

# GASTROENTEROLOGY

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## Diffuse Somatostatin-Immunoreactive D-Cell Hyperplasia in the Stomach and Duodenum

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*This paper presents the first case of extensive, diffuse, somatostatin-immunoreactive D-cell hyperplasia in the human stomach and duodenum. It occurred in a 37-yr-old woman, who showed clinical signs of dwarfism, obesity, dryness of the mouth, and goiter. The density of the distribution of D cells was increased 39-fold in the stomach fundus, 23-fold in the proximal antrum, 25-fold in the distal antrum, and 31-fold in the upper duodenum in comparison with normal values. At the same time, the gastrin-immunoreactive cells were increased 2.3-fold in the antrum. Although the range in size of the D cells was within normal limits in all regions examined, the G cells showed pronounced hypertrophy of up to 127%. A possible relationship between the immuno-histochemical findings and the clinical picture is discussed.*

Somatostatin is widely distributed in neurons and fibers in the central nervous system, especially in the hypothalamic region (1) and throughout the nervous

system of the digestive tract. It is also produced and stored in considerable amounts in the D cells in the intestinal mucosa and in the pancreas (2,3). Here, it may act (in part) in a paracrine, mainly inhibitory manner (4), but stimulated somatostatin also enters the circulation (5). Somatostatin controls hormones of the gastrointestinal tract and the pancreas (6), the endocrine function of the anterior pituitary (7), the thyroid gland (8), the salivary gland (9), and the urinary excretory system. It achieves homeostasis of nutrients in a wide range (10,11) and influences functional maturation, growth, and behavior (12-14).

Taking into account some deviations in different laboratories, somatostatin blood levels are highest in the portal vein at 100 pg/ml. This is a clear indication of the extensive production of somatostatin in the upper gastrointestinal tract. In the general circulation, physiologic levels in the fasting state are  $\sim 29 \pm 5$  pg/ml, and in the postprandial state after carbohydrate, protein, and fat they are  $48 \pm 7$ ,  $74 \pm 8$ , and  $80 \pm 9$  pg/ml, respectively (15). The level is highest after a mixed meal (16). At these levels somatostatin influences insulin and glucagon release, indicating its endocrine function (17). The somatostatin present in the cerebrospinal fluid ranges  $\sim 35.4$  pg/ml (18).

Since 1979, pathological increased levels of circulating somatostatin have been described in sporadic cases of solid somatostatin tumors and in somatostatinomas containing subpopulations of other endocrine cells (19,20). Like gastrinomas, the tumors were mostly malignant and with few exceptions were predominantly located in the pancreas: two tumors in the duodenum (21,22) and one in the jejunum (23). The clinical symptoms were heterogeneous and depended on the serum somatostatin levels and probably on the composition of the different molecular weight forms of the circulating

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An extract of this paper was presented at the 18th meeting of the European Association of Gastroenterology and Endoscopy and was awarded the first prize for the best presentation, March 14, 1986.

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hormones (24,25), the hormonal heterogeneity of some somatostatinomas, and probably on the varying degrees of target organ resistance to the increased hormone levels (26).

### Case Report

A 37-yr-old woman died suddenly exhibiting nausea and dyspnea. An autopsy was performed within 6 h. The fresh, macroscopically inconspicuous stomach was prepared for the purpose of studying the normal distribution of special cell populations, including the peptide hormone cells in the stomach mucosa.

Retrospective inquiry into the case history revealed the following. From early infancy on, the woman showed retarded growth, but she was slender until puberty. Later, she became obese. She was hypokinetic and except for an appendectomy, a tonsillectomy, and a motoring accident 7 mo before death, she never felt ill. She sometimes used contraceptives and had irregular menstrual cycles. On the whole, she displayed retarded sexual behavior and became increasingly lethargic and sleepy. Weight, and especially thirst, increased continuously until they reached pathological levels (>3L/day of liquids, some of which was cola-flavored soda). At death she was 146 cm tall and weighed 97 kg.

During the time when she was hospitalized for her accident, the following was observed: extreme dryness of the oral cavity and an unstable blood pressure reading between 120/80 mmHg and 180/110 mmHg. Some abnormal laboratory results were available from the 4–6-mo period before death (numbers in parentheses are normal values):  $\alpha_2$ -globulin, 12.30 relative % (4.7–9.5 relative %); serum cholesterol, 243 mg/dl (<220 mg/dl);  $\gamma$ -glutamyl-transpeptidase, 27.4 U/L (4–18 U/L); potassium level, 3.29 mmol/L (3.5–5.0 mmol/L). Urinalysis and creatinine clearance, as well as fasting glucose levels (82.0 and 95.0 mg/dl, normal = 50–120 mg/dl), were normal. She had very fragile bones with very thin corticalis. A slight trauma resulted in a humerus fracture followed by a very prolonged healing process.

Autopsy showed bilateral pulmonary embolism as the cause of death. The weights of various organs were as follows: brain, 1394 g; heart, 394 g; lungs, 660 g; liver, 2115 g; and spleen, 256 g. The enlargements were between 7% and 46%. The pancreas was of normal size and weight, she had a nodular goiter of considerable size, and abscess cavities were found at the upper pole of the left kidney.

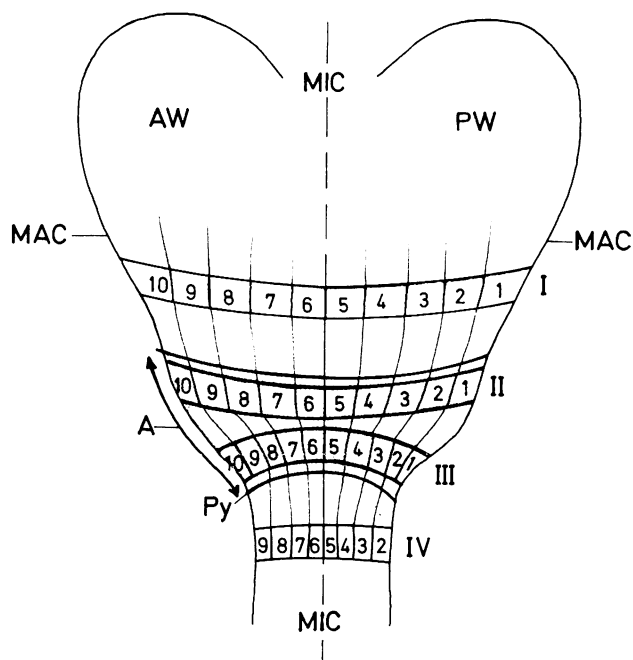
### Materials and Methods

After removal of its contents, the stomach was opened at the greater curvature, washed in ice water, prepared in 10 longitudinal strips, fixed in Bouin's fluid for 24 h, dehydrated, and embedded in paraffin. From the total material (including corpus-fundus, the total antrum, and the upper duodenum), complete sagittal sections from the surface to the muscle layers were prepared alternately as follows for differential cell counts: (a) hematoxylin and eosin dye for the total gland cells; (b) modified Zimmermann dye for the parietal cells and mucous neck cells;

(c) Masson–Fontana for the enterochromaffin cells; and (d) the peroxidase-antiperoxidase method after Sternberger (27) for gastrin-immunoreactive cells and somatostatin-immunoreactive cells.

The antisera came from rabbits after immunization with (a) synthetic human gastrin 17 and 34 from E. Wunsch (prepared and tested by W. G. Forssmann) and (b) synthetic somatostatin 28 (octacosapeptide) from E. Wunsch. L. Pradayrol prepared and tested the somatostatin 28 antibody serum by radioimmunoassay to exclude cross-reactivity against 18 gastrointestinal hormones at the 100-ng level. All antisera were used in a dilution of 1:1000, with an incubation time of 72 h. Sections incubated with antiserum inactivated by addition of an excess of the respective antigen (50  $\mu$ g of synthetic somatostatin 28 per milliliter of diluted antiserum) were used as controls.

Cell counts were carried out according to the method jointly developed with A. Schauer (28). In an area of 5000–8000 nuclei-containing gland cells, the specific cells were identified on a drawing microscope, outlined, counted, and determined by percentage of the total number of gland cells. The count method gives as a result the density of the cell population in the tissue. Each counted tissue block (~2 cm in length) was subdivided into an oral and aboral measuring area. The total antrum was exam-



AW	Anterior Wall	I	Fundus
PW	Posterior Wall	II	prox. Antrum
A	Antrum	III	dist. Antrum
Py	Pylorus	IV	Duodenum
MIC	minor curvature side	1-10	tissue blocks
MAC	major curvature side		

Figure 1. Diagram of the measuring fields in the stomach fundus-corpus, the proximal and distal antrum, and the proximal duodenum. Every numbered tissue block is subdivided into an oral and aboral measuring area.



Size of Somatostatin i.r. D-Cells in the stomach Fundus, prox. Antrum, dist. Antrum and Duodenum

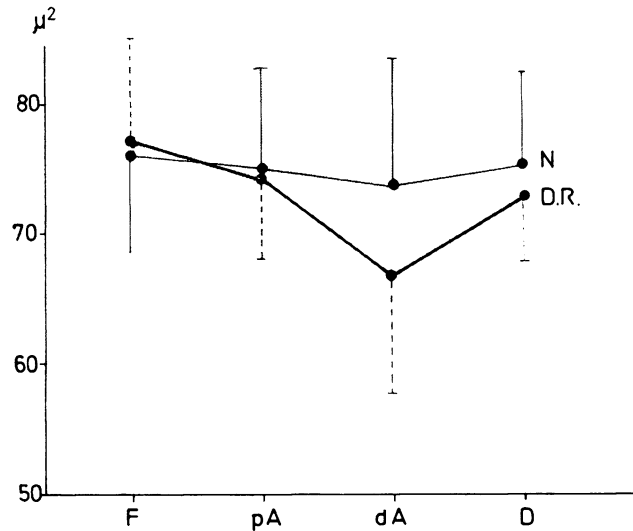
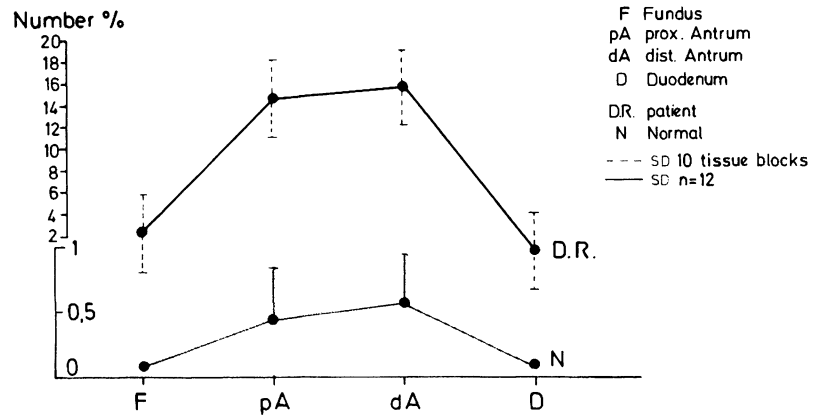


Figure 2. Evaluation of somatostatin-immunoreactive D cells in the upper gastrointestinal tract of patient D.R. in comparison with normal values (N). Top panel: size of D cells ascertained as an average of 100–150 cells. Bottom panel: percentage of D-cell population of each in an area of 500–8000 total mucosal gland cells.



Number % of Somatostatin i.r. D-Cell Population in the Stomach Fundus, Antrum and Duodenum

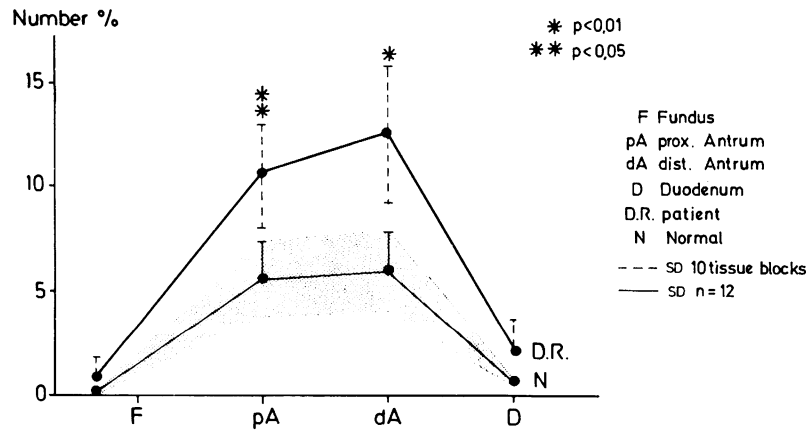
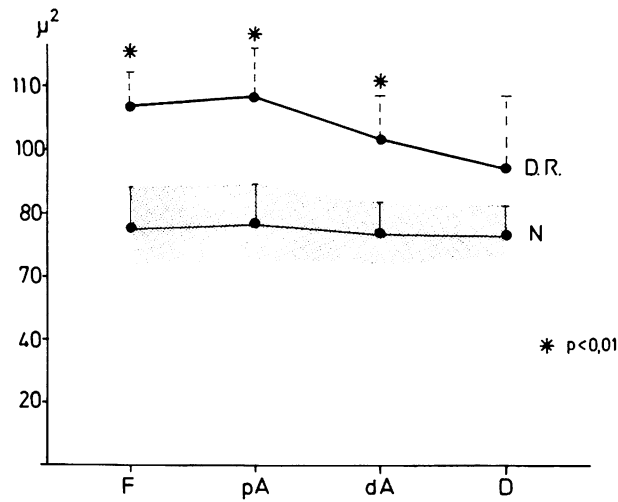
ined completely. Counting results for our patient were given from four representative circular strips: (a) the distal fundus, (b) the proximal antrum, (c) the distal antrum, and (d) the proximal duodenum (Figure 1). The data express the mean values of the results of all measured areas of the 10 and 8 tissue blocks from each total circumference.

G cells and D cells were surface analyzed using the semicomputerized Leitz ASM analytical system. The mean values of 100–150 nucleus-containing cells were determined for each examination. The mucosal thickness and the length of the histologic antrum were determined with the same equipment. The control values for comparison were taken from a separate study on the normal distribution of gastrin- and somatostatin-immunoreactive cells in the human stomach from 12 healthy subjects of different age and sex who died in accidents (G. E. Holle et al., in preparation). Bioptic material was also compared from peptic ulcer patients preoperatively and postoperatively (29,30).

**Results**

In the present case, the stomach was of normal size and shape. The length of the histologic antrum ranged from 4.5 cm at the lesser curvature to 6.2 cm at the major curvature. The mucosal thickness was  $1066 \pm 118 \mu\text{m}$  in the stomach fundus,  $869 \pm 73 \mu\text{m}$  in the proximal antrum, and  $833 \pm 63 \mu\text{m}$  in the distal antrum. The tubular-shaped course of the fundus glands showed high parietal cell numbers which were between 20% and 30% of the total number of fundus gland cells. The anatomic arrangement of the pyloric glands was regular. Likewise, scattered islets with inflammatory infiltration in the gastric antrum were within the normal range. The density of the somatostatin-immunoreactive D-cell population was  $2.38\% \pm 1.78\%$  in the fundus-corporus,  $14.46\% \pm 2.89\%$  in the proximal antrum,

### Size of Gastrin i.r. Cells in the Stomach Fundus, Antrum and Duodenum



### Number % of Gastrin i.r. Cell Population in the Stomach Fundus, Antrum and Duodenum

15.58%  $\pm$  3.59% in the distal antrum, and 1.53%  $\pm$  0.57% in the proximal duodenum. In comparison with the density of the somatostatin-immunoreactive cells in normal stomachs (0.06% in the fundus, 0.62% in the antrum, and 0.07% in the upper duodenum), this means a 39-fold increase in the density of the somatostatin-immunoreactive cells in the stomach fundus, a 23-fold increase in the proximal antrum, a 25-fold increase in the distal antrum, and a 21-fold increase in the upper duodenum (Figure 2).

In all regions, the size of the somatostatin-immunoreactive D cells was normal, with  $77 \pm 9 \mu\text{m}^2$  in the fundus,  $74 \pm 7 \mu\text{m}^2$  in the proximal antrum,  $65 \pm 9 \mu\text{m}^2$  in the distal antrum, and  $73 \pm 5 \mu\text{m}^2$  in the upper duodenum. In the antrum, somatostatin-immunoreactive D-cell sizes had a tendency to become smaller from the oral to the aboral area, but the differences are not significant.

In comparison to D-cell distribution, the fundus-

corpus showed only a few scattered G cells. The G cells in the proximal antrum amounted to 10.51%  $\pm$  2.58%, in the distal antrum 12.51%  $\pm$  3.34%, and in the proximal duodenum 1.95%  $\pm$  0.99%. This means a 2.3-fold increase in the number of G cells over the normal values. In addition, the G-cell sizes were increased by  $\sim$ 127% compared with normals, with mean values of  $106 \pm 4.8 \mu\text{m}^2$  in the stomach fundus,  $108 \pm 7.6 \mu\text{m}^2$  in the proximal antrum,  $102 \pm 7.33 \mu\text{m}^2$  in the distal antrum, and  $94 \pm 13 \mu\text{m}^2$  in the upper duodenum (Figure 3). The somatostatin/gastrin quotient, which is normally  $\sim$ 0.12, was far above 1 in all test regions.

### Discussion

The present study gives the first description of an excessive, diffuse somatostatin-immunoreactive D-cell hyperplasia in the stomach and duodenum,

Figure 3. Evaluation of gastrin immunoreactive cells in the upper gastrointestinal tract of patient D.R. in comparison with normal values (N). Top panel: size of G cells ascertained as an average of 150 cells. Bottom panel: percentage of G-cell population of each in an area of 5000–8000 total mucosal gland cells.

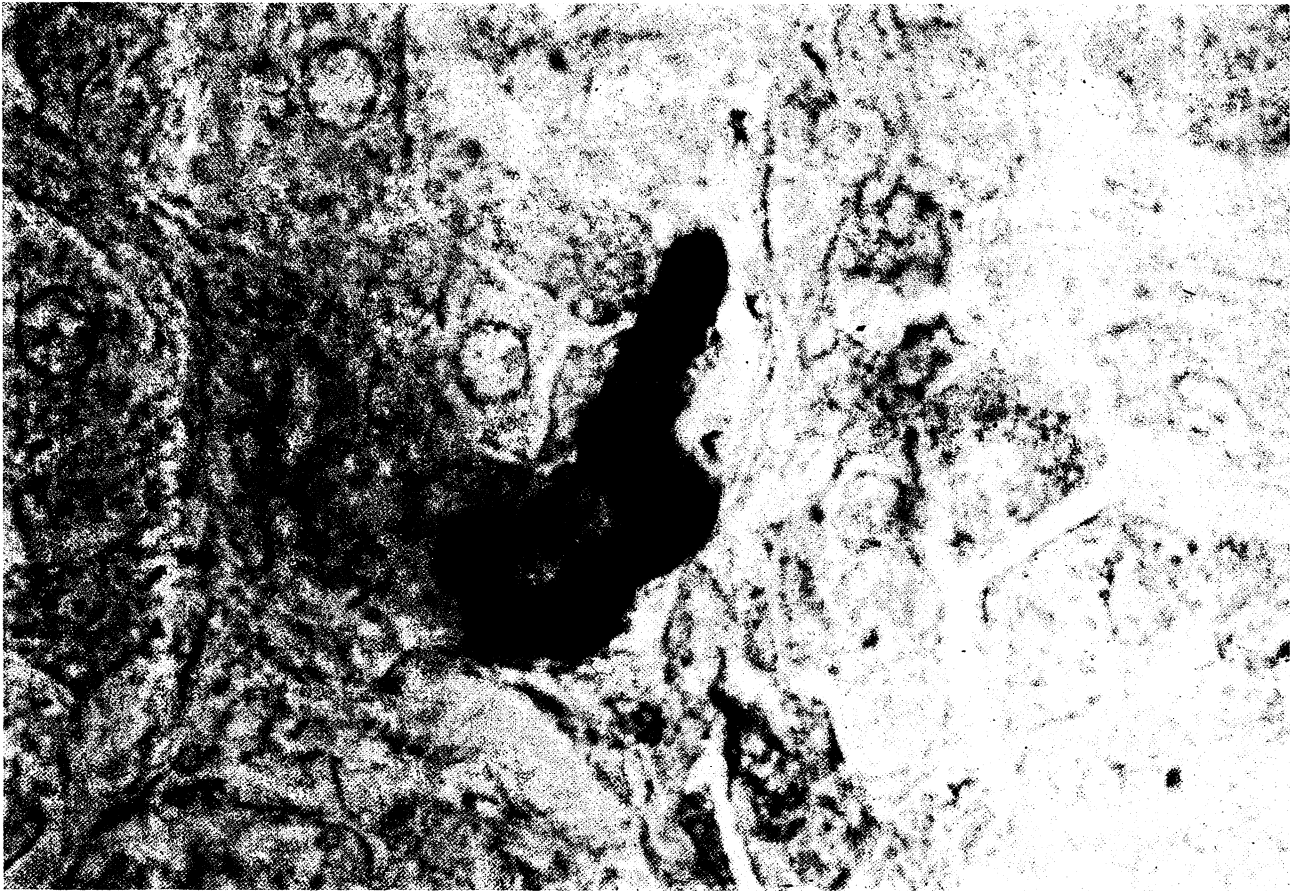


Figure 4. D cells in the stomach fundus-corpora approximate to parietal and chief cells. Stain: PAP,  $1 \times 1000$ .

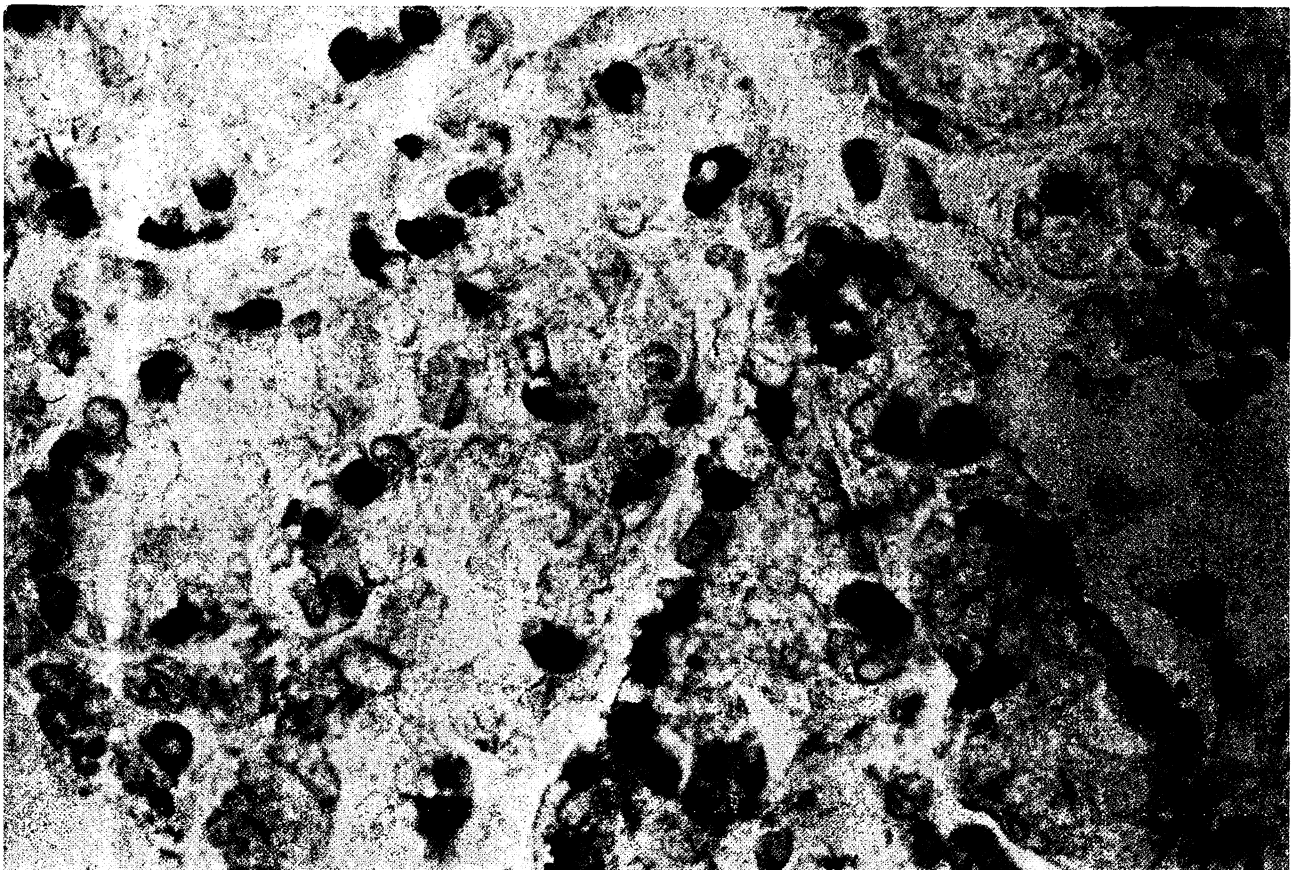


Figure 5. D-cell hyperplasia in the stomach antrum. Stain: PAP,  $1 \times 250$ .

with values between 20 and 40 times above normal. The diagnosis was ascertained postmortem in a woman with multiple clinical features, e.g., dwarfism (the height of an 11-yr-old female child), obesity, dryness of the mouth, and goiter. There was no evidence available as to whether a possible retarded splanchnic circulation resulting from an increased serum somatostatin level was responsible for the thrombosis.

The cytochemistry showed strong reactivity with somatostatin 28 antibody serum (Figures 4 and 5). L. Pradayrol detected, extracted, and described the structure of somatostatin 28 from the intestine (31), as we recognize somatostatin 28 as the main biologically active molecular form in the intestine (32). Hypothalamus and pancreas have been found to contain equimolar amounts of somatostatin 14 and somatostatin 28 (33). However, somatostatin 28 binds with 3.2 times greater affinity to receptors involved in the control of growth hormone secretion, and it acts there without prior cleavage to the smaller molecule (34). We should assume that in our case, somatostatin 28 predominated in the mucosa of the stomach and duodenum as well as in the general circulation.

Analogous to the elevated serum-gastrin levels in Zollinger–Ellison syndrome and antral G-cell hyperplasia, we conclude from the extensive somatostatin cell hyperplasia in the upper gastrointestinal tract of our patient, that elevated serum somatostatin levels may have been present. As our patient underwent continuous stimulation through polyphagia, we are even more convinced. Pathological increases of somatostatin serum levels of between 40-fold and 100-fold greater than normal values are known from somatostatinomas (9000–1300 pg/ml). These were accompanied by very low basal serum growth hormone levels (0.8 ng/ml), without any response to stimulation in hypothalamic and pituitary functional tests (20,21).

In considering the retarded growth of our patient in relation to a possible hypersomatostatinemia, we conclude that the endocrine abnormality in the upper gastrointestinal tract must have existed since early infancy, possibly as a developmental defect (35). It is known that circulating hormones have the ability to interfere with certain centers in the central nervous system (36). Especially in the paraventricular region of the third ventricle, highly permeable fenestrated capillaries pierce the blood-brain barrier (37) and permit a throttling of the growth hormone release and thyrotropin release (possibly also growth hormone releasing hormone) through chronically increased somatostatin blood levels (38,39). A parallel mechanism is known from ectopic growth hormone releasing hormone-producing tu-

mors accompanied by acromegaly (40,41). The latter can be influenced by somatostatin administration into the general circulation.

Further research, especially concerning circulating somatostatin serum levels [for example, in idiopathic growth hormone deficiency patients (42) or in disorders of the thyrotropin releasing hormone-thyrotropin system], could probably help to clarify syndromes like the one under discussion. By this connection, the mucosa of the gastrointestinal tract should be recognized as an integral endocrine organ, and a gut-brain axis can be assumed.

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