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Ultrastructural characterization of fundic endocrine cell hyperplasia associated with atrophic gastritis and hypergastrinaemia *

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Summary. Clinical and experimental evidence indicates that carcinoid tumours of the stomach fundic mucosa represent another example of hormone-dependent neoplasm, gastrin being the hormone involved in tumour induction. In this context hyperplasia of fundic endocrine cells associated with chronic atrophic gastritis (CAG) and hypergastrinaemia is regarded as the most frequent preneoplastic lesion. However, the cell type involved in this hyperplasia has not been clarified. To elucidate this problem fundic endocrine cells were characterized ultrastructurally in 9 patients from which endoscopic gastric biopsies were obtained. ECL cells were the most frequent cell type in 8 cases, in 4 of which they were more numerous than all other cell types taken together. D_1 cells were the most frequent type in one case while they were inconspicuous in the other cases. P cells were found with a frequency in each case intermediate between that of ECL cells and that of D_1 cells. These results indicate that fundic endocrine cell hyperplasia occurring in hypergastrinaemic CAG is in most cases cytologically similar to that found in other hypergastrinemic conditions, in which the gastrin-dependent ECL cells were already found to prevail. They also explain why fundic carcinoids arising in CAG are mostly composed of ECL cells. The relation between ECL, D_1 and P cells, if any, remains obscure.

Key words: Fundic mucosa – Endocrine cells – Atrophic gastritis – Gastrin – Trophic effect

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Abbreviations: EC, enterochromaffin cells, producing 5-hydroxytryptamine; ECL, enterochromaffin-like cells; D, somatostatin producing cells; D_1, cells with small granules showing some characteristics of granules of D cells; P, cells with small granules similar to those of pulmonary (P) endocrine cells; X, gastric endocrine cells with large, dense granules. Unless specified, the secretory product of these cells is unknown

The original suggestion that proliferative changes of endocrine cells of the stomach fundic mucosa may be dependent on the concomitant hypergastrinaemic levels of antral or extragastric origin (Bordi et al. 1975, 1976) has received growing support from several lines of evidence. Hyperplasia of fundic endocrine cells, in fact, was constantly seen in a series of patients with the longstanding severe hypergastrinaemia associated with the Zollinger-Ellison syndrome (ZES) (Solcia et al. 1980b). Several cases of fundic carcinoids associated with the same pathological condition have been reported (Solcia et al. 1970; Bordi et al. 1976; Rosai 1979; Carney et al. 1983) supporting the oncologic potential of such hyperplasia. In addition, hyperplasia and neoplasia of fundic endocrine cells were repeatedly found in patients with chronic atrophic gastritis (CAG) with or without pernicious anaemia (Larsson et al. 1978; Wilander 1981; Hodges et al. 1981; Harvey et al. 1985). In this condition an apparently obligate association with hypergastrinaemia was observed in all cases of fundic carcinoid tumours reported to date (Bordi et al. 1986). Finally, endocrine cell hyperplasia and carcinoid tumours of the fundic mucosa have recently been induced in rats during long-term, pharmacological inhibition of gastric acid secretion (Ekman et al. 1985). In full agreement with a leading role of gastrin in these experiments antrectomy was found to prevent the proliferation of fundic endocrine cells (Larsson et al. 1985).

From these observations carcinoid tumours of the fundic mucosa, which are malignant in a significant number of cases (Borch et al. 1985), may be regarded as a newly recognized example of hormone-dependent neoplasm. In this context, fundic endocrine cell hyperplasia represents the preneoplastic step in the series of events leading to the development of neoplasia (Solcia et al. 1979; Carney et al. 1980; Borch et al. 1985). However, previous studies suggested that the hyperplastic endocrine cell type may differ on the basis of the associated clinical or experimental condition. The cell type involved in the ZES as well as in rats given inhibitors of gastric acid secretion was identified as the ECL cell (Bordi et al. 1974; Solcia et al. 1975, 1979, 1980; Ekman et al. 1985), whose gastrin dependence is well recognized (Hakanson et al. 1976). In contrast, the cell type responsible for the endocrine cell proliferation in patients with CAG is questioned and frequently identified with the D_1 or the P cells (Rubin 1973; Solcia et al. 1975, 1979, 1980; Bordi et al. 1978, 1983). In addition, with the exception of a few cases in a previous paper from this laboratory (Bordi et al. 1978), the relation between gastrin levels and the type of hyperplastic endocrine cells in atrophic fundic mucosa was not investigated in previous studies. Therefore, the purpose of the present study is to provide the ultrastructural characterization of fundic endocrine cells in a series of 9 patients with endocrine cell hyperplasia and CAG of the fundic mucosa and with proven hypergastrinaemia.

Materials and methods

Patients. During routine histological examination of endoscopic gastric biopsies from unselected patients with upper gastrointestinal symptoms, 18 cases of severe hyperplasia of fundic

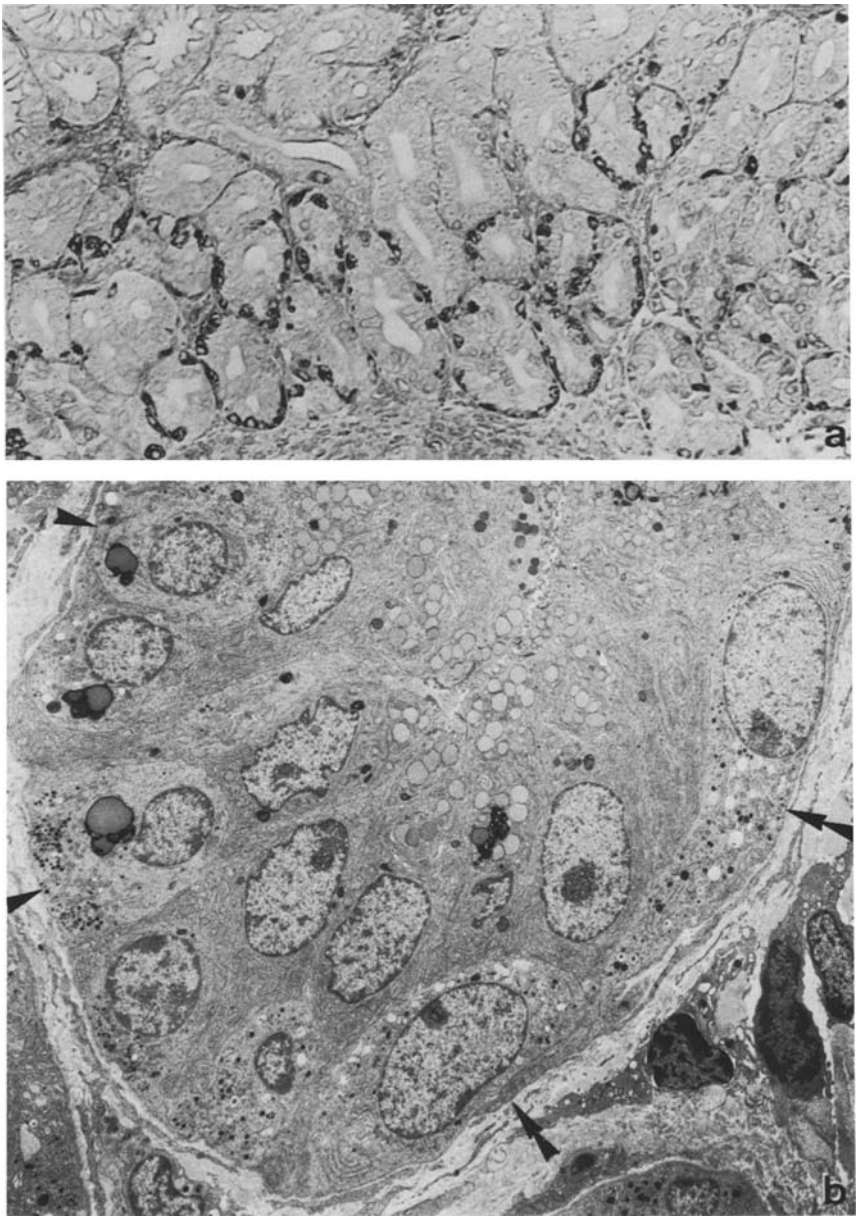

Fig. 1 a, b. Case 3. **a** Intraglandular hyperplasia of argyrophil cells in the atrophic fundic mucosa. Grimelius, ×230. **b** Ultrastructural survey of the bottom of a gland with numerous endocrine cells including both D_1 cells (*single arrowheads*) with prominent lipofuscin-like bodies and ECL cells (*double arrowheads*) with typical vacuolated granules and parallel arrays of rough endoplasmic reticulum. ×5,000

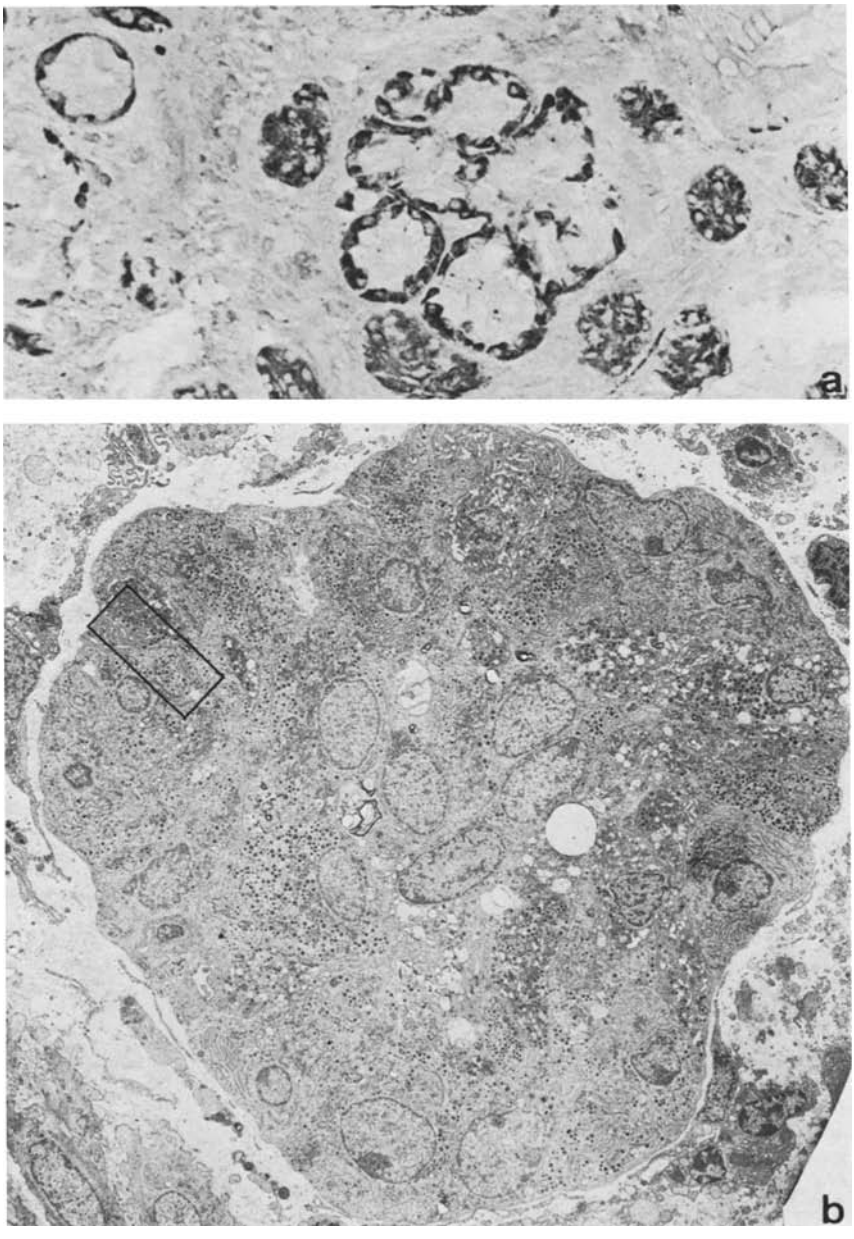

Fig. 2a, b. Case 6. **a** Argyrophil cell hyperplasia with numerous extraglandular nodules. Grimelius, ×270. **b** Ultrastructure of a nodule with granulated cells mostly identified as ECL cells with non vacuolated granules. For the granule ultrastructure see enlargement of the squared area in Fig. 3b. ×3,000

argyrophil cells associated with atrophic gastritis were identified with the use of the Grimelius silver method for argyrophil cells (Fig. 1a and 2a). When investigated, serum levels of gastrin were found to be constantly elevated and hypo- or, most commonly, achlorhydria was present. Only one patient showed pernicious anaemia, a condition frequently associated with fundic

endocrine cell hyperplasia in other series (Rubin, 1969; Borch et al. 1985). The detailed study of 18 patients is reported elsewhere (Bordi et al. 1986). Among these patients 9, from which informed consent was obtained, underwent a new endoscopic examination for the present ultrastructural investigation. All of them showed elevated blood levels of gastrin. Antral mucosa was regarded as the source of the hypergastrinaemia since G cell hyperplasia was demonstrated by immunocytochemistry in all patients. In addition, one of them (case No. 6) was found to have a duodenal carcinoid tumour showing a scattered population of gastrin-containing cells. Removal of this tumour without concomitant antrectomy, however, failed to induce a significant decrease of the patient's circulating gastrin. Another patient (case No. 1), also affected by extragastric plasmocytoma, presented hyperplastic gastric polyps. Gastric cancer or peptic ulcer were absent in all patients.

Methods. Gastric endoscopy was performed by standard techniques, with Olympus GIF-Q and GIF-B_3 fiberscopes. Three to four biopsy specimens were taken from the gastric body and antrum. Specimens from the body were taken rather high to avoid enlarged antral mucosa or intermediate zone between fundic and antral mucosa. Immediately after recovery, the specimens were cut perpendicular to the mucosal surface, into two fragments with the use of a razor blade: one fragment was processed for electron microscopy and was fixed in Karnovsky's (1963) paraformaldehyde-glutaraldehyde solution in 0.1 M phosphate buffer pH 7.3, post-fixed in 1% osmium tetroxide and embedded in Araldite. Thin sections, stained with uranyl acetate and lead citrate, were viewed under a Siemens Elmiskop 1A or a Zeiss EM 109 electron microscope. The other fragment was used for optical cytological investigations and was fixed in Bouin's fluid for six hours and embedded in paraffin. Sections cut at 6 μm were stained with haematoxylin-eosin, periodic acid-Schiff-alcian blue, Grimelius (1968) and Sevier-Munger (1965) methods for argyrophil cells, lead-haematoxylin (Solcia et al. 1969) for endocrine cells. In addition, immunocytochemical investigations using antisera against chromogranin, gastrin, somatostatin, glucagon (N-terminal region reacting with both pancreatic glucagon and intestinal glucagon-like material) were done, as detailed elsewhere (Bordi et al. 1986).

The ultrastructural identification of fundic endocrine cells was accomplished following the criteria described below. In each case a minimum of 100 (range 101–182, mean 143) cell profiles were sampled in non intestinalized areas of the fundic mucosa. All cells were photographed and examined on printed micrographs at a final magnification of 15,000×. The proportion of different cell populations in the fundic mucosa was expressed as a percentage.

Results

Differential ultrastructural characteristics of fundic endocrine cells

The present study mostly relies on the distinctive ultrastructural features of the different cell types which provided the basis for the cell classification. Therefore, these features, largely concerned with the structure of secretory granules, will first be specified. Guidelines for the cell characterization were provided by the studies of Solcia and his group (Vassallo et al. 1971; Capella et al. 1971, 1978; Solcia et al. 1975, 1979, 1981).

ECL cells. ECL cells are usually identified on the basis of the characteristic large, vacuolated granules (Solcia et al. 1975) (Figs. 1b and 3a). However, it is pertinent to the purpose of the present investigation to recall that vacuolated granules are not an exclusive feature of ECL cells but occur also in P cells (Solcia et al. 1979). Moreover, normal human ECL cells contain an additional, and often predominant, population of smaller, round

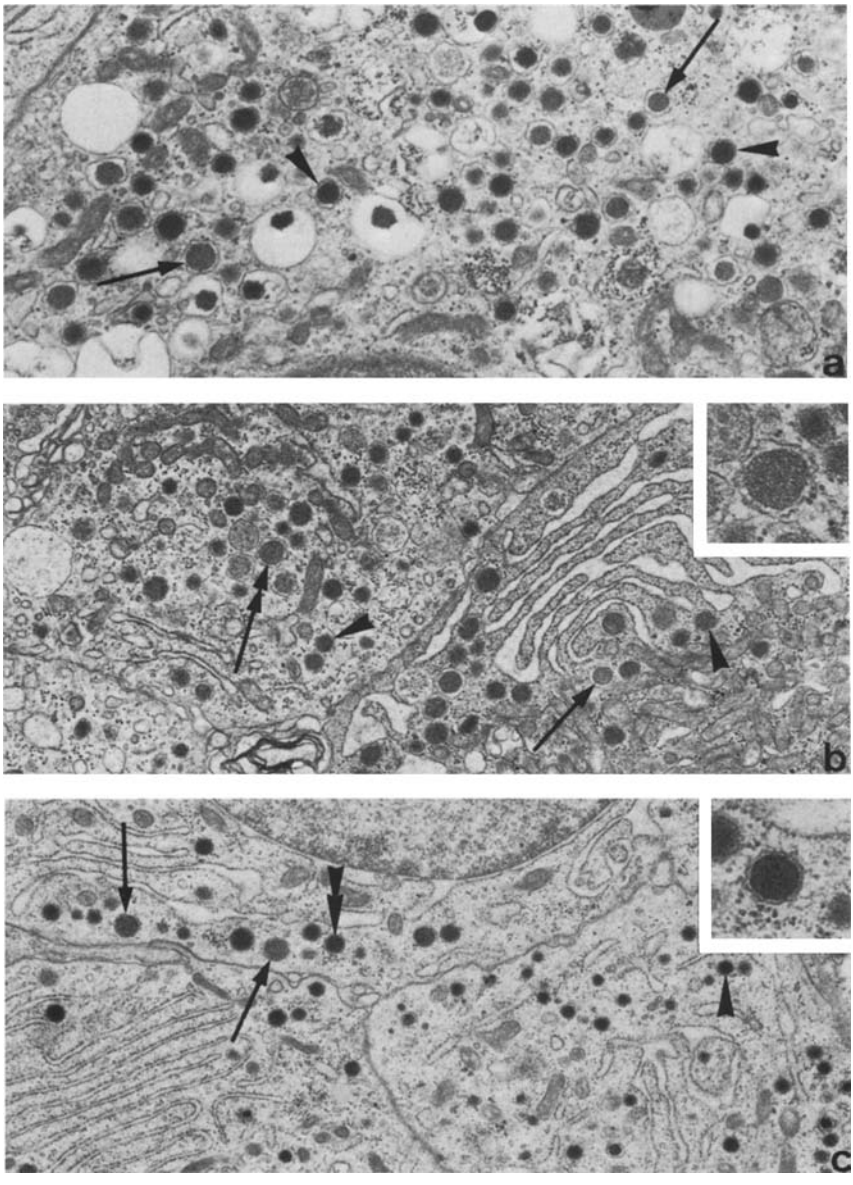

Fig. 3. Ultrastructure of granules in ECL cells with (**a**, case 8) and without (**b**, case 6, and **c**, case 5) typical vacuolated granules. Note the correspondence of non vacuolated granules with respect to the coarsely granular structure of larger granules (*arrows*, *inset* in **b**) and the wavy membrane of smaller, dense granules (*arrowheads*, *inset* in **c**). Double marks point to granules enlarged in insets. × 16,000; *inset*: × 58,000

and relatively dense granules (Vassallo et al. 1971; Capella et al. 1971). A coarsely granular texture of the granule core and a wavy appearance of the granule membrane, which is separated from the core by a thin, clear and sharply defined space, are distinctive, frequent features of these non

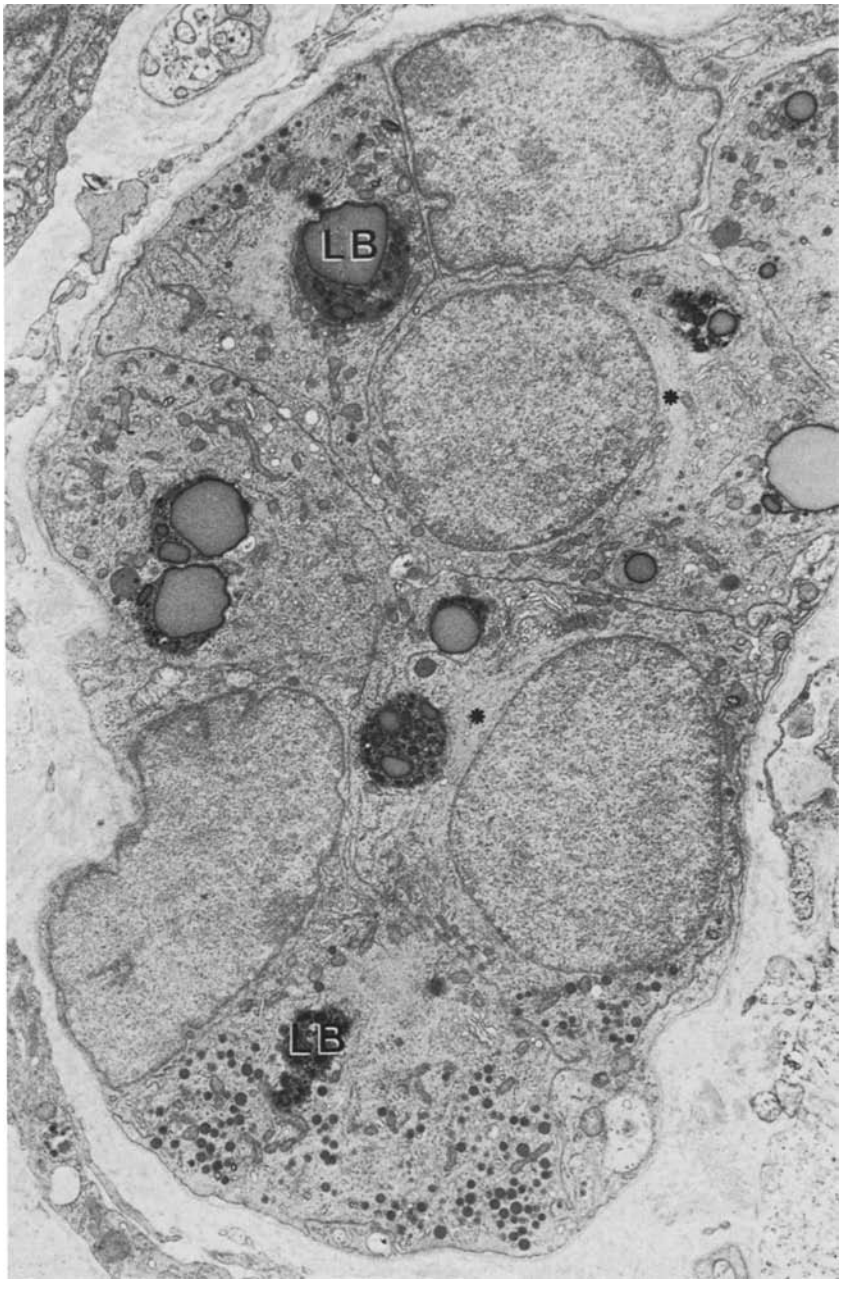

Fig. 4. Case 1. Ultrastructure of a nodule composed of D_1 cells. Note the abundance of lipofuscin-like bodies (LB) and of perinuclear filaments (*asterisks*). × 7,200

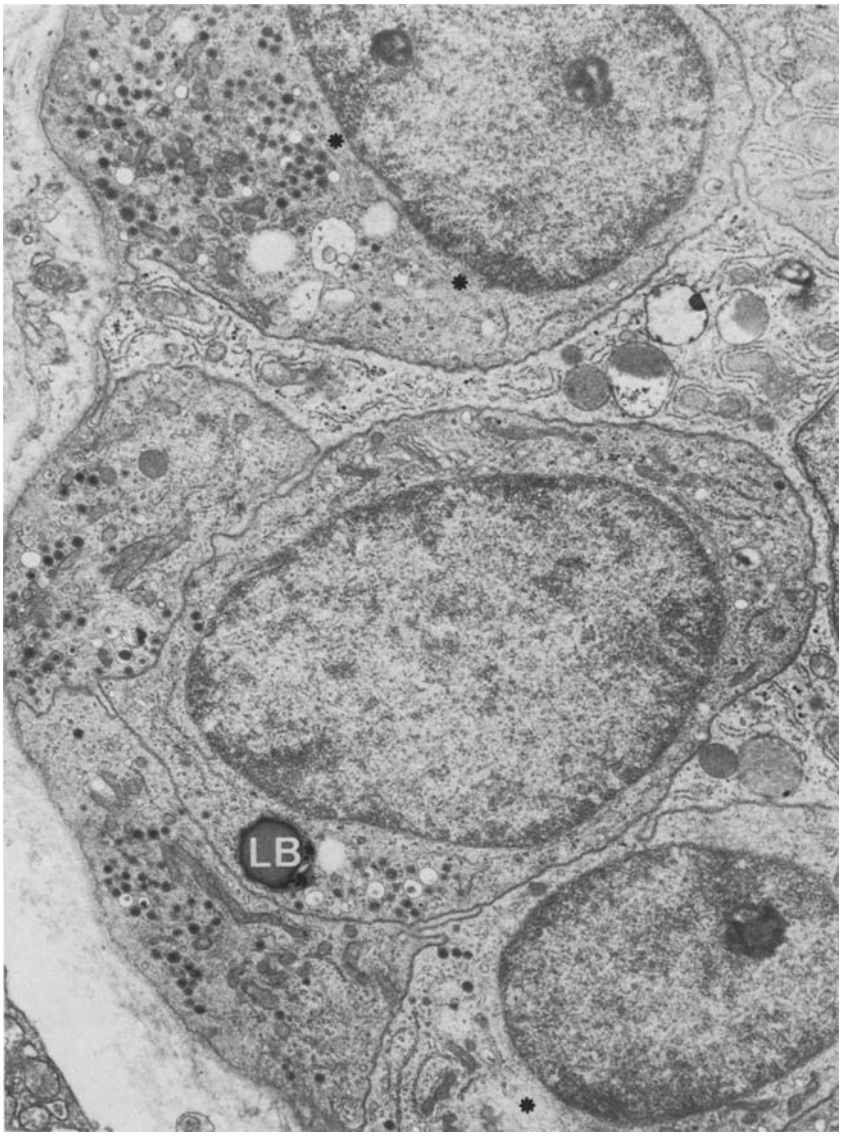

Fig. 5. Case 6. Several P cells within a fundic gland with frequent vacuolated or haloed granules. A lipofuscin body (*LB*) and moderate perinuclear filaments (*asterisks*) are also present. ×7,200

vacuolated granules (Solcia et al. 1975, 1979, 1981). In our study the latter features were found to be very useful in discriminating ECL cells without vacuolated granules from non-ECL cell types (Figs. 2b and 3). In addition, ECL cells were never found to contain microfilaments or large lipofuscin-like bodies while rough endoplasmic reticulum (RER), sometimes arranged in parallel or concentrical arrays of cisternae, and Golgi apparatus often were well represented (Figs. 1 and 3b, c).

D_1 cells. The granules of D_1 cells are round, homogeneous, of moderate to high density, with a diameter of 140–190 nm and a surrounding membrane closely apposed or separated from the core by a very thin space (Solcia et al. 1979, 1981). Abundant perinuclear filaments are commonly found in D_1 cells (Solcia et al. 1975). In addition, the present study revealed the frequent occurrence of large lipofuscin-like bodies (Figs. 1 and 4). RER profiles and Golgi apparatus were rarely conspicuous.

P cells. The differential features of these cells with respect to the D_1 cells are not well defined (Solcia et al. 1975, 1979, 1981). Cells classified as P cells in our study contained round, small (100–150 nm in diameter) granules. The granule core showed variable density and sometimes indistinct limits. It was usually separated from the surrounding membrane by a halo, which appeared either clear or of lesser density than the core itself (Capella et al. 1978; see in particular their Figs. 6 and 8a).

In addition, these cells frequently contained vacuolated granules identical to those of pulmonary P_1 cells (Capella et al. 1978) or of the enterocatecholamine cells described by Forssmann et al. (1969) in the gastric mucosa of the rat (Fig. 5). P cells were also found to contain lipofuscin bodies and perinuclear filaments, though less prominent than those of the D_1 cells; in contrast, RER profiles and Golgi apparatus were better represented than in the latter cells.

EC, D, and X cells. These cells, which were rarely encountered in our study, were defined by the typical appearance of their granules that were dense and pleomorphic, round, homogeneous and of weak density, and round, rather dense and large, respectively (Solcia et al. 1975, 1981).

Distribution of endocrine cells in the fundic mucosa

Table 1 illustrates the distribution of ultrastructurally identifiable endocrine cells of the fundic mucosa in the 9 patients investigated. ECL cells were the most frequent cell type in 8 cases, in 4 of which their number was higher than the cumulative number of all other cells. In all cases but two ECL cells containing only non-vacuolated granules were largely predominant over those also containing vacuolated granules (Fig. 2). D_1 cells were abundant only in one case (No. 1, the oldest patient of the series) in which they represented the most frequent cell type (Fig. 4). P cells usually ranged in intermediate position, in one case (No. 7) being virtually in the same frequency as the ECL cells (Fig. 5). The contribution of EC, D and X cells was very low or, often, negligible. In a varying but usually low proportion of cells mixed features of different cell types were seen. Unidentified cells, mostly because of the paucity of granules in the cell section examined ultrastructurally, were present in all cases and ranged up to 18 per cent. When cells forming intraglandular chains or extraglandular nodules were classified separatedly in individual patients, no differences were found. Therefore these data were cumulated.

Table 1. Classification of hyperplastic fundic endocrine cells in 9 patients with chronic atrophic gastritis and hypergastrinaemia

Case	Patient's Age (year) Sex	Serum gastrin levels[a] (pg/ml)	Number of endocrine cells examined	Endocrine cell types (%)							
				ECL	D_1	P	D	EC	X	mixed types	unclassified
1	73/F	>800	144	20.8	40.2	3.4	2	–	–	15.8	17.3
2	68/F	800	166	46.3	3	18	3	1.2	0.6	16.8	10.8
3[b]	63/F	720	101	71	4.2	7.4	3.2	1	–	4.2	8.5
4	62/F	600	105	42.8	3.8	21	3.8	6.6	0.9	3.8	17.2
5	61/F	700	123	88.6	0.8	2.4	0.8	0.8	1.6	4	0.8
6	49/F	520	182	45.6	4.3	28	3.2	1	–	8.7	8.7
7	47/F	950	162	38.8	0.6	33.9	0.6	5.5	–	2.4	17.9
8	39/F	450	137	82.4	2.2	5.8	0.7	1.4	–	4.3	2.9
9	16/F	300	167	80.2	0.6	12.5	–	1.7	–	2.4	2.4
Normal fundic mucosa[c]				40–60		5–10	10–20	5–10	1–5	–	–

[a] Normal values in our laboratory: less than 100 pg/ml
[b] This patient also presented pernicious anemia
[c] From Solcia et al. (1986)

Relation between optical and ultrastructural cytological findings

As described in greater detail elsewhere (Bordi et al. 1986), in light microscopy hyperplastic endocrine cells appeared to be argyrophil with both the Grimelius and the Sevier-Munger methods and immunoreactive for chromogranin. Moreover, a weak staining with lead-haematoxylin was observed in three cases (No. 1, 3 and 7). In contrast, antisera against gastrin, somatostatin, and glucagon reacted only with isolated, occasional cells in both fundic and intestinal metaplastic glands. These latter cells did not appear to be involved in the hyperplastic changes.

Although direct comparison of optical and ultrastructural findings with the consecutive semithin-thin section technique could not be performed, differences in the pattern of staining reactions were not found between cases with predominance of ECL cells and cases with a more heterogeneous cell composition.

Discussion

In the present study fundic endocrine cells of 9 patients with severe fundic argyrophil cell hyperplasia, CAG and proven hypergastrinaemia were classified on the basis of recent ultrastructural criteria for gastric endocrine cell characterization (Solcia et al. 1975, 1979; Capella et al. 1978). Electron microscopy remains the unique tool for the identification of the different types of fundic endocrine cells. Specific immunocytochemistry, in fact, is prevented by the absence of suitable antisera as the cell(s) hormonal product

has not been identified. Moreover, in our study staining methods for endocrine cells and immunocytochemistry using available antisera appeared to be ineffective in discriminating between cases which showed a ultrastructurally prevailing population of ECL cells from cases with significant involvement of the other cell types.

Our results indicate a heterogeneous composition of the hyperplastic endocrine cells. This heterogeneity may explain, at least in part, the variability in the results reported in previous studies (Rubin 1973; Solcia et al. 1975, 1979; Bordi et al. 1978, 1983). The ECL cells appeared to be the most frequent cell type in 8 of 9 hypergastrinaemic patients, a finding consistent with the dependence of the ECL cells on the trophic effect of gastrin (Hakanson et al. 1976). This result, therefore, shows that hyperplasia of fundic endocrine cells occurring in hypergastrinaemic CAG is similar to that found in other hypergastrinaemic conditions. Moreover, it offers an explanation for the fact that carcinoid tumours in patients with CAG are composed of ECL cells (Larsson et al. 1978; Capella et al. 1980; Hodges et al. 1981; Carney et al. 1983; Borch et al. 1985; Solcia et al. 1985). In our study most ECL cells contained only dense granules with absence of vacuolated granules characteristic of the same cell type in normal mucosa. The mechanism responsible for this absence is unknown while a role for gastrin seems unlikely since ECL cells of patients with Zollinger-Ellison syndrome were found to show abundant vacuolated granules (Bordi et al. 1974; Solcia et al. 1975).

D_1 cells were the most frequent cell type in one case while they were inconspicuous in other cases. P cells were well represented in most cases, in one patient being almost as abundant as the ECL cells (see Table 1). Owing to the low frequency of D_1 and P cells in normal fundic mucosa (Solcia et al. 1986), our data indicate that also these cells may proliferate in patients with CAG and hypergastrinaemia. Although this finding may suggest that also D_1 and P cells are dependent on gastrin influence, no conclusion can be drawn in the absence of more adequate functional and experimental evidence. Only one fundic carcinoid composed of D_1 and/or P cells has been described (Solcia et al. 1986). This suggests that hyperplastic D_1 and P cells have very low oncological potential.

Our results are not in accordance with previous studies reporting predominance of D_1 and P cells in CAG (Solcia et al. 1975, 1979, 1980a; Capella et al. 1978). Such discrepancy cannot depend on the cytological identification of these cells since similar criteria have been used. To explain these variations other factors may be considered in addition to gastrin. It is suggested that one of these factors may be age. Although our series is too small to allow definite conclusions, it is worth noting that the patient with preponderance of D_1 cells was the oldest one whereas the two patients with an age below 40 both presented a marked predominance of ECL cells. The ultrastructural appearance of ECL and D_1 cells was also consistent with a possible relationship of these cell types with age. ECL cells appeared as actively synthethizing cells showing well developed RER profiles and Golgi apparatus (Figs. 1–3). In contrast these structures were rather incon-

spicuous in D_1 cells while lipofuscin-like bodies and perinuclear bundles of filaments were abundant (Figs. 1 and 4). Cells with intermediate features were also observed consistent with previous findings in the fetal mucosa (Solcia et al. 1986). A further characterization of the relationship between the ultrastructural composition of fundic endocrine cells and their corresponding function appears to be warranted requiring, however, the development of markers for the still unknown specific secretory products of these cells.

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