GASTROINTESTINAL GANGLIONEUROMAS

Brief Review with Report of a Duodenal Ganglioneuroma*

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Ganglioneuromas are relatively uncommon, but not rare, tumors composed of ganglion cells and nerve fibers. They are preponderantly benign, containing mature-appearing ganglion cells. Undifferentiated or incompletely developed cells are present in about one fourth of the lesions, and such tumors are prone to malignant behavior, including metastasis.[1] Since the report of the first well authenticated case, that of Loretz[2] in 1870, more than 300 ganglioneuromas have been described in the literature. These case reports have been collected and reviewed from time to time; 47 such cases were found by Wahl[3] (1914), 94 by McFarland[4] (1931), 171 by Raška and Škorpil[5] (1936), and 243 by Stout[1] (1947). Published reports of about 75 additional ganglioneuromas have appeared since Stout's review.

These tumors are found most frequently along the sympathetic ganglion chains. The next common site of origin is the adrenal glands. While ganglioneuromas have been described arising in nearly every organ of the body, examples from the alimentary tract are extremely uncommon. We have found reports of only 11 such cases, exclusive of several such tumors in the pharynx and tongue. Five of these 11 tumors involved the appendix, two were situated in the terminal portion of the ileum, two in the stomach, and two involved a segment of intestine that included the terminal part of the ileum, the cecum, and the ascending colon (Table I). The report of the gastric lesion described by Dupuy[17] and listed as a ganglioneuroma by Raška and Škorpil[5] is not convincing, especially since an illustration was not provided. The present report is, to our knowledge, the first description of a ganglioneuroma in the duodenum.

Report of Case

A 49-year-old white housewife came to the Mayo Clinic in May, 1956, for removal of a polypoid duodenal lesion. Her previous personal history was not pertinent, and there was no history of familial disease. Approximately 6 weeks previously, she had become aware of mild abdominal distress, described by her as

* Received for publication, December 24, 1956.

† On assignment from the U.S. Air Force.

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TABLE I

Reported Cases of Gastrointestinal Ganglioneuromas

Author	Year	Age and sex	Symptoms, clinical findings or preoperative diagnosis	Organ involved	Pathologic findings	Accompanying disease or defects and remarks
Oberndorfer[6]	1921	28 M	Acute perforating appendicitis	Appendix	Perforated, diffusely enlarged appendix 16 cm. long, with relatively uniform hypertrophy of entire wall; neurofibromatous proliferation in meso-appendix and all coats of appendiceal wall; numerous ganglion cells especially in submucosa, but also as far out as meso-appendix	Dermal tumors, cutaneous pigmentation, low intelligence; mother and brother had Recklinghausen's disease
Schultz[7]	1922	57 M	Incidental finding at necropsy	Appendix	Thickened, hard appendix, with increased muscularis and submucosa; numerous ganglion cells, nerve fibers, and Schwann's cells in submucosa, muscularis, and meso-appendix	Death due to gastric carcinoma
Lichtenstein and Ragins[9]	1937	8 F	Acute appendicitis	Appendix	Appendix normal in size; mucosa in distal third diffusely thickened, projecting into lumen; increased stroma with numerous ganglion cells	
Martinez-Gutierrez[9]	1943	18 F	Abdominal pain for 4 months; pelvic mass	Appendix	Appendix 45 cm. long, 3.6 cm. in diameter; "neurinomatosis" of appendix and adjacent mesentery; muscularis hypertrophied; greatly increased ganglion cells in submucosa, muscularis, and mucosa	
Masson and Branch[10]	1945	34 F	Appendicitis	Appendix	Appendix 13 cm. long, 4.5 cm. in diameter, with walls to 2 cm. thick; hypertrophy of muscle layers; greatly increased ganglion cells of intrinsic plexuses; neurofibromatosis of adjacent mesentery	
Baltisberger[11]	1922	50 F	Peritonitis due to strangulated inguinal hernia	Terminal ileum	Large plexiform neuroma in mesentery of ileum, with increased thickness of wall of adjacent 48 cm. of ileum; increased ganglion cells in plexuses and along nerve trunks into mesentery	Numerous, soft, cutaneous tumors; horseshoe kidney; postoperative death; ganglioneuroma not in herniated intestine
Poate and Inglis[12]	1928	30 M	Flatulence, fullness, epigastric discomfort, sluggish bowels for 6 years	Terminal ileum, cecum, ascending colon	Confluent ganglioneuromatous tumors, 0.5 to 10 cm. in diameter, projecting into intestinal lumen; intervening cecal wall to 1 cm. thick; tumors believed to arise in region of Meissner's plexus	"Cystic retroperitoneal tumor" resected 8 years previously; chronic duodenal ulcer found at operation
Jentzer and Fatzer[13]	1937	17 F	Enlarging abdominal mass for 2 to 3 years, ascites	Terminal ileum, appendix, cecum, ascending colon	Plexiform neuroma with numerous ganglion cells in diffusely thickened intestinal wall; large neurofibroma and spindle cell sarcoma in adjacent mesentery	Low intelligence, oxycephaly, dilated cerebral ventricles, palatum ogivale; postoperative death
MacMahon and Davies[14]	1945	16 F	Loose bowels, nearly daily abdominal pain and vomiting since infancy; abdominal mass	Terminal ileum	Terminal ileum (22 cm.) enlarged to 5 cm. in diameter, with increase of all elements in wall; numerous ganglion cells in all layers; large nerve trunks in adjacent mesentery	
Bertini[15]	1936	66 M	Gastric ulcer	Stomach, anterior wall	Smooth, pedunculated, 3 cm. tumor containing ganglion cells, sympathoblasts, and neurofibrils	Lesser-curvature ulcer, not in proximity of ganglioneuroma
Pitts and Hill[16]	1947	68 F	Abdominal distention, eructation for 3 years; one episode of nausea and vomiting	Stomach, pyloric antrum	Smooth, discrete, ulcerated, 5 cm. tumor containing ganglion cells, apparently not involving muscularis propria, projecting into gastric lumen	

"bloating and swelling" of the abdomen and "heaviness" in the epigastrium. The discomfort occasionally was present when she awoke in the morning. It was relieved when she drank milk or ate, and it continued, but in diminishing severity, until the time of her admission to the clinic. Two weeks after the onset of these symptoms, she had fallen from a horse and fractured her left seventh rib. While recovering, with her thorax strapped, she had noted soreness in the left midabdomen. This discomfort disappeared spontaneously within 1 week. Roentgenologic examination shortly after the onset of these symptoms had disclosed a small polypoid tumor of the middle third of the second part of the duodenum.

General examination at the clinic disclosed no pertinent abnormalities. Roentgenologic studies confirmed the presence of the polypoid lesion of the duodenum (Fig. 1).

Laparotomy revealed a sharply circumscribed, firm, approximately spherical nodule, 12 mm. in diameter, covered except at the base by freely movable mucosa. The lesion projected from the medial wall of the duodenum into the lumen at a point 2.5 cm. proximal to the ampulla of Vater. A red, granular dimple, 2 mm. in diameter, in the otherwise smooth overlying mucosa suggested superficial ulceration. The lesion was separated from the apparently normal muscularis propria by sharp dissection. Grossly, the tumor resembled a leiomyoma because of its uniform, pale, yellowish pink color, smooth external surface, slightly whorled cut surface, and firmness.

Study of fresh frozen sections revealed large and small ganglion cells, occurring singly and in clusters, in a fibrillar and connective tissue stroma. A diagnosis of ganglioneuroma was made. The duodenal defect was closed without further resection. The patient was asymptomatic 4 months later.

Histopathologic Appearance

The bulk of the duodenal tumor was composed of non-myelinated nerve fibers coursing in all directions but not forming any conspicuous nerve bundles enclosed by perineurium. Many of the fibers were accompanied by Schwann's cells, but there was no proliferation of these cells. A thin capsule containing some collagenous connective tissue surrounded the tumor, separated it in most places from the overlying muscularis mucosae, and merged with the mass of the tumor. A single large cluster of Brunner's glands remained relatively undistorted within the tumor tissue. The muscularis mucosae was irregular in thickness and direction; it was duplicated in some places and discontinuous in others. It was heavily infiltrated by inflammatory cells and partially destroyed beneath a small mucosal ulcer (Fig. 2).

The number of ganglion cells varied greatly from place to place in the tumor (Figs. 3 and 4). Most cell bodies were arranged in clusters. Extremely few nerve fibers ran through these cellular aggregates. The largest ganglion cells occurred singly. The majority of ganglion cells of all sizes were multipolar, and none were pigmented. Chromophilic substance could not be demonstrated in their cytoplasm by staining with toluidine blue and cresyl violet. Their nuclei were vesicular, had little apparent chromatin, and contained prominent nucleoli. Occa-

sional cells had two, less commonly three, nuclei (Fig. 5). The nuclei of the smaller ganglion cells stained deeply with hematoxylin, but these cells also had abundant cytoplasm and often had well developed nerve processes. Mitotic figures were not found.

The mode of origin of most of the processes from the ganglion cells, in smooth continuity with the cytoplasm of the cells, suggested their dendritic nature. These silver-impregnated fibers frequently branched but rarely did so in close proximity to the cell body. The fibers varied in thickness but were nearly all less than 1 μ in diameter as measured by an ocular micrometer. Occasional nerve fibers, usually arising more abruptly, had twice that diameter. Beading or the formation of gemmules was encountered in extremely few fibers. As many as five or six fibers could be traced from a single cytoplasmic protrusion in some of the large ganglion cells. This feature may aid in explaining the apparent disparity in the number of ganglion cells and the fiber mass. None of the ganglion cells were surrounded by capsular or satellite cells. An occasional small cell with irregular cytoplasm, closely applied to the body of a ganglion cell, might be interpreted as a satellite cell (Fig. 6).

A few ganglion cells were found between the separated strands of the muscularis mucosae, and an occasional ganglion cell was present in the mucosa proper. An increase in nerve fibers within the mucosa was not evident. Degenerative changes in the ganglion cells, including cytoplasmic fraying and vacuolation, and frank cellular disintegration, were frequent, especially in the larger cells.

In the mucosa at one margin of the tumor, occupying a region approximately 2 mm. in greatest dimension, were a number of unusual gland-like structures. These extended from within the duplicated misshapen muscularis mucosae into the mucosal stroma to the tips of the crypts of Lieberkühn (Fig. 7). They were formed by oval to elongate, sometimes irregular cells with a homogeneous, usually abundant, eosinophilic cytoplasm. The nuclei of these cells were uniform, small and round to oval, containing small, deeply stained nucleoli. The cytoplasmic outlines were indefinite. In the more slender cells, the nuclei were near one end. These cells occurred in aggregates often suggesting an acinar arrangement. Their derivation from the duodenal glands did not appear probable. The cells did not contain mucus or any demonstrable intracytoplasmic granules. Small ganglion cells were associated intimately with some of the aggregates. Unfortunately, the pertinent region lay at the extreme margin of the specimen, where the tissue had been distorted, and adequate characterization of these structures was difficult. Sections from this zone were submitted to four surgical pathologists, whose comments included

"reminiscent of carcinoid," "perhaps aberrant pancreas," and "hamartomatous." All agreed that these structures did not appear to be an unusual arrangement of immature cells of the neurogenic series and that their precise classification apparently was impossible.

Comment

According to prevailing opinion, ganglioneuromas are true embryonic tumors in that they are considered to represent proliferation of ganglion cells from retained undifferentiated neural elements that have migrated to normal or abnormal locations from the neural crest or primitive brain or spinal cord. These cells are assumed never to have attained complete adult differentiation.[18,19]

The 12 tumors forming the basis of this report (the one just described plus the 11 in Table I) can be divided into two groups. The two ganglioneuromas from the stomach and the one from the duodenum were sharply delimited, not involving the muscularis propria. These three tumors had no large nerve trunks or neurofibromatous changes in the adjacent tissues, nor was there local or segmental hypertrophy of the wall of the affected viscus.

The group of nine tumors arising more distally in the gastrointestinal tract were much less definitely circumscribed. All but two of these lesions had more or less symmetric hypertrophy of the various layers of the affected intestinal wall, leading sometimes to a description of gigantism of the intestinal segment. These changes were least prominent in Lichtenstein and Ragins'[8] case and in Schultz's[7] case and were dramatic in most of the others. Eight of the nine tumors exhibited enlarged nerve trunks, plexiform neuromas, accumulations of Schwann's cells, or neurofibromatous proliferation intimately associated with the tumors, usually ramifying within the adjacent mesentery as well as in the entire thickness of the intestinal wall. Greatly increased numbers of ganglion cells were noted in each case. These were most prominent in the region of Meissner's plexus in eight of the nine cases but often were noted also in the region of Auerbach's plexus, in the mucosa, less commonly in the serosa, and occasionally even along nerve trunks in the adjacent mesentery.

The increase in thickness of the intestinal wall was brought about by hypertrophy of muscular and connective tissue elements and by proliferated nerve fibers, Schwann's cells, and ganglion cells. In the patients described by Jentzer and Fatzer[13] and by Baltisberger,[11] proliferation of nerve fibers and Schwann's cells within the mesentery formed the bulk of the tumor.

The relationship of the nine lesions under discussion to the neural

and muscular proliferation in the appendix described by Masson[20] has not been established. Whether such tumors as these nine should be called ganglioneuromas is debated. Pick[21] and Pick and Bielschowsky[22] objected to the applications of this term to the lesions described by Schultz[7] and by Oberndorfer[6] and to a similar tumor found by Pick in a horse. Pick and Bielschowsky preferred to think of these growths as resulting from a developmental aberration in which a defect in the intestinal anlage led to true hypertrophy of the affected intestinal segment in combination with local neurofibromatosis. Two of the nine patients, those described by Oberndorfer and by Baltisberger, had manifest stigmas of Recklinghausen's disease, and the former gave a family history of neurofibromatosis as well. Several of the patients had developmental anomalies, as listed in Table I.

The association of ganglioneuromas and neurofibromatosis has been recognized for a long time,[1,23-26] as has that of ganglioneuromas and developmental abnormalities.[23,27] Regardless of how one chooses to consider these growths in the intestine, they do contain ganglion cells in excess, and ganglioneuroma appears at present to be a good category for them. They have been listed as such by others.[1,5] A case reported by Montgomery and O'Leary[28] may be mentioned here. Multiple cutaneous nodules that proved to contain ganglion cells developed in a 26-year-old man who was under observation for another disease. His appendix, removed 1 year before onset of the cutaneous lesions, contained considerably increased numbers of ganglion cells, chiefly in Auerbach's plexus. The patient's colon was incompletely rotated. The cutaneous nodules subsequently underwent involution.[29]

Several features of the tumor described in the present report might be interpreted as indicating anomalous development, in part, of the lesion. The absence of submucosal glands, excepting a single, large, undistorted, glandular cluster retained within the tumor, the irregularities in the muscularis mucosae, not adequately explained on the basis of compression by tumor, and perhaps the peculiar unexplained structures in one region of the mucosa might be considered developmental errors. Nevertheless, the stigmas of proliferative activity of the ganglion cells, the occasional binucleated and trinucleated cells, the variation in cellular size, and the increased density of nuclear chromatin in the smaller cells, with their abnormal arrangement in loose clusters (Fig. 4), speak adequately for neoplastic activity. Although no one has been so bold as to favor the concept of dedifferentiation of ganglion cells in the natural history of these lesions, both Zimmermann[26] and Stout[1] have hinted strongly at it. Such dedifferentiation remains a possibility in the inception of some ganglionic tumors, especially since good evi-

dence exists that adult sympathetic ganglion cells are not absolutely post-mitotic.[30]

Ganglioneuromas may be considered to be part of a continuous spectrum with regard to malignancy. Completely undifferentiated, highly malignant neuroblastomas stand at one end of this spectrum, and quiescent mature ganglioneuromas are at the other. Metastatic lesions from tumors with the degree of cellular maturity present in the duodenal lesion have not been described. Classically, ganglioneuromas exhibit histologic evidence of malignancy in one of two ways.[1] They may be composed of diffusely intermixed cells in various stages of immaturity and mature ganglion cells, or they may contain completely neuroblastomatous regions in a tumor that in other parts has only mature ganglion cells. Two of the 12 tumors from the gastrointestinal tract presented malignant histologic features. The polypoid gastric lesion described by Bertini[15] contained intermixed, small, darkly stained cells interpreted as sympathoblasts. Neither metastasis nor invasion of the adjacent gastric wall apparently occurred, although follow-up was not available. The tumor described by Jentzer and Fatzer[13] was not malignant in the classic fashion but was associated with a spindle cell sarcoma arising in a zone of neurofibromatous proliferation in the mesentery adjacent to the ganglioneuroma in the intestinal wall. The authors' illustration showed a neoplasm that may have been a malignant schwannoma. Both Oberndorfer[6] and Schultz[7] described syncytial cells in the lesions reported by them; they considered these syncytia to represent intermediate forms in the development of ganglion cells. Pick and Bielschowsky,[22] who subsequently reviewed sections from these tumors, considered these syncytial cells to be proliferating Schwann's cells. With the exception of Jentzer and Fatzer's case, none of the 12 ganglioneuromas from the gastrointestinal tract were clinically malignant, and none recurred in the stated follow-up period, which was usually short. Two of the patients died in the immediate postoperative period (Table I).

There are no specific signs or symptoms to point to a preoperative diagnosis of ganglioneuroma of the alimentary canal. The clinical histories and findings in three of the five patients who had appendiceal lesions led to a preoperative diagnosis of appendicitis. One of the appendices was ruptured, and an inflammatory reaction explained the acute symptoms in the other two. The varied symptoms in the remaining patients are summarized in Table I. The complaints that necessitated surgical operation in three of these patients undoubtedly were related to disease processes other than the ganglioneuroma.

Ganglioneuromas are not radiosensitive, and complete surgical ex-

tirpation is the accepted treatment. That incompletely removed ganglioneuromas, even those not found to contain undifferentiated cells, can recur and grow rapidly is illustrated in the case reported by Wyman and associates.[31]

SUMMARY

Detailed pathologic studies have been made in a case of ganglioneuroma of the duodenum. This apparently is the first such lesion in this part of the intestine to be reported.

Search of the available literature revealed records of 11 ganglioneuromas of the gastrointestinal tract. Five of these tumors were in the appendix, two in the ileum, and two in the stomach; the remaining two involved the ileum, cecum, and ascending colon. One of the 12 tumors was clinically malignant, and one other had histologic features of malignancy.

Complete surgical extirpation is the accepted treatment.

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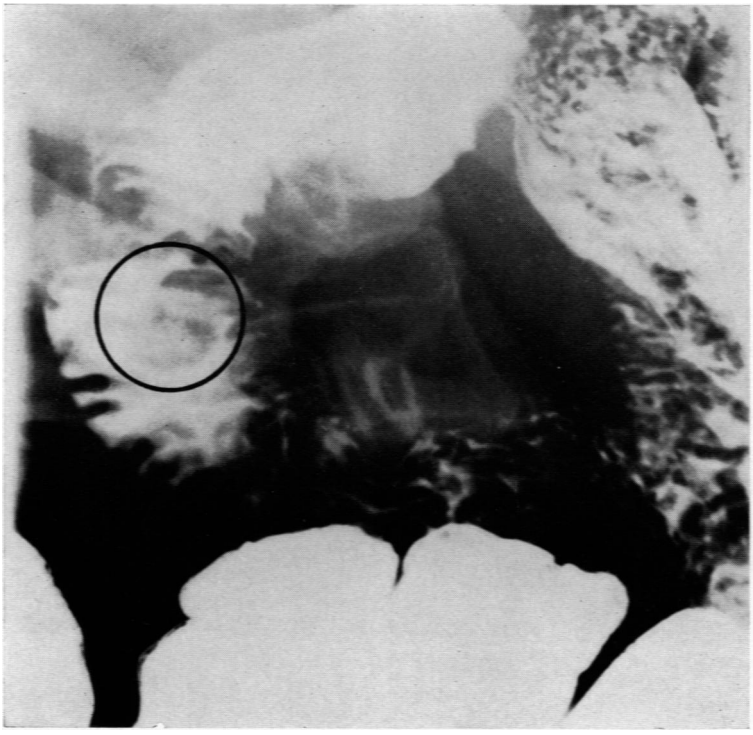
[*Illustrations follow*]

LEGENDS FOR FIGURES

FIG. 1. Polypoid lesion in second part of duodenum, outlined by barium.

FIG. 2. Section of entire tumor, with small mucosal ulcer at upper right. Single cluster of Brunner's glands is seen within the tumor. Capsule is not shown at left because of oblique cut through tissue. Hematoxylin and eosin stain. × 12.



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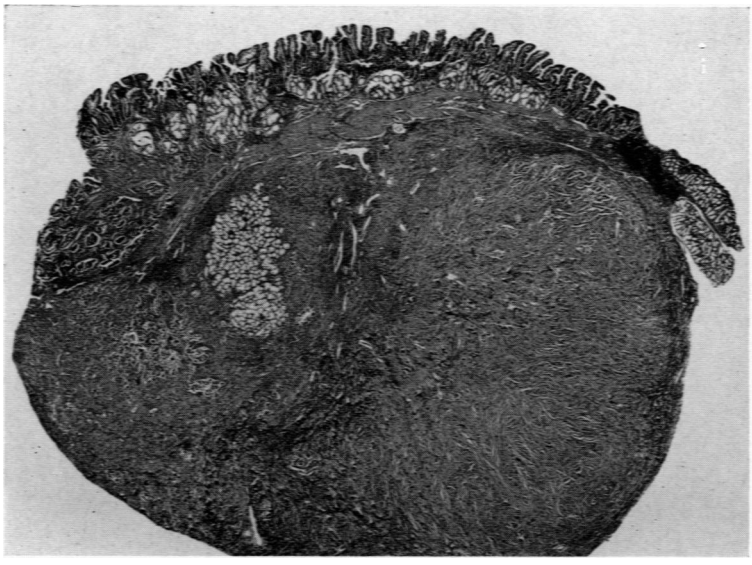

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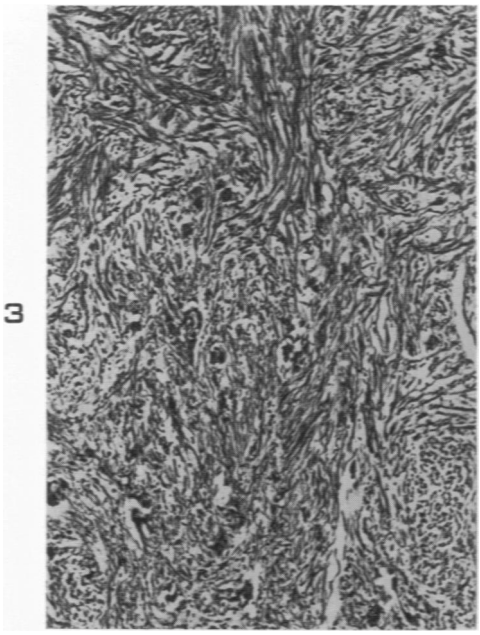

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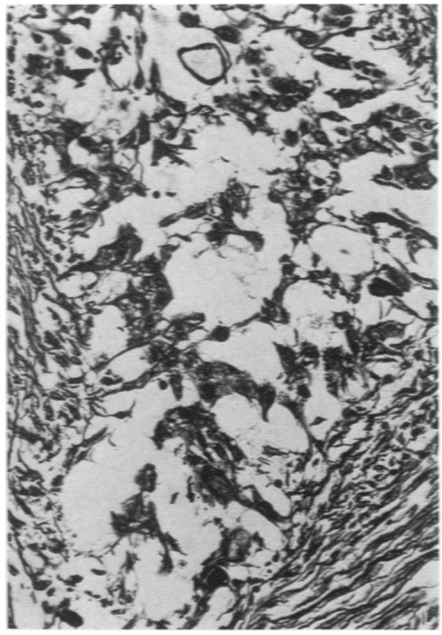

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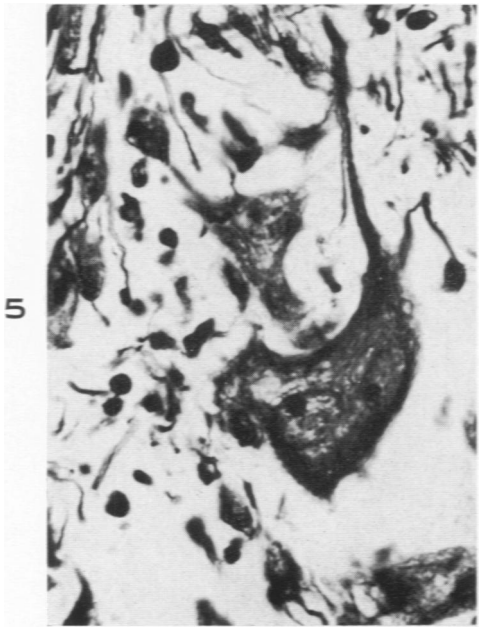

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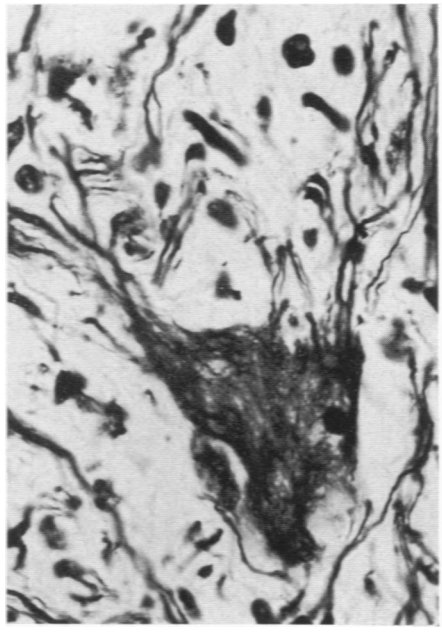

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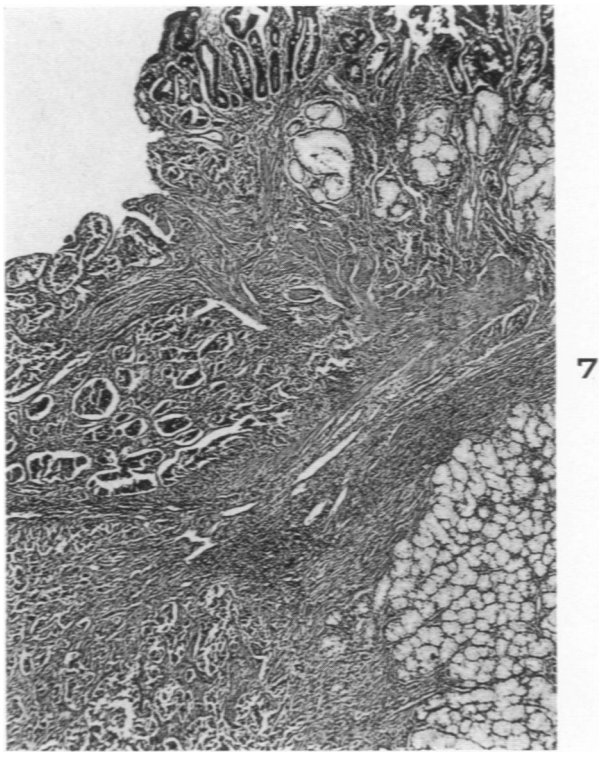

FIG. 3. Ganglion cells sparsely scattered in predominantly neurofibrillar stroma. Bodian stain. × 75.

FIG. 4. Loose cluster of small ganglion cells. Bodian stain. × 200.

FIG. 5. Large, binucleate, multipolar ganglion cell and several smaller ganglion cells. Bodian stain. × 700.

FIG. 6. Large ganglion cell with multiple processes and a satellite. Bodian stain. × 700.

FIG. 7. Unusual gland-like structures within mucosa at left. Duplication and distortion of muscularis mucosae may be noted. Hematoxylin and eosin stain. × 40.