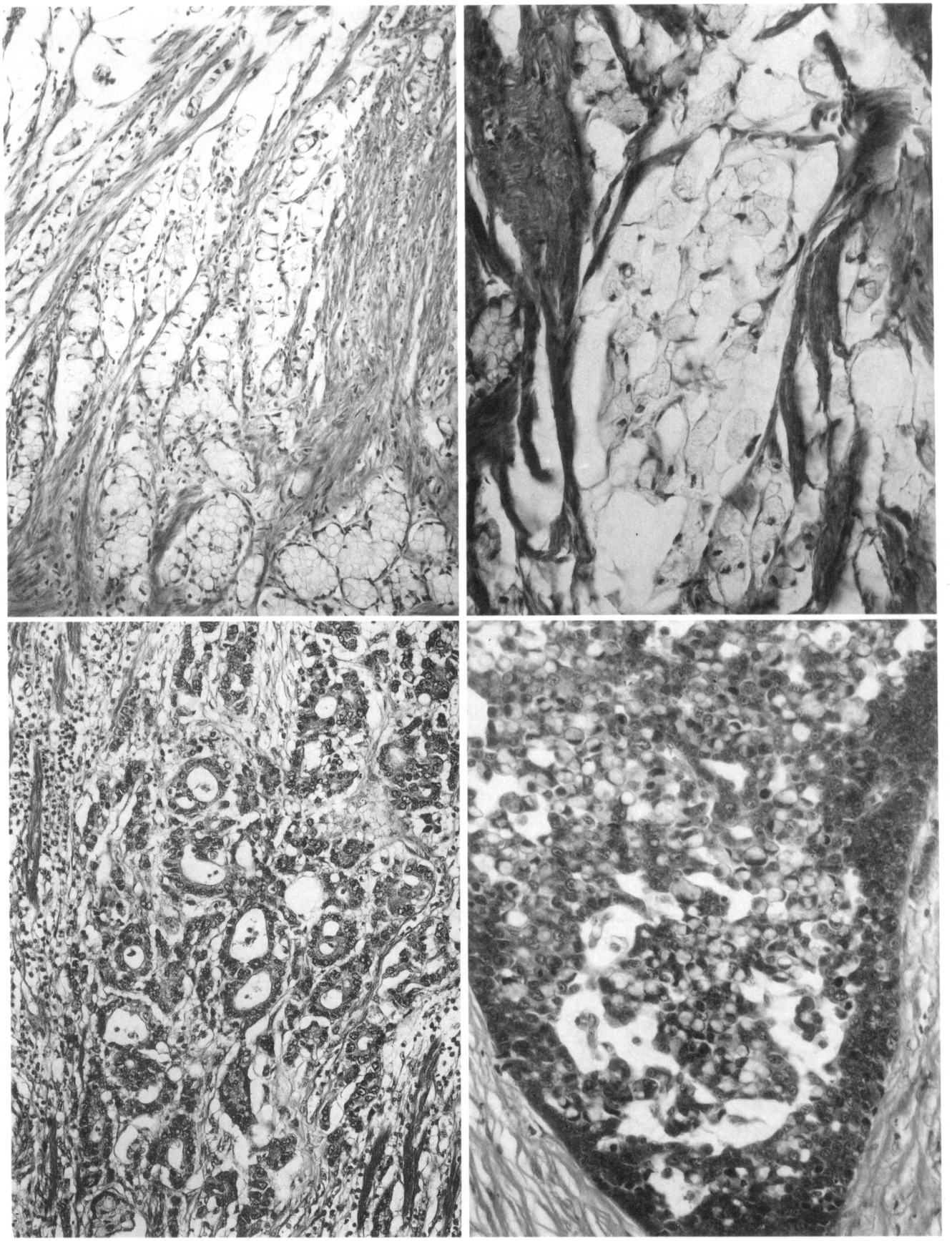
## Discussion

The tumors in this study have the following features in common: they all primarily occupy the submucosa or wall rather than being in the lumen; they all contain mucin; they are all strongly carcinoembryonic antigen positive; and they show evidence of endocrine differentiation. Tubular, trabecular, glandular, goblet cell, and frankly carcinomatous growth patterns are encountered and can

FIG. 8 (*upper*). Mixed carcinoid-adenocarcinoma. *A* (*upper, left*). Focal extracellular mucin. In contrast to Figure 5, the tumor nests are fused into elongated complex structures, without forming goblet cell groups or crypts (×125). *B* (*upper, right*). Higher power demonstrates fusion of signet ring cells. In other areas there was typical goblet cell carcinoid composed of nests separated by stroma (×125).

FIG. 9 (*lower, left*). Mixed carcinoid-adenocarcinoma. Adenocarcinoma, glandular pattern. Other areas of the tumor were typical goblet cell carcinoid (×250).

FIG. 10 (*lower, right*). Mixed carcinoid-adenocarcinoma. Poorly differentiated solid areas containing numerous mucin-filled signet ring cells as well as serotonin-positive cells (*not shown*). Other areas of the tumor were typical goblet cell carcinoid (×300).



overlap in individual tumors. We have separated these tumors into three groups based on the predominant feature: tubular carcinoid, goblet cell carcinoid, and mixed carcinoid–adenocarcinoma. This conforms to the WHO histologic classification,[14,17] except that the WHO classification groups tubular carcinoids with typical carcinoid tumors.

We have shown that tubular carcinoids are nonargentaffin and invariably express glucagon, unlike other glandular and nonglandular appendiceal carcinoids. Tumors that are predominantly of this pattern appear to be clinically benign, corresponding to most typical carcinoids of the appendix. They can be classified simply as "carcinoid" even if small portions of the tumor show crypt cell or goblet cell areas. The mucin in these tumors is entirely intraluminal, with the exception of those few tumors with rare goblet cells. Separating tubular from goblet cell carcinoids correlates well with clinical findings because patients with tubular carcinoids are younger and have smaller tumors that are confined to the tip of the appendix.

Goblet cell carcinoids are often large and circumferential, unlike the tubular variety. They are easily diagnosed when they are of pure type. The diagnosis is still appropriate when the goblet cell component is mixed with mucus-filled crypts or mucin lakes in the stroma, because this does not appear to affect stage or prognosis, which in our short-term follow-up is quite good. Although we recognize that crypt cell differentiation (with or without Paneth's cells) occurs in this group of tumors, and can occasionally be the predominant growth pattern, we prefer to avoid the additional category of "crypt cell carcinoma" because crypt cell differentiation did not adversely affect prognosis.

All of the follow-up patients with goblet cell carcinoid in our study did well without evidence of metastasis, whether or not hemicolectomy was performed. Few of the tumors showed residual tumor at hemicolectomy, and in every instance only a small area at the base of the appendix was involved. Goblet cell carcinoids do not form discrete tumors and are not always suspected at surgery or at gross examination. For this reason, the line of resection should be examined microscopically in all appendectomy specimens, especially in older patients, in whom these tumors most often occur. The role of right hemicolectomy in the absence of positive margins remains uncertain before longer follow-up studies are performed. However, after our retrospective reclassification of the original tumors studied by Warkel and associates,[22] no patient with pure goblet cell carcinoid died of disease after a follow-up interval averaging several years.

The diagnosis of mixed carcinoid–adenocarcinoma, which had a bad prognosis in our study, required a predominance of carcinomatous growth and smaller areas of goblet cell or other carcinoid component. The presence of carcinomatous growth patterns correlated well with extension into adjacent organs and a poor prognosis, justifying this diagnostic category. Warkel and associates[22] studied 39 goblet cell carcinoids and found that mitoses and atypia were important in predicting outcome. We were unable to find a useful cut-off for mitotic rate but found carcinomatous growth more significant and have added the term "carcinoma" because of their poor prognosis and the histologic appearance of the carcinomatous areas. We believe that since the description of goblet cell carcinoid, many adenocarcinomas with areas of endocrine growth have been included under this diagnosis, possibly explaining why goblet cell carcinoids have been considered more aggressive than the typical appendiceal carcinoid.

In our study, all of the metastasizing tumors were classified as mixed carcinoids–adenocarcinomas on the basis of the growth pattern, and all that metastasized had done so at the time of initial surgery. In most reports of metastasizing "goblet cell carcinoids," the patients presented with spread beyond the appendix at first diagnosis.[2,7,9,10,12,16,20,25] Three of the patients of Warkel and colleagues[22] presented without extraappendiceal spread, yet metastases developed later, which is in contrast to most findings. However, in two of these three patients, spread into adjacent organs was found within two months, suggesting that the initial surgical evaluation may have been inaccurate.

In conclusion, based on this retrospective study, we do not believe that all mucin-producing carcinoids of the appendix have the same prognosis. Tubular carcinoids should be considered clinically as typical carcinoids. Those with carcinomatous areas are much more aggressive than the tubular or goblet cell types and deserve to be classified separately and treated as carcinomas. The treatment of goblet cell carcinoids remains questionable, although hemicolectomy is indicated if margins are involved.

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