Mixed Endocrine Gastric Tumors Associated With Hypergastrinemia of Antral Origin

L.-I. Larsson, MD, J. F. Rehfeld, MD, R. Stockbrügger, MD, G. Blohme, MD, I.-M. Schöön, MD, G. Lundqvist, MD, L. G. Kindblom, MD, J. Säve-Söderberg, MD, L. Grimelius, MD, and L. Olbe, MD

A patient with atrophic gastritis and excessively raised serum gastrin concentrations (4000 to 5000 pg/ml) was found to have multiple polypous tumors of the gastric corpus mucosa. Following gastrectomy, serum gastrin concentrations decreased to undetectable levels. The tumors consisted of a mixed population of endocrine cells. The majority of tumor cells were of the ECL type, but, in addition, enterochromaffin cells of various subtypes as well as agranular cells were found. The tumors were locally invasive and invaded the walls of submucosal blood vessels. The surrounding mucosa showed a severe atrophic gastritis with intestinalization and contained numerous goblet cells, enterochromaffin cells, and cholecystokinin cells. Cholecystokinin cells do not occur in the normal oxyntic mucosa. Hence, the observation of this cell type in intestinalized gastric epithelium suggests that "intestinalization" also is associated with changes in endocrine cell populations. Gastrin has been shown to affect the function of the ECL cells. Indications for a trophic action of gastrin on these cells have been obtained. It is discussed whether greatly raised serum gastrin levels in patients with atrophic gastritis may be associated with increased risks for the development of certain types of gastric tumors. (Am J Pathol 93:53–68, 1978)

APART FROM THE WELL-KNOWN FEATURES of the Zollinger–Ellison syndrome,[1] hypergastrinemia may be associated with other changes that seem related to the trophic effects of gastrin on certain cell systems. Such changes include the voluminous hyperplasia of parietal cells [2,3] and endocrine cells (so-called ECL cells) of the gastric corpus mucosa [4-6] as well as pancreatic islet cell hyperplasia.[1,7-9] Recognition of such long-term effects are important for the understanding of the pathophysiology of hypergastrinemia.

In the following report we describe a patient with hypergastrinemia of antral origin associated with multiple mixed endocrine tumors of the gastric corpus mucosa.

Clinical Data

The patient was a 57-year-old woman with a 28-year history of insulin-treated, uncomplicated, diabetes mellitus. In 1964 the patient underwent

From the Institute of Medical Biochemistry, University of Aarhus, Aarhus, Denmark; the Departments of Medicine Surgery, and Pathology, Sahlgrens Hospital, Gothenburg; and the Departments of Clinical Chemistry and Pathology, University Hospital, Uppsala, Sweden.

Grant support from Landsforeningen til Kraeftens bekaempelse and the Danish Medical Research Council.

Accepted for publication May 23, 1978.

Address reprint requests to L.-I. Larsson, MD, Institute of Medical Biochemistry, University of Aarhus, DK-8000, Denmark.

0002-9440/78/1010-0053$01.00

a thyroidectomy due to benign goiter, and substitution therapy with thyroid hormones (sodium levothyroxine [Levaxin]) was instituted. In the same year she underwent surgery for a benign tumor of the left breast. In 1976, screening tests on diabetic patients revealed that this patient had excessively raised serum gastrin levels (varying between 4000 and 5000 pg/ml; normal levels are below 100 pg/ml). A pentagastrin test revealed achlorhydria. Despite previous slight anemia, serum concentrations of iron, vitamine B_{12}, and folic acid were normal. Serum levels of insulin, secretin, vasoactive intestinal polypeptide, pancreatic polypeptide, glucagon, parathormone, TSH, and cortisol were within the normal range. Gastrointestinal x-ray series revealed no abnormalities, but on gastroscopy, multiple (approximately 20) polypous lesions were detected in the corpus mucosa. The antral mucosa appeared normal. Biopsies from the polypous lesions revealed endocrine-like tumors with local infiltration of the submucosa and blood vessels. A total gastrectomy was performed in 1976. Subsequently, serum gastrin levels decreased to unmeasurable concentrations (below 10 pg/ml). The patient tolerated the operation well and her insulin requirements fell. One year following surgery, no evidence of metastases has been detected and she is now working part-time.

Materials and Methods

Material from the tumors and from the antral mucosa was obtained at gastroscopy and at surgery. For light microscopy the material was fixed in 10% neutral formalin or in Bouin's fluid and was subsequently embedded in paraffin. Electron microscopic material was fixed in a 3% formaldehyde and 2% glutaraldehyde mixture in 0.1 M sodium phosphate buffer, pH 7.3, for 3 to 4 hours, washed in the buffer, postfixed in 1% osmic acid, dehydrated, and embedded in Epon 812.

Light Microscopy

Paraffin sections were stained with van Gieson–hematoxylin, hematoxylin and eosin, periodic acid–Schiff, or silver according to Grimelius,[10] Sevier and Munger[11] (argyrophil reactions), or Singh[12] (argentaffin reaction).

Fluorescence Microscopy

Three-micron sections were deparaffinized and mounted in Entellan (Merck). They were subsequently analyzed in a Zeiss standard 18 fluorescence microscope equipped for epiillumination using an HBO 50 mercury lamp as light source and selective filters for excitation at 405 nm. Under these conditions, cells that contain large amounts of 5-hydroxytryptamine (such as the enterochromaffin cells) are detected due to their intense formaldehyde-induced yellow fluorescence.[13] Specificity of the reaction was confirmed by comparing the distribution of fluorescent cells with that of argentaffin cells. Exposure of the sections to a sodium borohydride solution considerably lowered the fluorescence intensity, which subsequently could be made to reappear by renewed exposure to formaldehyde.[14]

Immunocytochemistry

Three-micron paraffin sections were subjected to an indirect immunocytochemical method for the demonstration of gastrin and cholecystokinin (CCK) immunoreactivity. Gastrin antiserums Nos. 4562 and 4710 and CCK antiserum No. 4698 were employed as described in detail elsewhere.[15-17] Gastrin antiserum No. 4562 recognizes the COOH terminal portion of both gastrin and cholecystokinin, whereas antiserum No. 4710 is specific for the mid portion of human gastrin-17.[16] CCK antiserum No. 4698 is specific for the region 25–30 of CCK-33[16-17]; hence, it fails to bind any gastrins or to react with antral gastrin cells.[16] The antiserums were applied in appropriate dilutions for 24 hours at 4 C. The site of antigen–antibody reaction was revealed either by the PAP procedure of Sternberger [15-18] or with fluoresceinisothiocyanate (FITC)-labeled sheep antirabbit IgG (SBL, Stockholm, Sweden). Controls were those recommended by Sternberger [18] and included the application of antigen-inactivated antiserums (10 μg of synthetic human gastrin I [ICI, Alderley Park, Cheshire, England] or purified porcine cholecystokinin [kindly provided by Prof. V. Mutt, Department of Biochemistry, Karolinska Institute, Stockholm, Sweden] per milliliter of diluted antiserum). Immunofluorescence preparations were analyzed in the fluorescence microscope employing a xenon XBO 75 lamp as light source and selective interference filters to obtain excitation at 490 nm (the excitation maximum for FITC). The number of antral gastrin cells was obtained by counting immunoreactive cells in perfect transverse sections. The result was expressed as number of gastrin cells per field of vision (objective 10 ×, eye-piece 12.5 ×), according to previously established methods.[15,19] The values were compared with those obtained in a previous study of antral gastrin cells in normal and achlorhydric patients.[19]

Electron Microscopy

Ultrathin sections were cut on an LKB III ultrotome and contrasted on grids with lead citrate and uranyl acetate. The preparations were examined in a Jeol JEM 100 C electron microscope.

Gastrin Radioimmunoassay

Serum samples were analyzed in triplicate with a specific gastrin radioimmunoassay employing antiserum No. 2604 and ^{125}I-labeled synthetic human gastrin I. In addition, gel chromatography on preoperative serum samples was carried out on Sephadex G-50 superfine columns (Pharmacia Fine Chemicals, Uppsala, Sweden), as monitored by the above assay (for details see References 20 and 21).

Results

Gross Appearance

The gastric resection measured 27 cm on the greater curvature and 22 cm on the lesser curvature. Within the corpus region approximately 20 pale gray-white polyps up to 7 mm in diameter were seen (Figure 1).

Light Microscopy

The corpus mucosa was atrophic and revealed prominent intestinalization of the epithelium. Villi-like structures, goblet cells, Paneth cells, and pseudopyloric glands were frequently encountered. No parietal cells could be detected. The polypous tumors were found to be covered

either with typical gastric surface epithelium or, more commonly, with the intestinalized epithelium. Beneath the epithelium, cords and whorls of tumor cells were detected (Figures 2 and 3). Most of the tumor cells were fairly small, uniform, and rounded, with light-staining, vesicular nuclei and a pale, slightly eosinophilic cytoplasm (Figure 2). Mingling with these cells were occasional smaller cells with dark-staining hyperchromatic nuclei (Figure 2C). The tumors were mostly delimited to the mucosa, although a few of the polyps contained tumor cell cords which infiltrated and penetrated some thin-walled mucosal and submucosal vessels. Most of the tumor cells stained strongly with silver according to Grimelius [10] and Sevier and Munger [11] (Figure 3).

Fluorescence Microscopy

Strongly yellow fluorescent enterochromaffin cells were detected in both the antral mucosa and in the intestinalized epithelium of the gastric corpus. In the latter location, the cells assumed the typical flask-shape of intestinal enterochromaffin cells. In addition, similar yellow-fluorescent enterochromaffin cells were scattered in the gastric tumors.

Immunocytochemistry

Antral Mucosa

Scattered gastrin cells occurred in the antral mucosa, which was devoid of cholecystokinin (CCK) cells. The gastrin cell number was low and averaged 10 to 20 cells per field of vision (in normal patients the corresponding value is 50 to 60 cells per field of vision [15,19]). No evidence of antral tumor tissue was obtained.

Corpus mucosa

The tumors were devoid of gastrin and CCK immunoreactive cells. CCK immunoreactive cells were, however, detected in the intestinalized epithelium overlying the tumors (Figure 4). These cells reacted with the specific CCK antiserum (No. 4698) as well as with the cross-reacting gastrin antiserum (No. 4562), whereas they failed to react with the gastrin-specific antiserum (No. 4710). Their identity with CCK cells was thus proved. The CCK cell frequency was low and roughly equaled one third to one fourth of the duodenal CCK cell frequency in humans and experimental animals. All immunologic and staining controls confirmed the specificity of the immunocytochemical reactions.

Electron Microscopy

The gastric tumors were built up of a multiplicity of cells, the majority of which contained the characteristic cytoplasmic granules of endocrine cells. The predominating cell type contained large nuclei and corresponded to the uniform, rounded cells with vesicular nuclei seen in the light microscope. Ultrastructurally, these cells were characterized by the presence of vesicular cytoplasmic granules, containing a small electron-dense core that often was eccentrically placed in the granules (Figures 5 and 6). The halo between the dense core and the surrounding membrane was electron-lucent and usually wide. The cells contained a variable number of granules as well as considerable amounts of granular endoplasmic reticulum and a well-developed Golgi apparatus (Figures 5 and 6). The ultrastructure of these cells is identical with that of the ECL cells described in the 1977 Lausanne nomenclature.[22] ECL cells were calculated to represent more than 70% of the total tumor cell population. In addition, few (1 to 2%) cells containing the characteristic pleomorphic, electron-dense granules of enterochromaffin cells [22] were detected (Figure 7). The size of the enterochromaffin cell granules varied considerably and at least two types could be discerned: one containing small pleomorphic granules of the type seen in enterochromaffin cells of normal human gastric mucosa and another type containing much larger, pleomorphic granules of the type seen in intestinal epithelium and in mid-gut carcinoids.[22] These cells probably correspond to the yellow-fluorescent cells seen by fluorescence microscopy of formalin-fixed material. The remainder of the tumor cells were smaller and devoid of cytoplasmic granules and contained hyperchromatic nuclei.

Radioimmunoassay

Preoperative serum samples were found to contain high gastrin concentrations (4000 to 5000 pg per ml). Gel chromatography of the samples on Sephadex G-50 superfine columns revealed the presence of gastrin components I through IV, eluting in a pattern corresponding to that seen in other patients with atrophic gastritis. Following total gastrectomy, serum gastrin concentrations fell considerably (to below our detection limit: 10 pg/ml), an observation strongly in favor of an antral origin of the raised gastrin levels.

Discussion

The high serum gastrin concentrations detected in the present patient by far exceed those seen in most patients with atrophic gastritis.[19] The

pronounced fall in serum gastrin concentrations seen after gastrectomy confirms that the stomach was the source of the hypergastrinemia. However, the frequency of antral gastrin cells was slightly below normal, whereas the gastrin cell frequency is usually raised in hypergastrinemic, achlorhydric patients. Hence, the possibility of a gastric gastrin-producing tumor must be considered. Only two well-investigated such cases are on record: in both patients these tumors occurred in the antropyloric gland area.[7,23] No antropyloric tumors were found in the present case. Immunocytochemical studies on material from the tumors of the present patient did not reveal any gastrin immunoreactive cells. Electron microscopy revealed that the tumors were composed of cell types distinctly different from both normal gastrin cells and cells seen in gastrin-producing tumors. Hence, we believe that they are unlikely to represent the source of hypergastrinemia. The reasons for this may be summarized as follows: a) no gastrin-producing tumors have ever been encountered in the body mucosa and only two such tumors have been found in the antral mucosa, b) the immunocytochemical and electron microscopic results show that the tumor cells were distinct from gastrin-producing cells, and c) in some hypergastrinemic achlorhydric patients the antral gastrin cell frequency is low.[19] Hence, we believe that in the present case the antral gastrin cells were hyperactive, releasing excessive amounts of gastrin to the circulation. Immunocytochemistry detects only tissue stores of gastrin. Possibly, some hyperplastic antral gastrin cells may have stored gastrin in amounts below the detection limit of the immunocytochemical technique.

The tumors of the body mucosa consisted mainly of the so-called ECL cells, which made up 70 to 80% of the tumor cells. Due to their ultramorphologic and cytochemical similarity to well-known peptide-hormone–producing cells, they are supposed to secrete an as yet unidentified hormone.[cf 22] In some rodents, the ECL cells are known to store and synthesize histamine, but it is very doubtful whether they do so in other mammals.[24,25] In the rodent *Mastomys* (*Praomys*) *natalensis*, tumors similar to those of the present patient have been shown to produce large quantities of histamine and to cause increased gastric acid secretion.[26,27] In rats, ECL cells respond promptly to stimulation by exogenous or endogenous gastrin by activation of the histamine-forming enzyme histidine decarboxylase.[24]

Experiments producing chronic changes in serum gastrin concentrations have indicated that gastrin exerts a trophic action on the ECL cells. Hence, antrectomy, producing low serum gastrin concentrations, is associated with a reduction in the number of ECL cells, whereas portacaval shunting greatly increases the number of ECL cells.[28] Antrectomy partly

prevents the proliferation of ECL cells seen after portacaval shunting, supporting the notion that the effects of the latter operation are, at least partly, mediated by gastrin.[28] In addition, numerous observations have indicated the occurrence of ECL cell hyperplasia in states of hypergastrinemia in humans.[4-6] These data suggest that the trophic actions of gastrin are not restricted to exocrine cell populations. In accordance with this notion, proliferation of pancreatic islet cells is frequently encountered in patients with hypergastrinemia,[1,7-9] and preliminary evidence suggests a trophic effect of gastrin on the pancreatic islet cell population.[29]

Interestingly, the gastric tumors were mixed in that they, in addition to ECL cells, contained enterochromaffin cells of at least two types as well as agranular cells. Mixed endocrine tumors seem to be comparatively common and have been noted to occur in, for example, the pancreas.[1,30]

A feature worthy of note was that the severely intestinalized epithelium of the body mucosa not only contained villi and goblet cells but also cholecystokinin cells, which are restricted to the duodenal and jejunal epithelium under normal conditions. Hence, the changes associated with gastric atrophy and intestinalization may include also endocrine cell populations.

It is tempting to speculate that in the patient in this study the primary lesion was achlorhydria due to gastric atrophy with intestinalization of her corpus mucosa. The subsequently raised serum gastrin levels, caused by decreased acid feedback inhibition, may have been instrumental in bringing about hyperplasia and neoplasia of the ECL cells. Although still conjectural, the possible combination of achlorhydria, hypergastrinemia, and the development of gastric endocrine tumors deserves more study.

References

1. Creutzfeldt W, Arnold R, Creutzfeldt C, Track NS: Pathomorphologic, biochemical, and diagnostic aspects of gastrinomas (Zollinger-Ellison syndrome). Hum Pathol 6:47–76, 1975
2. Neuburger PH, Lewin M, DeRecherche C, Bonfils S: Parietal and chief cell populations in four cases of the Zollinger-Ellison syndrome. Gastroenterology 63:937–942, 1972
3. Johnson LR: The trophic action of gastrointestinal hormones. Gastroenterology 70:278–288, 1976
4. Solcia E, Capella C, Vassallo G: Endocrine cells of the stomach and pancreas in states of gastric hypersecretion. Rendic Gastroenterol 2:147–158, 1970
5. Rubin W: A fine structural characterization of the proliferated endocrine cells in atrophic gastric mucosa. Am J Pathol 70:109–118, 1973
6. Bordi C, Costa A, Missale G: ECL cell proliferation and gastrin levels. Gastroenterology 68:205–206, 1975
7. Larsson L-I, Ljungberg O, Sundler F, Håkanson R, Svensson SO, Rehfeld JF, Stadil F, Holst J: Antropyloric gastrinoma associated with pancreatic nesidioblastosis and proliferation of islets. Virchows Arch [Pathol Anat] 360:305–314, 1973

8. Larsson L-I: Endocrine pancreatic tumors. Hum Pathol (In press)
9. Larsson L-I: Two distinct types of islet abnormalities associated with endocrine pancreatic tumours. Virchows Arch [Pathol Anat] 376:209–219, 1977
10. Grimelius L: A silver nitrate stain for A_2 cells in human pancreatic islets. Acta Soc Med Upsal 73:243–270, 1968
11. Sevier AC, Munger BL: A silver method for paraffin sections of neural tissue. J Neuropathol Exp Neurol 24:130–135, 1965
12. Singh I: A modification of the Masson-Hamperl method for staining of argentaffin cells. Anat Anz 115:81–82, 1964
13. Enerbäck L: Specific methods for detection of 5-hydroxytryptamine in carcinoid tumors. Virchows Arch [Pathol Anat] 358:35–43, 1973
14. Corrodi H, Hillarp N-Å, Jonsson G: Fluorescence methods for the histochemical demonstration of monoamines. 3. Sodium borohydride reduction of the fluorescent compounds as a specificity test. J Histochem Cytochem 12:582–586, 1964
15. Larsson L-I, Håkanson R, Sjöberg NO, Sundler F: Fluorescence histochemistry of the gastrin cell in fetal and adult man. Gastroenterology 68:1152–1159, 1975
16. Larsson L-I, Rehfeld JF: Evidence for a common evolutionary origin of gastrin and cholecystokinin. Nature 269:335–338, 1977
17. Larsson L-I, Rehfeld JF: Characterization of antral gastrin cells with region-specific antisera. J Histochem Cytochem 25:1317–1321, 1977
18. Sternberger L: Immunocytochemistry. Englewood Cliffs, N.J., Prentice-Hall, Inc., 1974
19. Stockbrügger R, Larsson LI, Lundqvist G, Angervall L: Antral gastrin cells and serum gastrin in achlorhydria. Scand J Gastroenterol 12:209–213, 1977
20. Rehfeld JF, Stadil F, Rubin B: Production and evaluation of antibodies for the radioimmunoassay of gastrin. Scand J Clin Lab Invest 30:221–232, 1972
21. Stadil F, Rehfeld JF: Preparation of ^{125}I-labelled synthetic human gastrin I for radioimmunoanalysis. Scand J Clin Lab Invest 30:361–368, 1972
22. Solcia E, Polak JM, Pearse AGE, Forssman WG, Larsson LI, Sundler F, Lechago J, Grimelius L, Fujita T, Creutzfeldt W, Gepts W, Falkmer S, Lefranc F, Heitz PH, Bordi C, Hage E, Buchan AMJ, Bloom SR, Grossman MI: Lausanne 1977 classification of gastroenteropancreatic endocrine cells. Gut Hormones. Edited by SR Bloom. Edinburgh, Churchill Livingstone, 1978, pp 40–48
23. Royston CMS, Brew DStJ, Garnham JR, Stagg BH, Polak J: The Zollinger-Ellison syndrome due to an infiltrating tumour of the stomach. Gut 13:638–642, 1972
24. Håkanson R, Larsson L-I, Liedberg G, Sundler F: The histamine-storing enterochromaffin-like cells of the rat stomach. Chromaffin, Enterochromaffin and Related Cells: A NATO Foundation Symposium. Edited by RE Coupland, T Fujita. Amsterdam, Elsevier Scientific Publishing Co., Inc., 1976, pp 243–263
25. Håkanson R, Owman C: Letter to the editor: Histochemical localization of histamine in the human gastric mucosa. Am J Gastroenterol 60:417–419, 1973
26. Håkanson R, Larsson LI, Owman C, Snell KC, Sundler F: Fluorescence and electron microscopic histochemistry of endocrine-like cells in gastric mucosa and argyrophil tumour of Praomys (Mastomys) natalensis. Analysis of 5-hydroxytryptamine, histamine, histidine decarboxylase and aromatic amino acid decarboxylase. Histochemie 37:23–38, 1973
27. Capella C, Solcia E, Snell KC: Ultrastructure of endocrine cells and argyrophil carcinoids of the stomach of Praomys (Mastomys) natalensis. J Natl Cancer Inst 50:1471–1485, 1973
28. Håkanson R, Larsson L-I, Liedberg G, Oscarson J, Sundler F, Vang J: Effects of antrectomy or portacaval shunting on the histamine-storing endocrine-like cells in oxyntic mucosa of rat stomach: A fluorescence histochemical, electron microscopic and chemical study. J Physiol 259:785–800, 1976

29. Larsson LI, Høiriis-Nielsen J, Rehfeld JF: Presence and possible physiological significance of pancreatic gastrin. Diabetologia 12:404, 1976
30. Larsson LI, Stadil F, Holst J, Angervall L, Sundler F: Mixed endocrine pancreatic tumours producing several peptide hormones. Am J Pathol 79:271–284, 1975

Acknowledgments

We thank Professor A. Maunsbach, Institute of Anatomy (A), University of Aarhus, Aarhus, Denmark, for generously putting electron microscopic facilities at our disposal. Excellent technical assistance was provided by Mrs. J. B. Lauridsen and Mrs. E. Petersen.

[*Illustrations follow*]

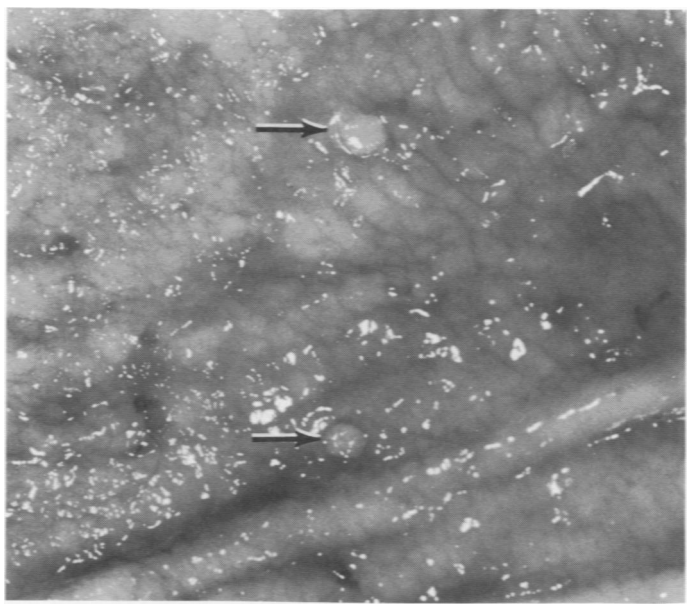
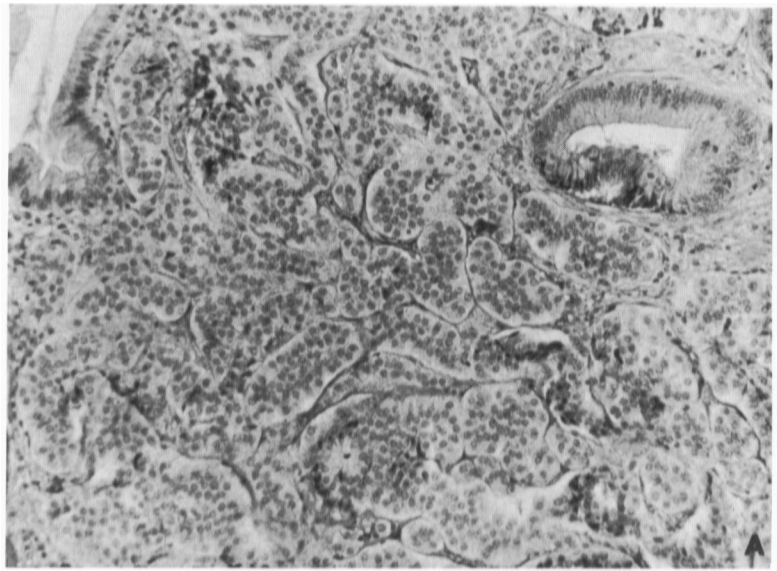
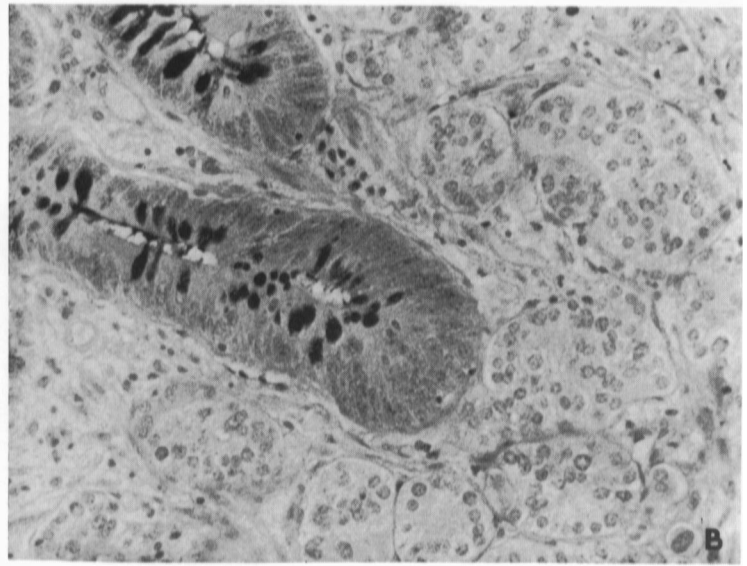


Figure 1—Gastric corpus mucosa (natural size). Two small polypous tumors are seen (*arrows*).





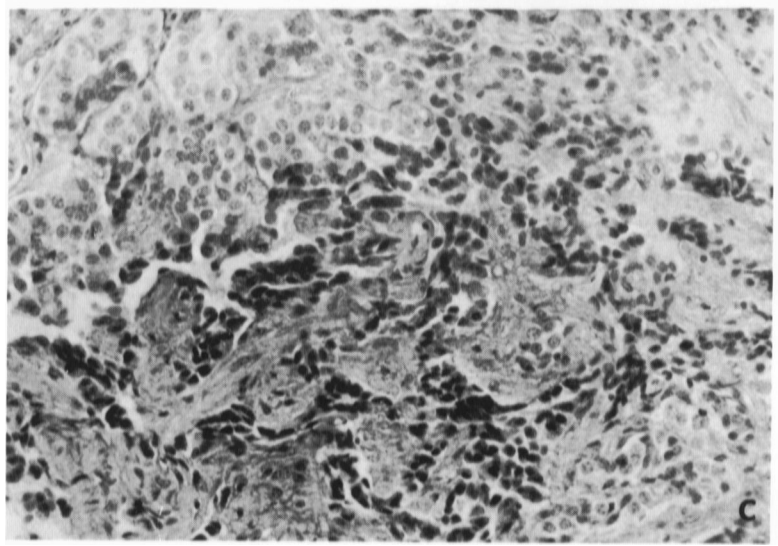


Figure 2—Sections of the tumors of the corpus mucosa. **A**—Hematoxylin and eosin staining reveals cells with pale vesicular nuclei growing in whorls and cords with scanty connective tissue. **B**—Periodic acid–Schiff/hematoxylin staining shows the PAS-negative tumor cells growing adjacent to the villi of the intestinalized epithelium. **C**—Hematoxylin and eosin staining reveals both apparently well-differentiated tumor cells as well as cells with scanty cytoplasm and hyperchromatic nuclei. (**A**, × 180; **B**, × 288; **C**, × 288) (with printing reduction of 4%)

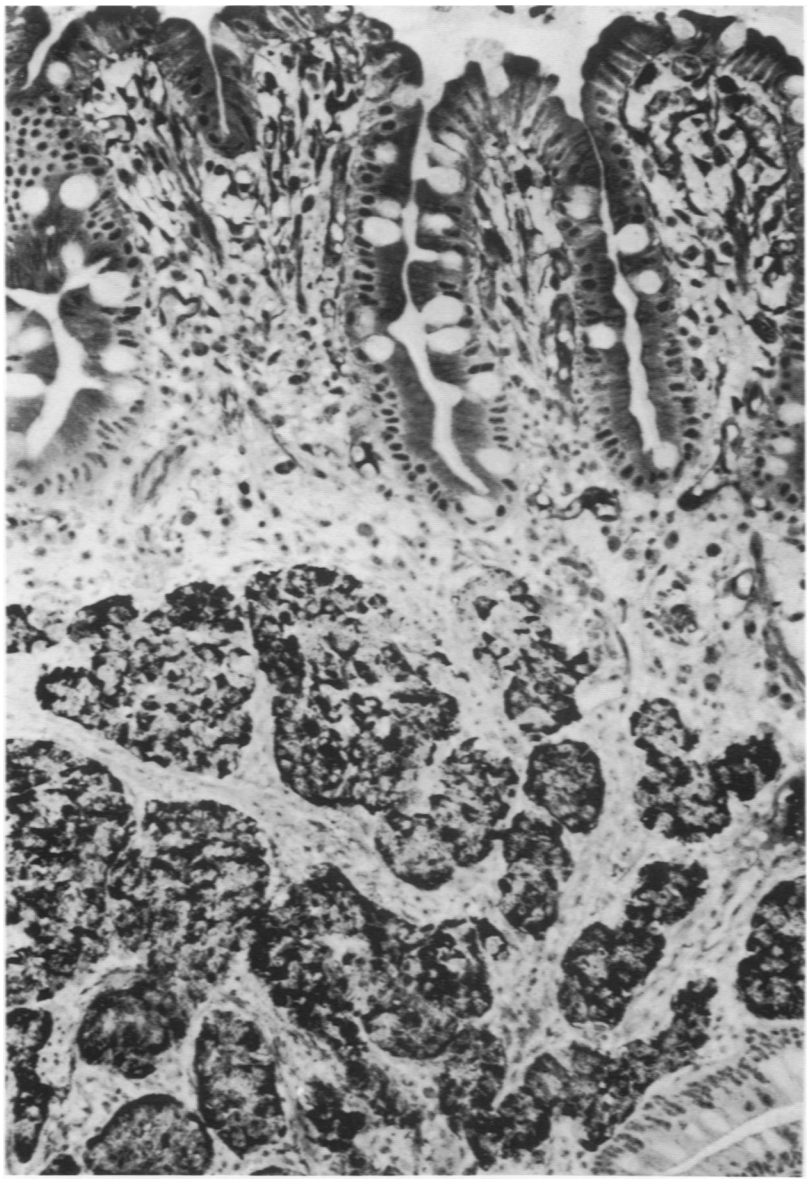
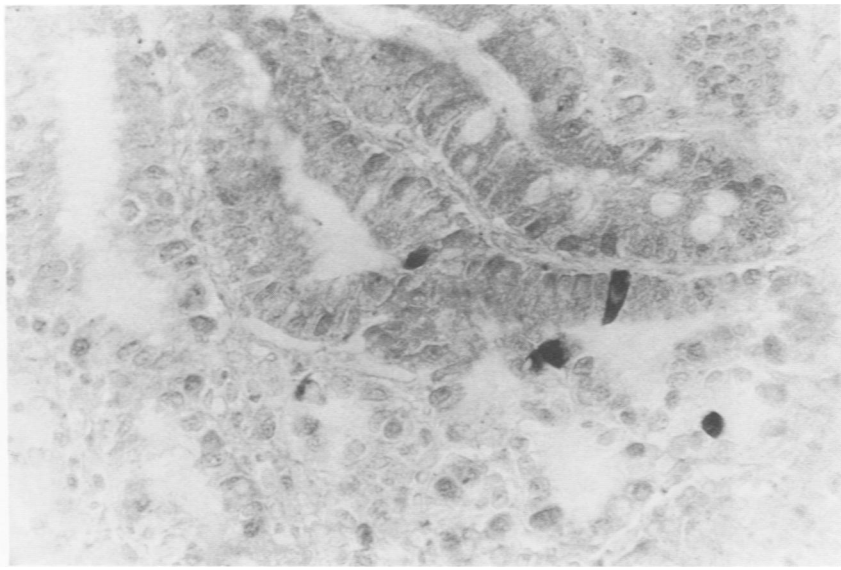


Figure 3—Corpus tumor stained with silver according to Sevier and Munger.[11] Note the intact overlying intestinalized epithelium and the intensely argyrophil tumor cells. (× 230)



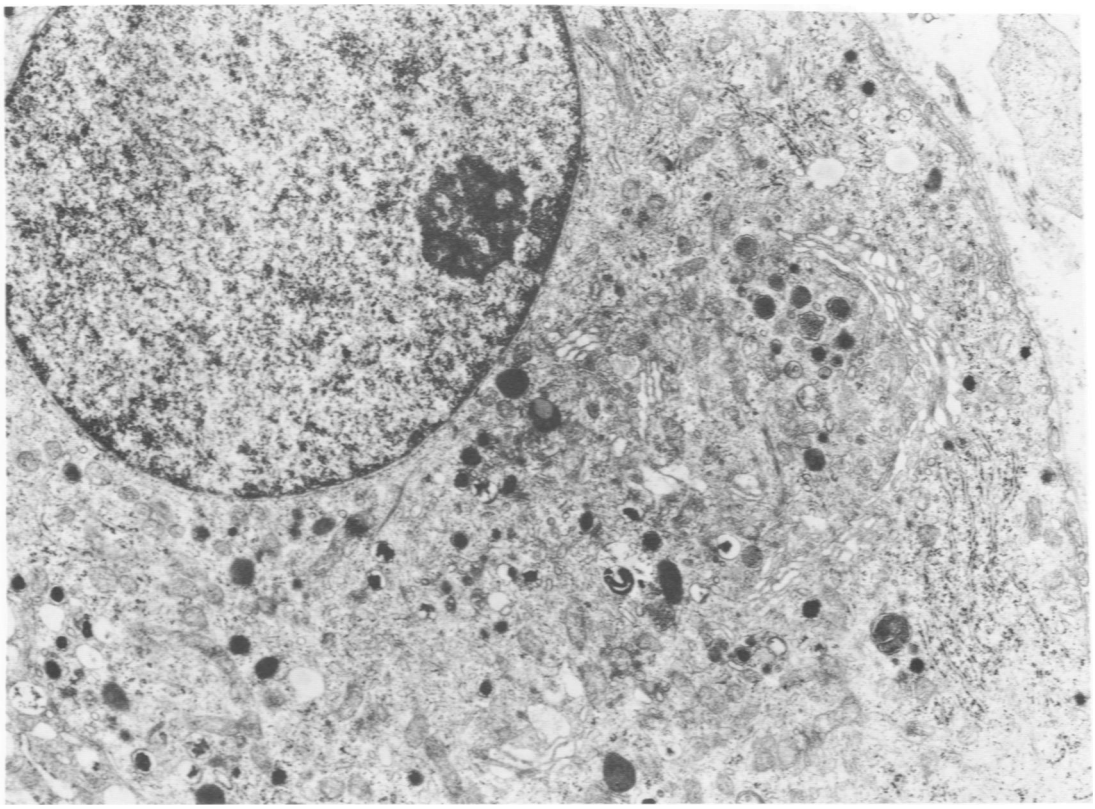


Figure 4—Intestinalized epithelium immunocytochemically stained for CCK (Antiserum No. 4698; PAP technique). Several strongly immunoreactive CCK cells are seen. The oxyntic mucosa is normally devoid of CCK cells. (× 430) **Figure 5**—Electron micrograph of a gastric corpus tumor. The tumor cells contain numerous granules as well as well-developed endoplasmic reticulum and a prominent Golgi apparatus, indicating active peptide or protein synthesis. The cytoplasmic granules belong to the ECL cell variety, although in this electron micrograph the space between the dense core and the surrounding membrane is less wide than is usually seen. (See Figure 6). In most of the neoplastic ECL cells, granules of the type shown in this figure were seen in the vicinity of the Golgi apparatus, whereas larger and more vesicular granules occurred more peripherally. This may indicate that the smaller granules are newly formed. (× 12,500)

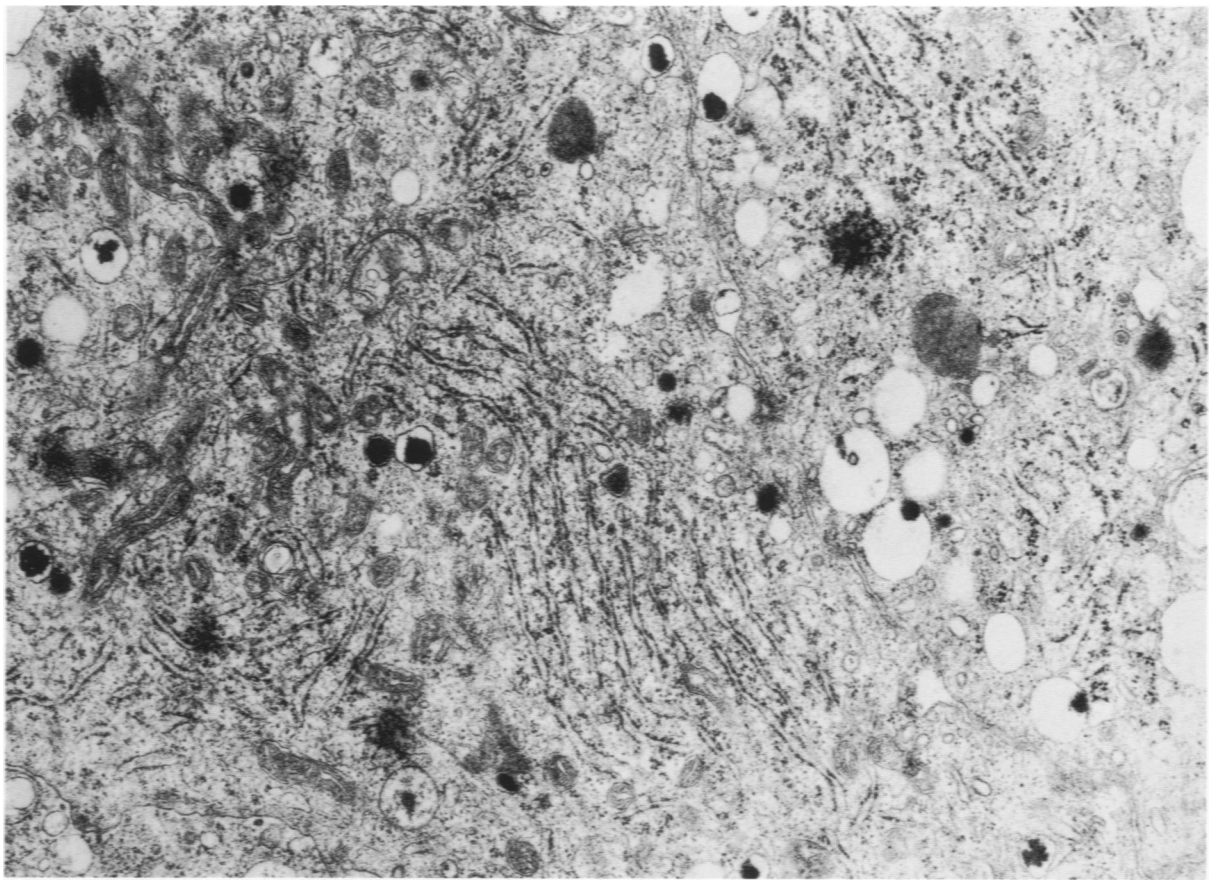


Figure 6—Electron micrograph of gastric corpus tumor cell of the ECL type. Note the occurrence of both smaller cytoplasmic granules and large granules containing a wide space between the small dense core and the surrounding membrane. Granules of the latter type are characteristic of ECL cells. (× 20,200)

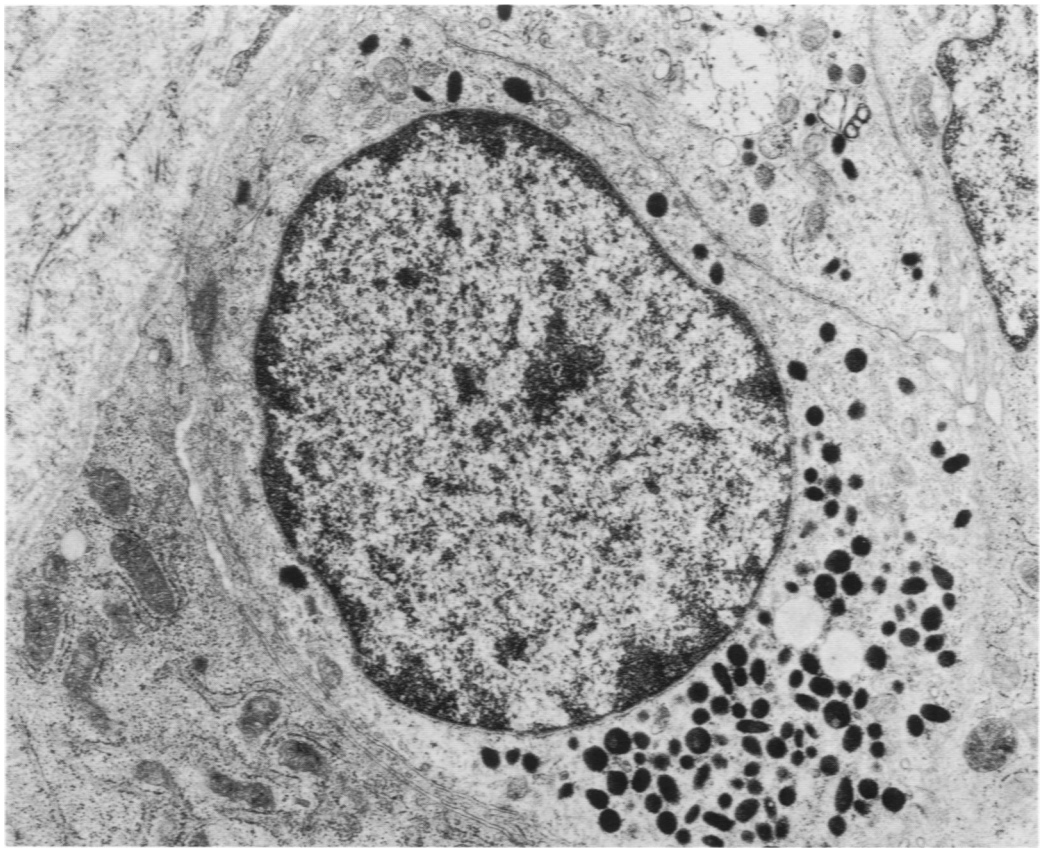


Figure 7—Electron micrograph of tumor cell containing small, pleomorphic and highly electron-dense cytoplasmic granules. These granules are characteristic for one subpopulation of enterochromaffin (EC) cells known to produce 5-hydroxytryptamine. (× 13,200)