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HISTOLOGIC, IMMUNOHISTOCHEMICAL AND MORPHOMETRIC STUDY OF THE MUCOSA OF THE TOTAL GASTRIC ANTRUM IN PATIENTS WITH CARCINOMA OF THE STOMACH

G. E. Holle, M.D., M. Stiegelmeier, M.D, J. Riedel, M.D., R. Ringel, M.D., R. Siewert, M.D., W. Eisenmenger, M.D., *and* F. Holle, M.D., F.A.C.S.(HON.), *Munich, Germany*

Examination of gastrin-immunoreactive G-cells, somatostatin-immunoreactive D-cells, enterochromaffin cells and 5-hydroxytryptamine-immunoreactive (5-HT-immunoreactive) cells of the completely mapped histologic antrum (70 to 100 tissue blocks) was done in 20 normal stomachs of persons between 17 and 94 years of age (from forensic autopsy). Results were compared with those of nine patients between 48 and 76 years of age with total gastrectomy for carcinoma of the proximal part of the stomach. Cell counts and morphometric examinations were performed. Results were summarized for the proximal (I), middle (II) and distal (III) one-third of the antrum and for the major (A) and minor (B) curvature side.

In normal stomachs, the G-cell count was 2.52 percent of the total gland cell count in AI; 4.25 percent in AII and 4.77 percent in AIII. In BI, the numbers were 2.5 percent, in BII, 3.73 percent and 4.06 percent in BIII. The D-cell count was 0.47 percent in AI, 0.62 percent in AII and 0.58 percent in AIII. The numbers were 0.44 percent in BI, 0.51 percent in BII and 0.51 percent in BIII. In the antrum of the stomach with carcinoma, the G-cells revealed a nonsignificant 20 to 70 percent lower cell count, while the D-cell count was reduced insignificantly by as much as 35 percent in all areas.

The 5-HT-immunoreactive cell count in normal stomachs is 0.25 percent in AI of the total gland cells, 0.32 percent in AII and 0.39 percent in AIII. In B, it shows numerically no difference to that of A. Contrary to the cell count in normal stomachs, the carcinoma antrum revealed a 200 to 400 percent increase in 5-HT-immunoreactive cell count, highly significant in every area of the antrum. Because 5-HT is known as a growth stimulant, especially for tumors, an increase in 5-HT-immunoreactive cells may be a factor that contributes to the initial histologic changes observed during the early phase of gastric tumor. *Surg. Gynecol. Obstet.*, 1993, 176: 65-72.

THE MEANS for diagnostically assessing the mucosa of the upper part of the gastrointestinal tract have increased greatly and have been differentiated because of routinely taken endoscopic biopsies and through the ability to demonstrate, immunohistochemically, specific bioactive cells in this tissue (1). Both of these developments, however, raise new questions. Is it not necessary to redefine the difference between normal and pathologic tissue? Furthermore, what is the diagnostic validity of a sample as small as that obtained at biopsy? Neither a quantitative nor a qualitative diagnosis seems to be possible from a biopsy sample, for example, because of the frequent focal occurrence of endocrine cells and degeneration in the gastric mucosa (2). However, definition of what is "normal" healthy stomach mucosa is lacking, although it could provide the basis for evaluating pathologic alterations, such as those that occur in carcinoma of the stomach. Although there are numerous histologic and cytologic studies of carcinoma of the stomach, most deal with the tumor and the immediate proximity (3–6) or with the mitotic activity (7). The current study was undertaken to evaluate the histologic factors, immunohistochemically and morphometrically, of specific mucosal cells of the human gastric antrum of normal postmortem stomachs (fresh forensic material and transplantation ma-

From the Gastroenterology Research Laboratories, Walther Straub Institute, Institute of Forensic Medicine, Ludwig Maximilians University, Department of Surgery, Technical University and the Surgical Policlinic, Ludwig Maximilians University, Munich.

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Reprint requests: Dr. G. E. Holle, Ludwig Maximilians University, Gastroenterology Research Laboratories, Walther Straub Institute, Pettenkoferstr. 8a, 8000 Munich 2, Germany.

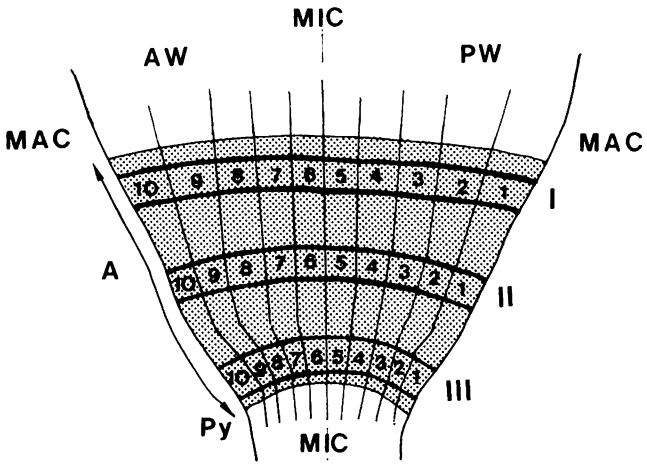

FIG. 1

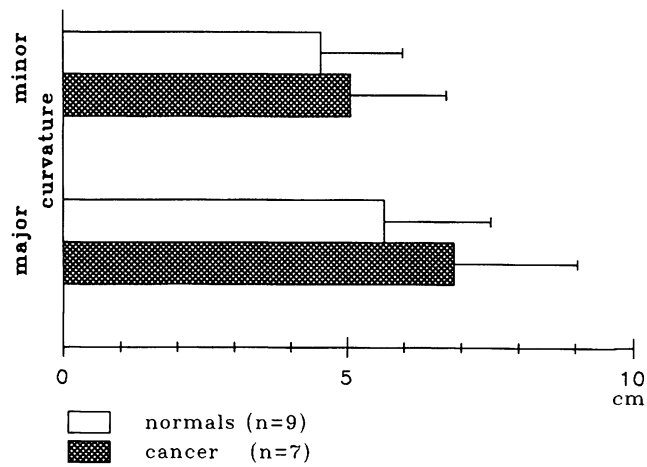

FIG. 2

FIG. 1. Three representative strips from proximal antrum, I (transitional zone), middle antrum, II, and prepyloric antrum, III, of the completely mapped antrum (70 to 100 tissue blocks) were examined for histologic factors, immunohistochemically and morphometrically. *AW*, Anterior wall; *PW*, posterior wall; *A*, antrum; *Py*, pylorus; *MIC*, minor curvature; *MAC*, major curvature, and 1 to 10, tissue blocks.

FIG. 2. Length (distance orad to aborad border) of the histologic antrum measured at the major and minor curvature side. The shrinkage factor (approximately 10 to 15 percent) because of tissue preparation was not taken into account. Open bar, normal stomach (n=9) and cross-hatched bar, stomachs with carcinoma (n=7).

terial); to perform the same examinations on the antrum that is free of tumor of resected stomachs from patients with carcinoma of the gastrointestinal tract whose tumors were located exclusively in the proximal part of the stomach, and to compare the results of both examinations for possible histologic differences.

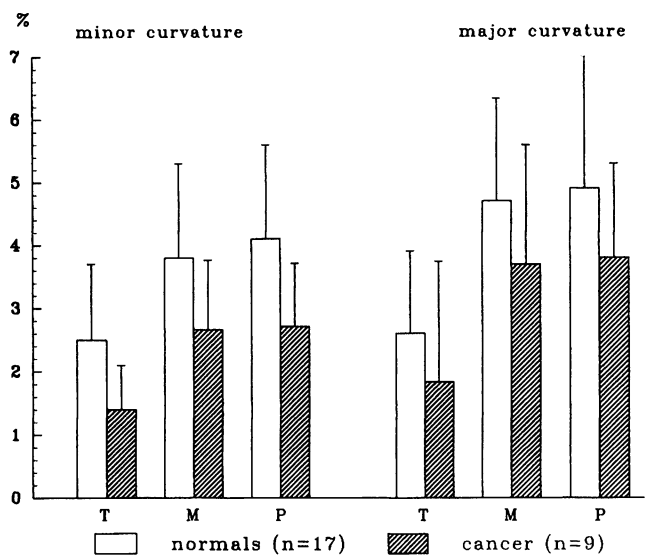

FIG. 3. G-cell count in three areas of the minor and major curvature side each in normal stomach and stomachs with carcinoma.. *T*, Transitional zone, *M*, middle and *P*, prepyloric antrum. G-cell were given as number percent of the total gland cells (8,000 to 12,000 per area counted). Open columns, normal stomach (n=7), and cross-hatched columns, stomachs with carcinoma (n=9).

MATERIALS AND METHODS

Twenty fresh human stomachs from forensic autopsy no later than four hours postmortem or from transplantation were examined. The stomachs came from persons who were between 17 and 94 years of age, who had no gastric symptomatology. The results were compared with those of nine stomachs of patients between 48 and 76 years of age who had carcinoma of the upper part of the stomach and who had undergone total gastrectomy. Ninety percent of the tumors had metastases. In all instances, the antrum was unaffected by the carcinoma.

After removal of the contents, the stomachs were opened at the greater curvature side, washed in ice water, prepared in ten to 12 longitudinal strips (Fig. 1), and fixed in Bouin's fluid for 24 hours. Some strips were fixed in 10 percent formalin solution for 48 hours, dehydrated and embedded in paraffin. From the total antrum, including the corpus-antrum and antrum-duodenum transitional zones (70 to 100 tissue blocks), 5 micrometers thick serial transversal sections (from the surface to the muscle layers) were prepared alternately for differential cell counts as described recently (8) with hematoxylin-eosin for the total gland cells, modified Zimmermann dye for parietal cells, Masson-Fontana for enterochromaffin cells and the peroxidase-antiperoxidase method after Sternberger (9) for gastrin-immunoreactive

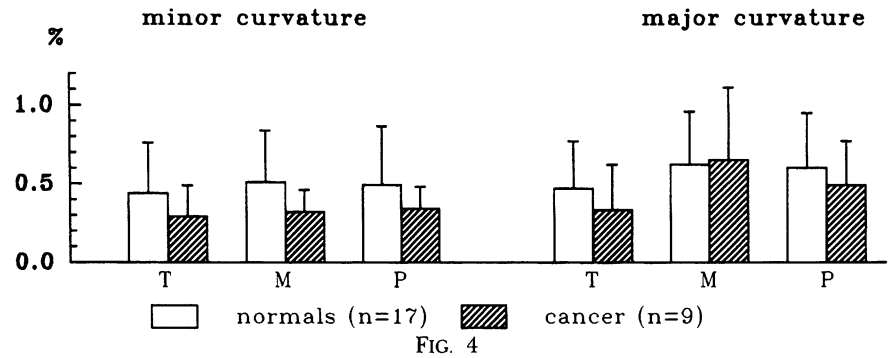

FIG. 4

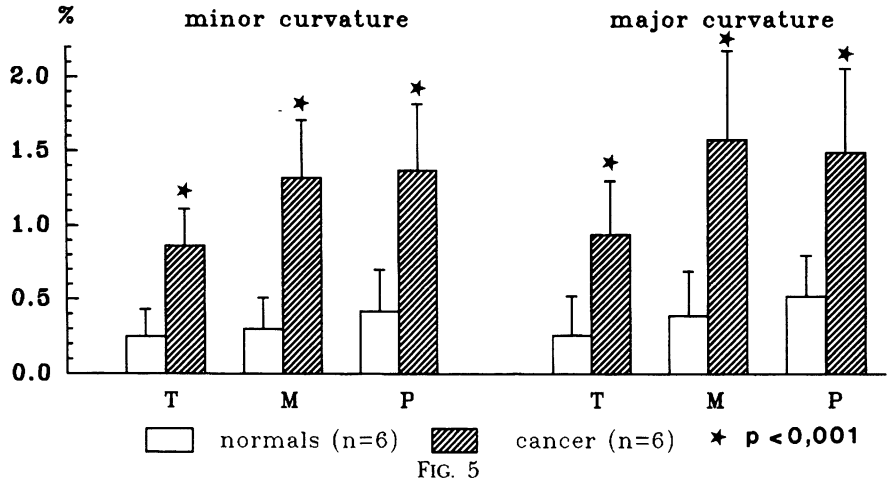

FIG. 5

FIG. 4. D-cell count like G-cell count in Figure 3 from normal stomachs (n=17) and those of patients with carcinoma of the stomach (n=9). *T*, Transitional zone; *M*, middle, and *P*, prepyloric. Open columns, normal stomachs, and cross-hatched columns, stomachs with carcinoma.

FIG. 5. 5-Hydroxytryptamine-immunoreactive cell count from normal stomachs and those of patients with carcinoma of the stomach. The differences are all highly significant ($p<0.001$). *T*, Transitional zone; *M*, middle, and *P*, prepyloric. Open columns, normal stomachs (n=6), and cross-hatched columns, stomachs with carcinoma (n=6).

G-cells, somatostatin-immunoreactive D-cells and 5-hydroxytryptamine-immunoreactive (5-HT-immunoreactive) cells. The antisera came from rabbits after immunization (a) with synthetic human gastrin-17 and gastrin-34 from E. Wünsch prepared and tested by W. G. Forssmann, (b) synthetic somatostatin-28 (octacosapeptide) from E. Wünsch prepared and tested by L. Pradayrol and (c) the serotonin polyclonal antibody PSE 003 (10). Antibodies a and b were diluted 1:1000 and incubated for 72 hours. Antibody c was diluted 1:20 with an incubation time of three hours. Cell counts were done according to the method jointly developed with A. Schauer. In every tissue block, two areas comprising 8,000 to 12,000 nuclei-containing gland cells were counted and the specific cells were identified in alternate sections, outlined, on a drawing microscope, counted and determined as a percentage of the total gland cells. The count method gives as a result the density of the cell population in relation to the total gland cell count in the area counted. The total antrum was completely examined. The oral border line was identified by the occurrence of the pyloric glands, the rapid decrease of parietal cells and the increase of gastrin immunoreactive G-cells. Data were given as mean values of the counting results of the tissue blocks of three representative circular strips of I the proximal, II the middle and III the prepyloric antrum. Minor and major curvature sides were differentiated (Fig. 1).

The length of the antrum (from the proximal transitional zone to the border of the duodenal mucosa) was determined at the minor and major curvature side by measuring the length of the muscularis externa in representative sections of the consecutive tissue blocks. Two parallel longitudinal strips were measured at the major and minor curvature side with the help of the semi-

FIG. 6. VI Gastrin-immunoreactive G-cells (peroxidase-antiperoxidase stain after Sternberger) from the antrum of a 66 year old patient with carcinoma of the proximal part of the stomach show irregular G-cell distribution within the mucosa. Arrows, G-cells in the upper portion of the glands and near the muscularis mucosae. Calibration bar equals 100 micrometers.

computerized Leitz ASM analytical system. The average values from the two strips were given as the actual measurements. This did not take into account the shrinkage factor by the tissue preparation, which amounts to 10 to 15 percent. However, it requires a definite determination of the orad and aborad (proximal and distal) histologic borderline of the antrum.

For statistical analysis, the Student's *t* test for paired values was used. Data are expressed as mean values with standard deviation, with $p>0.05$ indicating significance.

RESULTS

In normal stomachs, the orad-aborad distance of the histologic antrum measured 4.527 ± 1.44 centimeters at the minor curvature side and 5.59 ± 1.6 centimeters at the major curvature side. In the antrum of stomachs with carcinoma, this measurement was 5.165 ± 1.47 centimeters and 6.872 ± 2.16 centimeters, respectively (Fig. 2).

Because the size of the histologic antrum varies greatly, the increased carcinoma antrum did not reach significance. The height of the mucosa measured in zone I was 724 ± 180 micrometers; in zone II, 667 ± 152 micrometers, and in zone III, 647 ± 129 micrometers. In the carcinoma antrum, this measurement was significantly increased and reached $1,168 \pm 201$ micrometers in zone I, $1,136 \pm 161$ micrometers in zone II and $1,102 \pm 226$ micrometers in zone III. The mucosa height decreased from orad to aborad in the antrum of normal stomachs and that of the patients with carcinoma of the stomach. The measurement of the muscularis mucosae was reversed. It increased from orad to aborad and measured 105 ± 28 micrometers in zone I in the normal stomach, and 131 ± 34 and ± 28 micrometers in zone II and III. In the stomachs with carcinoma, the measurements are 130 ± 37 micrometers, 140 ± 37 micrometers and 167 ± 77 micrometers, respectively. The height of the gland-bearing area in the mucosa was 457 to 425 micrometers from orad to aborad in normal stomachs and from 560 to 517 micrometers in the carcinoma antral mucosa. Cell count of the G-cells, D-cells and 5-HT-immunoreactive cells gave results as a mean of the 20 healthy stomachs. At the minor curvature side, the G-cell numbers amounted to 2.5 ± 1.2 percent in zone I, 3.8 ± 1.5 percent in zone II and 4.1 ± 2.1 percent in zone III. At the major curvature side, the values were 2.6 ± 1.3, 4.7 ± 1.6 and 4.9 ± 2.1 percent of the total gland cells, respectively. In the antrum with carcinoma, the G-cell values were insignificantly different from the normal stomachs, even though decreased between 44 and 30 percent at the minor curvature side and between 35 and 21 percent at the major curvature side (Fig. 3).

To exclude deviations due to age differences between the two groups (normal stomachs and carcinomas), we additionally examined normal stomachs from persons between 40 and 94 years of age. This latter group consisted of nine stomachs. It gave a nonsignificant lower G-cell count of 30 percent in zone I and II and of 10 percent in zone III of the antrum in comparison with the total group of normal stomachs (n=20).

Somatostatin immunoreactive D-cell numbers, which are ten times lower than the G-cell numbers in the human antrum of normal stomachs, had values of 0.44 ± 0.32 percent in zone I, $0.51 \pm$

0.33 percent in zone II and 0.52±0.34 percent in the prepyloric zone III at the minor curvature side and 0.47±0.3 percent, 0.63±0.34 percent and 0.6±0.34 percent, respectively, at the major curvature side. In the stomach with carcinoma, the values were approximately 36 percent lower at the minor curvature side and nonsignificantly lower in zones I and III at the major curvature side (Fig. 4). In the D-cell count of the older normal stomachs (n=9), we found a 40 percent lower value in zone I, 28 percent lower value in zone II and 30 percent lower value in zone III of the antrum in comparison with the values of the total normal stomachs (n=20).

The 5-HT-immunoreactive cell numbers displayed contrary behavior. From a cell count of 0.25±0.18 percent in zone I, 0.3±0.21 percent in zone II and 0.42±0.28 percent in zone III at the minor curvature side and a cell count of 0.26±0.2, 0.39±0.3 and 0.52±0.28 percent, respectively, at the major curvature side in the antrum of normal stomachs, these cells were highly significantly increased in the antrum of patients with carcinoma of the gastrointestinal tract in all areas examined between 226 and 340 percent at the minor curvature side and 187 and 305 percent at the major curvature side (Fig. 5). This increase in 5-HT-immunoreactive cell count in the group with carcinoma was still stressed when being compared with the values of the older normal stomachs (n=9), which displayed a decreased 5-HT-immunoreactive cell count compared with the total normal stomachs (n=20).

The *pattern* of the distribution of the bioactive mucosal cells was also altered in the stomach with carcinoma. While in normal stomachs the G-cells were found in a relatively close band over the pyloric glands in the middle one-third of the mucosa, in stomachs with carcinoma, the G-cells are scattered over the entire antral mucosa and were, in single instances, found to be invaded in the muscularis mucosae layer (Fig. 6). On the other hand, the decreased D-cells in the stomach with carcinoma showed focal accumulations, usually in regions of inflammatory infiltration and in the flattened epithelium of cystic degeneration, while on the other side wide areas were unoccupied by D-cells (Fig. 7).

The increased 5-HT-immunoreactive cells were scattered over the entire antral mucosa from the epithelium to the pyloric glands in the antrum of the stomach with carcinoma and sometimes reached the region of the muscularis mucosae (Fig. 8). Although the areas of examination were

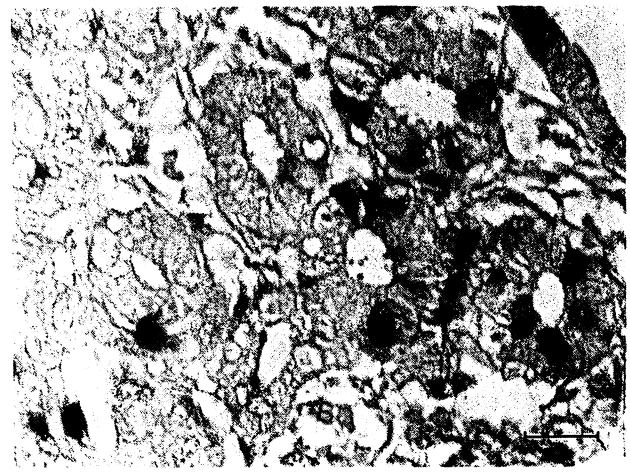

FIG. 7. Somatostatin immunoreactive D-cells (antibody L. Pradayrol, solution 1:1000, incubation time 72 hours). Prepyloric antrum of patient with proximal carcinoma of the stomach. Calibration bar equals 80 micrometers. Peroxidase-antiperoxidase stain after Sternberger.

outside the actual malignant process, all types of degeneration could be found in the antral mucosa (Fig. 9): hyperplasia and dysplasia of the glands with cystic dilatation, necrobiosis of the superficial epithelium in some instances, intestinal metaplasia of all degrees and also inflammatory infiltrations and fibrosis. All together, the hyperplastic gastropathy increase the mucosal thickness by 61 to 70 percent. The severity of the changes increased according to the proximity of the tumor, while the 5-HT-immunoreactive cell count showed the highest 5-HT-immunoreactive cell frequency in the distal parts of the antrum away from the tumor (Fig. 5).

It is worth mentioning that we could not find a single antrum without any alterations, even in the mucosa of normal stomachs. In young volunteers, for example, 17 years of age, there are mostly focal infiltrations, sometimes invading in a small band the entire mucosal thickness. Only in the elderly did we observed focal intestinalization of the epithelium, as well as inflammatory infiltration through the entire wall or more expanded under the surface epithelium.

DISCUSSION

On the basis of the current study of the normal stomach of healthy persons, some features have to be considered as regular phenomena. One such conspicuous feature is the manifestation of a limited number of endocrine cells in a type-specific distribution in the gastric mucosa. For the G-cells, the values range from 2.5±1.2 to 4.9±2.1 percent of the glandular cells counted

FIG. 8. 5-Hydroxytryptamine-immunoreactive cell hyperplasia in the prepyloric antrum of a patient with carcinoma of the proximal part of the stomach. Calibration bar equals 80 micrometers. Peroxidase-antiperoxidase stain after Sternberger.

in the gastric antrum, found in a band shape in the middle one-third of the mucosa above the pyloric glands. In the results of an earlier study on material taken at biopsy from healthy persons and from patients with ulcers in the duodenum and gastrointestinal tract, we determined that the lower limit for hyperplasia was around 10 percent G-cell count (11). In the present study of the entire mapped antrum, we found that the number of G-cells in the stomach of an older, but healthy, person was between 10 to 20 percent lower, but not significantly reduced. The localization within the mucosa was also normal, although these stomachs were occasionally marked by islands of intestinal metaplasia.

The somatostatin immunoreactive D-cells, of which there were a power of ten fewer than the G-cells, are distributed in the antrum over the entire mucosa, but concentrated in the lower two-thirds, where they gave a cell count of 0.545 percent. An increase of up to 1.95 percent D-cells has been described from biopsies of the antrum in stomachs with ulcers in the gastrointestinal tract after selective proximal vagotomy (12). A pathologic increase in D-cells in the entire upper part of the gastrointestinal tract was also reported (8). In the older but normal stomachs (n=9), a nonsignificant decrease of D-cells of approximately 30 percent compared with the total normal stomachs (n=20) can be observed in this study. In normal antrum mucosa, the 5-HT-immunoreactive cells are also primarily found in the basal portion of the mucosa, where the 5-HT-containing enterochromaffin cells can be stained with silver and chromium salts (13, 14). The 5-HT-immunoreactive cells are, in contrast with the enterochromaffin cells, also frequently present in the upper sections of the mucosa and are of the "open" cell type (Fig. 8). In the current study, in normal stomachs, these specific bioactive cells were never encountered outside the mucosa and were never dislocated within it. They were numerically nonsignificantly reduced between 18 and 40 percent in the selected group of the older normal stomachs (n=9).

In contrast with these definite criteria of the physiologic state, the finding of focal lymphocyte and plasmacyte infiltration in adolescents and the focal manifestation of intestinalization in the antrum of the stomach of older, but healthy, persons are so common that a limited number of biopsy samples do not suffice to reliably indicate a pathologic state.

One criterion that can be derived from comparison of results for stomachs with carcinoma is that the antrum of the stomach with carcinoma is large. The expanded proximal carcinomas in the present study do not permit a reliable estimate of the size of the entire stomach. One investigator (15) described the stomach with gastric ulcer and stomach with carcinoma with a mean size of 715 square centimeters as being small in comparison with a normal one with a mean size of 803 square centimeters and with those with duodenal ulcers with a mean size of 938 square centimeters. Therefore, the dimensions we determined must indicate an enlarged antrum, defined by histologic factors in a stomach with carcinoma.

Although G-cell and D-cell counts are low in the antral mucosa in a stomach with carcinoma, they are still in the lower range of normal. This can partly be explained by the lower G- and D-cell count, which was found in the selected group of older normal probands. The group with carcinoma ranged in age between 48 and 76 years. The stomach with carcinoma is subacid.

We know that serotonin inhibits the release of stomach acid and gastrin (16) and possibly also the maturation of G-cells. The reason for the alteration in the cell distribution within the mucosa may be the degeneration of the antrum mucosa in carcinoma of the stomach. It is questionable whether or not this also explains the invasion of endocrine cells near the muscularis mucosae.

The extensive 5-HT-immunoreactive cell hyperplasia in the antral mucosa of all the stomachs with carcinoma we studied was impressive, probably a manifestation of the disease. Based on the results of earlier studies of carcinomas of the stomach, argentaffin cells were present in carcinomas and surrounding tissue in from less than 2 percent (17, 18) to 31 percent of the instances (3). The results of subsequent immunohistochemical studies showed scattered serotonin containing tumor cells in 31 percent of the adenocarcinomas; they were always restricted to small areas of the tumor (19). Mitosis of these cells was never demonstrated (7, 19). Despite this, we cannot explain why a 5-HT-immunoreactive cell can mature in an undifferentiated adenocarcinoma. Some possible mechanisms are described; for example, cell fusions between carcinoma and enterochromaffin cells (19, 20).

From the G-cells, we know that they are absent in intestinalized glands (21). The 5-HT-immunoreactive cells seen in poor differentiated adenocarcinoma may arise from mucosal stem cells still equipped to generate differentiating cells within the tumor. The occurrence of 5-HT-immunoreactive cells in undifferentiated tumors is actually rare (focal appearance only in some tumors). This is in contrast with the regularly observed 5-HT-immunoreactive cell hyperplasia in the antrum of the stomachs with carcinoma, most marked in areas away from the tumor. It is also worth mentioning that the intestinal degenerations observed in the gastric antrum of stomachs with carcinoma occurred more frequently in the more proximal portion of the antrum near the tumor.

From all of these observations, we conclude that the antrum mucosa of the stomach with carcinoma is the primary site of 5-HT-immunoreactive cell hyperplasia. The significant increase in 5-HT-immunoreactive cells and the enlarged antrum in the stomach with carcinoma is a source of overproduction of serotonin. It has been shown that intraperitoneal injections of small doses (10 micrograms per kilogram) of serotonin result in an increase of the cell mitotic rate selectively in the tumor (22). The 5-HT-immunoreactive cell hyperplasia described in the present study contributes to the tumor growth and possibly to the initial tumor development in the human stomach. This initial tumor development, however, seems to evolve particularly in areas in which the mucosal degeneration is most marked.

FIG. 9. Intestinalization of the glands, cystic degeneration and inflammatory infiltration in the middle antrum of a patient with a adenocarcinoma of the proximal part of the stomach. Hematoxylin and eosin stain. Calibration bar equals 100 micrometers.

SUMMARY

Examination of the completely mapped antrum revealed in the normal stomach (n=20) an endocrine cell count of gastrin immunoreactive G-cells of 2.52, 4.25 and 4.77 percent in relation with the total epithelial cell count in the upper (I), middle (II) and prepyloric (III) region of the antral mucosa at the minor curvature side. Corresponding somatostatin immunoreactive D-cell count showed 0.47 and 0.51 percent, respec-

tively, and 5-HT-immunoreactive cell counts were 0.25, 0.32 and 0.39 percent, respectively. In comparison, cell count of the antrum in proximally located carcinoma of the stomach showed nonsignificant lower G-cells (minus 20 to 70 percent) and D-cells (minus 35 percent), but displayed increased 5-HT-immunoreactive cell numbers by 200 to 400 percent ($p<0.0001$) in the entire antrum, most frequently in the region away from the tumor, while inflammatory degeneration was mostly pronounced near the tumor.

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