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Endocrine-Amphicrine Enteric Carcinoma of the Nasal Mucosa

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Summary. A 39-year-old bus driver had been suffering for 2 years from a malignant polypoid mucosal proliferation of the upper nasal concha-ethmoid region, resembling a highly differentiated, villous-glandular adenocarcinoma of enteric type. There were numerous mono- and amphicrine cells and a massive quantity of oxyphilic, frequently Paneth-like goblet cells in the tumor. Immune-histochemically, a number of gastrin- and fewer glucagon-positive cells were identified. The somatostatin level in the serum was clearly increased. Electron-microscopically, 7 different endocrine cell types were identifiable, in order of decreasing frequency: A-like- and G-cells, both types of 5-HT-cells, A-cells, EG- and K-cell-like elements. Particularly impressive were the muco-argyrophilic amphicrine cells, containing A-granules.

The unusual enteric character of the carcinoma seems to result from boundary movements and tissue displacements in an ecto-entodermal embryonic border region.

There was no history of occupational wood dust inhalation.

Key words: Adenocarcinoma – Nasal adenocarcinoma – Enteric nasal carcinoma – Endocrine cells – Amphicrine cells – Paneth cells.

Zusammenfassung. Ein 39jähriger Lastwagenfahrer leidet seit 2 Jahren an einer malignen polypösen Schleimhautwucherung der oberen Nasenmuschel-Siebbeinregion, nach Art eines hoch differenzierten, zottigdrüsigen Adeno-

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** Dedicated to Prof. Wilhelm Doerr, M.D., on the occasion of his 65th birthday

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carcinoms enteralen Typs mit zahlreichen mono- und amphikrinen endokrinen Zellen und massenhaft oxyphilen, oft Paneth-ähnlichen Becherzellen. Immunhistochemisch sind reichlich Gastrin- und spärlichere Glukagon-positive Zellen nachgewiesen. Dagegen ist im Blutserum der Somatostatinspiegel deutlich erhöht. Elektronenoptisch können 7 verschiedene endokrine Zelltypen nachgewiesen werden, der Häufigkeit nach: A like- und G-Zellen, beide 5-HT-Zelltypen, A-Zellen, EG und K-zellartige Elemente. Besonders auffällig sind die mukoargyrophilen amphikrinen Zellen, sie enthalten A-Granula.

Der ungewöhnliche enterale Charakter des Carcinoms resultiert offenbar aus Grenzverschiebungen und Gewebsverwerfungen in einem entwicklungsgeschichtlich ento-ektodermalen Grenzbereich.

Es muß besonders betont werden, daß in unserem Fall beruflich nie ein Kontakt mit Holzstaub erfolgte.

Introduction

A 39-year-old bus driver had been suffering for $1^1/_2$ years from highly secretory, polypoid mucosal proliferations of the middle nasal concha. At surgical resection these were found to extend to the ethmoid cells and possibly originated from them.

Clinical and Occupational History

Bronchial asthma since 1960, for appr. one year pain in the right side of the nose with bloody, yellowish secretion from the right nostril. Painful swelling at the root of the nose on the left side during the last 2 months before admission. X-ray shows ethmoidal sinusitis on the right and a polypoid, marginally situated mucosal swelling in the right maxillary sinus, no bone destruction. The first operation entailed removal of greater than walnut-sized, soft, fragmented tumour masses destroying the ethmoid. Radical excision was not possible.

First recurrence after about 2 months. Gradual worsening of general condition, continually under alkaloids during the last months due to severe pain. No clinical signs of metastases of the nasal carcinoma. No indication that the nasal carcinoma is a secondary (metastatic) carcinoma of a primary tumour of the gut.

After finishing school (at 14 years of age) he had been occupied as an electrician. During the last 4 years he was employed as driver by a company producing glue, but was not in direct contact with glue production, although he was occasionally exposed to the fumes arising therefrom. He was never employed in the wood-working industry and had only a slight measure of contact with wood and wood dust while building his own home.

Material and Methods

For examination in the *light microscope,* material obtained surgically was fixed in formaldehyde and embedded in paraffin. The sections were stained with H+E, PAS and van Gieson. Four methods of silver impregnation were carried out: Masson-Hamperl, Grimelius, Sevier-Munger and Bodian. Amphicrine cells were identified by combining the silver impregnations Masson-Hamperl, Grimelius and Sevier-Munger with mucus stains; either Alcian-blue or mucicarmine. Immunecytochemical examination was carried out with the unlabeled antibody-enzyme method (peroxidase-

antiperoxidase method) according to Sternberger. For examination in the *electron microscope*, material removed intraoperatively was immediately cut into pieces 1 mm^3 in size and pre-fixed for 2 h in 3% glutaraldehyde (buffered with sodium cacodylate at pH 7.3). After rinsing in cacodylate buffer, the tissue samples were post-fixed, or pre-contrasted, for 2 h in 1% osmium tetroxide solution and, following dehydration in graded ethanol solutions, were embedded in Epon 812. The ultrathin sections, prepared with a Reichert OmU 2 ultramicrotome, were stained with lead citrate and uranyl acetate solutions, and electron micrographs were made, using a Philips EM 200 at 80 kV beam voltage. *Semi-thin sections* stained with toluidin-blue were also examined.

Results

Under the light microscope and with H + E staining the polypoid tumour shows a clearly villous-adenomatous structure, with frequent crypt-like pitting of the generally simple, occasionally pseudostratified columnar epithelium. In some areas atypical nuclei and numerous goblet cells were seen (Fig. 2a). Especially remarkable are numerous oxyphilic, obviously granulated, Paneth-like cells (Fig. 1A), while transitional forms between the goblet cells and these oxyphilic granulated cells occasionally appear, most impressively in the PAS-stain. Further s surprising number of "Helle Zellen" (light cells; Pearse 1977: clear cells)

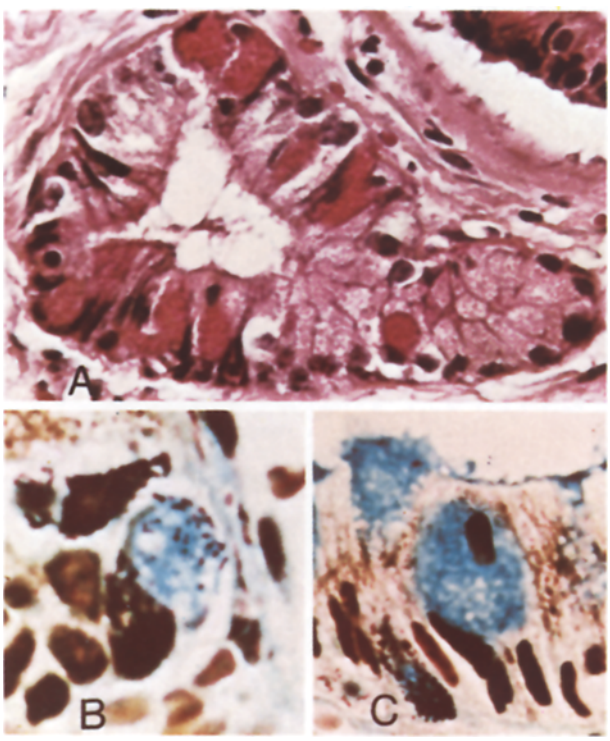

Fig. 1. A numerous, oxyphil granulated, Paneth-like cells, sparse "Helle Zellen" (light cells). Paraff. H.-E. ×200. **B** and **C** two amphicrine cells of varying exocrine secretory type. Paraff. Grimelius-Alcian-blue, ×500

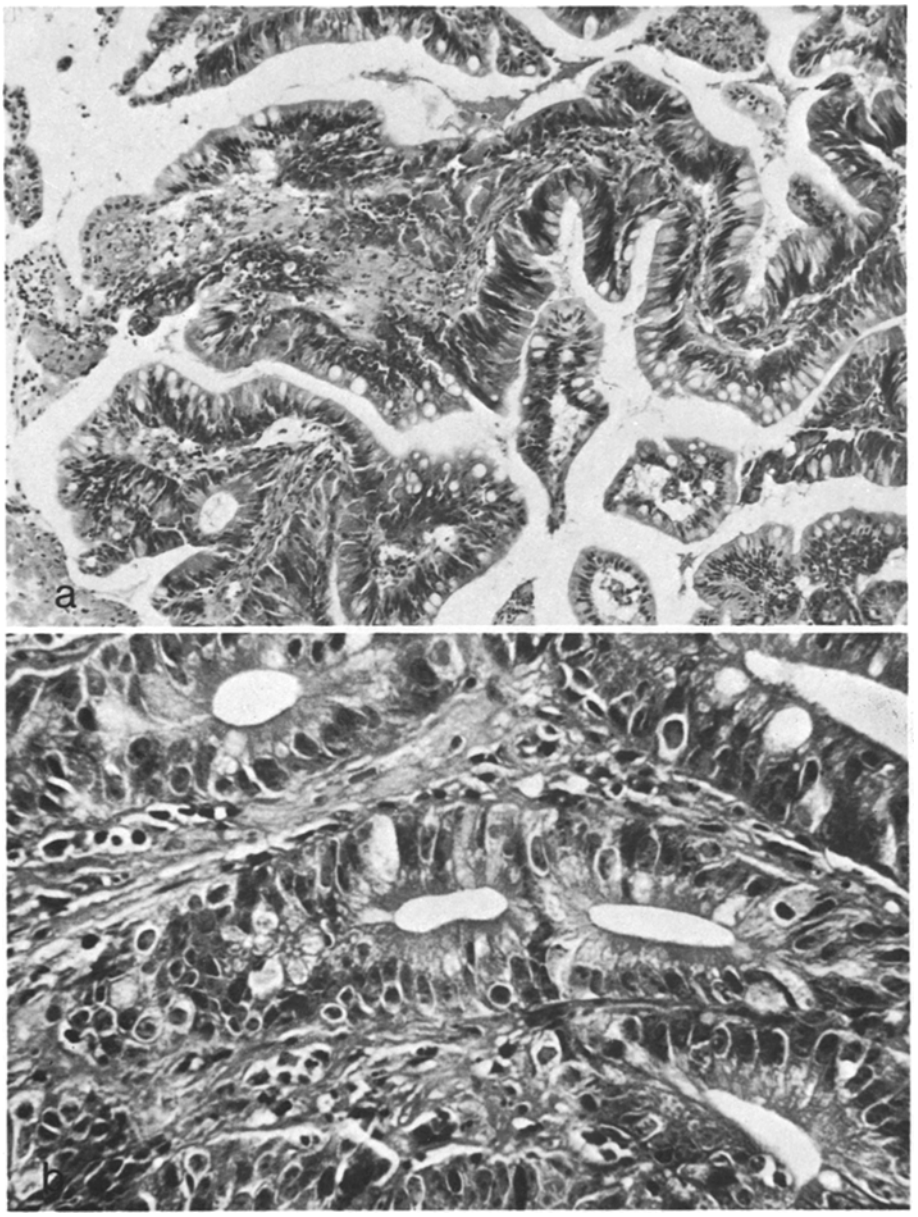

Fig. 2.a Mature, polypoid-papillary, enteric adenocarcinoma with frequent crypt-like pitting and numerous goblet cells. Paraff., H.-E. ×63. **b** Detail with numerous "Helle Zellen" = light cells (E-cells) in the cancerous epithelium. Paraff., H.-E. ×125

are discernible in a primarily basal position (Fig. 2b); these correspond, for the most part, to argyrophilic polypeptide cells as demonstrated by the Sevier-Munger technique (Fig. 3b). Silver impregnation (Masson-Hamperl) reveals argentaffin cells (Fig. 3a). An attempt to identify mucoargentaffin cells by the combined Masson-Hamperl-Alcian-blue stain was unsuccessful, but the Grime-

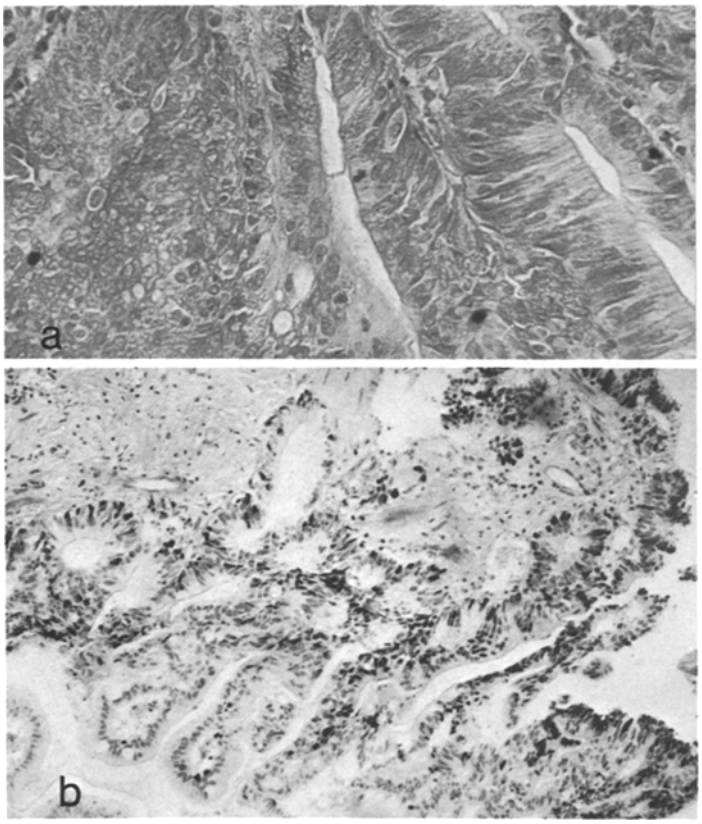

Fig. 3. a A number of argentaffin cells in the canccerous epithelium. Paraff., silver impregnation accord. to Masson-Hamberl, × 125. **b** Great number of argyrophilic cells. Paraff., silver impregnation accord. to Sevier-Munger, × 25

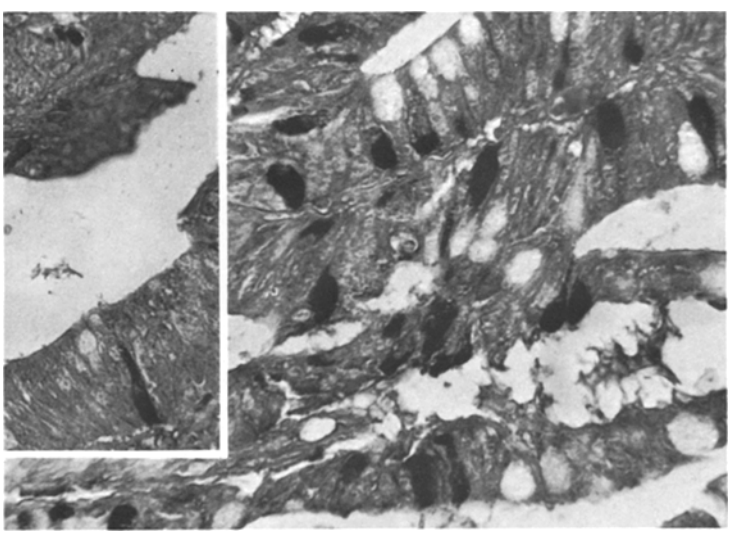

Fig. 4. Immune-histochemically, numerous gastrin-positive cells. Left insert: glucagon-positive cell. Antiperoxidase method, paraff., × 250

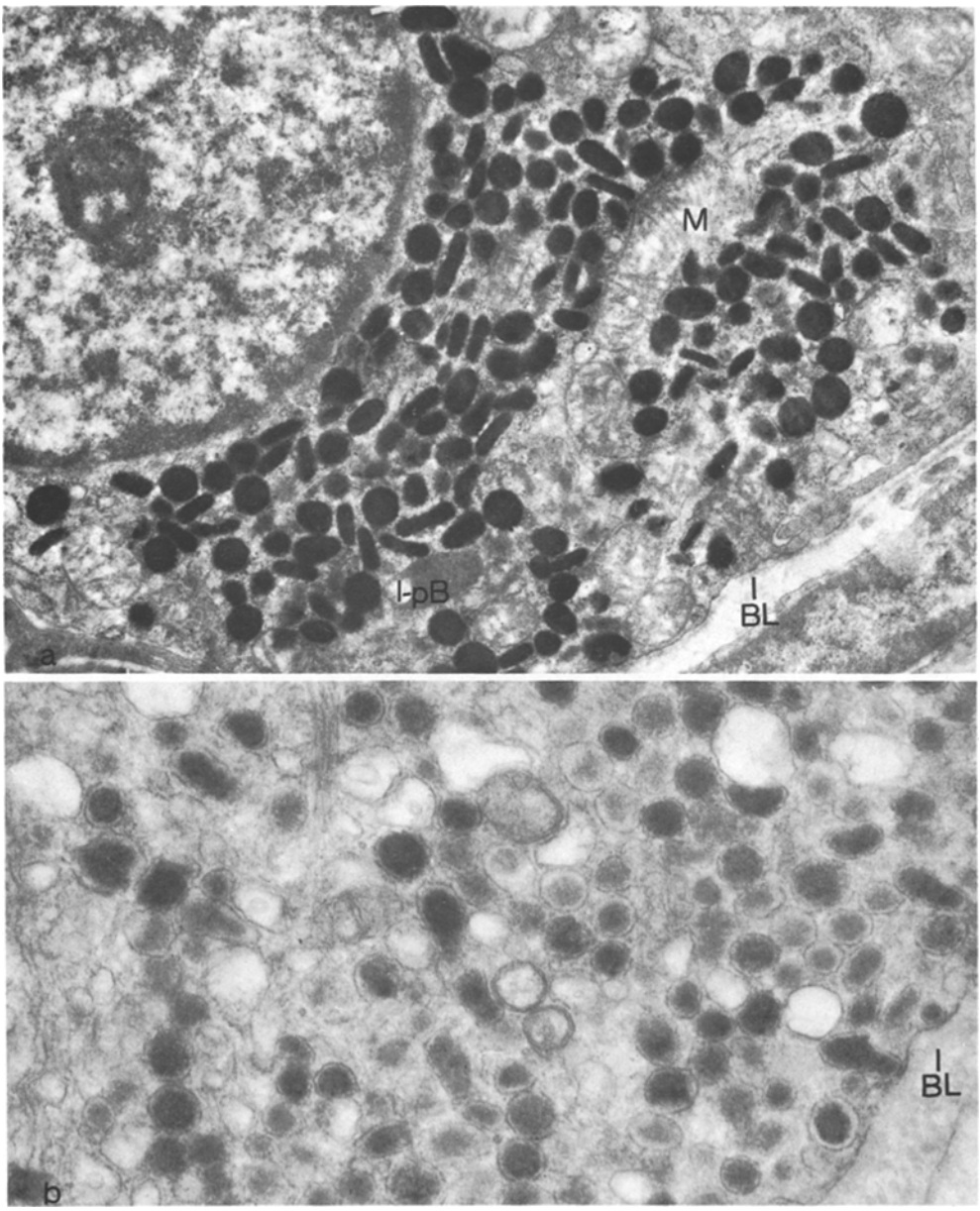

Fig. 5. **a** 5-HT-cell of type I (EC^1-cell), just above the basal lamina (BL), with numerous, electron-dense, frequently longish to dumbbell-shaped endocrine secretory granules; mitochondria (M), lipid-pigment bodies (l-pB), ×24,000. **b** 5-HT-cell of type II (EC^2-cell) at the basis of the tumour epithelium (basal lamina, BL) with ovoid to round-sectioned, endocrine secretory granules, varying electron-density. ×25,000

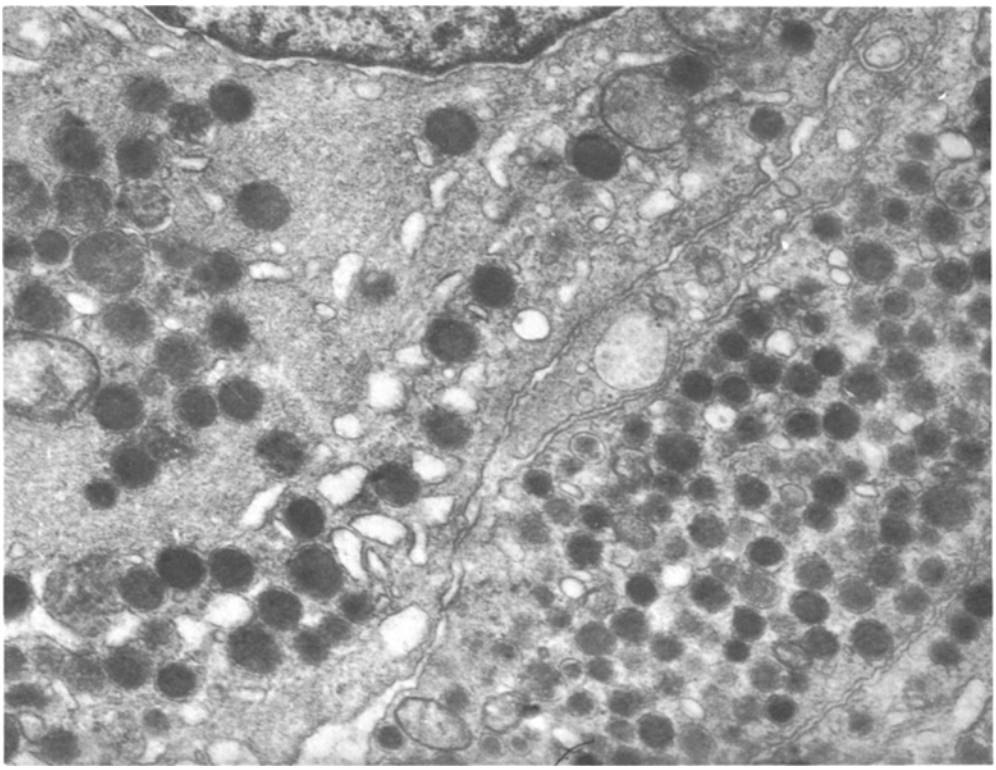

Fig. 6. Two neighbouring endocrine tumour cells, K-cell at left, Al-cell at right, with electron-dense secretory granules of varying dimensions (K-cell: 500–580 nm. Al-cell: 320–350 nm). × 23,200

lius-Alcian-blue method reveals numerous muco-argyrophilic cells of various types (Fig. 1 B and C).

Immune-cytochemically, the antiperoxidase method (Sternberger) shows a relatively large number of gastrin-positive (Fig. 4a) and a few glucagon-positive cells (Fig. 4b). Quantitative serum-hormone analysis revealed an obviously increased somatostatin level (2250 pg/ml, normal up to 800 ph/ml), a slightly increased value for gastrin at 175 pg/ml instead of the normal 70 pg/ml, and a glucagon value approximately one fifth above the maximum normal level. The levels of motilin, insulin, parathyroid hormone and calcitonin lay within the normal range.

Electron-microscopic fine granule ultrastructure and morphological details was used to differentiate 7 endocrine cell veriants. The first is the EC_1 cell of the "intestinal" type (Fig. 5a). These cells are situated along the basal lamina and do not reach the glandular lumen. The most important electron-microscopic characteristic of this cell type are the polymorphic, longish, dumbell-shaped endocrine secretory granules, membrane-enclosed and very electron-dense. Their longitudinal diameter averages 455 nm. Higher magnification permits the identification of a narrow halo. The second cell is the duodenal type EC_2 (Fig. 5b).

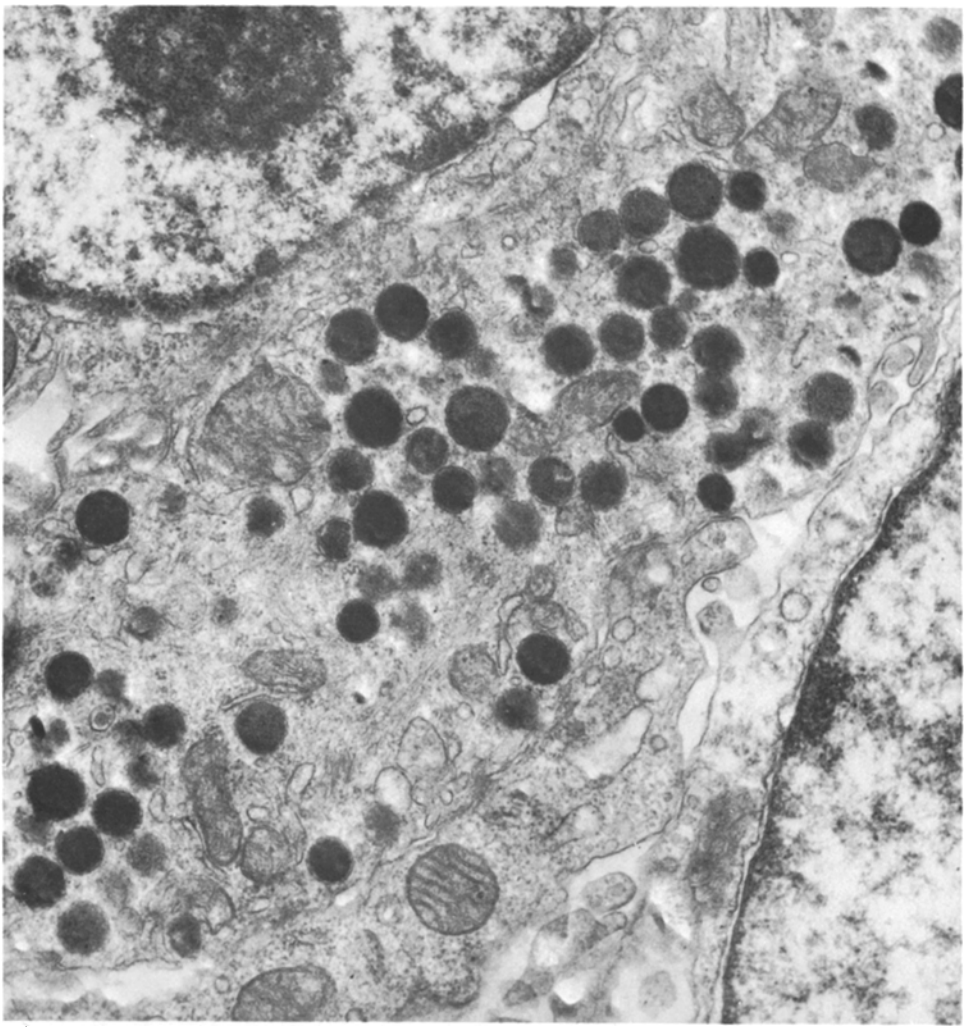

Fig. 7. Tangential section of a tumour cell with the finemorphological characterisitics of a G-cell, having round-sectioned, highly electron-dense secretory granules (diameter: 220–260 nm). ×42,000

There is no real difference in localisation and fine structure, from the cell-type EC_1, but the secretory granules are obviously different; these show remarkable polymorphism with less osmophilia, are primarily ovoid or round, more rarely polygonal or even curved, with a clearly recognizable halo and a distinct enveloping membrane. The diameter of the granules is appr. 430 nm.

The most common cell type is the A-like cell (Fig. 6, right, and Fig. 9, right), with almost exclusively round secretory granules measuring 320 to 350 nm in diameter, a homogeneous, finely granulated core of varying osmophilia, separated from a well-defined membrane by a halo of varying width.

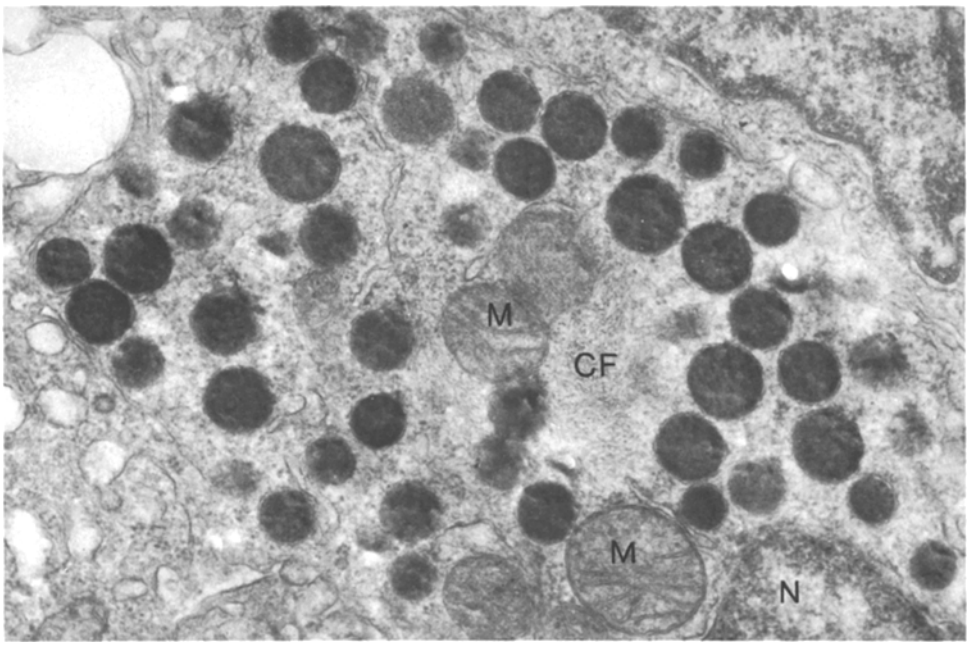

Fig. 8. Tangential section of an EG-cell with large, membrane-enveloped secretory granules (diameter: 400–420 nm); tangentially sectioned nucleus (*N*), mitochondria (*M*), cytofilaments (*CF*). × 33,000

The next type is the K-cell (GIP-cell, left in Fig. 6). Its principal electron-microscopic characteristic is the presence of large, round, very electron-dense secretory granules, whose size varies between 500 and 580 nm. They have a distinct membrane and only a narrow halo and are scattered randomly throughout the cytoplasm. They possess large, regularly formed nuclei, numerous cytofilaments and well-developed Golgi-complexes and granular endoplasmatic reticulum, as well as numerous good-sized mitochondria. A further cell type (Fig. 7) was classified with the G-cells on the basis of relatively small, uniform, highly electron-dense endocrine secretory granules, sized 220–260 nm. Clearly distinguishable from these cells were relatively coarsely granulated cells, granule diameter 400–420 nm, with a round, regular cross-section and a very narrow halo between the well-discernible membrane and the granule core, similar to the EG-cell (Fig. 8).

The most impressive cells morphologically were the amphicrine cells of the muco-argyrophilic typ (Fig. 10). Their main fine – morphological characteristic is the intracellular coexistence of endocrine secretory granules with exocrine mucus droplets. The former show a round cross-section with a diameter of appr. 310 nm; the osmiophilic core is separated from the surrounding membrane by a narrow halo. The form and diameter of the granules permit their classification with the A- or A-like cells. The endocrine granules are, for the most part situated below the nucleus in the basal portion of the cell, occasionally they are also seen above the nucleus. The mucus droplets are considerably

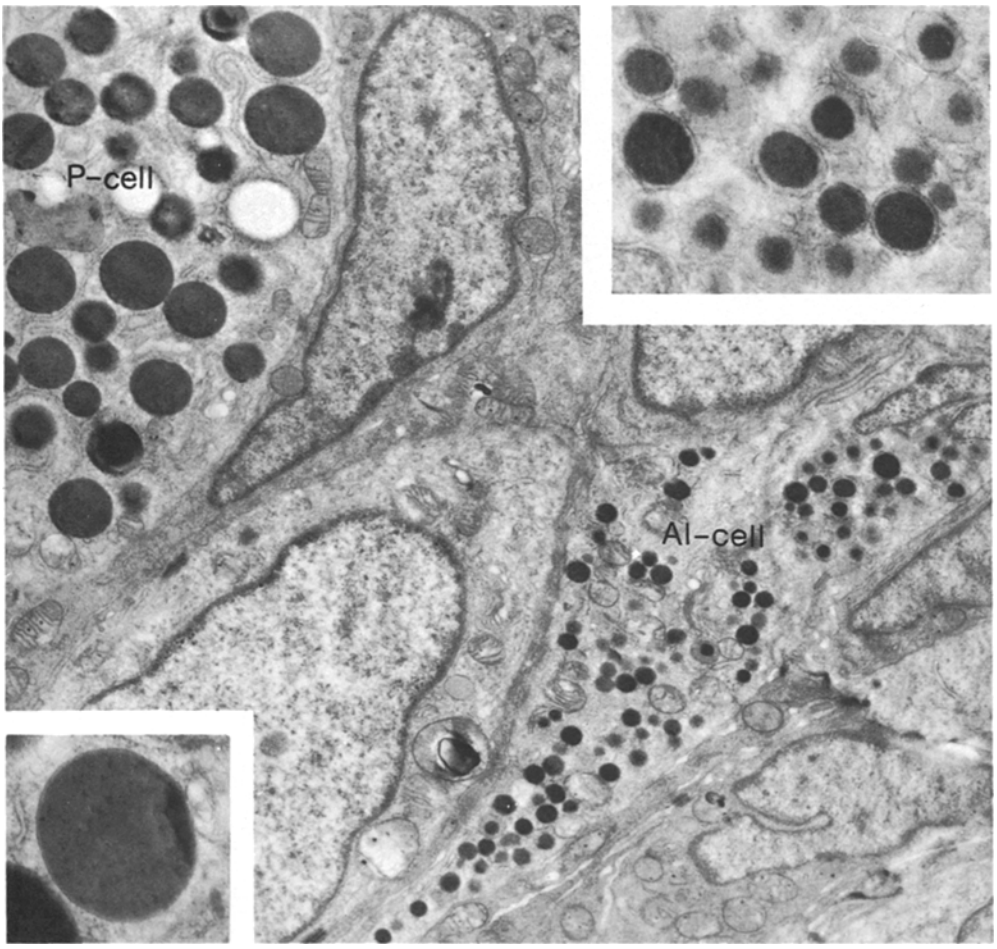

Fig. 9. Tumour epithelium with tangentially sectioned Al-cell (granule diameter 320–340 nm) and a Paneth-cell (P-cell) with granules appr. 800–900 nm in diameter; highly magnified secretory granules of both cell-types in the two inserts. ×35,100

larger, up to appr. 1000 nm in diameter, and are surrounded by a clearly perceptible membrane. Their contents are finely granular or cloudy with excentrically situated densities (patches). They lie mainly in a basal position; the cell has no access to the lumen (an appearance due either to the section plane or to the possibility of actual excretion of the mucus into the stroma). Mucoargyrophilic A-cells have few other cytoplasmic structures, including a sparsely developed granular endoplasmic reticulum, which contrasts with the well-developed endoplasmic reticulum of the mucous cells. Numerous cytoplasmic filaments, relatively small mitochondria and very large lipid-like cell inclusions are present. Junctional structures are responsible for the connection to neighboring cells.

A few cells may be characterized as Paneth-cells (Fig. 9, left). Their halo-free granules show an average diameter of 800–900 nm, are for the most part homoge-

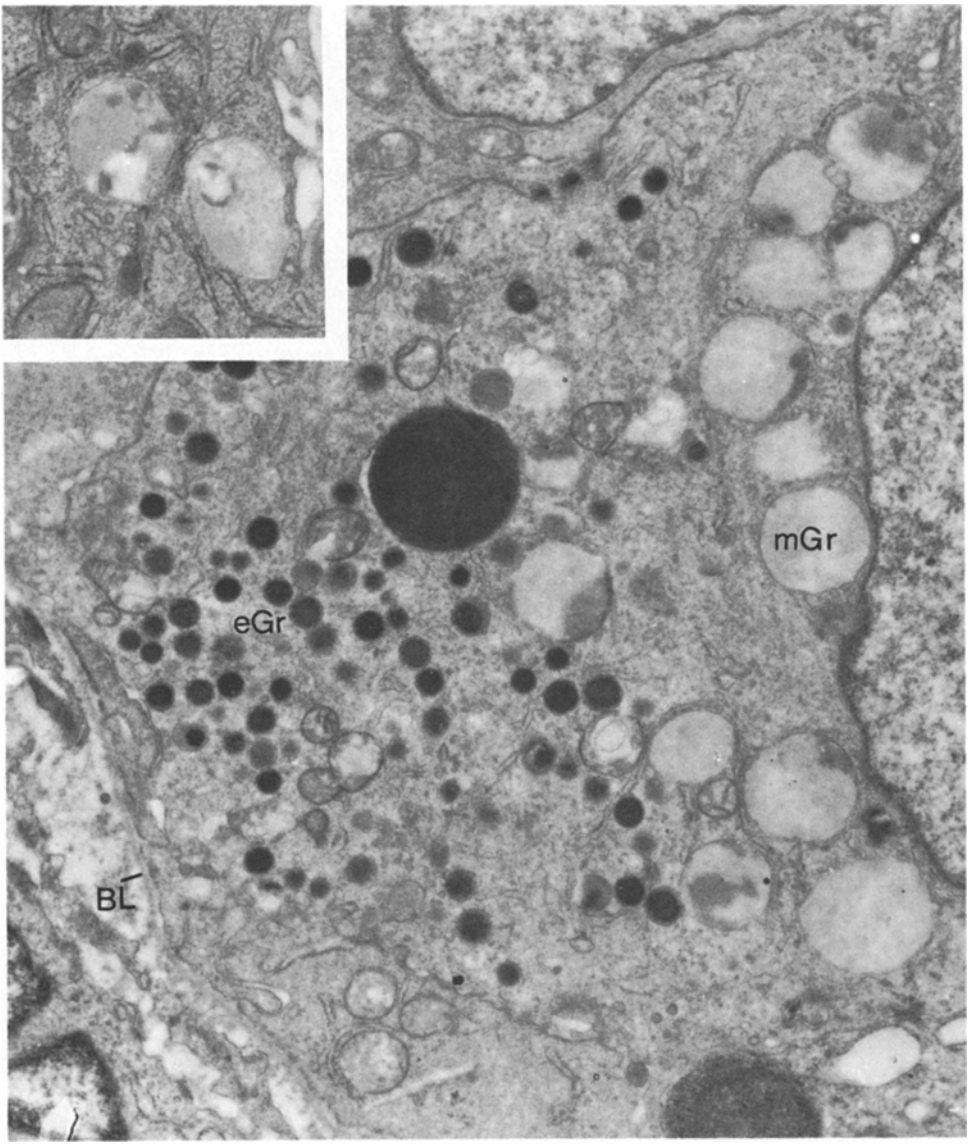

Fig. 10. Amphicrine, muco-argyrophilic tumour cell, containing small, osmiophilic endocrine secretory granules (*eGr;* diameter: 300 nm) of the A-cell type, interspersed with large, finely-granular mucous granules (*mGr;* diameter: 1000 nm). Basal lamine (*BL*). ×20,100. *Inset:* Two mucous granules in a normal mucous cell of the duodenum. ×21,000

neously osmiophilic, and only rarely permit distinction between an "externum" and an "internum" (see Otto, 1974, p. 11). The granule size corresponds roughly to the G 3-type ("mature granule"). The somewhat reduced endoplasmic reticulum is therefore not an unexpected finding in association with this sign of reduced granulopoietic activity. Forms transitional between the Paneth- and the goblet cells were occasionally observed.

Discussion

Although primary adeocarcinomas of the enteric type in the nasal ethmoid region are rare, they are well described (Järvi, 1944; Simard and Jean, 1953; Batsakis et al., 1963; Sanchez-Casis et al., 1971; Di Rago et al., 1975; Gamez-Araujo et al., 1975; Walter et al., 1976). Järvi was first to stress the occurrence of argentaffin cells in these carcinomata, as did Simard and Jean and Sanchez-Casis et al. According to Feyrter (1953, 1969), the cells of the Helle Zellen organ of the nasal mucosa are, under regular conditions, argyrophobic, but may develop an argyrophilic or even argentaffin granulation later in life, particularly in tumours of the upper turbinate-ethmoid region. As the time of these reports a more detailed classification of the silver staining granules was not possible. In our case, the number of argyrophilic elements and their widely varied type were particularly remarkable. In addition the total impression fitted with a mature, villous adenocarcinoma with small-intestinal characteristics, having interspersed argentaffin EC-cells. In this tumour there were the following three, previously undescribed cell series:

1. A prodigious number of eosinophilic Paneth-like cells,
2. 7 different types of argyrophilic and argentaffin polypeptide cells, in decreasing order of frequency: Al-cells, G-cells, the two 5-HT-(ec-)cell types, A-cells, EG-cells and K-cell-like elements.
3. A few amphicrine cells.

The numerous Paneth-like, oxyphilic granulated cells in the carcinomatous region (see Fig. 1 A) show all gradations of oxyphilia, even within the cytoplasm of a single cell. These oxyphilic granulated cells do not only represent varying stages of degeneration in oxyphilic goblet cells (Otto) but also true Paneth-cells, as the electron micrograph (Fig. 9) shows.

The type of peptide cell most common in our tumour, the Al-cell, possesses secretory granules that show great similarity with those of the animal pancreatic A-cell under the electron microscope (see Mitschke, 1977), but is probably not an enterospecific A-cell. Functionally, the Al- and the A-cell seem connected with glucagon production. The second-most frequent cell, the G-cell, occurs in the human stomach (pylorus and antrum. Fujita) and in the small intestine (Heitz, 1977) and is believed to form gastrin.

The EG(L)-cell is found typically in the small and large intestine (Heitz), but not in the stomach of the human being (see Mitschke), and is considered to be an entero-glucagon producer. The K (G–I–P)-cell occurs exclusively in the human small intestine (see Heitz, Mitschke); its product is gastrin-inhibitory protein (GIP). The comparison of the electron-microscopic with the immune-histochemical results reveals an unexpected reciprocal relationship in the frequency of gastrin- and glucagon-producing cells, a fact that may be attributable to quantitatively different cell frequency ratios in the tissue samples examined with the electron microscope and those analysed histochemically. The obvious increase of the somatostatin level, revealed by quantitative serum-hormone determination, is not explicable on the basis of electron-microscopic or immune-histochemical examination, as neither method provided evidence of D-cells which normally produce somatostatin. Since our case involves tumour cells variable

differentiation with a capability for somatostatin production as an unusual partial function of one or more of the E-cells identified, or of endocrine tumour cells, is conceivable.

The third distinctive characteristic of the tumour is its impressive content of *amphicrine cells* (see colour plate and Fig. 9). These were recognized and categorized, first electron-microscopically (Ratzenhofer and Leb, 1965; Ratzenhofer et al., 1969) and later with the light microscope (Ratzenhofer, 1977, 1979) as a separate species of cell in both the normal and, more frequently, in the pathologically differentiated gastro-enteric epithelium. Amphicrine cells occur in the appendiceal crypts of neurogenic appendicitis, in metaplastic gastric glands during chronic gastritis and in colonic epithelium in the vicinity of a carcinoma. Metaplastic development leads to goblet-cell carcinoids (primarily appendix, Subbuswamy et al., 1974; Abt and Carter, 1976, more rarely in colon and duodenum).

The amphicrine cell is a mixed endo- and exocrine cell which involves the entire spectrum of silver-staining cell granules with respect to its endocrine behaviour, while its exocrine activity seems to be limited to the production of mucus.

In our case, only the muco-argyrophilic variant of the amphicrine cell was to be found. This showed both basal and apical mucus production (see Fig. 1B and C), basal production being manifest as mainly intermediately situated mucous particles; electron-microscopically, only basally situated mucous granules were identifiable. The endocrine granules of the amphicrine cells in our case resembled the A- or A-like cell only. Different theories are offered to explain the rather typical, although unusual localisation of these primary adenocarcinomata of enteric type, in the vicinity of the upper nasal concha – ethmoid region. Since this area involves an embryonic ento-ectodermal border zone, Järvi (1944) postulates a congenital entodermal germinal displacement in the sense of Cohnheim (heterotopia of islands of intestinal mucosa), but Feyrter vigorously opposes this idea. In his opinion, these growths arise from a changed external stimulus acting later in life. We find merit in Stark's comment (1975), that precise classification of the enteric tube cannot be based on genetic considerations exclusively because, in the course of individual development, boundary movements and displacements must be taken into account. This may well be relevant in the formation of the nasal cavity from the ectodermal nasal pit and the entodermal foregut in our opinion, and the assumption of a "germinal displacement" is therefore unnecessary. With regard to the exogenous stimulus postulated by Feyrter, injurious occuptational influences seem to be of particular interest: In England, especially be Acheson's team (1967, 1968), attention has been drawn to the very significantly increased incidence of carcinomata, particularly of adenocarcinomata in the nasal mucosa and the paranasal sinuses, believed to be caused by wood dust (hard-wood). These observations were later confirmed by similar reports from Belgium, Holland, Denmark, France and Australia (Ironside and Matthews 1975). In 1976, Walter and co-workers found that, of 22 enteric nasal cancers, 15 patients were members of wood-working occupations. In 1979, Walter even reported on 34 patients with nasal adenocarcinoma from the wood-working industry, out of a total of 51 nasal cancer cases.

Wood dust can be eliminated as a carcinogen in our patient's case; he was first an electrician and has been a bus-driver for the last 4 years. No occupational connection with his nasal carcinoma seems apparent. It should be noted that Walter (1979) neither identified argentaffin or argyrophilic cells, nor did he find endocrine cells with the electron microscope.

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Note Added in Proof

The highly emaciated patient died after $2-^1/_2$ years. Autopsy showed a fist-sized, extensively exulcerated, local recurrent cancer with widely destructive encroachment into the right orbita and into the basal cranium. Furthermore, a massive, purulent, frontobasal leptomeningitis was found. The entire digestive tract, as well as the liver, were free of cancer. Only one walnut-sized metastasis in the right upper pulmonary lobe, and a pea-sized metastasis in the left lower pulmonary lobe were to be found. The recurrent cancer was histologically very similar to the primary cancer, while the two pulmonary metastases showed a slight decrease in differentiation.