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Oxyntic endocrine cells of hypergastrinaemic patients. Differential response to antrectomy or octreotide

T D'Adda, B Annibale, G Delle Fave, C Bordi

Abstract

***Background/aims*—To evaluate the response of endocrine cells of the gastric oxyntic mucosa in hypergastrinaemic patients to either antrectomy or treatment with the somatostatin analogue octreotide.**

***Patients*—(a) Two patients with enterochromaffin-like (ECL) cell carcinoid and chronic atrophic gastritis, treated with antrectomy; (b) four patients with Zollinger-Ellison syndrome, treated with octreotide.**

***Methods*—Oxyntic endocrine cells were examined by ultrastructural morphometry on full thickness biopsy specimens taken: (a) before and four months after antrectomy, (b) before and after three months' treatment with octreotide 200 μg daily.**

***Results*—Both treatments induced prompt, significant reduction of gastrinaemia and a significant decrease of the volume density of the whole endocrine cell mass and of the cross sectional area of all nucleated endocrine cell profiles (antrectomy: −38%, $p<0·04$ and −31%, $p<0·04$, respectively; octreotide: −59%, $<0·007$ and −26%, $<0·04$, respectively). Assessment of the relative proportion of individual endocrine cell types showed a different response to antrectomy or octreotide. After antrectomy, in fact, only the volume fraction of ECL cells was significantly reduced, from 56·5% to 22·5% (−60%, $p<0·04$). After octreotide treatment, in contrast, the proportion of all endocrine cell types remained remarkably constant, showing that all cell types took part in the observed overall decrease.**

***Conclusions*—Postantrectomy reduction of oxyntic endocrine cells mostly reflects the withdrawal of the specific trophic stimulus of hypergastrinaemia on ECL cells. In contrast, the inhibitory response to octreotide seems to be exerted on virtually all types of oxyntic endocrine cells, probably reflecting a universal occurrence of somatostatin receptors.**

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Keywords: antrectomy, octreotide, hypergastrinaemia, enterochromaffin-like cells, gastric carcinoids, somatostatin receptors.

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Enterochromaffin-like (ECL) cells of the oxyntic (fundic) mucosa of the stomach are one of the main targets of the trophic stimulus of gastrin and proliferate in response to chronic hypergastrinaemia.[1] This is well reported not only in experimental conditions, including longterm administration of inhibitors of gastric acid secretion,[2–7] but also in human hypergastrinaemic states, such as Zollinger-Ellison syndrome and chronic atrophic gastritis.[8–12] The persistent stimulus of longstanding hypergastrinaemia, therefore, leads to ECL cell hyperplasia, which may progress to dysplasia and, eventually, evolve into carcinoid tumours.[13–17]

In different clinical settings, two procedures, antrectomy and octreotide administration, have been proposed for the control of ECL cell growths associated with hypergastrinaemia. Antrectomy removes the bulk of gastrin producing G cells, therefore leading to the normalisation of serum gastrin concentrations. Its ability in inducing regression of fundic endocrine cell hyperplasia and, even, ECL cell carcinoids has been reported.[18–21] Octreotide, the most widely used somatostatin analogue, is known to inhibit proliferations that depend on the stimulus of trophic hormones.[22] Its effectiveness in lowering gastrin concentrations and in leading to the regression of fundic endocrine cell growths has been proved both in rodents[23] and in humans,[24] although the relation between these two effects has not been properly investigated yet.

In previous studies, however, the oxyntic endocrine cell regression was investigated with light microscopy alone, a methodology not permitting discrimination between ECL cells and the other types of endocrine cells of the oxyntic mucosa in humans. For this purpose, only electron microscopy, identifying the characteristics of the cell secretory granules, is adequate.[25] In this paper, therefore, we have applied ultrastructural morphometry, the unique methodology that simultaneously provides quantitative data and reliable identification of each endocrine cell profile, with the aim of evaluating the specific fundic endocrine cell type(s) target of the inhibitory effects of antrectomy and octreotide. The study was performed on biopsy specimens of oxyntic mucosa collected before and after treatment from six hypergastrinaemic patients, two that underwent antrectomy as a part of treatment for ECL cell gastric carcinoids, and four treated with octreotide for Zollinger-Ellison syndrome

Methods

PATIENTS AND TREATMENT

The study was performed in the following six

TABLE I *Blood concentrations of fasting gastrin (ng/l)* in chronic atrophic gastritis (n=2) and Zollinger-Ellison syndrome (n=4) patients before and after (antrectomy) or during (octreotide) treatment*

Patient	Sex	Age (y)	Before treatment†	After/During treatment (days) 7	30	60	90‡/120§
Chronic atrophic gastritis/antrectomy							
1	M	72	1100	81	255	216	130
2	F	45	1150	20	10	15	20
Zollinger-Ellison syndrome/octreotide							
3	M	38	7750	6800	2300	3000	12500
4	F	59	315	45	90	65	120
5	M	56	472	280	250	300	425
6	M	60	2650	360	310	800	1312

*Normal values <100 ng/l. †Data are the mean value of at least three blood samples collected before the beginning of treatment. ‡After octreotide treatment. §After antrectomy.

patients, all showing high fasting concentrations of circulating gastrin before treatment (Table I): (a) two patients underwent Billroth II gastric resection, inclusive of antrectomy, for ECL cell carcinoid(s) of the gastric body in chronic atrophic gastritis. Pernicious anaemia was present only in patient 1. Data from one of these cases have been previously reported as single case study;[26] (b) four patients affected by Zollinger-Ellison syndrome were treated for three months with the somatostatin analogue octreotide (SMS 201-995, Sandoz, Milan, Italy), given subcutaneously in two doses of 100 μg at 7 am and 7 pm, respectively. All patients showed positive test for secretin stimulated gastrin release, corresponding to an at least 200 ng/l increase of blood gastrin over basal values after intravenous bolus of 2 U/kg secretin (Bachem, Bubendorf, Switzerland). They were not affected by multiple endocrine neoplasia type 1. During treatment, one patient did not require further antisecretory therapy, while the others received famotidine in daily doses ranging from 30 to 60 mg. All pharmacological treatments were suspended at least 24 hours before blood and biopsy specimen collection. These cases were part of previous studies on light microscopy morphometry of endocrine cells and on gastric acid secretion.[24 27]

STUDY DESIGN

Tissue sampling for electron microscopy

For each patient, three biopsy specimens were obtained from the mid part of the gastric body mucosa, along the great curvature, approximately 4–5 cm from the corpus-antrum border. Endoscopy examinations were performed: (a) before and four months after antrectomy; (b) before and after three months of octreotide treatment.

Biopsy specimens were immediately fixed in Karnovsky's solution (4% paraformaldehyde and 5% glutaraldehyde in 0·1 M phosphate buffer, pH 7·2), for three hours at room temperature, postfixed in 1% osmium tetroxide, dehydrated in graded acetone, and embedded in Araldite. Thin sections were collected on Formvar-coated Robertson multiple-slot grids, having a slot width of 75 μm, stained with uranyl acetate and lead citrate, and examined in a Zeiss EM 109 electron microscope.

Ultrastructural morphometry

The methodology applied in this study is essentially the same used in previous works from our laboratory.[25 28 29] For each of the three fundic biopsy specimens, one mucosal area comprised between two bars of the Robertson grid was analysed. Only fields comprising the whole thickness of the mucosa, from muscularis mucosae to the superficial epithelium, and not including areas of intestinal metaplasia or lymphoid nodules, were selected for the morphometric evaluation. For each selected area, low magnification electron micrographs (890×) were sequentially mounted to reconstruct the entire thickness of the mucosa. The very same section was then carefully scanned at higher magnification and micrographs (12 500×) of all endocrine profiles were taken. All the morphometric evaluations were then performed by the point-counting method, using a Weibel's grid (measuring 224×199 mm and containing 896 sampling points) superimposed on electron micrographs. This morphometric procedure provided quantitative data on the whole endocrine population of the fundic mucosa of the stomach, consisting of an estimate of the fractional volume of all endocrine cell profiles, using the epithelial compartment as the reference volume, and the cross sectional area of nucleated endocrine profiles. In addition, the respective proportion of each specific endocrine cell type (ECL, EC, D, X, P, non-granulated) in the whole endocrine cell population was evaluated. Ultrastructural criteria used for identification of the various endocrine cell types are described in our previous paper.[25 30] According to recent criteria for gastric endocrine cell classification,[31] however, cells formerly identified as D_1 have been mostly classified as X cells. The fraction of cytoplasm occupied by organelles such as secretory granules, rough endoplasmic reticulum, Golgi apparatus, lysosomes, vacuoles, and cisternae filled with proteinaceous material, were also quantitatively evaluated.

Statistical analysis

All the results were expressed as median and range of data obtained from the three fields morphometrically analysed in each patient. Comparisons between pre- and post-treatment values (12 determinations in Zollinger-Ellison syndrome and six in chronic atrophic gastritis patients at each time) were performed by the two tailed Wilcoxon signed rank test. p Values less than 0·05 were considered significant.

Results

GASTRIN VALUES

After antrectomy

In both patients, blood gastrin concentrations were considerably reduced one week after surgery (Table I; Fig 1). Such decrease reached a stable state four months after antrectomy, and still persisted 10–12 months later (data not shown).

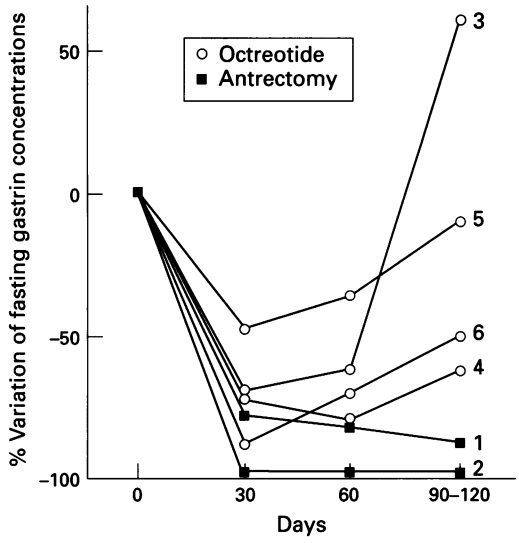

Figure 1: Variation of serum gastrin concentrations, expressed as per cent of the pre-treatment value, during three months' period of octreotide administration and four months' period after antrectomy.

After octreotide

In all four patients, blood gastrin concentrations were promptly reduced by the treatment, reaching their maximum decrease within one month (Table I; Fig 1). However, normal values of gastrin were obtained in only one case. Though with pronounced variations from one patient to another, a progressive escape of this inhibitory effect was found in all cases in later periods of treatment (Table I; Fig 1).

ELECTRON MICROSCOPY

General morphometric data

The fractional volumes of epithelium and lamina propria were not significantly modified by either treatments (Table II). A significant decrease of the volume density of the whole endocrine cell population and of the cross sectional area of nucleated endocrine cell profiles was apparent in both groups of patients (Table III). Table IV shows the evolution of the former parameter in individual patients.

Morphometry of individual endocrine cell types

After antrectomy, only ECL cells showed a significant regression of their volume density (Table V). A relative post-treatment increase in the volume density of P and X cells was found, although the statistical significance was reached only in the case of P cells (Table V). After octreotide, in contrast, the relative distribution of the different endocrine cell types remained remarkably constant (Table V), showing that the decrease in the volume density of the entire endocrine cell population was distributed over different cell types, including ECL, EC, P, and D cells. Analysis of the evolution of the volume fraction of ECL cells in individual patients (Table VI) showed a post-treatment decrease, although consistently below the values found after antrectomy, in at least two patients. Thus, in these cases ECL cells regressed more than the average of other cell types. It is worth noting that such a more pronounced decrease of ECL cells was absent in the single patient characterised by total escape of the gastrin lowering effects of octreotide.

TABLE II *Volumetric composition of the oxyntic mucosa of chronic atrophic gastritis (n=2) and Zollinger-Ellison syndrome (n=4) patients before and after the respective treatment*

	Before treatment	*After treatment*	*p Value*
Chronic atrophic gastritis/antrectomy			
Epithelium (%)*	57·1 (46·1–73·1)	72·0 (54·0–81·0)	NS
Lamina propria (%)*	42·9 (26·9–53·9)	28·0 (19·0–46·0)	NS
Zollinger-Ellison syndrome/octreotide			
Epithelium (%)*	64·0 (41·1–73·4)	61·8 (43·5–73·3)	NS
Lamina propria (%)*	36·0 (26·6–58·9)	38·2 (26·7–56·5)	NS

Comparisons have been based on three determinations for each patient and for each time and have been performed with the Wilcoxon test. NS: not significant. *Values are expressed as medians (range).

TABLE III *Ultrastructural morphometry of the whole fundic endocrine cell population in chronic atrophic gastritis (n=2) and Zollinger-Ellison syndrome (n=4) patients, before and after the respective treatment*

	Before treatment	*After treatment*	*p Value*
Chronic atrophic gastritis/antrectomy			
Volume density*	4.2 (2.5-15.3)	2.6 (1.9-3.9)	0.03
CSA†	51.8 (42.3-69.8)	35.7 (29.6-42.7)	0.03
Zollinger-Ellison syndrome/octreotide			
Volume density*	2.7 (0.8-11.7)	1.1 (0.6-4.0)	0.007
CSA†	53.0 (44.7-81.3)	39.4 (27.1-68.1)	0.03

Comparisons have been based on three determinations for each patient and for each time and have been performed with the Wilcoxon test. Values expressed as medians (range).
*Expressed as percentage, the reference volume being the epithelial compartment.
†CSA, cross sectional area of nucleated cell profiles, expressed in μm^2.

Cytological findings of ECL cells

None of the cytoplasmic organelles investigated, including secretory granules, rough endoplasmic reticulum, Golgi apparatus, lysosomes, and vacuoles were significantly changed by either treatments (data not shown). Punctate secretory granules, a finding restricted to ECL cells in hypergastrinaemic states,[32] were present in a subset of ECL cells

TABLE IV *After treatment evolution of the volume density* of the whole fundic endocrine cell population in individual patients with chronic atrophic gastritis or Zollinger-Ellison syndrome*

Patient	*Before treatment*	*After treatment*	*Difference (%)*
Chronic atrophic gastritis/antrectomy			
1	4·3	2·7	−36
2	3·5	2·5	−30
Zollinger-Ellison syndrome/octreotide			
3	9·5	3·4	−64
4	2·4	0·8	−67
5	3·6	1·4	−59
6	2·4	1·1	−53

*Expressed as percentage, the reference volume being the epithelial compartment. Each value represents the median of three determinations.

TABLE V *Quantitative distribution of the different endocrine cell types* in chronic atrophic gastritis (n=2) and Zollinger-Ellison syndrome (n=4) patients, before and after the respective treatment*

	Before treatment	After treatment	p Value
Chronic atrophic gastritis/antrectomy			
ECL cells	56·5 (26·1–73·6)	22·5 (0·6–38·0)	0·03
EC cells	6·1 (0·6–31·0)	3·8 (2·1–7·1)	NS
D cells	1·8 (0–16·4)	4·2 (0–13·7)	NS
P cells	8·0 (3·5–18·4)	23·7 (11·2–38·8)	0·03
G cells	6·4 (0–22·7)	4·8 (0·3–15·8)	NS
X cells	2·4 (0–6·1)	9·9 (0–43·8)	NS
Non-granulated cells	18·9 (12·0–49·2)	31·0 (12·7–43·9)	NS
Zollinger-Ellison syndrome/octreotide			
ECL cells	65·8 (37·5–76·4)	63·5 (33·9–76·7)	NS
EC cells	4·8 (0–21·7)	3·4 (0–11·0)	NS
D cells	3·3 (0–16·8)	3·3 (0–17·7)	NS
P cells	5·1 (0–20·7)	6·2 (0–39·3)	NS
X cells	0·4 (0–3·2)	1·3 (0–16·5)	NS
Non granulated cells	20·6 (6·3–36·1)	22·1 (12·6–35·3)	NS

Comparisons have been based on three determinations for each patient and for each time and have been performed with the Wilcoxon test. NS: not significant. *Data are expressed as percentage of the total endocrine cell area (range).

in the Zollinger-Ellison syndrome patient having the highest basal values of gastrin (7750 ng/l) and were not modified by octreotide treatment. Before treatment, intracytoplasmic vacuoles (Fig 2) were a prominent feature of ECL cells in four cases, two with chronic atrophic gastritis and two with Zollinger-Ellison syndrome (up to 33·0% of the cytoplasmic volume). They were considerably reduced in three patients, after either antrectomy or octreotide. Cisternae filled with proteinaceous material were well represented in the cytoplasm of ECL cells of two Zollinger-Ellison syndrome cases before octreotide (1·75% and 2·71% of the cytoplasmic volume, respectively) (Fig 3a) and were not significantly modified after treatment (0·58% and 2·53% of the cytoplasmic volume, respectively) (Fig 3b).

Discussion

Our results show a different response of fundic endocrine cells to antrectomy and octreotide, supporting different mechanisms of inhibition of the cell proliferation associated with hypergastrinaemia by the two procedures. The study confirmed that both treatments are able to cause substantial reduction, or even normalisation, of serum gastrin values in humans. Gastrin stimulates the proliferation of ECL cells,[5] mostly through mitotic self replication of mature cells as shown by experiments in rodents.[4 33] Withdrawal of the gastrin trophic stimulus, therefore, has been regarded as the most reasonable factor responsible for the overall quantitative decrease of fundic endocrine cells seen in previous light microscopic studies after correction of hypergastrinaemia.[20 21 24] In full agreement with these results, our ultrastructural data show that antrectomy and octreotide exert the same effects on the whole endocrine cell population, reflected by global reduction of the volume density and cross sectional area of nucleated endocrine cell profiles.

Previous studies based on non-specific light microscopy stainings, however, were unable to discriminate between the different, functionally heterogeneous types of endocrine cells of the human oxyntic mucosa. In this regard, the crucial advantage of this study using ultrastructural morphometry resides in its ability of evaluating the involvement of individual cell types in the fundic endocrine cell regression that follows antrectomy or octreotide. Although deteminations performed in very thin mucosal areas inherent in our methodology coupled with the uneven distribution of oxyntic endocrine cells may expose to potential sampling errors, we have repeatedly proved the reproducibility of data obtained with ultrastructural morphometry by showing their consistent relation with those yielded in the same patients by light microscopy morphometry of sections stained for endocrine cells from differently processed biopsy specimens.[29 30] A similar relation was obtained also in this study (data not shown).

Using ultrastructural morphometry, therefore, we have been able to show that the effects of the two treatments on fundic endocrine cell types were different. Despite the limitations inherent in the small number of cases of such a rare condition, antrectomy was found to induce selective, significant regression of ECL cells, by reducing both volume density and cross sectional area of these cells. This result is explained by the loss of the specific trophic effect exerted by gastrin on ECL cells.[1 28 34] Thus, antrectomy can be considered as a model in which the withdrawal of a trophic stimulus (hypergastrinaemia) directly induces regression of the specific target cell (ECL cells). Elucidation of this mechanism is important in that antrectomy has been found to induce not only inhibition of ECL cell hyperplasia, as confirmed by this study, but also regression and, even, disappearance of gastrin dependent ECL cell carcinoid tumors.[18 19 21] Administration of gastrin receptor antagonists may represent an additional, probably more specific model for studying the effects of withdrawal of gastrin activity on ECL cells. To date, however, these drugs have been used only in animal studies,[6 35] none of which discriminated among ECL cells and other oxyntic endocrine cell types.

TABLE VI *After treatment evolution of the ECL cell volume fraction* in individual patients with chronic atrophic gastritis or Zollinger-Ellison syndrome*

Patient	Before treatment	After treatment	Difference (%)
Chronic atrophic gastritis/antrectomy			
1	35·0	23·4	−33
2	68·4	21·3	−69
Zollinger-Ellison syndrome/octreotide			
3	61·9	67·3	9
4	65·1	47·6	−27
5	68·4	54·5	−20
6	73·9	68·5	−7

*Expressed as percentage of the total endocrine cell area.

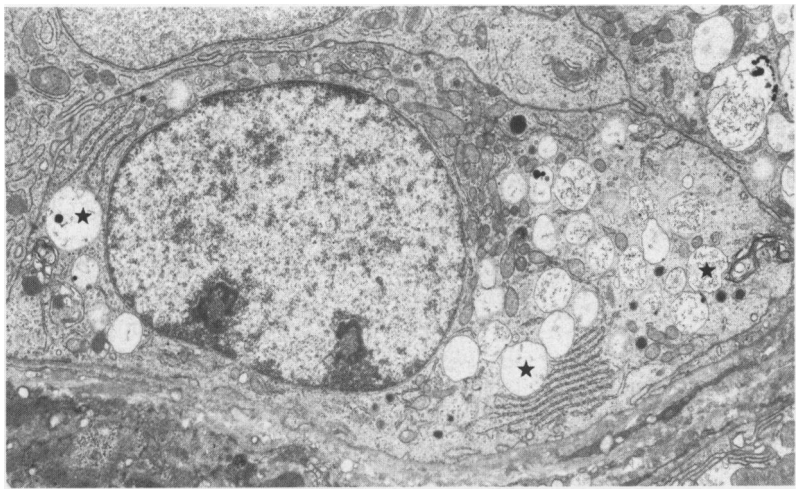

Figure 2: Pre-treatment abundance of intracytoplasmic vacuoles (stars) in an ECL cell of a Zollinger-Ellison syndrome patient, in which the vacuole cytoplasmic fraction was reduced from 33·0% to 1·6% after octreotide administration (×6840).

On the contrary, the relative proportion between the different types of fundic endocrine cells remained virtually identical after octreotide treatment. This result shows that the overall decrease in endocrine cell volume density was distributed over most cell types, including ECL, EC, P, and D cells. It follows that the trophic inhibitory activity exerted by the drug is effective on all these types and probably reflects the almost universal occurrence of somatostatin receptors in the heterogeneous endocrine cell population of the oxyntic mucosa. Five different subtypes of human somatostatin receptors have been recently cloned and octreotide was found to have high affinity for the subtype 2 (SSTR2).[36] Our data, therefore, support the expression of SSTR2 in human oxyntic endocrine cells, a finding in agreement with the recent demonstration of these somatostatin receptors in ECL cells of the rat.[37] These findings suggest a direct inhibitory effect of octreotide on human ECL cell proliferation.

To what extent the concomitant lowering of gastrin and its trophic effect may contribute to the inhibition of proliferating ECL cells in octreotide treated hypergastrinaemic patients is difficult to evaluate. Results of previous studies, either experimental or in Zollinger-Ellison syndrome patients, are controversial. Even if variations in methodology and drug dose should be taken into account, studies in omeprazole stimulated rats supported a direct inhibitory effect of somatostatin analogues on ECL cells, without concomitant decrease of circulating gastrin.[38–40] In contrast, data from loxtidine treated mastomys[23] and from Zollinger-Ellison syndrome patients[41] suggest an indirect effect mediated by the decrease of circulating gastrin. Our results support a potentiating role of gastrin lowering in ECL cell regression after octreotide treatment. In fact, the post-treatment decrease of the volume fraction of ECL cells in some Zollinger-Ellison syndrome patients indicates that these cells regressed more than the average of other cell types. In addition, such a more pronounced ECL cell decrease was not seen in the single patient in which total escape of the gastrin lowering effect of the drug was found.

Thus, it is conceivable that the inhibitory activity of octreotide on ECL cells depends on a combination of indirect (lowering of gastrin concentrations) and direct (through somatostatin receptors) effects, as already postulated to explain the mechanism through which somatostatin analogues inhibit tumour growth in a variety of experimental tumour models.[22] The specific affinity of octreotide for SSTR2 receptors is of clinical relevance because octreotide treatment was found to be effective only in human endocrine tumours expressing these receptors.[36] Our results may support the potential effectiveness of the drug in carcinoid tumours originating from ECL cells, as found by Modlin *et al*[23] in gastrin dependent ECLomas of the rodent mastomys. It should be noted, however, that a single patient affected by Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1 was reported to develop fundic carcinoids during longlasting treatment with octreotide and omeprazole.[17]

The absolute decrease of the D cell volume density after octreotide (as shown by the persistence of the same cell fraction in an endocrine cell population reduced by 59%) supports the existence of somatostatin receptors on human fundic D cells. This hypothesis is in agreement with the finding of similar receptors on canine fundic D cells by Park *et al.*[42] In that study these receptors were found to be involved in autoregulation of fundic D cell secretion as confirmed by the ability of somatostatin to inhibit its own release from these cells. By analogy, our results suggest that somatostatin can also autoregulate the trophism of the very same cell from which it is secreted.

The relative volume fraction of P and X cells was found to be increased after antrectomy, although statistical significance was obtained only for the first of these. As they refer to a cell population that was greatly reduced as a whole, these results do not imply an absolute increase of these cells but, at least, show that P and,

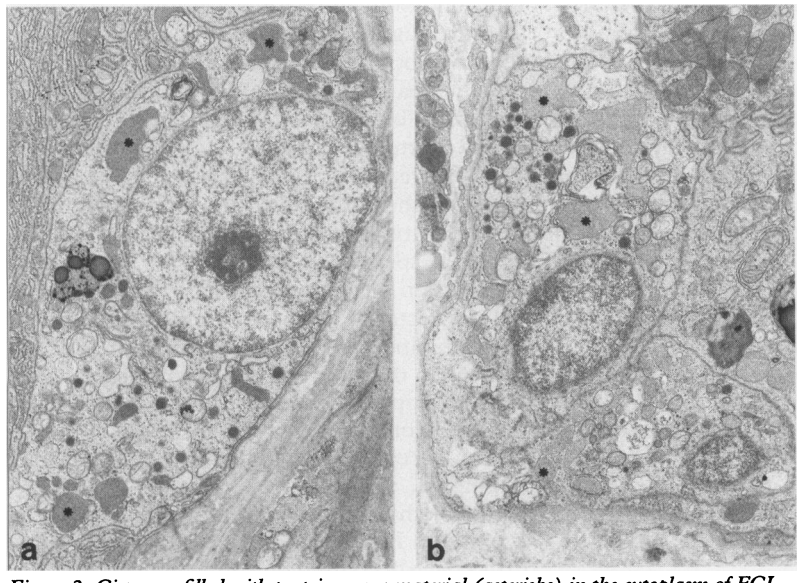

Figure 3: Cisternae filled with proteinaceous material (asterisks) in the cytoplasm of ECL cells of the same Zollinger-Ellison syndrome patient before (a) and after (b) three months' treatment with octreotide (×6510).

probably, X cells are insensitive to withdrawal of the trophic stimulus of hypergastrinaemia.

It is known that in chronic atrophic gastritis patients G cells, normally located in the antral mucosa, commonly occur in areas of pseudopyloric metaplasia of the body-fundus mucosa, where they are associated with typical ECL cells.[43 44] In our study such heterotopical G cells were not significantly influenced by antrectomy. They may be responsible for the postantrectomy persistence of slightly increased serum gastrin concentrations in one of our patients. Such persistence, however, did not prevent the regression of ECL cell proliferation.

Some cases showed peculiar ultrastructural findings of ECL cells. Cytoplasmic vacuoles were abundant in four patients, including the two with chronic atrophic gastritis, and were decreased in three cases after either antrectomy or octreotide treatment. As, in the rat, similar vacuoles have been found to reflect the cell content of histamine,[45] our results suggest that both treatments may decrease the histamine content of ECL cells. This hypothesis is in accordance with data from experimental studies showing decrease of histidine decarboxylase activity and histamine concentration in the oxyntic mucosa consistent with a decreased histamine production by ECL cells after administration of somatostatin analogues.[38 39] In two Zollinger-Ellison syndrome patients, ECL cells were characterised by occurrence of endoplasmic cisternae filled with proteinaceous material, a finding pointing to derangement of the cell protein synthesis. This change was not influenced by octreotide treatment. Nevertheless, its consistent demonstration in samples taken at three month intervals shows the longterm persistence of a changed ECL cell function in Zollinger-Ellison syndrome patients, which has never been reported before.

In conclusion, we have found that the overall regression of fundic endocrine cell proliferation induced by antrectomy and octreotide in hypergastrinaemic conditions, implied a different cell response to the two treatments. In fact, antrectomy selectively induced regression of ECL cells, showing inhibition of endocrine growth by removal of the trophic effects exerted by gastrin. On the contrary, octreotide inhibited virtually all fundic endocrine cell types, a finding probably reflecting the universal occurrence of somatostatin receptors on these cells.

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