

Achylia and the Development of Gastric Carcinoids

Erik Wilander

Department of Pathology, University of Uppsala, P.O. Box 553, S-751 22 Uppsala, Sweden

Summary. Twenty-four patients with gastric carcinoids¹ were examined retrospectively with regard to the presence of achylia and pernicious anaemia (PA). Six patients (25%) had achylia preoperatively and half of these had an associated PA. The gastric carcinoids occurring in an achylic stomach were almost exclusively located to the corpus area and tended to be multiple. Further, the majority of cells in most of them were argyrophil (Sevier-Munger) positive, indicating that they were of the enterochromaffin-like cell type. At present, achylia with or without concomitant PA appears to be the most distinct condition associated with gastric carcinoids. The pathogenesis of these tumours which develop in an achylic stomach is discussed.

Key words: Stomach – Carcinoids – Achylia – Pernicious anaemia – Argyrophil reaction

Introduction

The first report of gastric carcinoids was published by Askanazy in 1923. Since then sporadic cases have occurred and in 1961 Christodouloupoulos and Klotz reviewed the literature and collected a total number of 79 cases, of which only five were associated with the carcinoid syndrome. There have also been a few reports of the Zollinger-Ellison syndrome (Royston et al. 1972; Larsson et al. 1973) and Cushing's syndrome (Hirata et al. 1976) due to hormone secretion from gastric carcinoids, but on the whole endocrine symptoms from the tumours seem to be infrequent and unpredictable.

A recent report indicated that achylia with or without pernicious anaemia (PA) is associated with gastric carcinoids in a higher frequency than has been suspected previously and that a relatively large number of these tumours may

Offprint requests to: E. Wilander at the above address.

¹ The term carcinoid is used here to mean a primary endocrine tumour of the digestive tract irrespective of the presence or absence of 5-hydroxytryptamine (5-HT) (Dawson 1976)

contain a majority of tumour cells of the enterochromaffin-like (ECL) type (Wilander 1980). In an attempt to get further information about the frequency of these tumours and to study the observed clinico-pathological correlation in an unselected material, all available gastric carcinoids recorded in the Cancer Registry of the National Board of Health and Welfare in Sweden (1958–1974) and at the Department of Pathology in Uppsala (1975–1980) were collected and analysed retrospectively with regard to the clinical picture, morphology and the staining properties with different silver techniques.

Material and Methods

The material comprised paraffin blocks of gastric carcinoids obtained at surgical resection from 24 patients in different hospitals in Sweden between 1958 and 1980. About 4 µm thick sections were cut from the blocks, deparaffinized and stained with haematoxylin and eosin, the argentaffin staining technique of Masson-Hamperl as described by Singh (1964) and two argyrophil stains, namely the Grimelius (1969) and the Sevier-Munger (1965) stain. In addition to a study of the light microscopic morphology in routinely stained sections, the Grimelius stain was used to classify the tumours, since this stain is non-discriminating and stains almost all the different types of normal endocrine cells of the gastro-intestinal mucosa (Grimelius and Wilander 1980) as well as carcinoids – irrespective of their location (Wilander et al. 1977a and b, 1979a). Only gastric carcinoids with an argyrophil reaction (Grimelius stain) in the majority of the tumour cells were accepted for the study. The findings at preoperative radiography and the morphology of the gastric mucosa close to the tumours were decisive for the establishment of the location of the carcinoids in the stomach.

Results

Clinical Data

Of the 24 patients, 10 were men and 14 were women, with an age range of 32–79 years. Seven patients had concomitant achylia (Table 1). The condition was diagnosed preoperatively except in one patient (No. 9), in whom diagnosis was settled postoperatively after a local resection of the tumour. Of the achylic patients four had associated PA (three of these cases have been described before – Wilander et al. 1979a and b). The PA was diagnosed preoperatively in three patients. In one, who preoperatively had an anaemia of unknown cause, the PA was established one year after a subtotal gastrectomy performed for multiple gastric carcinoids (case 23). Four patients had multiple gastric carcinoids (cases 20, 21, 22 and 23). They were all located in the body of the stomach (Table 1). No carcinoid syndrome or other endocrine syndrome was present in any of the patients.

Light Microscopy

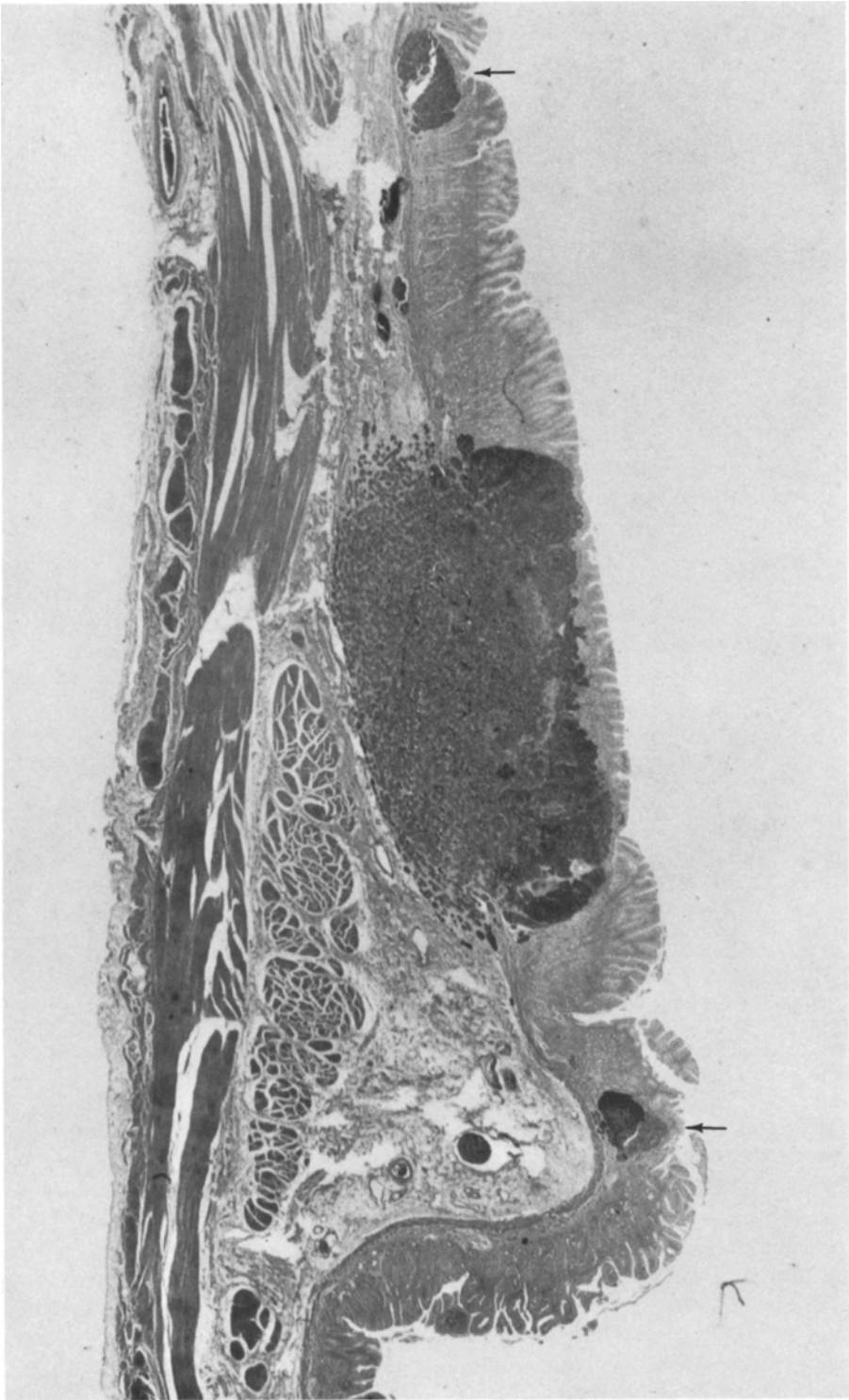
All tumours showed the microscopic picture of carcinoids, with regular tumour cells growing in solid sheets, buds, tubular and ribbon-like structures. They were all “atypical” compared with the morphology of the “classical” carcinoids of the mid-gut as described by Williams and Sandler (1963). The majority of the tumour cells were argyrophil with the Grimelius technique in all cases,

Table 1. Clinical observations and histopathology of 24 gastric carcinoids

Case No.	Sex	Age yrs	Location	Diameter (cm)	Multiple tumours	Argyrophil reaction ^a	Achyilia	Pernicious anaemia
1	M	65	Antrum	0.7	—	+	—	—
2	M	40	Antrum	0.8	—	—	—	—
3	F	79	Antrum	0.6	—	—	+	—
							(11 years preop)	
4	F	51	Antrum	1.2	—	+	—	—
5	F	68	Antrum	6	—	+	—	—
6	F	65	Antrum	8	—	—	—	—
7	M	69	Antrum	9	—	+	—	—
8	M	60	Corpus	0.6	—	+	+	+
							(preop)	(22 years preop)
9	F	52	Corpus	0.9	—	+	+	—
							(postop)	
10	M	62	Corpus	1.5	—	+	—	—
11	M	52	Corpus	1.5	—	+	—	—
12	M	49	Corpus	1.5	—	+	—	—
13	F	68	Corpus	2	—	+	+	+
							(33 years preop)	(8 years preop)
14	F	55	Corpus	1.2	—	+	+	—
							(preop)	
15	F	38	Corpus	1.5	—	+	—	—
16	F	45	Corpus	1.6	—	+	—	—
17	F	57	Corpus	2	—	+	—	—
18	F	60	Corpus	3	—	—	—	—
19	M	79	Corpus	5	—	+	—	—
20	M	76	Corpus	1–2	+(2)	+	+	+
							(preop)	(preop)
21	F	39	Corpus	<0.6	+(4)	+	+	—
							(many years)	
22	F	32	Corpus	<1	+(5)	+	—	—
23	F	41	Corpus	<2	+	+	—	+
					(several)			(1 year postop)
24	M	62	Cardia	5	—	—	—	—

^a + indicates argyrophil cells with the Sevier-Munger technique in the majority of tumour cells

which, as mentioned in Material and Methods, was a criterion for inclusion in the study. With the Sevier-Munger argyrophil silver stain the majority of the tumour cells were stained in 19 cases, and most of these tumours were located in the corpus (Table 1). All multiple tumours were Sevier-Munger positive. The Masson stain yielded only a very few scattered argentaffin cells in some tumours but was otherwise negative, indicating negligible amounts of 5-hydroxytryptamine in the tumours. In case 22, in addition to the five macroscopically visible tumours there were several small nodules of argyrophil (Sevier-Munger) tumours which were observable only at the light microscopic level.



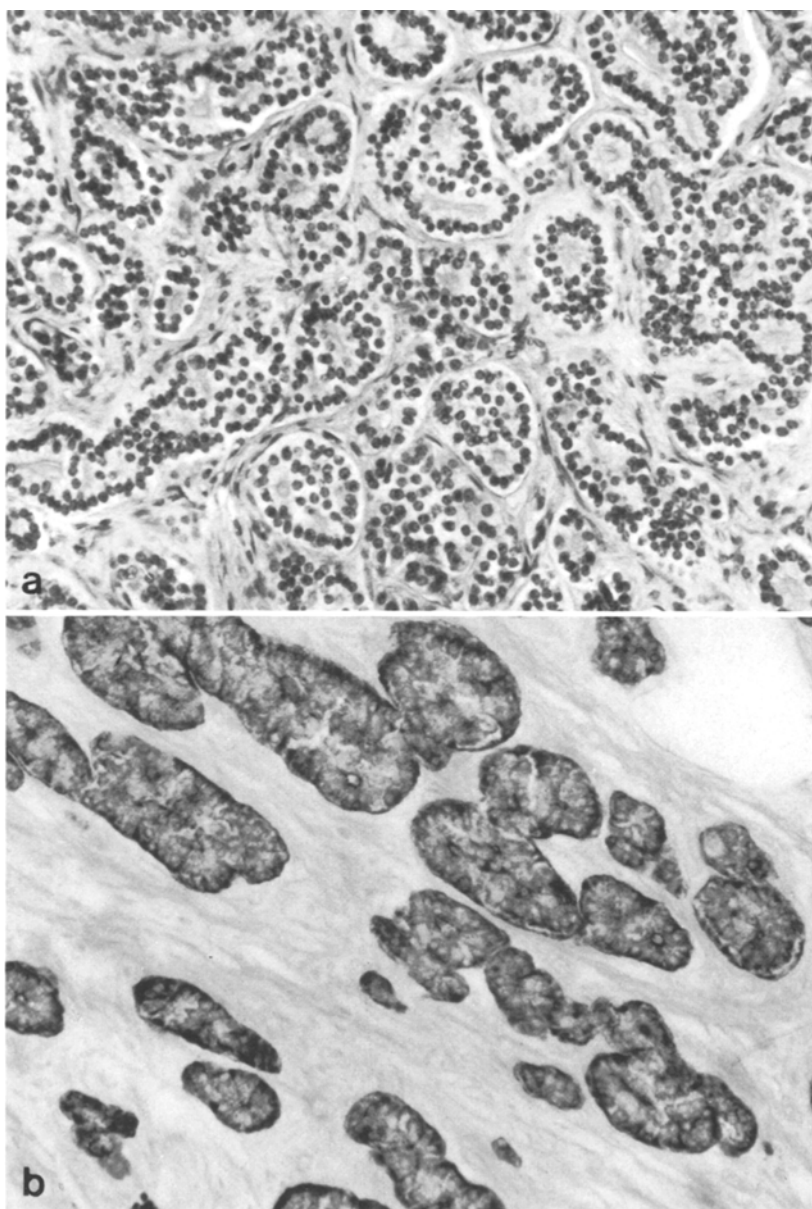


Fig. 2. **a** Haematoxylin-eosin stain of the same tumour as in Fig. 1. $\times 250$. **b** Grimelius stain $\times 250$

Fig. 1. Low-power view of microscopic section of the gastric specimen from case 22. In the gastric mucosa and submucosa of the corpus area, a carcinoid tumour is seen. Peripheral to the main tumour there are also two small mucosal tumour nodules which were diagnosed light microscopically (*arrows*); Grimelius stain $\times 8$

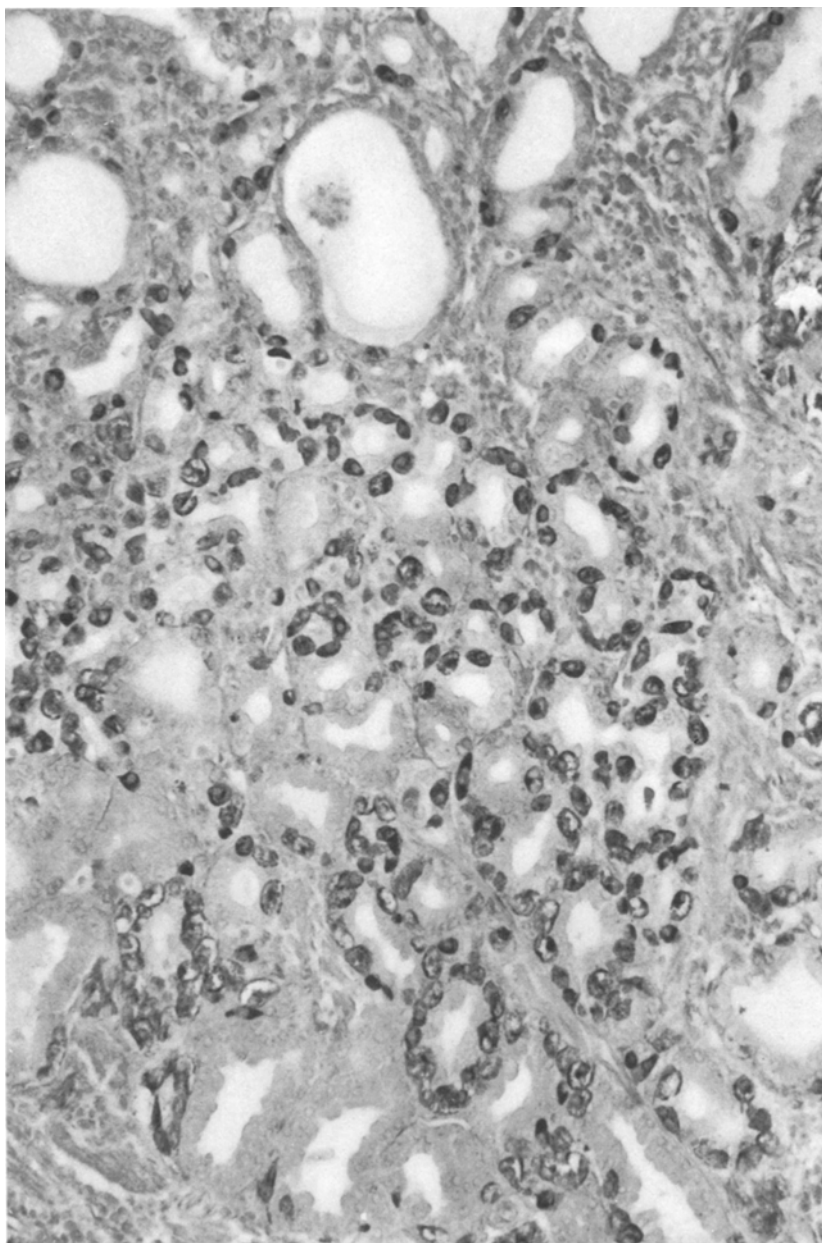


Fig. 3. Photomicrograph of the gastric mucosa (corpus area) of case 23, showing the pronounced hyperplasia of argyrophil cells; Grimelius stain $\times 250$

These were located in the deeper part of the mucosa and did not penetrate through the *lamina muscularis mucosa* (Figs. 1, 2a and b). The gastric mucosa of case 23 presented a morphology which was not observed in any of the other patients. The basal part of the mucosa of the corpus harboured endocrine cells which showed pronounced hyperplasia and an argyrophil reaction with the Grimelius and the Sevier-Munger stain (Fig. 3). The hyperplastic cells were diffusely spread but sometimes had the appearance of multiple isolated microtumours. There was no sharp border between these diffuse or nodular hyperplastic cells and the macroscopically identified argyrophil tumours.

Discussion

The incidence of cancer of the stomach is increased in patients with PA (Elsborg and Mosbech 1979), a disease in which atrophic gastritis and achlorhydria are important features. It has been observed that the mean nitrate concentration in gastric juice from fasting patients with PA is nearly fifty-fold greater than that of age-matched controls. The nitrate is essential for the formation of volatile nitrosamines, which possess carcinogenic properties, and a high concentration of nitrosamines in the achylic stomach has been suggested as an important pathogenic factor in the development of gastric cancer (Ruddell et al. 1978).

Gastric cancer in patients with PA is more frequent in the corpus and fundus region of the stomach than gastric cancer in patients without PA, indicating a difference in the pathogenesis of cancer of the stomach between patients with and without PA (Elsborg and Mosbech 1979). Since patients with PA often have high plasma gastrin concentrations, caused by decreased acid feedback inhibition (Ganguli et al. 1971), and since gastrin is a trophic hormone for the corpus and fundus of the stomach, it has been presumed that high gastrin levels promote the development of gastric cancer in patients with PA (Elsborg and Mosbech 1979).

In the present study 25% of the patients with gastric carcinoids were achylic preoperatively and half of these had associated PA. The tumours that developed in the achylic stomach showed a predilection for the corpus area. This situation resembles that of gastric cancer and indicates similarities in the pathogenesis of these two types of epithelial neoplasms of the stomach.

Almost all of the gastric carcinoids associated with achyilia examined contained a majority of tumour cells which were argyrophilic with the Sevier-Munger silver stain. The silver reaction indicates that the tumour cells are ECL cells (Solcia et al. 1970; Hage and Hage 1976; Larsson et al. 1978; Capella et al. 1980) storing an unknown hormone. Several studies in man have revealed hyperplasia of ECL cells in association with increased plasma gastrin levels and achyilia (Solcia et al. 1970; Rubin 1973; Bordi et al. 1976). It may be postulated that a trophic action of gastrin on the ECL cells and high concentrations of carcinogenic nitrosamines are pathogenetic factors in the development of argyrophil gastric carcinoids in the achylic stomach, as illustrated in Fig. 4. The formation of ECL cell tumours may be preceded by nodular or diffuse ECL cell hyperplasia (Black et al. 1968; Hodges et al. 1981) as indicated in cases twenty two and twenty three.

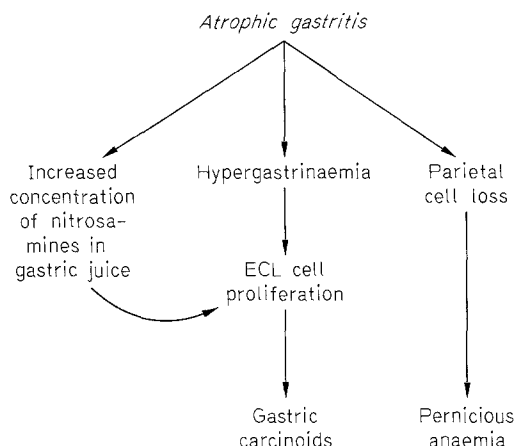


Fig. 4. Presumed pathogenesis of gastric carcinoids which develop in an achylia stomach

At least ten cases of pernicious anaemia in association with gastric carcinoids have been documented in the literature by other authors (Martin and Atkins 1952; Cattani et al. 1955; Pestana et al. 1963; Sheahan et al. 1971; Gueller and Haddad 1975; Bader et al. 1977; Harris and Greenberg 1978; Hodges et al. 1981) and seven cases of gastric carcinoids in association with achylia (Lützow-Holm 1952; Hines and Savage 1955; Eklöf 1967; Gueller and Haddad 1975; Bordi et al. 1976). The occurrence of endocrine syndromes in connection with gastric carcinoids is rare. Postlethweit (1966) collected a total number of eight cases with the carcinoid syndrome. The findings in the present study are in agreement with the observation that achylia, sometimes with concomitant PA, is the most distinct clinical condition associated with gastric carcinoids, especially those which tend to be multiple and are located in the corpus area of the stomach.

Acknowledgements. This investigation was supported by grants from the Swedish Medical Research Council (Project No. 102). The technical assistance of Monalill Lundqvist is appreciated.

References

- Askanazy M (1923) Zur Pathogenese der Magenkrebsse und über ihren gelegentlichen Ursprung aus angeborenen epithelialen Keimen in der Magenwand. *Dtschr Med Wochenschr* 49:49–51
- Bader LV, Lykke AWJ, Hinterberger H (1977) Multiple biogenic amine-secreting "carcinoid" tumour of the stomach: A case report: *Pathology* 9:353–358
- Black WC, Haffner HE (1968) Diffuse hyperplasia of gastric argyrophil cells and multiple carcinoid tumours. A histological and ultrastructural study. *Cancer* 21:1080–1099
- Bordi C, Costa A, Missale G (1975) ECL cell proliferation and gastrin levels. *Gastroenterology* 68:205–206
- Bordi C, Senatore S, Missale G (1976) Gastric carcinoid following gastro-jejunostomy. *Am J Dig Dis* 21:667–671
- Capella C, Polak JM, Timson CM, Frigerio B, Solcia E (1980) Gastric carcinoids of argyrophil ECL cells. *Ultrastruct Pathol* 1:411

- Cattan R, Nallet J, Libeskind M, Habib R, Pariente Pu (1955) Carcinoïde de l'estomac et anémie de Biermer. Société nationale française de gastro-entérologie, Juillet:922-928
- Christodouloupoulos JB, Klotz AP (1961) Carcinoid syndrome with primary carcinoid tumour of the stomach. *Gastroenterology* 40:429-440
- Dawson IMP (1976) The endocrine cells of the gastrointestinal tract and the neoplasms which arise from them. *Curr Top Pathol* 63:221-259
- Eklöf O (1967) Carcinoid tumours of the stomach, 3 cases reported. *Acta Chir Scand* 121:118-126
- Elsborg L, Mosbech J (1979) Pernicious anaemia as a risk factor in gastric cancer. *Acta Med Scand* 206:315-318
- Ganguli PC, Cullen DR, Irvine WJ (1971) Radioimmunoassay of plasma-gastrin in pernicious anaemia, achlorhydria without pernicious anaemia, hypochlorhydria and in controls. *Lancet* i:155-158
- Grimelius L (1969) A silver nitrate stain for A₂-cells in human pancreatic islets. *Acta Soc Med Upsal* 73:243-270
- Grimelius L, Wilander E (1980) Silver stains in the study of endocrine cells of the gut and pancreas. *Invest Cell Pathol* 3:3-12
- Gueller R, Haddad JK (1975) Gastric carcinoids simulating benign polyps. Two cases diagnosed by endoscopic biopsy. *Gastrointest Endosc* 21:153-155
- Hage E, Hage J (1976) A gastric carcinoma identified as an ECL-oma associated with acanthosis nigricans. In: Fujita (ed) *Endocrine gut and pancreas*, Elsevier, Amsterdam, pp 359-369
- Harris AI, Greenberg H (1978) Pernicious anaemia and the development of carcinoid tumours of the stomach. *JAMA* 239:1160-1161
- Hines CR, Savage JL (1955) Carcinoid tumours of the stomach. *Ann Intern Med* 43:859-867
- Hirata Y, Sakamoto N, Yamamoto H, Masukura S, Imura H, Okada S (1976) Gastric carcinoid with ectopic production of ACTH and B-MSH. *Cancer* 37:377-385
- Hodges JR, Isaacson P, Wright R (1981) Diffuse enterochromaffin-like (ECL) cell hyperplasia and multiple gastric carcinoids: a complication of pernicious anaemia. *Gut* 22:237-241
- Larsson L-I, Ljungberg O, Sundler F, Håkanson R, Svensson SO, Rehfeld JF, Stadil F, Holst J (1973) Antropyloric gastrinoma associated. *Virchows Arch [Pathol Anat]* 360:305-314
- Larsson L-I, Rehfeld J, Stockbrügger R, Glohne G, Schöön IM, Lundqvist G, Kindblom L, Sæve-Söderberg J, Grimelius L, Olbe L (1978) Mixed endocrine gastric tumours associated with hypergastrinaemia of antral origin. *Am J Pathol* 93:53-68
- Lützw-Holm G (1952) Carcinoid tumours of the stomach. Two cases. *Acta Chir Scand* 104:193-200
- Martin JD, Atkins EL (1952) Carcinoid of the stomach. Review of reported cases. *Surgery* 31:698-704
- Pestana C, Beahrs OH, Woolner LB (1963) Multiple (seven) carcinoids of the stomach. Report of cases. *Proc Mayo Clin* 38:453-456
- Postlethwait RW (1966) Gastrointestinal carcinoid tumours. A review *Postgrad Med* 40:445-454
- Royston CMS, Brew DSJ, Garnham JR, Stagg BH, Polak J (1972) The Zollinger-Ellison syndrome due to an infiltrating tumour of the stomach. *Gut* 13:638-642
- Rubin W (1973) A fine structural characterization of the proliferated endocrine cells in atrophic gastric mucosa. *Am J Pathol* 70:109-118
- Ruddell WS, Bone ES, Hill MJ, Walters CL (1978) Pathogenesis of gastric cancer in pernicious anaemia. *Lancet* i:521-523
- Sevier AC, Munger BL (1965) A silver method for paraffin sections of neural tissue. *J Neuropathol Exp Neurol* 24:130-135
- Sheahan DG, Horowitz SA, Zamchek N (1971) Deletion of epithelial ABH isoantigens in primary gastric neoplasms and in metastatic cancer. *Am J Dig Dis* 16:961-969
- Singh J (1964) A modification of the Masson-Hamperl method for staining of argentaffin cells. *Anat Anz* 115:81-82
- Solcia E, Capella C, Vassallo G (1970) Endocrine cells of the stomach and pancreas in states of gastric hypersecretion. *Rendic Gastroenterol* 2:147-158
- Wilander E (1980) Letter to the editor: Achylia, pernicious anaemia, ECL-cells and gastric carcinoids. *Virchows Arch Pathol [Anat]* 387:371-373
- Wilander E, Grimelius L, Lundqvist G, Skoog V (1979a) Polypeptide hormones in argentaffin and argyrophil gastro-duodenal carcinoids. *Am J Pathol* 96:519-530

- Wilander E, Portela-Gomes G, Grimelius L, Lundqvist G, Skoog V (1977a) Enteroglucagon and substance P-like immunoreactivity in argentaffin and argyrophil rectal carcinoids. *Virchows Arch [Cell Pathol]* 25:117–124
- Wilander E, Portela-Gomes G, Grimelius L, Westermark P (1977b) Argentaffin and argyrophil reactions of human gastrointestinal carcinoids. *Gastroenterology* 73:733–736
- Wilander E, Sundström C, Grimelius L (1979b) Pernicious anaemia in association with argyrophil (Sevier-Munger) gastric carcinoid. *Scand J Haematol* 23:415–429
- Williams ED, Sandler M (1963) The classification of carcinoid tumours. *Lancet* i:238–239

Accepted August 18, 1981