15 Neuroendocrine Gastro-Entero-Pancreatic (GEP) Tumors

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Summary

Neuroendocrine gastro-entero-pancreatic (GEP) tumors are rare but present with variable, sometimes dramatic clinical syndromes. The majority of these tumors is non-functioning and most functioning and non-functioning tumors are malignant. This chapter describes the various clinical entities, has a special focus on histopathology of these tumors as a reliable source for prognosis and summarizes current state and new trends in diagnosis and treatment of these tumors. The management of neuroendocrine GEP-tumors needs a multidisciplinary approach. Therefore, diagnostic and therapeutic aspects of this chapter recognize the important contributions of surgery, pathology, radiology, nuclear medicine and gastrointestinal endocrinology.

Definition

Several terms for endocrine tumors of the gastrointestinal tract are currently applied to describe the same pathological entity: "carcinoid", "neuroendocrine tumor", "neuroendocrine carcinoma", "APUDoma", "gastro-entero-pancreatic (GEP) tumor", "islet cell tumor" (in case of pancreatic origin). The term "carcinoid" was introduced by S. Oberndorfer in 1907 to distinguish carcinoids as less rapidly growing and well-differentiated epithelial tumors of the small intestine from the more aggressively growing adenocarcinoma of the gut and, thus, recognizing the decisive difference to carcinomas which is the very slow growth of most endocrine tumors and which is frequently associated with an uncompromized life quality. Strictly speaking is the term "carcinoid" reserved for endocrine tumors of the gastrointestinal tract (Table 2) and not for those of the pancreas (Table 1). Endocrine pancreatic tumors are assumed to arise from islets of Langerhans although their origin from the dif-

fuse endocrine cell system scattered within the mucosa of the gastrointestinal tract and the pancreatic duct system cannot be excluded. At least in vertebrates, the islets of Langerhans arise within an independent islet organ which melts together with the exocrine pancreas during ontogenesis. The blurredness of the term "carcinoid" results from its histological features which are almost identical with those of endocrine pancreatic tumors. Therefore, even pathologists frequently use the term "carcinoid" to describe an endocrine pancreatic tumor. To avoid the dilemma, the term "carcinoid" should be used only for well-differentiated endocrine tumors of the gut and the term "malignant carcinoid" to designate the corresponding well differentiated endocrine carcinoma [1]. If a "carcinoid" is associated with a clinical syndrome as a Zollinger-Ellison syndrome in the case of a gastrin-producing endocrine tumor of the duodenum, the respective "carcinoid" should better be called gastrinoma.

The term "neuroendocrine" reflects the origin of the endocrine cells of the gastrointestinal tract fom the embryonic neural crest. They have been designated as "Helles Zellenorgan" by F. Feyrter. The acronym "APUDoma" (amine precursor uptake and decarboxylation) describes the potency of endocrine tumors to synthesize in addition to hormones biogenic amines as serotonin and other peptides characteristic to cells originating from the neural crest first described by A.E.G. Pearse.

Endocrine tumors of the gastrointestinal tract are epithelial tumors and differ histologically from neuronal tumors as neuroblastomas, pheochromocytomas and paragangliomas which also arise from the diffuse neuroendocrine system and are, therefore, of neural crest origin.

Amphicrine and mixed endocrine-exocrine tumors will not be discussed within this survey since their prognosis and biological features are determined by the exocrine cell department with a predominantly unfavourable prognosis.

Table 1

Classification and leading symptoms of the most frequent endocrine tumors of the gastrointestinal tract

Name (Syndrome)	Leading Symptoms	Responsible Hormone	Other Hormones in the Tumor	Malignancy (%)	Localization of primary	Extra-pancreatic Localization
Insulinoma	Hypoglycaemia	Insulin	Glucagon, PP	5–10	Pancreas	very rare
Gastrinoma (Zollinger-Ellison syndrome)	Peptic Ulcers, Diarrhea, Reflux Disease	Gastrin	Insulin, PP, Glucagon, ACTH, Somatostatin, Chromogranin A	>90	Pancreas	Duodenum, Stomach, Mesenterium
Carcinoid syndrome	Flush, Diarrhoea, Bronchial Obstruction	Serotonin	Tachykinins, Prostaglandins, Chromogranin A	100	Ileum	Pancreas (rare)
VIPoma (Verner-Morrison syndrome), Pancreatic Cholera	Intractable Diarrhea, Hypokalemia	VIP, PHI	PP, Glucagon, Somatostatin, Chromogranin A	75	Pancreas	
Glucagonoma	Erythema necrolyticans migrans, Diabetes	Glucagon	PP, Insulin, Somatostatin, Chromogranin A	50	Pancreas	Rare
Somatostatinoma	Diabetes, Steatorrhea, Gallstones	Somatostatin	PP, Insulin, Calcitonin	50	Pancreas	Duodenum
GHRHoma	Acromegaly	GHRH	Somatostatin, Gastrin, Insulin, Chromogranin A	100	Pancreas	Lung
CRHoma, ACTHoma	Cushing's syndrome	CRH	Gastrin, PP, Chromogranin A	>90	Pancreas	Lung

ACTH Adreno-corticotrophic hormone; *CRH* Corticotropin releasing hormone; *GHRH* Growth hormone releasing hormone; *PHI* Peptide histidine isoleucine; *PP* Pancreatic peptide; *VIP* Vasoactive intestinal polypeptide.

Table 2

Characteristics of extra-pancreatic endocrine gastrointestinal tumors ("carcinoids")

Localization	% of all carcinoids	Peptides and hormones	Functional activity	Endocrine cell type	Malignancy
Esophagus	0.04	Chromogranin A	rarely	Grimelius positive, NSE positive	>50%
Stomach	2–3	Chromogranin A (histamine, gastrin), Ghrelin, VMAT-2	very rarely	ECL-cells, rarely EC-cells, rarely G-cells	highly variable
Duodenum and proximal jejunum	22	5-HT, gastrin, somatostatin, PP, calcitonin, ACTH	Zollinger-Ellison syndrome or functional inactive	EC-cells, G-cells, somatostatin-cells	50%
Distal jejunum and ileum	23–28	Chromogranin A, serotonin, substance P, tachykinins, others	mostly inactive; carcinoid syndrome in 5–7%	EC-cells	>50% in tumors larger then 1 cm
Appendix	19	Serotonin, GLP-1, GIP-2, PP/PYY	mostly inactive; carcinoid syndrome extremely rare	EC-cells, L-cells	risk factor size >2 cm and invasion of mesoappendix
Cecum	8	Serotonin	carcinoid syndrome in 5%	EC-cells	> 50%
Ascending Colon	8	GLP-1, GLP-2 PP/PYY		L-cells	
Rectosigmoid	20	Serotonin,	no	EC-cells	15% depends on tumor size and invasion
Rectum	20	GLP-1, GLP-2 PP/PYY		L-Cells	

Classification

Endocrine GEP tumors can be subdivided according to their origin into those originating from the foregut (esophagus, stomach, duodenum, proximal jejunum, pancreas), midgut (distal jejunum, ileum, appendix, cecum, right-sided colon) and hindgut (left-sided colon and rectum). This classification is based on the embryologic assignment of the different parts of the gut. Vary rarely endocrine tumors of the same histology can arise in the ovary, extrahepatic bile ducts, the liver, the kidney, testis, spleen, breast and larynx and other organs as the broncial system and thymus.

Clinically more relevant is a classification according to the functional activity of endocrine GEP tumors. Most benign and malignant endocrine GEP tumors are functionally inactive and patients commonly present with abdominal pain, weight loss, obstructive jaundice and intestinal obstruction depending on the localization and size of the tumor. Noteworthy, many tumors are asymptomatic even in the presence of metastases and are discovered incidentally during routine imaging procedures.

Survival of patients with GEP tumors is even in the metastatic state much more favourable than in patients with other malignancys and depends on the site of the primary tumor and the extent of metastatic spread. Of pancreatic endocrine tumors the best prognosis is associated with insulinomas which are in more that 95% of patients solitary and benign. In contrast, most of the other pancreatic entities are malignant (see Table 1).

As shown in Tables 1 and 2 the majority of functionally active endocrine tumors arise within the pancreas (see Table 1) whereas functionally active tumors within the gastrointestinal tract can cause the Zollinger-Ellison syndrome if originating from the duodenum or cause a Carcinoid syndrome due to a metastatic tumor of the ileum.

Endocrine GEP tumors may be benign or malignant. The majority of endocrine pancreatic tumors are malignant and present with metastases mostly to the liver (see Table 1). The malignancy rate of endocrine tumors within the gastrointestinal tract is highly variable and mostly depending on the size of the carcinoid.

Endocrine GEP tumors can arise sporadic or as part of the Multiple Endocrine Neoplasia (MEN) syndromes (Table 3). MEN-I syndrome is an autosomal dominantly inherited disorder characterized by the synchronous or metachronous occurrence of tumors in multiple endocrine organs, predominantly the pancreas, parathyroid, pituitary and duodenum. The genetic locus was ascribed to a segment of the long arm of chromosome 11, where the menin gene – a tumor suppressor gene – is located which is in MEN-I syndrome mutated [2, 3]. MEN-I syndrome is present in 20% of patients with gastrinoma

Table 3
MEN syndromes

Syndrome	Affected organ	Alterations
MEN-1 (Wermer's syndrome)	Parathyroid gland	Hyperplasia, multiple adenomas
	Pancreas	Islet cell tumors (insulinoma, gastrinoma, VIPoma, glucagonoma)
	Pituitary (anterior)	Adenoma (prolactin, ACTH, STH, GH, non-funtioning)
MEN-2A (Sipple's syndrome)	Thyroid gland	C-cell hyperplasia, medullary thyroid carcinoma
	Adrenal medulla	Phaeochromocytoma
	Parathyroid gland	Hyperplasia, multiple adenomas
MEN-2B	Thyroid gland	C-cell hyperplasia, medullary thyroid carcinoma
	Adrenal medulla	Phaeochromocytoma
	Mucosa	Neuromas
	Other abnormalities:	
	Marfanoid habitus,	
	Megacolon	

[4], 4% of patients with insulinoma [5] and 13–17% of patients with glucagonoma [6]. However, in MEN-I syndrome most endocrine pancreatic tumors are non-functional containing mostly pancreatic polypeptide or glucagon [5].

Epidemiology

Endocrine GEP tumors are rare events. The exact incidence and prevalence of these tumors is difficult to ascertain because many are asymptomatic. From autopsy studies an annual incidence of 8.4 gastrointestinal endocrine tumors (carcinoids) per 100.000 people has been calculated [7, 8] (Table 4). 90% of these tumors were incidental autopsy findings. For endocrine pancreatic tumors an annual incidence of 0,1–0,4 tumors per 100.000 has been reported. [8]. Table 4 summarizes the published annual incidence rates for the most common gastrointestinal (carcinoids) and pancreatic endocrine tumors. Endocrine tumors originating in the midgut encompass by far the majority of all endocrine tumors followed by the pancreatic endocrine tumors.

Almost all endocrine tumors originating within the hindgut are asymptomatic and do not create symptoms as a consequence of hormone overproduction. The reason for that is unknown since many of these tumors contain peptides and hormones which are also pro-

Table 4
Epidemiological data of endocrine GEP tumors

Localization	Incidence cases per 100.000 people per year	Remarks (% of all gastro-intestinal carcinoids)	Mean age [years] (range)
Stomach	0.002–0.1	(11–14%) type I: 74% type II: 6% type III: 13% poorly differentiated: 6%	50–60 63 [15–88] 50 [28–67] 55 [41–61]
Duodenum		(22%) Gastrin-producing: 62% Somatostatin-producing: 21% Gangliocytic pasaganglioma: 9% Undefined tumors: 5,6%	59 [30–90]
Proximal Jejunum		(1%)	
Distal Jejunum/Ileum [30–99]	0.28–0.89	(28%)	60–70
Appendix [6–80]		(19%) more frequent in females	32–45
Colon	0.07–0.21	(right-sided colon: 8%) (left-sided colon: 20%)	58
Rectum	0.14–0.76		60
Pancreas			
all	0.01 – 0.3		
Insulinoma	0.1–0.2		47 [8–82]
Gastrinoma	0.05–0.15		[33–53]
VIPoma	0.005–0.02		
Glucagonoma	0.001–0.01		

duced in tumors responsible for the carcinoid syndrome. The same is true for most gastric carcinoids and carcinoids arising in the distal ileum. Even in metastatic tumors a hormone mediated symptomatology is mostly absent. Of the endocrine pancreatic tumors almost 50% are functionally inactive as well [8]. The incidence rates of the functionally active tumors with insulinoma as the most frequent tumor are listed in table 4.

According to an analysis of 8305 cases of carcinoid tumors identified by the "Surveillance, Epidemiology, and End Results" (SEER) program of the American National Cancer Institute (NCI) from 1973 to 1991 and by an earlier NCI program 5-year survival of patients was 50.4% [7]. The presence of regional and distant metastases reduced survival rate to 21,8%. If survival rates are calculated separately for tumors arising in the foregut, midgut and hindgut 5-year survival rates were 44.5%, 61% and 72% respectively [7]. Most favourable survival have appendiceal carcinoids with 85.9%. Surveillance rates for endocrine GEP tumors of specific localizations will be discussed in more detail later in this chapter.

Etiology

The etiology of endocrine GEP tumors is unknown. It is comprehensible to assume that they originate from cells or rather precursor cells of the diffuse neuroendocrine cell system. Endocrine tumor cells display certain cytochemical properties with endocrine cells scattered within the mucosa of the gastrointestinal tract and with the constituents of the islets of Langerhans as the expression of neuron-specific enolase, synaptophysin and chomogranin A and C [1, 16]. Chromogranins are acidic glycoproteins present in almost all endocrine and neuronal tissues. They are released into the circulation and can serve as tumor markers since they are found in more than 90% of patients with endocrine GEP tumors. Although endocrine pancreatic tumors are also called "islet cell tumors" it is unproven that pancreatic insulinomas, gastrinomas, VIPomas etc. originate from the islets of Langerhans. In favour of this assumption are findings in experimental settings which clearly demonstrate that insulinomas in rats can under defined conditions arise from islets. However, some endocrine pancreatic tumors produce hormones and peptides as gastrin or VIP which are not synthesized from islet cells

after birth. Therefore, it is conceivable to assume that islet tumors originate from endocrine pancreatic multipotent precursor cells which are constituants of the pancreatic duct epithelium [13].

General Pathophysiology

The key event occurring in functionally active endocrine GEP tumor cells is the loss of capacity to store their hormonal product as insulin in insulinomas, gastrin in gastrinomas etc. within the tumor cell. Therefore, inappropriately released hormones and peptides not responding to the physiological feedback inhibition are responsible for the clinical manifestation of the disease. According to the concept of an impaired storage capacity of tumor cells, it has been shown, that insulinoma cells contain less insulin than normal β-cells, and the mean total insulin content of insulinomas was even lower than the mean insulin content of the whole pancreas of the respective patient [14]. Very similar is the gastrin content of the majority of gastrinomas lower compared to the gastrin content of the whole antral mucosa which contains more gastrin-producing cells than the tumor [15].

Histopathology

Most endocrine GEP tumors display a solid, trabecular or glandular arrangement of well-different (Fig. 1a–c) [1, 16]. However, not in every case these features permit recognition of the endocrine nature of the tumor. In these tumors special staining methods as silver methods or immunohistochemical staines for general endocrine markers as chromogranins (Fig. 1e), synaptophysin or neuron-specific enolase are needed for tumor identification [1, 16]. To characterize the tumor cell further with regard to their hormone/peptide production specific antibodies against polypeptide hormones are needed to identify a tumor cell as insulin-, gastrin-, glucagon- or other hormones producing cell (Fig 2a, b) [16]. Endocrine tumors with predominant insulin production can be classified as insulinoma, those with predominant glucagon- or gastrin production as glucagonoma or gastrinoma. This does not indicate that a tumor which histologically has been diagnosed as insulinoma or glu-
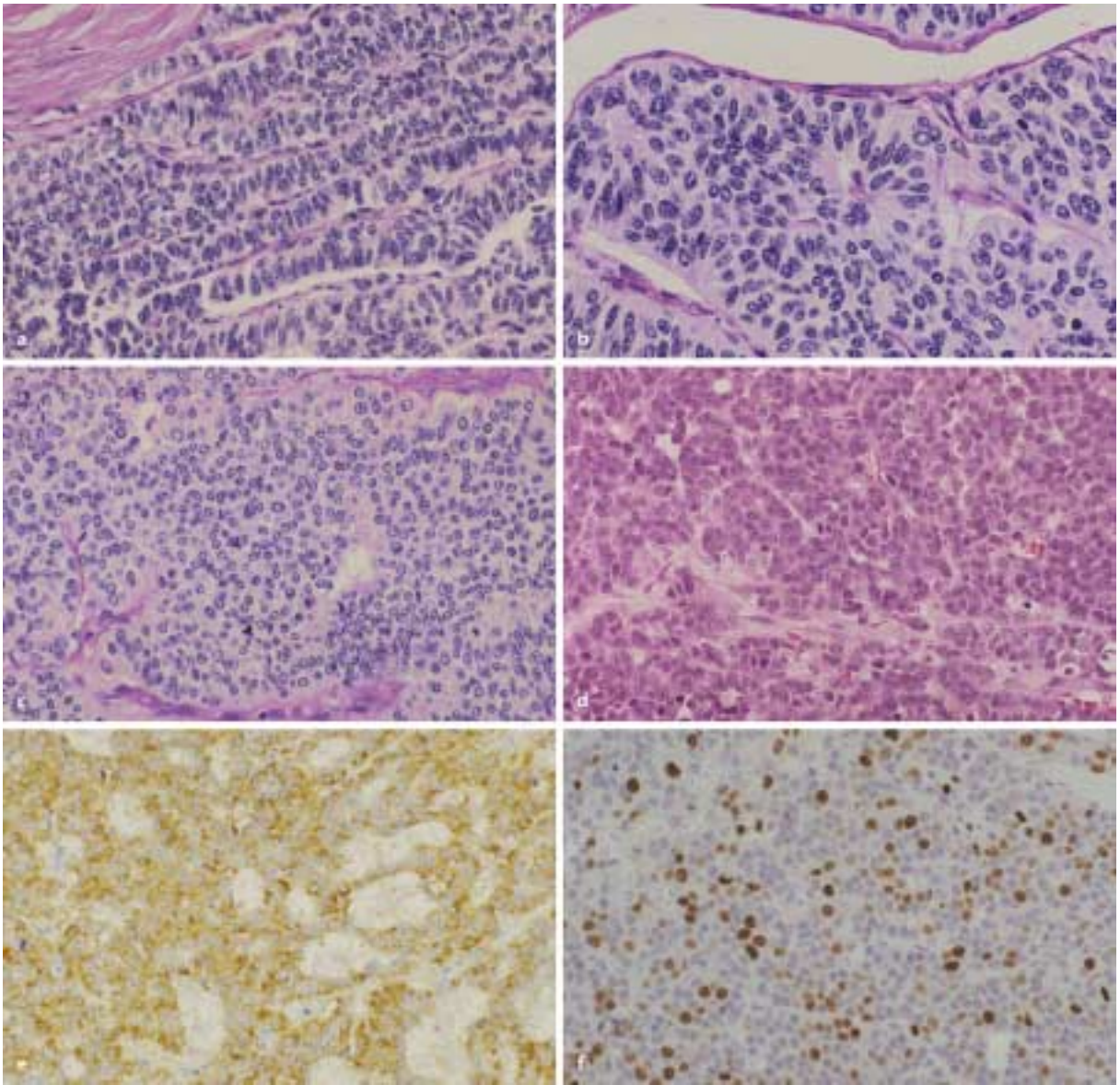
Figure 1a–f
Histopathological patterns in pancreatic endocrine tumors. a trabecular pattern; PAS staining; **b** glandular pattern; PAS staining; **c** solid pattern; PAS staining; **d** poorly differentiated neuroendocrine tumor; PAS staining; **e** staining with the endocrine marker chromogranin A; **f** staining with an antibody against the proliferation marker Ki-6

cagonoma acts as a functionally active endocrine tumor responsible for hypoglycemic attacks in the case of an insulinoma or giving rise to the typical symptoms of a glucagonoma syndrome. Functional activity or inactiv- ity cannot be deducted from histology. Correspondingly and most characteristicly, many endocrine tumors as part of the MEN-I syndrome are functionally inactive [18].
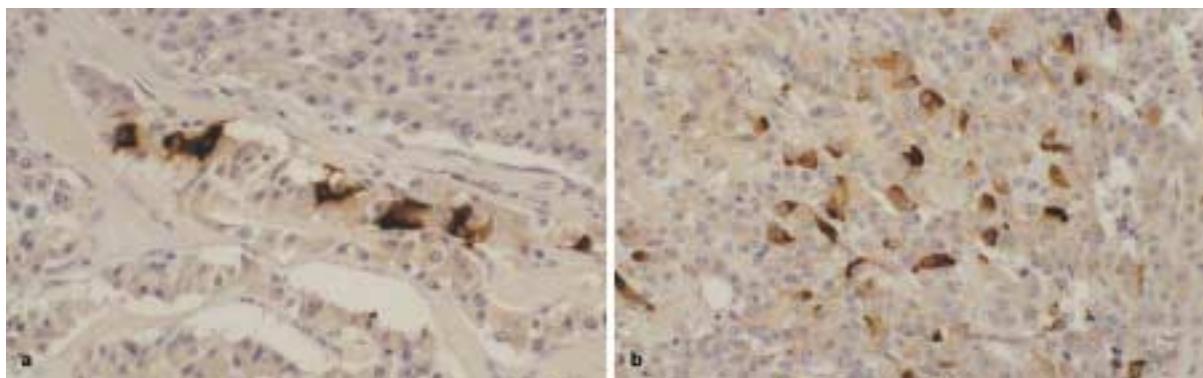
Figure 2a,b
Demonstration of several hormones present within the same endocrine Pancreatic tumor. **a** immunohistological staining for insulin; **b** immunohistological staining for gastrin

Most endocrine tumors are composed of more than one cell type. An endocrine pancreatic tumor with predominant insulin-producing cells can contain additional somatostatin- or glucagon- or pancreatic polypeptide-producing cells [15]. This feature is independent on the functional status of the tumor and can be observed in functionally active and inactive tumor [15]. It is unclear, why in the presence of multiple hormones within a single endocrine tumor only one or no clinical syndrome occurs. Nevertheless, in few patients, a second clinical syndrome can be present initially or develop later. This occurs preferably in patients with metastatic endocrine pancreatic tumors or in patients with MEN-I syndrome and multiple endocrine pancreatic tumors [4]. According to own observations which are in accordance with reports from the literature the combination of ectopic ACTH-producing and gastrin-producing pancreatic tumors giving rise to a combination of Cushing's syndrome and Zollinger-Ellison syndrome is frequent, although the condition itself with two functionally active tumors is a rare event.

Since most endocrine tumors are well-differentiated, their mitotic index visualized by the Ki67 labelling (Fig. 1f) index [9] is low which is in accordance with their slow growth behaviour. Therefore, it is difficult to predict the biological behaviour of well-differentiated tumors using classical histopathological malignancy criteria as cellular or structural atypia, necrosis, mitotic activity or microscopic invasion. A panel of international pathologists has, therefore, proposed to classify benign and malignant endocrine tumors into the categories listed in table 5 [1]. The basis for distinguishing a well-differentiated endocrine tumor from a well-differentiated endocrine carcinoma is the presence of metastases and/or evidence for local invasion. Benign or low risk endocrine tumors are distinguished from tumors with greater risk of malignancy on the basis of a combination or features such as tumor size, local extension, angioinvasion, cellular atypia, proliferative activity and the expression of hormones regularly found in the specific organ ("eutopic" hormone production) or the expression of "ectopic" hormonal products (as ACTH in an endocrine pancreatic tumor).

Poorly differentiated small cell carcinoma (Fig. 1d) is for experienced pathologists easy to distinguish from well-differentiated endocrine tumors on the basis of cellular atypia, the presence of markedly hyperchromatic nuclei, a high nuclear/cytoplasmic ratio, focal necrosis and high mitotic activity. To classify such an indifferentiated tumor as endocrine, tumors must react for

Table 5
General endocrine tumor categories

1	Well-differentiated endocrine tumor
2	Well-differentiated endocrine carcinoma
3	Poorly differentiated endocrine (small cell) carcinoma
4	Mixed exocrine-endocrine tumor
5	Tumor-like lesions

cytosolic neuroendocrine markers as synaptophysin and neuron-specific enolase [1]. However, these tumors are frequently negative for markers of endocrine granules as chromogranin and for specific hormonal products.

Additional histopathologic characteristics and tumor classifications will be discussed later when specific tumors are described in more detail.

Molecular Pathogenesis

Sporadic GEP Tumors

In sporadic pancreatic endocrine tumors (PETs) an allelic deletion of the tumor-suppressor gene MEN-I located on chromosome 11q13 has been found very frequently [3, 17]. However, the mutational frequency of MEN-I is different in functional and non-functional PETs: 30% of functional but only 8% of non-functional PETs showed mutations of the MEN-I gene [17, 18]. Furthermore, there are differences within the group of functional PETs: Alterations in MEN-I have been found in 54% (15/28) of gastrinomas, 50% (4/8) of VIPomas, 2/3 glucagonomas, 1/1 somatostatinoma but only in 7% (4/54) of insulinomas [17]. While such findings support the relevance of MEN-I for the pathogenesis of endocrine neoplasms, it is important to note that the incidence of MEN-I alteration is obviously tumor-type related and found more frequently in gastrinomas and non functional PETs than in insulinomas. Other frequent genetic abberations found in 25–50% of PETs analyzed are chromosomal deletions on 3p, 3q, 6q, 10q, 11q, 11p, 16p, 20q, 21q, 22q, Xq and Y. In up to 25% of PETs gains on chromosomes 5q, 7q, 7p, 9q, 12q, 17p and 20q were found.

The p53 tumor suppressor gene located on chromosome 17p13 encodes a nuclear protein which is involved in multiple cellular processes like cell cycle, DNA repair, replication, transcription, apoptosis and cell differentiation. p53 alterations are detectable in almost all cancers but are extremely rare in PETs. However, increased p53 protein concentrations were found in malignant insulinomas most likely due to inactivating mutations resulting in an increased stability or posttranslational events leading to overexpression [19].

The p16 (INK4a, MTS1) gene located on chromosome 9p21 encodes a protein that binds to cyclin-dependent kinase 4 inhibiting its interaction with cyclin. p16 alterations do not play a role in non-functional PETs and insulinomas. Since p16 was found abnormal in 42% of 8 gastrinomas analyzed [20] it might play a role in gastrinoma tumorigenesis. However, further studies are necessary to confirm this assumption.

DPC4/Smad4 is a tumor suppressor gene located on chromosome 18q21 encoding a protein which is involved in the TGF-β signaling pathway. Previous data suggested that Smad4 mutations seem to be common in non-functional PETs [21]. However, based on a more recent study it is unlikely that Smad4 plays a role in tumorigenesis of endocrine tumors.

Of the oncogenes c-myc, c-fos, K-ras and c-erbB-2 only K-ras was found to be overexpressed in PETs. However, only 10 of 90 PETs analyzed in the literature showed a ras mutation indicating that this is a rare event in these tumors. Most PETs with ras mutations were malignant insulinomas suggesting that alterations of ras might play a role in the pathogenesis of these tumors.
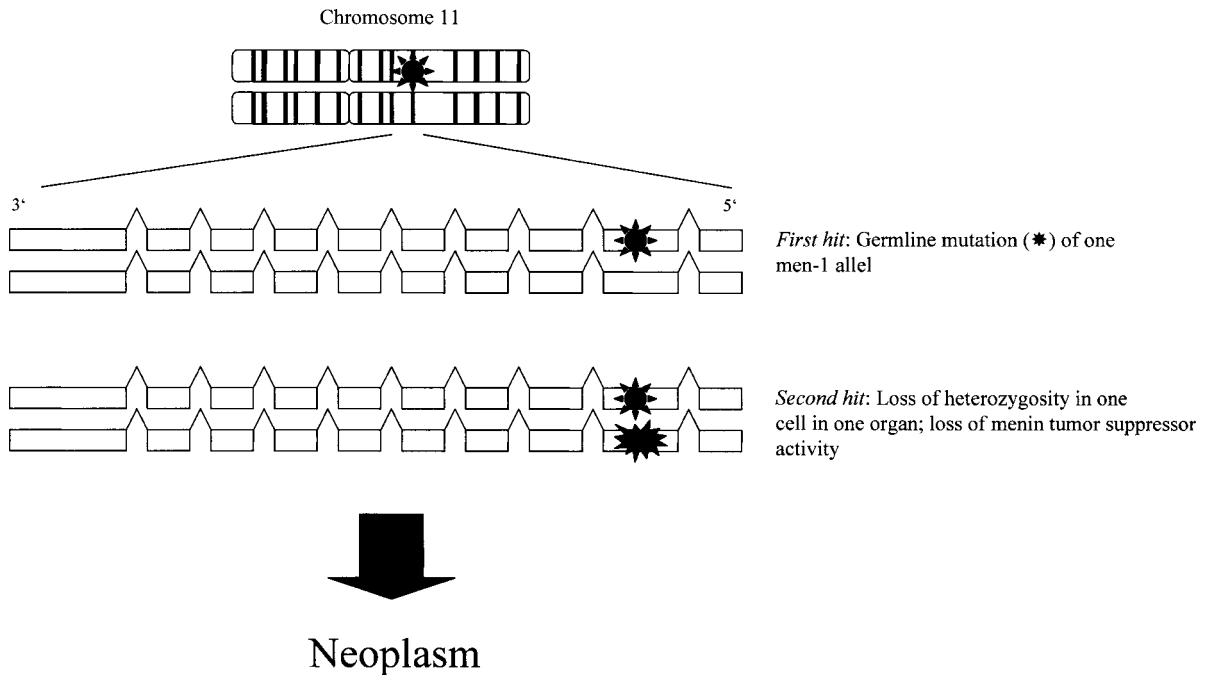
Recent data indicate that losses of sex chromosomes are common in PETs and are associated with presence of metastases, local invasion and poor survival.

Up to date the pathogenesis of neuroendocrine tumors of the gastrointestinal tract is not well characterized. Allelic loss of the MEN-I gene located on chromosome 11q13 was identified in type II ECL cell tumors and carcinoids of the jejunum and ileum. In type I ECL cell tumors abnormal RegIalpha gene was observed. In poorly differentiated neuroendocrine neoplasms allelic loss of p53 located on chromosome 17p13 were found in 4 of 9 cases suggesting a role for p53 in the development of these aggressive tumors.

Multiple Endocrine Neoplasia-Type 1

Multiple endocrine neoplasia-type 1 (MEN-I; Wermer's syndrome) is characterized by a combined occurrence of primary hyperparathyroidism, pancreatic endocrine tumors and pituitary adenomas [5]. The development of additional tumors in other endocrine or non-endocrine tissues indicates that the protein menin encoded by the MEN-I gene might have a function in a wide variety of tissues. Most MEN-I patients (90%) exhibit primary hy-

Chromosome 11

3'   5'

First hit: Germline mutation (✳) of one men-1 allel

Second hit: Loss of heterozygosity in one cell in one organ; loss of menin tumor suppressor activity

Neoplasm

Figure 3
Tumorigenesis in MEN-1 according to the two hit model described by Knudson. Patients show a germline mutation of the MEN-1 gene. Later they acquire another mutation in the wild-type allele resulting in an loss of suppressor function of the gene

perparathyroidism. Pancreatic endocrine tumors occur in ~60% and are usually benign and non-functional [5]. The most common functional tumors are insulinomas and gastrinomas. The prevalence of pituitary adenomas is between 15–50%. A recent large study including 324 MEN-I patients showed pituitary adenomas in 42% of the cases which were larger in size and more aggressive than without MEN-I.

MEN-I is an autosomal dominant inherited syndrome and is related to mutations of the MEN-I gene located on chromosome 11q13 [2, 3]. The tumorigenesis of MEN-I is supposingly a process according to the two hit model by Knudson (Fig. 3). Patients inherit a mutated MEN-I gene and later aquire another mutation in the wild-type allel (loss of heterozygosity) in vulnerable endocrine tissue. This results in a loss of the tumor suppressor function of the MEN-I gene. The MEN-I gene contains 10 exons encoding the protein menin consiting of 610 amino acids [2]. Two transcripts have been identified which are most likely due alternative splicing.

A 2.9 kb transcript was detected in all tissues while a 4.2 kb transcript was found in pancreas, stomach and thymus only [2]. Menin contains two nuclear localization sites and is predominantly a nuclear protein. However, during cell cycle menin was shown to shuttle from nucleus to cytoplasm.

In Ras-transformed NIH3T3 cells overexpression of menin resulted in decreased proliferation, suppression of clonogenicity in soft agar and inhibition of tumor growth in mice. Menin directly interacts with JunD, a transcriptional factor of the AP-1 complex, via three JunD interacting domains and inhibits JunD activation of transcription [22]. However, since JunD inhibits growth of Ras-transformed NIH3T3 cells the repressive effect of menin should result in enhanced growth. This indicates that the mechanism of action of menin is more complex than we know today and probably involves other genes and proteins. This assumption is supported by a recent observation that menin interacts with NF-κB proteins and inhibits NF-κB-mediated transactivation).

Up to date more than 400 mutations of the MEN-I gene have been identified. Most mutations were unique but some occurred twice or more in unrelated families (107, 110–112). Of 262 mutations observed in MEN-I patients between 1997 and 1999 approximately 22% are nonsense mutations, 48% frameshift deletions and insertions, 8% inframe deletions and insertions, 5% donor-splice site mutations and 17% missense mutations. The majority of mutations result in an inactivation of the MEN-I gene. There is no genotype-phenotype correlation in MEN-I. However, most patients with agressive phenotypes show truncating mutations.

Multiple Endocrine Neoplasia-Type 2

The term multiple endocrine neoplasia-type 2 (MEN-2) describes the combined occurrence of inherited forms of medullary thyroid carcinoma (MTC) with other malignomas. In MEN-2A (Sipple's syndrome) MTC is combined with pheochromocytoma and primary hyperparathyreoidism. MEN-2B (Gorlin's syndrome) is characterized by the occurrence of MTC, pheochromocytoma, neurinomas of the gastrointestinal tract and a marfanoid habitus [23].

Men-2 is caused by germline mutations of the RET gene located on chromosome 10q11–2 encoding a transmembrane tyrosine kinase receptor with cadherin-like and cystein-rich extracellular domains and a tyrosine kinase intarcellular domain [23]. RET genomic size is 60 kb and the gene contains 21 exons. GDNF (glia cell line-derived neurotrophic factor), neurturin, artemin and persephrin act as RET protein ligands inducing homodimerization through the cystein-rich region resulting in an activation of the tyrosine kinase domain and the Ras-MAP-kinase pathway. 95% of MEN-2A patients show mutations of the cystein-rich extracellular domain. The most common mutation affects codon 634 (Cys→Arg/Tyr/Gly). Missense mutations have also been identified in codons 609–611, 618 and 620. Approximately 98% of MEN-2B patients exhibit mutations in the intracellular tyrosine kinase domain (codon 918; Met→Thr). While mutations in the cystein-rich region result in the formation of constitutive active RET dimers, mutations in the intracellular tyrosine kinase domain lead to a switch to an abnormal signalling pathway.

Germline RET mutations were observed in approximately 100% of men-2 families. Therefore, genetic analysis of RET is advisable to identify young asymptomatic gene carriers and perform prophylactic thyroidectomy.

Other Inherited Syndromes Associated with GEP Tumors

In a recent report 12% of 158 patients with von Hippel-Lindau (VHL) syndrome had neuroendocrine tumors [24]. These patients showed no symptoms due to hormonal hypersecretion suggesting that the endocrine tumors were non-functioning. The VHL syndrome is caused by a germline mutation of the VHL gene which is located on chromosome 3p35–36 coding for a 213-aa protein. The VHL gene product is a component of an Skp1-Cdc53-F-box-like ubiquitin-ligase complex targeting the α-subunits of the hypoxia-inducible factor heterodimeric transcription factor for polyubiquitylation and proteasomal degradation. Somatostatinomas have been described in patients with von Recklinghausen's neurofibromatosis. Neurofibromatosis is caused by alterations of the NF1 gene located on chromosome 17q11.2 coding for neurofibromin which is a 2485-aa protein.

Growth Characteristics and Metastatic Spread and Secondary Non-Endocrine Malignancies

As recognized as early as in 1907 by S. Oberndorfer who introduced the term "carcinoid", endocrine GEP tumors grow slowly even in the metastatic state compared to adenocarcinomas of the gastrointestinal tract. However, the spontaneous tumor growth varies from one patient to another. Some tumors remain unchanged in size for months or even years without therapy, others grow slowly independent of any antiproliferative measures and still others exhibit exploding growth. The latter tumors are poorly differentiated and mostly small cell carcinomas. Even spontaneous tumor regression without any treatment has been reported in well-differentiated tumors. A schematic presentation, how malignant GEP tumors can grow is shown in fig. 4.

Unfortunately the use of proliferative markers and immunostaining of tumors for oncoproteins, tumor suppressor genes, and adhesion molecules gave contradic-
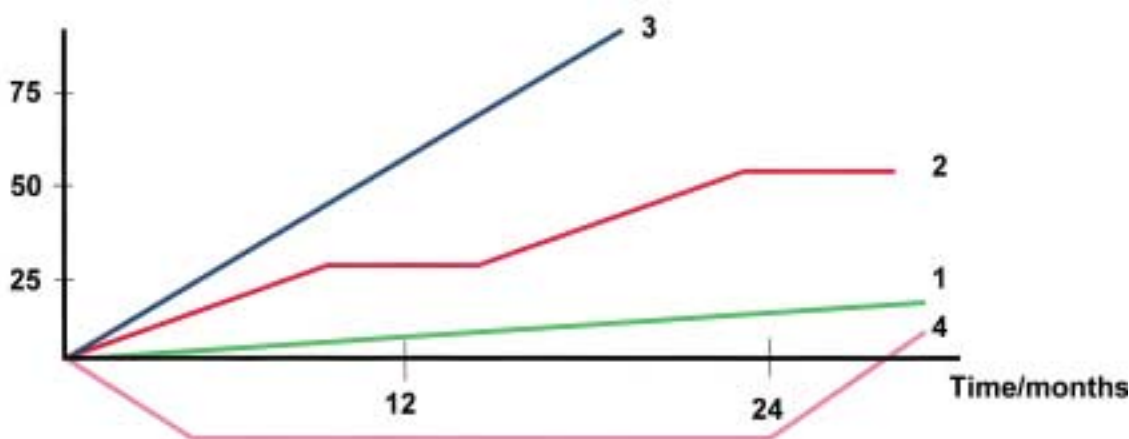
Figure 4
Schematic presentation how endocrine GEP tumors can grow. Some tumors grow so slowly that they do not meet the 25% increase according to the accepted NIH criteria of tumor progression even after 18 months (*1*). Tumor (*2*) displays an intermediate tumor growth. Tumor (*3*) grows very rapidly corresponding to its histology of a small cell neuroendocrine carcinoma. Tumor (*4*) decreased spontaneously in size, remained constant for 2 years and started to grow after 24 months of observation without any treatment

tory results. One study was performed in gastrointestinal carcinoid tumors and indicated that expression of p53, cyclin D1, Rb, bcl-2 and Ki-67 does not correlate with malignant behaviour, whereas p21 overexpression did. Others concluded from studies in bronchial carcinoid tumors and in gastrointestinal carcinoid tumors that high expression of ki-67, a tumor size >3 cm and a high mitotic index (in the case of ECL cell tumors of the stomach) is malignancy predictive. Possibly, these findings are dependent on the site of the primary tumor since in carcinoid tumors of the duodenum and ampulla of vater an aggressive behaviour of the tumor was not associated with higher proliferative indices as proliferating cell nuclear antigen (PCNA), Ki-67 and p21.

Malignant GEP tumors can spread in almost all organs: lymphnodes, peritoneal spread, liver, spleen, kidney, lung, skin, brain and bones. Table 6 is an example of the metastatic spread of patients with malignant gastrinoma and patients with carcinoid syndrome observed in the institution of the authors.

It is noteworthy that patients with malignant endocrine GEP tumors tend to synchronous and metachronous non-endocrine malignancies. In a 20-year retrospective study of 150 patients with gastrointestinal

Table 6

Metastatic spread in different endocrine GEP tumors (own data, values in percent)

Site	Non-functioning tumor	Carcinoid syndrome	Gastrinoma
Lymph nodes	64	76	54
Liver	61	88	57
Bones	13	17	11
Lung	9	14	7
CNS	2	0	4
Peritoneal	17	23	4
Other	28	24	4

carcinoids followed up for a median of 66 months 22% developed synchronous non-carcinoid tumors and 10% metachronous tumors. In another retrospective study on 69 patients with gastrointestinal carcinoid tumors 42% hat synchronous and 4% metachronous tumors. The most common site for the secondary primary malignancy was the gastrointestinal tract with carcinoma of the colon and rectum. Patients with colorectal carcinoids have, in addition, an increased risk for cancer in the colon, ano-rectum, small bowel, esophagus, stomach, lung, urinary tract and prostate.

Staging of Endocrine GEP Tumors

Staging of tumors is a useful and essential tool in oncology to define tumor size, invasion and infiltration into adjacent tissues and metastatic spread into regional lymph nodes, liver and other organs. This is important for further management using surgical, radiotherapeutic and chemotherapeutic approaches. For this, TNM classification has been elaborated for specific tumor entities as published by the AICC Cancer Staging Manual and UICC. No corresponding TNM classifications exist for endocrine GEP tumors and their malignant variants because management of endocrine tumors depends even in metastatic tumors primarily on growth behaviour (see Fig. 4) and functional activity. Insulinomas must be removed because they produce life-threatening symptoms independent on the size of the tumor which may be too small to be visualised by available imaging techniques. Metastatic insulinomas have to be partially resected if possible to reduce tumor burden and, thus, to facilitate control of hypoglycemic symptoms. In patients with very slowly growing metastatic GEP tumors the beneficial effect of many therapeutic measures is unsettled. The same applies for non-functioning small endocrine pancreatic tumors in patients with MEN-I syndrome for whom resection has not been shown to influence patient's outcome.

In an attempt to classify endocrine GEP tumors not having metastasized at diagnosis a panel of pathologists has recently proposed a classification of endocrine GEP tumors and assigned the tumors according to the categories summarised in table 5 [1]. The basis of distinguishing well differentiated endocrine carcinomas from other well differentiated endocrine tumors was usually the presence of metastases and/or evidence of local invasion. Benign or low risk endocrine tumors were distinguished from tumors with greater risk of malignancy on the basis of a combination of features such as tumor size and site, local extension, angioinvasion, cellular atypia and proliferative activity. Differentiation of poorly differentiated endocrine small cell carcinoma from well-differentiated endocrine tumors was performed by conventional histological characteristic features including high-grade cellular atypia, markedly hyperchromatic nuclei, focal necrosis and high proliferation.

In tables 7–11 these major principles have been transferred to endocrine tumors arising in different organs of the GI tract as the pancreas (Table 7), stomach (Table 8), the duodenum and upper jejunum (Table 9), the ileum, cecum, colon and rectum (Table 10) and the appendix (Table 11).

Clinical Entities: Symptoms and Laboratory Findings

Insulinoma

Epidemiology

Around 40% of endocrine pancreatic tumors are insulinomas. Based on a review of 224 insulinoma patients over a 60-year period the medium age was 47 (range 8–82) years and 41% of patients were male [25]. The yearly incidence is 0,5 to 4 per one million population and 5,8% had malignant insulinoma [25]. In 7,6% of patients the insulinoma was part of the MEN-I syndrome [4, 25]. Almost all insulinomas are situated in or close to the pancreas. 1–3% of insulinomas have been reported to arise in the duodenum, ileum and lung [26]. Insulinomas are evenly distributed within the pancreas [26]. Based on a study in 1067 cases most insulinomas are small: 5% smaller then 0.5 cm, 34% were 0.5 to 1 cm, 53% 1 to 5 cm and only 8% larger then 5 cm in size. With the exception of the rare malignant insulinomas prognosis of patients with a benign insulinoma and curative resection is excellent. For definition of "benign" insulinoma see Table 7.

Table 7

Clinicopathological staging of endocrine tumors of the pancreas. (Mod. according to [1])

1	Well-differentiated endocrine tumor
1.1	Benign behaviour: confined to the pancreas, nonangioinvasive, <2 cm in size*, ≤2 mitoses and ≤2% Ki67 positive cells/10HPF
1.2	Uncertain behaviour: confined to the pancreas ≥2 cm in size, >2 mitoses, >2% Ki67 cells/10 HPF, or angioinvasive
2	Well-differentiated endocrine carcinoma
2.1	Low grade malignant with gross local invasion and/or metastases
3	Poorly differentiated endocrine carcinoma – small cell carcinoma, high grade malignant

*<2 cm in size implies close to 100% probability of benign behaviour, >3 cm corresponds to 90% probability of malignancy. Functioning, associated with pertinent clinical syndrome of endocrine hyperfunction; nonfunctioning, not associated with pertinent clinical syndrome, irrespective of hormone detection in blood or tumor tissue.

Table 9

Clinicopathological staging of endocrine tumors of the duodenum and upper jejunum. (Mod. according to [1])

1	Well-differentiated endocrine tumor – carcinoid
1.1	Benign behaviour: nonfunctioning, confined to mucosa-submucosa, ≤1 cm in size, nonangioinvasive
1.1.1	Gastrin-producing tumour (proximal duodenum)
1.1.2	Serotonin-producing tumor
1.1.3	Gangliocytic paraganglioma, any size and extension (ampullary region)
1.2	Uncertain behaviour: confined to mucosa-submucosa >1 cm in size or angioinvasive
1.2.1	Gastrin-producing tumor, functioning (Zollinger-Ellison syndrome) or nonfunctioning, sporadic, or MEN-1-associated
1.2.2	Somatostatin-producing tumor (ampullary region) with or without Recklinghausen disease
1.2.3	Serotonin-producing tumor, nonfunctioning
2	Well-differentiated endocrine carcinoma – malignant carcinoid
2.1	Low grade malignant. extending beyond submucosa or with metastasis
2.2	Gastrin-producing carcinoma, functioning (Zollinger-Ellison syndrome) or nonfunctioning, sporadic, or MEN-1-associated
2.3	Somatostatin-producing carcinoma (ampullary region) with or without Recklinghausen disease
2.4	Serotonin-producing carcinoid, nonfunctioning or functioning (any size or extension) with carcinoid syndrome
2.5	Malignant gangliocytic paraganglioma
3	Poorly differentiated endocrine carcinoma – small cell carcinoma
4	High grade malignant (ampullary region)

Table 8

Clinicopathological staging of endocrine tumors of the stomach. (Mod. according to [1])

1	Well-differentiated endocrine tumor – carcinoid
1.1	ECL-cell carcinoid
1.1.1	ECL-cell carcinoid type I associated with type A gastritis
1.1.2	ECL-cell carcinoid type II associated with Zollinger-Ellison syndrome
1.1.3	Sporadic ECL-cell carcinoid
1.2	ECL-cell carcinoid
1.3	G-cell carcinoid
2	Small cell carcinoma – poorly differentiated endocrine tumor
3	Tumor like lesions: Hyperplasia, Dysplasia

Table 10

Clinicopathological staging of endocrine tumors of the ileum, cecum, colon and rectum. (Mod. according to [1])

1	Well-differentiated tumor – carcinoid
1.1	Benign behaviour: confined to mucosa-submucosa, nonangioinvasive, ≤1 (small int.) or ≤2 cm (large int.) in size
1.2	Uncertain behaviour: nonfunctioning, confined to mucosa-submucosa, >1 cm (small int.) or >2 cm (large int.) in size, or angioinvasive
2	Well-differentiated endocrine carcinoma – malignant carcinoid, low grade malignant, deeply invasive (muscularis propria or beyond), or with metastases
3	Poorly differentiated endocrine carcinoma – small cell carcinoma, high grade malignant
4	Mixed exocrine-endocrine carcinoma – moderate to high grade malignant

Table 11

Clinicopathological staging of endocrine tumors of the appendix. (Mod. according to [1])

1	Well-differentiated endocrine tumor – carcinoid, benign behaviour, nonfunctioning, confined to appendiceal wall, nonangioinvasive, ≤2 cm in size
1.1.1	Serotonin-producing tumor
1.1.2	Enteroglucagon-producing tumor – uncertain behaviour, nonfunctioning, confined to subserosa, >2 cm in size, or angioinvasive tumor
2	Well-differentiated endocrine carcinoma – malignant carcinoid
2.1	Low grade malignant, invading the mesoappendix or beyond, and/or with metastasis
2.2	Serotonin-producing carcinoid with or without carcinoid syndrome
3	Mixed exocrine-endocrine carcinoma
3.1	Low grade malignant – goblet-cell carcinoid

Pathophysiology

Insulinoma cells fail to respond adequately to low blood glucose levels. This is indicative of a defective negative feedback which maintains euglycemia in healthy subjects. In addition, the storage capacity of insulinoma cells is impaired, resulting in an inappropriate insulin release [14].

Symptoms

Insulinoma symptoms are the consequence of neuro-hypoglycemia and superimposed by symptoms which are the consequence of adrenergic counter regulation as sweating, tremulousness, palpitation (Table 12). As a rule, the frequently nonspecific symptoms are associated with fasting and occur more often after muscular exercise and during late night or early morning and when a meal is delayed. Whipple's triad is highly suggestive of an insulinoma and comprises of hypoglycemic symptoms, a parallel demonstration of low blood glucose levels less then 50 mg/dl (2.8 mmmol/l) and improvement of symptoms after administration of glucose [12, 25, 26]. There is often a long-lasting delay between onset of clinical signs and diagnosis, because symptoms listed in table 12 are unspecific and do not appear in a clear sequence. The mean duration of symptoms prior to diagnosis varies between 15 months and more then 3 years [12, 25]. Each patient displays his/her own pattern of symptoms which differ from patient to patient. Since regular food intake prevents the occurrence of symptoms, patients are used to eat regularly and often gain weight. If misinterpreted, severe and longer lasting hypoglycemia can progress to seizure and permanent brain damage. Some insulinoma patients are diagnosed only in psychiatric hospitals, having been admitted with misdiagnosed symptoms.

Differential Diagnosis

In addition to insulinoma hypoglycemia can have several causes which are summarised in table 13. Factitious hypoglycemia secondary to self-administration of insu-

Table 12

Clinical symptoms in patients with insulinoma

Symptoms of neurohypoglycemia	Symptoms of adrenergic catecholaminergic response
Diplopia	Anxiety
Blurred vision	Sweating
Confusion	Tremulousness
Abnormal behaviour	Hunger
Weakness	Nausea
Amnesia	Fatique
Aphasia	Tremor
Transient motor defects	Palpitation
Dizziness	
Speech difficulty	
Headache	
Seizure	
Memory loss	
Lethargy	
Disorientation	
Mental change	
Convulsion	
Coma	
Obesity	

Table 13

Other causes of hypoglycemia

|	
Insulin or insulin-like-mediated	Factitious hypoglycemia (153)
	Tumor associated hypoglycemia (151, 152)
	insulin autoantibodies (154)
	Transient hypoglycemia of infancy
	Nesidioblastosis
Postprandial (reactive) hypoglycemia	Previous gastric surgery (Billroth I and II gastrectomy)
	Idiopathic
Food stimulated	Ethanol
	Unripe kakee fruit (159)
Hormone deficiency	Addison's disease
	Growth hormone deficiency
	Hypothyroidism
Hepatic diseases	End-stage liver failure
	Glycogen storage disease
	Glycogen synthetase deficiencies
	Fructose-1,6-disphosphate deficiency
Metabolic diseases	Severe malnutrition
	Sepsis
Drugs	Sufonylureas (155)
	Quinine (156)
	Disopyramide (157)
	Haloperidol (158)
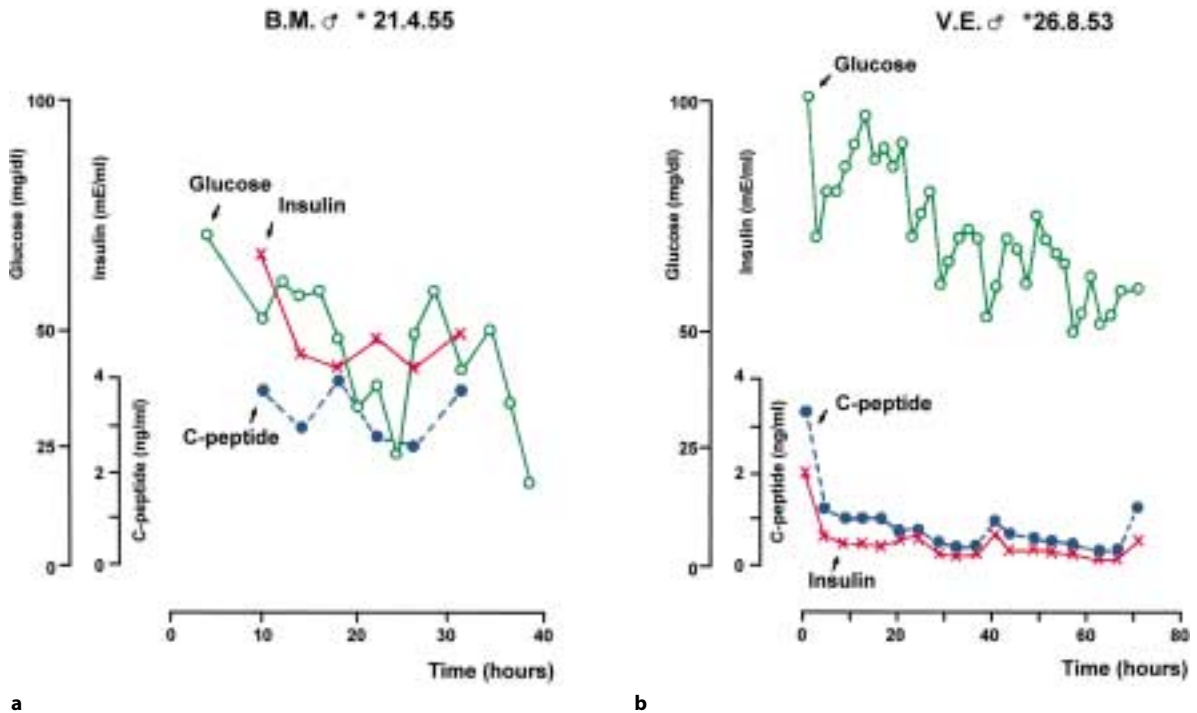
Fig. 5a,b
Blood glucose, insulin and C-peptide levels during a 40 h fast, suggesting an insulin producing tumor since insulin and C-peptide levels remained inadequately elevated despite low blood glucose levels (**a**). In **b** insulin and C-peptide levels dropped down to very low levels during a 72 hour fast

lin or oral intake of hypoglycemic agents should be considered if an insulinoma cannot be ascertained by diagnostic measures. In the author's institution the following conditions are mostly the cause of hypoglycemic episodes if an insulinoma could be excluded: postprandial hypoglycemia (late dumping syndrome) even in the absence of gastric resection (Billroth I and II resection) due to rapid gastric emptying; mesenchymal tumors, such as fibrosarcoma, liposarcoma, rhabdomyosarcoma, hemangiopericytoma, mesothelioma, leiomyosarcoma, IGF-II-producing tumors; endstage of liver cirrhosis.

Diagnosis

Biochemical testing. The gold standard for the diagnosis of an insulinoma is the "72 h fast" test. About 75% of insulinoma patients will develop symptoms and blood glucose levels of <40 mg/dl (2.2 mmol/l) within the first

24 h of the fast (Fig. 5), 90% within 48 h, and 100% within 72 h. The test should be performed using a standardised protocol as follows:

1. begin the test immediately after the last meal (breakfast); insert a capped intervenous cannula;
2. allow intake of calorie-free fluid ad lib (water);
3. encourage physical activity (walking);
4. analyze plasma glucose, insulin and C-peptide in the same specimen every 6 h until blood glucose drops to <60 mg/dl; then increase sampling to every 1–2 h;
5. terminate the test when the patient develops symptoms of hypoglycemia *and* glucose is <40 mg/dl. If the patient is asymptomatic, prolong the test until suggestive symptoms appear; sample always blood glucose, insulin and C-peptide at the end of the test;
6. when symptoms arise, give 10% glucose intravenously or orally until the patient is asymptomatic.

The pathophysiologic background of the prolonged fast test is that steadily decreasing blood glucose levels signal to the normal b-cell of the islets of Langerhans to turn down insulin and C-peptide levels which decrease to either not measurable or very low levels. In insulinoma patients insulin and C-peptide are inadequately suppressed despite even lower blood glucose levels then observed in healthy controls (see Fig. 5). Importantly, plasma insulin in insulinoma patients go rarely beyond levels normally found in the fasted and fed state of normal subjects; however, they are inappropriately high for the prevailing blood glucose concentration. Therefore, plasma insulin and C-peptide levels must always be assessed in relation to the corresponding blood glucose levels. Some authors have advised to calculate a ratio of insulin to glucose because borderline low levels of insulin have been reported in some patients with proven insulinoma in association with hypoglycemia. However, also these ratios do not reliably differentiate between insulinoma patients and healthy subjects since there is not in every subject a linear correlation of insulin and glucose levels. Normal subjects rarely exceed a ratio of plasma insulin (in µU/ml) to glucose (in mg/dl) of 0.3 which is based on the observation that insulin levels are in normals less than 6 µU/ml when blood glucose levels decrease to less than 40 mg/dl. For example: if plasma insulin measures 8 µU/ml and blood glucose is 40 µg/dl, than the ration is 8: 40=0.2. However, neither this ratio or an amended variation of such a ratio do reliably discriminate between insulinoma patients and healthy subjects because there is not in every patient a clear linearity between plasma insulin and glucose levels.

Some experts recommend estimation of proinsulin in insulinoma patients which is elevated in most insulinoma patients to more than 20% of the total plasma insulin levels. Indeed, some insulinomas produce and secrete predominately proinsulin.

In previous literature, various stimulatory and suppressive tests have been recommended because they are believed to facilitate the diagnosis of an insulinoma as C-peptide suppression test, tolbutamide test, glucagon test, calcium infusion test, euglycaemic clamp procedure and others. These tests are neither specific nor sensitive and due to the possibly harmful side effects of prolonged hypoglycemia in case of the tolbutamide and calcium infusion not favoured in the more recent literature.

Figure 6a–f

Localization of endocrine GEP tumors by various imaging techniques. **a** Endoscopic ultrasound showing a small (11 mm) pancreatic insulinoma; **b** CT imaging of desmoplastic reaction in a patient with carcinoid syndrome due to an ileum carcinoid; **c** OctreoScan showing wide metastatic spread in a patient with a non-functioning endocrine pancreatic tumor; **d** MRT imaging of liver metastases in a patient with non-functioning endocrine pancreatic tumor; **e** MRT imaging of two brain metastases in a patient with malignant gastrinoma; **f** endoscopic demonstration of a rectal carcinoid. Notice the *yellow colour*   ▶

To exclude other causes of hypoglycemia as factitious hypoglycemia or postprandial hypoglycemia measurement of plasma sulfonylurea should be performed to exclude surreptitious use of these drugs and an oral glucose load with estimation of blood glucose and insulin levels in 30 minutes intervals for 3 h should be considered if reactive hypoglycemia is considered.

Localization. Imaging studies to localize an insulinoma should only be performed once the diagnosis of an insulinoma is highly suggestive by biochemical testing. Experienced surgeons claim that the most sensitive localization instrument is the finger of the skilled surgeon during intraoperative abdominal exploration and recommend no preoperative localization procedures. Indeed, almost all insulinomas are situated in the pancreas and only 1–3% found ectopically. On the other side, there is no localization procedure available with an 100% detection rate. At the institution of the authors, 50 patients with biochemically proven insulinoma had undergone operative exploration within the last 10 years and all insulinomas have been identified at the first operation (R. Rothmund, personal communication). These results have been confirmed by some but not all authors. The latter claim that 10–27% of insulinomas remained undetected and advocated, therefore, the need for preoperative localization procedures.

The most accurate and sensitive imaging procedure to localize and to stage (see table 7) an insulinoma is endoscopic ultrasound (EUS) which localizes an insulinoma in up to 85% and thus being superior to other imaging studies as CT, MRT, conventional ultrasound and arteriography (Fig. 6a). Of course, detection rate is mostly dependent on the experience of the investigator and expert investigators will detect tumors less than 0.4 cm in diameter. In such institutions EUS will be the

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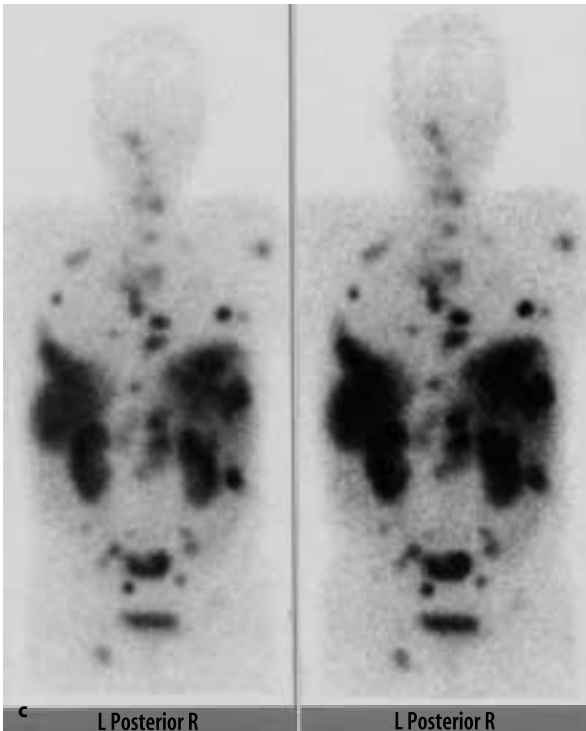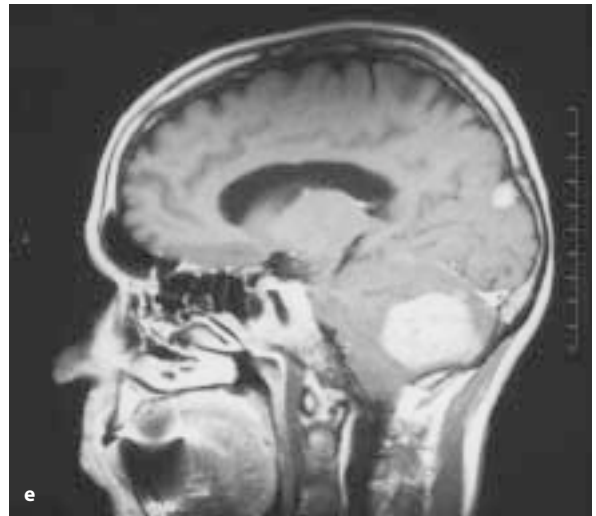
Table 14

Sensitivity of imaging studies in the detection of endocrine GEP tumors

	SRS [%]	CT [%]	MRI [%]	EUS [%]
Gut tumors	72–96%	33%	n.d.	-
Pancreatic tumors	58–100%	25–38%	24–71%	58–86%
Insulinoma	12–50%	29%	13%	81–94%

primary and exclusive diagnostic modality for tumor imaging. Sensitivity of other imaging procedures are summarised in table 14. Angiography was for many years the preferential method in localising insulinomas due to the characteristic high blood supply of the tumor. In earlier reports successful tumor localization of up to 90% has been described whereas more recent data indicated a sensitivity of only 30–50%. The method is invasive, expensive and requires considerable experience in data interpretation. Therefore, both computed tomography (CT) with rapid-sequence spiral CT, with oral and intravenous contrast enhancement and magnetic resonance imaging (MRI) with the use of dynamic gadolinium enhancement and fat suppression have replaced angiography in many centers that prefer an exact preoperative tumor localization. Somatostatin receptor szintigraphy which recognizes high numbers of somatostatin receptors present on most endocrine GEP tumors detects, in contrast to other GEP tumors, only 50% of insulinomas due to the inconsistant frequency of somatostatin receptor subtype 2 on insulinomas. Therefore, negative somatostatin receptor scintigraphy does not exclude the presence of an insulinoma.

Treatment. The primary treatment option in patients with a biochemically proven insulinoma is surgery. Once the tumor is localized pre- and intraoperatively surgeons will decide whether the tumor can be enucleated or whether proximal or distal pancreatic resection is the perfered method. Total pancreatectomy or "blind" distal resection should be avoided if the insulinoma cannot be identified intraoperatively. In this case laparotomy should be terminated and tumor localization repeated. Surgery is also indicated in metastatic insulinoma since operative tumor debulking has been shown to provide long-lasting symptomatic improvement. Symptomatic

antisecretory therapy is indicated in the pre-operative phase and in metastatic disease. To prevent hypoglycemic events regular intake of carbohydrates in required and a light carbohydrate meal in the late evening is important. If diet does not prevent hypoglycemia, oral administration of diazoxide and subcutaneous long-acting somatostatin analogues are the therapeutic priciples of choice to prevent hypoglycemia whereas β-blocking agents, glucocorticoids, calcium-channel blockers and phenytoin have been used earlier but with limited therapeutic effects.

Diazoxide is a non-diuretic benzothiadizine that inhibits the release of insulin from the secretory granules of normal β-cells and of insulinoma cells. Unfortunately, not all insulinoma patients respond to diazoxide but it should be tried with starting dosages of 25 μg b.i.d. and the dose can be escalated up to 200 μg t.i.d. Side effects including cardiac arrhythmia, cardiomyopathy, bone marrow depression, sodium retention and peripheral edema should be noticed and can force to discontinue therapy.

Also long-acting somatostatin analogues (Fig. 7) as octreotide and lanreotide suppress insulin secretion. They have been first introduced for the treatment is disabling acromegaly and later for functionally active endocrine GEP tumors to supress hormone secretion [27]. Octreotide, lanreotide and octreotide LAR are modifications of the naturally occuring somatostatin (Fig. 7). Lanreotide and octreotide-LAR bound to polylactidglycolide microspheres permit sustained release allowing single subcutaneous injections of lancreotide every 2 weeks and of octreotide-LAR every 4 weeks. Somatostatin and its analogs act through a family of at least 5 receptors (sstr 1–5). Most encocrine GEP tumors express sstr 2, whereas the other 4 sstr are less frequently or not expressed (179). Unfortunately, long acting somatostatin analogs are effective in only 50% of insulinoma patients since sstr 2 is only expressed in 50% of insulimas. Therefore, the hypoglycemia preventing effect of somatostatin analogs is unpredictable. Importantly, somatostatin analogs can even aggravate hypoglycemic symptoms because they suppress also the counter regulatory hormone glucagon. Therefore, insulinoma patients must be monitored carefully if somatostatin analogs are considered to prevent hypglycemia. Treatment should be started with 50 μg short-acting octreotide b.i.d. and increased to 200 μg t.i.d. according to the patients re-
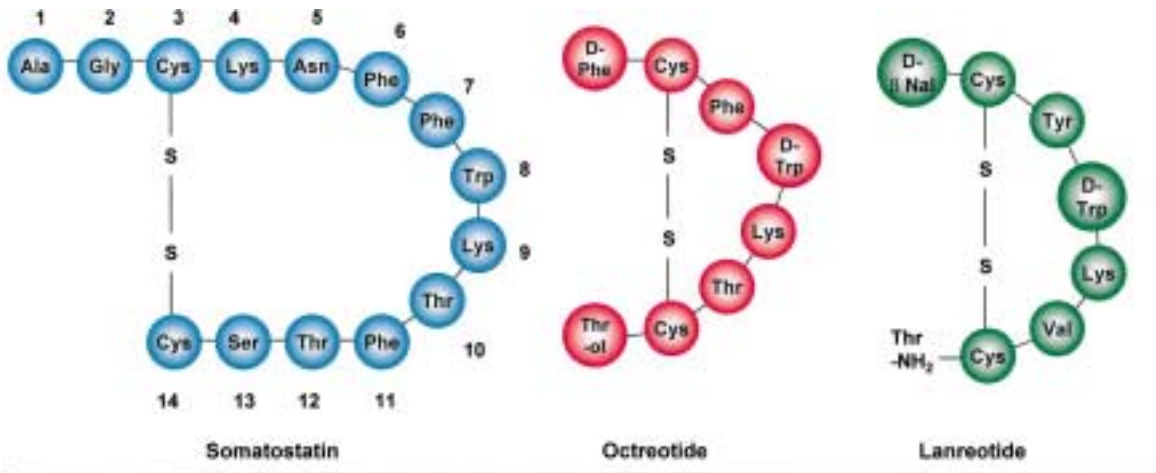
Figure 7
Structure and characteristics of native somatostatin and its long-acting analogues octreotide and lanreotide

sponse. If they respond adequately to the short lasting somatostatin formulations, the longer lasting octreotide-LAR and lanreotide-LAR which have to be administered only every 2 weeks (lanreotide-LAR) or every 28 days (octreotide LAR) can be offered.

In patients with malignant and metastatic insulinoma several therapeutic options have to be considered including palliative surgery, embolisation of liver metastases and chemotherapy with streptozotocin combinations (for further details see "General aspect of management" under "Medical treatment of symptoms")

Persistent Neonatal Hyperinsulinemic Hypoglycemia (PNHH). Persistent neonatal hyperinsulinemic hypoglycemia was earlier called "nesidioblastosis" and originally described by Laidlow in 1938 [28]. He called cells which originated from the pancreatic ductal epithelium nesidioblasts, their proliferation nesidioblastosis and the resulting

tumor nesidioblastoma. Today, the term "nesidioblastosis" is substituted by the term "persistent neonatal hyperinsulinemic hypoglycemia (PNHH). This entity is characterized by the occurrence of hyperinsulinemic hypoglycemia in the absence of an endocrine pancreatic tumor. As in insulinomas hypoglycemia occurs in the fasting state and insulin secretion is not adequately suppressed. The disease affects newborn children within the first 6 months of life and only very rarely adults [28]. The term nesidioblastosis is misleading since it implies general islet cell hyperplasia which does not exist. The pancreas of the newborn enfant has physiologically much more and smaller islets of Langerhans compared to the situation in later life. The morphological abnormalities of the endocrine pancreas that underly PNHH are heterogeneous and encompass small endocrine tumors (insulinoma), unifocal or multifocal adenomatosis characterized by local and excessive proliferation of islet

cells, hyperplasia of islets of Langerhans and frequently even no recognizable pathomorphological abnormalities [28]. In the latter situation, a functional defect of the pancreatic β-cells is assumed to cause unrestrained insulin release. PNHH occurs in a sporadic and a familial autosomal recessive form [28]. In the familial variant of PNHH a genetic defect has been identified on the short arm of chromosome 11p14–15.1. The respective gene codes for the sulfonylurea receptor which is mutated in the familial form of PNHH. This mutation results in abnormal insulin secretion and altered sensitivity of the β-cell to glucose. The genetic defect responsible for the sporadic form of PNHH is also identified. A recent report suggests a dysfunction in the adenosine triphosphate-sensitive potassium channel present in the plasma membrane of pancreatic β-cells [29].

Clinically, the respective infants present with non-specific symptoms resulting from neuroglucopenia. Medical management includes continuous glucose infusion via a central venous catheter, diazoxide and long-acting somatostatin analogs. Recently, it has been demonstrated that calcium channel blocking agents can be used with efficacy and safety to control hypoglycemia in PNHH. However, definitive cure requires in most patients subtotal pancreatectomy.

Adult onset PNHH is very rare and requires the same multimodal therapeutic approach as in the infantile form.
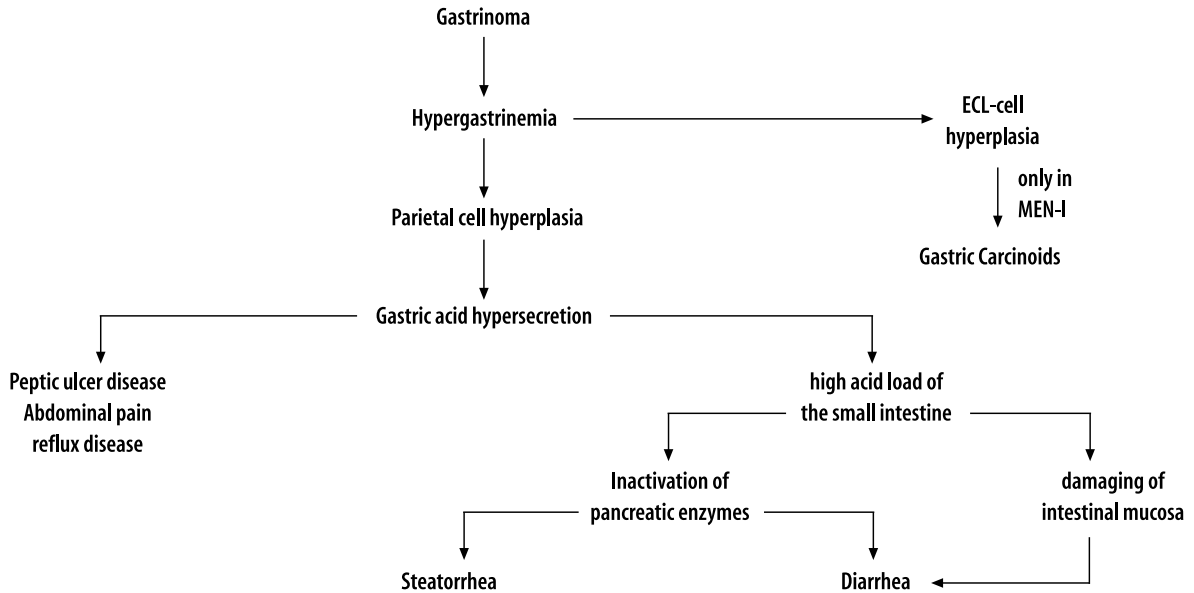
Gastrinoma

Epidemiology and Prognosis

Gastrinomas are as insulinomas very rare tumors. The yearly incidence is 0,5 to 3 per one million population [4, 8]. The mean age at diagnosis is 50 years. Unlike insulinomas, the majority of gastrinomas is malignant. Gastrinomas are in 30–50% part of the MEN-1 syndrome [8]. In a recent study with 151 patients with surgically removed non-metastasised gastrinoma, of whom 128 were part of MEN-1 syndrome, it has been shown that 34% of patients with sporadic gastrinoma but none of patients with MEN-1 syndrome were disease free after 10 years [30]. This demonstrates that in sporadic gastrinoma definitive cure can be achieved in a substantial proportion by surgery. In contrast, patients with gastrinoma as part of MEN-1 syndrome have either multiple gastrinoma or have metastatic disease at operation.

Whereas insulinomas are almost exclusively located in the pancreas and are not located in a special part of the pancreas, the vast majority of gastrinomas occur in the "gastrinoma triangle". This region is defined by the junction of the neck and body of the pancreas, the junction of the second and third part of the duodenum and the confluence of the cystic and common bile duct. 50% of gastrinomas are located in the duodenum. Very rarely, gastrinomas arise in the antrum, omentum, liver, lymph node or elsewhere [8]. In MEN-1 gastrinomas are more frequently located in the duodenum where they are mostly very small and multifocal. Sporadic gastrinomas, in contrast, occur more frequently in the pancreas. The malignant potential of sporadic gastrinomas and those arising in patients with MEN-1 syndrome is not uniform. Recent studies indicate that approximately one fourth of patients with sporadic gastrinomas persue an aggressive growth pattern, with a 10-year survival of 30%, whereas in the remaining 75% of patients gastrinomas display a less aggressive growth pattern with a 10 year survival of 95% [30]. Similarly, in patients with metastatic gastrinomas to the liver aggressive growth was demonstrated only in a minority of patients whereas the majority displayed indolent growth [30]. Tumor related deaths occur almost entirely in the aggressive growth group. According to a recent investigation in patients with gastrinoma and MEN-1 syndrome growth behaviour is also not uniform. 23% of patients with gastrinoma and MEN-1 syndrome developed liver metastases and 14% had an aggressively growing gastrinoma. Aggressive growth of the primary gastrinoma but not of liver metastases growing less aggressively was associated with decreased survival [30]. High serum gastrin levels, a primary tumor size of >3 cm and the presence of bone and liver metastases were associated with an aggressive gastrinoma growth [30].

Pathophysiology

The pathophysiological events occurring in patients with Zollinger-Ellison syndrome are summarized in Fig. 8. Hypergastrinemia as the result of unrestrained hormone release from the tumor displays two effects: stimulation of gastrid acid secretion from the parietal cell and stimulation of parietal and ECL-cells both located in the oxyntic mucosa of the proximal stomach. The consequences of gastric acid hypersecretion are summarized in Fig. 8. All patients with gastrinoma develop diffuse,

Gastrinoma

↓

Hypergastrinemia → ECL-cell hyperplasia

↓ (Hypergastrinemia)   ↓ only in MEN-I

Parietal cell hyperplasia   Gastric Carcinoids

↓

Gastric acid hypersecretion

↓ (left)   ↓ (right)

Peptic ulcer disease / Abdominal pain / reflux disease

high acid load of the small intestine

↓   ↓

Inactivation of pancreatic enzymes   damaging of intestinal mucosa

↓   ↓   ↓

Steatorrhea   Diarrhea ← (from damaging of intestinal mucosa)

Figure 8
Pathophysiology of Zollinger-Ellison syndrome

Symptoms

Clinical presentation of patients with Zollinger-Ellison syndrome has changed considerably in the last two decades mainly due to the availability of potent anti-secretory drugs. Before the discovery of H_2-blockers and proton pump inhibitors patients presented with severe relapsing peptic ulcer disease and its sequelae: life-threatening bleeding and perforation. Patients died from complications and not from the tumor itself. This has dramatically changed. Most patients with gastrinoma present today with severe and medically resistant reflux disease requiring higher than standard dosages of PPIs. More then 90% of gastrinoma patients suffer from epigastric discomfort and peptic ulcer disease. Most ulcers are situated in the duodenal bulb or the distal stomach, whereas ulcers located in atypical sites (distal to the duodenal bulb, jejunum) are the exception. 30% of gastrinoma patients have helicobacter pylori infection, but eradication has virtually no influence on peptic ulcer relapse rate. 5–10% of patients do not have peptic ulcer disease and present with secretory diarrhea (Fig. 8). Patients report on watery stools arising during late night and early morning with some improvement after intake of meals. Secretory diarrhea is present in more than 50% of gastrinoma patients. A history of nephrolithiasis and the presence of hypercalcemia are suspicious for hyperparathyroidism as part of MEN-1 syndrome. The association between Zollinger-Ellison syndrome and Cushing's syndrome due to ectopic ACTH production by the endocrine pancreas tumor is rare and patient's survival depends mainly on the control of hypercorticism (see later).

Differential Diagnosis

Differential diagnosis of Zollinger- Ellison syndrome encompass few states of relapsing ulcer disease, hypergastrinemia and gastric acid hypersecretion. Antral G-cell hyperfunction is are rare event and results, ac-

Table 15
Differential diagnosis of hypergastrinemia

With gastric acid hypersecretion	With hypo- or achlorhydria
Antral G-cell hyperfunction	Typ-A gastritis
Massiv resection of small bowel	Renal insufficiency
"excluded antrum"	Prolonged acid-suppressive medication

cording to recent reports, from *H. pylori* infection. In these patients *H. pylori* inhibits antral somatostatin release much more powerfully then in other *H. pylori* infected individuals and leads to hypergastrinemia because antral gastrin producing G- and somatostatin-producing D-cells are situated in close vicinity. After food intake serum gastrin increases in patients with antral G-cell hyperfunction to much higher levels then in patients with normogastrinemic ulcer disease. Cure of infection prevents further peptic ulcer relapse and fasting and postprandial hypergastrinaemia normalize.

The "excluded antrum syndrome" is currently extremely rare and was more frequent in earlier decades when patients with peptic ulcer disease have been subjected to distal gastric resection (Billroth II). In this condition, a small part of the distal antrum adjacent to the duodenal bulb was inadvertently left on the blind loop. Hypergastrinemia results from the neutral environment of this part of antral mucosa and produces acid hypersecretion with the consequence of relapsing ulcer disease in the remaining stomach or around the gastro-jejunal anastomosis.

Diagnosis

Biochemical Testing. The triad: "excessive gastric acid hypersecretion, intractable peptic ulcer disease and the presence of a non-insulin-producing pancreatic endocrine tumor" was recognized as entity in 1955 by Zollinger and Ellison. Biochemically, diagnosis of a Zollinger-Ellison syndrome is based on the simultaneous presence of elevated serum gastrin levels and low intragastric pH. Elevated serum gastrin levels alone do not prove a gastrinoma since it can be found in several conditions mostly as consequence of reduced or absent gastric acid. Examples are the intake of PPIs, the presence of chronic atrophic gastritis (type A gastritis) and severe *H. pylori*

associated chronic gastritis (Table 15). Therefore, diagnosis of Zollinger-Ellison syndrome is easily made if elevated serum gastrin levels combined with gastric acid hypersecretion exists. Since most patients with Zollinger-Ellison syndrome are under long-term PPIs, treatment should be stopped and shorter lasting H_2-blockers offered. Ten days after discontinuation of PPI-treatment basal acid secretion and serum gastrin should be studied after 12 hours withdrawal of H_2-blockers. A serum gastrin level of greater 500 pg/ml in the absence of conditions summarized in table 14 but in the presence of elevated basal acid output (BAO) are highly suggestive of Zollinger-Ellison syndrome. BAO is generally above 10 mEq/hr in an intact stomach and above 5 mEq/hr in patients after Billroth I and II resection. If serum gastrin levels are in the upper normal range or only moderately elevated Zollinger-Ellison syndrome can be confirmed by a secretin provocative test. After intravenous rapid injection of 2 U/kg secretin, serum gastrin rises "paradoxically" within 15 minutes by more then 50% or 200 pg/ml in patients with Zollinger-Ellison syndrome. Blood for gastrin measurement should be taken at times – 5 min and immediately before secretin and after 2, 5, 15 and 30 minutes post secretin. The mechanism of gastrin increase after secretin is not completely understood. There are no other conditions with gastrin increase after secretin. In contrast, hypergastrinemia due to chronic atrophic gastritis or "excluded antrum" declines after secretin (Fig. 9). The sensitivity of the secretin test is below 100% since in some gastrinoma patients no or only small increases of serum gastrin occur.

Localization. During the past decade significant advances in the localization of endocrine GEP tumors could be achieved. Imaging studies in patients with gastrinoma are focused on the detection of the primary (pancreas, duodenum, elsewhere) and to the presence of metastases. As other malignant endocrine tumors malignant gastrinomas tend to metastasize into lymph nodes, liver, bones and other sites as skin and brain. Somatostatin receptor szintigraphy using [111]indium-labelled octreotide (OctreoScan) has changed the imaging strategies of gastrinomas and other endocrine pancreatic tumors since somatostatin subtype 2 (sst_2) receptors have been demonstrated in approximately 90% of gastrinomas using in vitro autoradiography. It could be shown that OctreoScan has a sensitivity of 71–75% and a specificity of up to 82% (see Fig. 7c). According to a recent report in

which OctreoScan was compared with conventional imaging procedures in 80 gastrinoma patients, OctreoScan was the most sensitive modality for detection of primary and metastatic gastrinoma. However, size of the primary gastrinoma was an important factor and tumors smaller then 0.5 cm could not be visualized. According to this study 33% of primaries, especially small duodenal gastrinomas that could be detected later intraoperatively, were missed by OctreoScan [8]. Somatostatin receptor szintigraphy and MRI were the most sensitive imaging procedures to detect bone metastases and OctreoScan was the only method to distinguish small liver metastases from small hemangiomas. Therefore, OctreoScan is presently the imaging procedure of choice to localize the primary and to define the extent of metastatic spread. As in insulinomas endoscopic ultrasound is highly accurate in the localization of small pancreatic and duodenal gastrinomas whereas contrast medium enhanced CT and MRT have been shown to have sensitivities of approximately 80–85% [32].

The most important questions which have to be answered are:

▸ Is the biochemically and clinically highly suggestive gastrinoma sporadic or part of the MEN-1 syndrome?
▸ Is the gastrinoma malignant and has spread to lymph nodes, to the liver and elsewhere?
▸ What is the potential benefit of surgical intervention?

Figure 9a–d
Serum gastrin levels after secretin injection in patients with **a** Zollinger-Ellison syndrome; **b** antral G-cell hyperfunction; **c** patient with "excluded antrum"; **d** patients with regular duodenal ulcer disease

If the size of a gastrinoma is greater then 2 cm in case of a pancreatic tumor (see Table 7) and greater then 1 cm in case of a duodenal tumor (see Table 9) malignant behaviour is likely and the effect of surgical intervention with respect to cure the disease uncertain. In patients with MEN-1 syndrome frequently more then only 1 endocrine pancreatic tumor can be visualized. In this condition it is almost impossible to identify the tumor which is responsible for the Zollinger-Ellison syndrome.

For practical reasons one should always start with OctreoScan. If the primary as well as metastatic spread have been detected by OctreoScan the findings should be further confirmed by contrast-medium enhanced CT or MRT (see Fig. 7e). If a solitary gastrinoma, no primary and no metastases are found by OctreoScan and upper abdominal CT and/or MRT careful upper gastroduodenoscopy should be performed to confirm the presence of a duodenal primary. Endoscopic ultrasound should complete endoscopy. In case of a solitary primary
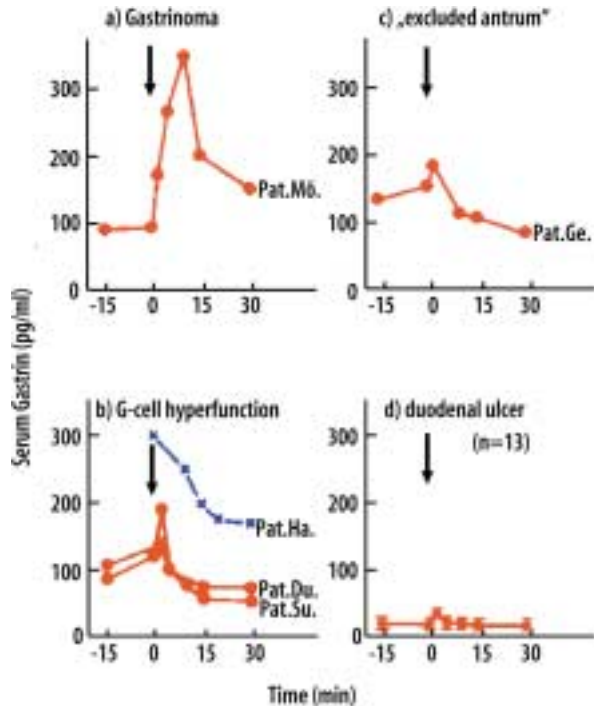
and if no primary and no metastases exist laparotomy is indicated to localize and to remove the primary tumor within the "gastrinoma triangle".

Treatment. The sequelae of gastric acid hypersecretion as reflux disease, peptic ulceration and watery diarrhea can be effectively controlled by proton pump inhibitors (PPI). They have completely substituted surgical procedures as total gastrectomy and vagotomy. They are superior to all available histamin-H_2-blockers. For all currently available PPIs a comparable therapeutic efficacy and safety has been demonstrated. However, the exact dosage necessary for symptomatic control and for inhibition of gastric acid secretion has to be determined for every individual patient. The dosage can range from normal and 3–4 times elevated dosages. One should start with the regular PPI dose bid (2×20 mg Omeprazole; 2×30 mg Lanzoprazole; 2×40 mg Pantoprazole; 2×40 mg Rabeprazole etc.) and increase the dosage until patients are

symptom-free and BAO decreased to less then 5 mEq/hr in patients with intact stomach. BAO should be studied prior to the next scheduled dose. If BAO is around 0 mEq/hr PPI dosage should be reduced if desired.

There is no place for long-acting somatostatin analogs which have to be administered subcutaneously and which do not control acid secretion as reliably as PPIs.

In case of a sporadic non-metastasized gastrinoma, surgical removal should always be desired [31]. In patients with a gastrinoma as part of MEN-1 syndrome available data do not indicate whether removal of the primary has an survival advantage for the patient. In addition it is difficult to define which of several pancreatic tumors is the tumor responsible for the Zollinger-Ellison syndrome. Therefore, laparotomy in Zollinger-Ellison syndrome and MEN-1 syndrome is a controversial issue.

For management of metastatic disease see under "General aspect of management".

Glucagonoma

Definition, Epidemiology and Prognosis

Glucagonomas are endocrine pancreatic tumors that contain predominantly glucagon. However, only some of these tumors secrete excessive amounts of glucagon into the circulation and cause the glucagonoma syndrome. The latter tumors are malignant, sized 5 cm in diameter and even larger, frequently solitary but they can spread to the liver, lymphnodes, bone and other sites. Most glucagonomas, especially small tumors found in most patients with MEN-1 syndrome are non-functioning and not associated with a clinical syndrome. Their malignant potential is small.

All glucagonomas whether functionally inactive or active encompass less then 1% of all endocrine tumors of the GEP system. Whereas functionally inactive small and benign glucagonomas are found not only in patients with MEN-1 syndrome but even by chance at autopsy the glucagonoma syndrome is rare if compared with insulinoma and gastrinoma.

The prognosis of small functionally inactive glucagonomas is likely favourable whereas in the malignant variant as cause of the glucagonoma syndrome prognosis depends on the aggressiveness of tumor growth and the response to antiproliferative measures.

Pathophysiology

Elevated glucagon levels have metabolic consequences which explain some but not all clinical features in patients with glucagonoma syndrome. Weight loss results from the catabolic effects of glucagon and from a recently described anorectic substance found in animals with transplantable glucagonoma. Glucagon stimulates glycogenolysis and gluconeogenesis leading to impaired glucose tolerance and diabetes mellitus as found in most Patients with glucagonoma syndrome. Since exogenous administration of glucagon decreases erythropoiesis in animals anemia which is frequently observed in these patients can be attributed to glucagon hypersecretion. However, the role of hyperglucagonemia in the pathogenesis of thromboembolic complications including pulmonary embolism is poorly understood. The necrolytic migratory erythema (Fig. 10) is believed to be related to hypoaminoacidemia present in most but not all patients and not the consequence of hyperglucagonemia. Skin lesions disappear despite high glucagon levels if plasma amino acid levels normalize. They are similar to those observed in patients with zink deficiency and zink suplementation has been shown to improve skin lesions in some patients as well. According to the authors experience skin lesions can disappear after resection of the primary without normalization of hyperglycagonemia and hypoaminoacinemia due to metastases to the liver suggesting a still undetected substance released by the tumor as cause of the necrolytic migratory erythema.

Symptoms

Main symptoms in patients with glucagonoma syndrome are skin lesions, diabetes mellitus, weight loss and anorexia present in up to 90% of patients with glucagonoma syndrome. Less frequently normochromic and normocytic anemia, venous thrombosis and pulmonary embolism occur. Diarrhea and steathorhea are present in 14% of patients. Their etiology is unclear. Rare clinical features include, in addition, psychiatric disturbances including depression and complex neurologic symptoms with dementia and optic atrophy, possible related to protein hypercatabolism that can recover after treatment with long-acting somatostatin analogs.

Figure 10
Necrolytic migratory erythema
in two patients with glucagonoma
syndrome

The necrolytic migratory erythema is one of the most impressive clinical symptoms in patients with glucagonoma syndrome. Skin lesions involve the lower abdomen, groin perineum, face, armpits (Fig. 10) and distal extremities. They start with an erythematous lesion which becomes papular. The erythema spreads peripherally and becomes raised with superficial central blistering. Lesions begin to heal in the center with a raised erythematous ring. Healing is followed by hyperpigmentation. The sequence of skin manifestations take 1–2 weeks while new lesions appear elsewhere. Skin lesions frequently precede the diagnosis of the syndrome for many years and are misdiagnosed as acrodermatitis enteropathica, psoriasis, contact dermatitis and other skin disorders.

Diagnosis

Diagnosis is based on the presence of a mostly large pancreatic tumor with and without metastases to the liver or elsewhere, clinical symptoms described in detail in "Symptoms" and the demonstration of high plasma glucagon levels. Total plasma aminoacids should be determined and support the diagnosis if they are markedly decreased. In most patients the pancreatic tumor can be visualized by conventional US. Fine-needle biopsy proves the endocrine nature of the tumor. Somatostatin receptor szintigraphy, CT and MRT imaging are helpful in evaluating tumor burden outside the pancreas [32].

Treatment

Surgical removal of the primary and of resectable liver metastases should always be considered because tumor debulking has been shown to have a favourable effect on clinical symptoms including skin lesions.

Medically, long-acting somatostatin analogs have been shown to be currently the medical principle of choice in the control of skin lesions, to improve symptoms as weight loss, anemia and diarrhea. Most studies recommend 200–600 µg per day or 10–20 mg octreotide-LAR every 28 days. Unfortunately, long-acting somatostatin analogs are not effective in up to 50% of patients. In these individuals debulking operation, embolization of liver metastases and chemotherapy with streptozotocin combinations or dacarbazine should be considered. For details see "General aspect of management".

Verner-Morrison Syndrome (VIPoma)

Epidemiology and Prognosis

An endocrine tumor mostly located within the pancreas and responsible for a syndrome characterized by extreme watery diarrhea, hypochlohydria and hypokalemia was first discribed by Priest and Alexander in 1957 and by Verner and Morrison in 1958. Alternative acronyms are "Verner-Morrison syndrome", "VIPoma" (due to the hormone vasoactive intestinal polypeptide responsible for the diarrhea), "WDHH (watery diarrhea, hypokalemia, hypochlorhydria) syndrome" and "Pancreatic Cholera". In adults VIPomas are mostly located in the pancreas and rarely outside the pancreas in the retroperitoneum, liver, small intestine and bronchial system. In children, a ganglioneuroma or an ganglioneuroblastoma can cause a VIPoma syndrome. Most VIPomas are malignant and have metastasized to the liver at diagnosis. VIPomas are as glucagonomas, somatostatinomas and endocrine pancreatic tumors with ectopic hormone production very rare. Prognosis of this malignant tumor was prior to the availability of long-acting somatostatin analogues unfavourable and patients died from the consequences of excessive watery diarrhea as dehydratation and pulmonary embolism. Presently, prognosis depends on the aggressiveness of tumor growth which differs between VIPomas and their responsiveness to chemotherapy.

Pathophysiology

Although VIPomas produce frequently several hormones as Peptide Histidine-Methionine-28 (PHM-27), secretin, pancreatic polypeptide and prostaglandines, vasoactive intestinal polypeptide (VIP) which is elevated in all patients with Verner-Morrison syndrome is the cause of watery diarrhea and electrolyte disturbances. VIP induces massive small intestinal net secretion of water and ions, especially potassium with an inconsistent effect on water absorption in the colon. If VIP is infused intravenously in healthy individuals in amounts reflecting circulating VIP-levels in patients with Verner-Morrison syndrome, subjects develop massive secretory diarrhea, hypokalemia and hypochloremic metabolic acidosis. VIP reduces water and sodium absorption from the colon and induces potassium secretion, thus explaining hypokalemia which may induce secondary hypoaldosteronism. In addition, VIP inhibits gastric acid secretion. Fluid secretion from the small intestine is attributed to activation of adenylate cyclase and cyclic adenosine monophosphate in intestinal cells. Some patients develop hypercalcemia which is attributed to the stimulation of bone osteolytic activity by VIP.

Symptoms

Patients with Verner-Morrison syndrome present with excessive watery diarrhea up to 5–10 L per day. Chronic diarrhea is a constant feature in 50% of patients but may be intermittent in others. Diarrhea decreases only slightly during fasting or exclusive parenteral nutrition proving its secretory nature. Untreated diarrhea leads to dehydration, weight loss, hypkalemia and hypomagnesemia resulting in paresthesia, muscle weakness and cardiac arrhythmia. Before the availability of long-acting somatostatin analogs patients died from the consequences of dehydration and electrolyte loss as cardiac arrhythmia and pulmonary embolism. 25% of patients report flushing episodes.

Differential Diagnosis

Secretory diarrhea of other origin as diarrhea in patients with Zollinger-Ellison syndrome, carcinoid syndrome, medullary carcinoma of the thyroid is mostly less pronounced compared to diarrhea in VIPoma patients. A stool volume of less then 700 ml per day excludes a VIPoma and is suggestive for other causes of secretory diarrhea. The most important differential diagnosis is laxative abuse and Münchhausen's syndrome. Repeatedly normal VIP-levels should induce search for laxatives in stool and urine.

Diagnosis

The combination of excessive watery diarrhea, hypokalemia and elevated plasma VIP-levels together with a pancreatic mass visualized by conventional US or CT/MRT imaging are highly suggestive for a VIPoma. The endocrine nature of the tumor can be ascertained by fine needle biopsy.

Treatment

Surgical intervention should always be considered if the primary is resectable and liver metastases could be removed with tenable risk for the patients. Medical therapy and patient's prognosis have been dramatically changed through the currently available long-acting somatostatin analogs. They substituted a number of drugs tried earlier to control diarrhea as loperamide, prednisone, clonidine, phenothiazines, indomethacin, lithium and others. Octreotide is in most patients effective and doses of 200–600 µg per day in two to three single injections are recommended. If the short lasting formulations are effective, long-acting depot formulations as octreotide-LAR 20 mg every 28 days can be offered. Unfortunately, some patients escape from treatment with long-acting somatostatin analogs after an initial longer lasting response. The mechanisms behind tachyphylaxis and/or desensitisation are not completely understood. Treatment should be terminated and started again after few weeks.

Somatostatinoma

Epidemilogy and Prognosis

Somatostatinoma is an endocrine tumor containing somatostatin as shown by immunihistology and arises either in the pancreas or in the duodenum where it is located close to the ampulla vateri. Most duodenal somatostatinomas are solitary and small (<1,5 cm) whereas pancreatic somatostatinomas tend to be larger. Malignancy rate in large tumors is 50–90% and metastases to liver, lymph nodes and bones have been described. According to table 9 duodenal somatostatinomas tend to metastasize if they are larger then 2 cm.

Approximately 90% of these tumors are functionally inactive and only 10% are cause of the somatostatinoma syndrome. Non-functional somatostatinomas located in the region of ampulla vateri are associated with von Recklingshausen's disease. Small pancreatic somatostatinomas of the pancreas can be part of MEN-1 syndrome. Prognosis of somatostatinomas seems to be favourable in small, non-metastasized tumors. In larger tumors it depends on the aggressiveness of tumor growth.

Pathophysiology

Somatostatin inhibits the release of gastrointestinal hormones as CCK and gastrin, inhibits basal and simulated gastric acid secretion and stimulated pancreatic secretion and inhibits the absorption of food constituents from the intestine. Through inhibition of CCK release somatostatin inhibits gallbladder emptying. Inhibition of pancreatic secretion is believed to cause diarrhea and steatorrhea in the somatostatinoma syndrome. Since somatostatin inhibits insulin release impaired glucose tolerance is a frequent finding in patients with somatostatinoma syndrome.

Symptoms

Leading symptoms in patients with somatostatinoma syndrome are cholecystolithiasis, diabetes mellitus, diarrhea and steatorrhea, hypochlorhydria and as a consequence of a tumor situated close to the ampulla vateri obstructive jaundice. However, the reported symptoms are rarely present in all patients with somatostatinoma syndrome. Other symptoms are epigastric pain, weight loss and nausea.

Since symptoms in patients with somatostatinoma syndrome can arise although in other conditions as cholecystolithiasis, diabetes mellitus and diarrhea and steatorrhea some authors question the existence of this entity.

Treatment

Medical treatment should be directed to correct symptoms associated with cholecystolthiasis, diabetes mellitus and diarrhea. Few observations suggest that diarrhea and diabetes mellitus can improve by exogenous somatostatin. But this suggestion is clearly experimental. Surgery should considered to be reduce tumor burden.

Tumors with Ectopic Hormone Production

Epidemiology, Classification and Prognosis

Most benign and malignant endocrine GEP tumors produce more then one hormone within the same tumor. Insulinomas contain next to insulin frequently somato-

statin-producing and glucagon-producing cells, gastrinomas additional pancreatic-polypeptide-, insulin- and somatostatin-producing cells (see Fig. 2). As a rule the additional hormones are not released into the circulation and do not produce hormone-mediated symptoms. In patients with MEN-1 syndrome, however, two clinical syndromes from two independent pancreatic or one pancreatic and one duodenal endocrine tumor can arise, mostly the combination of a gastrin-producing tumor situated in the duodenal bulb with the clinical symptoms of Zollinger-Ellison syndrome and a pancreatic functionally active insulinoma. In the latter condition additional endocrine pancreatic tumors exist, mostly glucagonomas and somatostatinomas which are functionally inactive.

Apart from tumors producing multiple hormones regularly synthetized in the normal islets of Langerhans of adults (insulin, glucagon, pancreatic polypeptide, somatostatin) or during fetal life (gastrin) (eutopic hormone production) endocrine pancreatic tumors can produce hormones uncommon for the endocrine pancreas (ectopic hormone production) as growth hormone-releasing factor (GRF), ACTH or corticotropin-releasing factor (CRF) and parathyroid hormone-related peptide (PTH-RP) or an unknown hypercalcemic substence mimicking the action of PTH. These tumors are mostly malignant and very rare. In addition, few patients with neurotensin-producing tumors have been described. Tumor prognosis depends on the aggressiveness of tumor growth and the success of antiproliferative measures.

Clinical Symptoms, Pathophysiology and Diagnosis

GRFoma. The association of acromegaly with endocrine bronchial, intestinal and pancreatic tumors is rare and approximately 150 patients with this syndrome have been described. Pancreatic GRFomas are mostly large but multiple GRFomas have also been reported. They are part of MEN-1 syndrome. Different from pituitary adenoma GRFomas arise 3 times more frequent in females then in males. They can be associated with other endocrine syndromes as gastrinoma, insulinoma, Cushing's syndrome and pheochromocytoma. In 30–40% metastatic disease which spreads mostly to the liver is present.

Clinically, patients present with characteristic signs indistinguishable from pituitary derived acromegaly with elevated GH and IGF-1 levels. If GRFomas are associated with other endocrine functionally active tumors, symptoms of acromegaly could be blurred by hypoglycemia resulting from an insulinoma etc.

Treatment includes surgical resection of the primary and debulking procedures and, medically, the suppression GRF levels by long-acting somatostatin analogs.

ACTH-Producing Tumors. According to a recent report from the Mayo Clinic in 106 patients ectopic ACTH or CRF production results in 25% from bronchial carcinoids, 16% from malignant islet cell tumors, 16% from medullary thyroid carcinoma, 11% from small cell carcinoma of the lung, 7% from disseminated neuroendocrine tumors with unknown primary source, 5% from thymic carcinoids and 3% from pheochromocytoma. Whereas in MEN-1 syndrome Cushing's disease results from a pituitary adenoma ectopic ACTH-production in the case of an islet cell tumor has been found mostly in sporadic gastrinomas. In the latter condition the gastrinoma is metastatic and the prognosis poor.

In a recent prospective study Cushing's syndrome in patients with Zollinger-Ellison syndrome due to a solitary malignant gastrinoma was an independent predictor for poor survival. Patients with ectopic ACTH syndrome differ from those with pituitary adenoma because they present with muscle waisting and weight loss which is more frequently observed then the classic features of Cusing's syndrome.

Possibly, symptom differences in patients with ectopic and eutopic ACTH-production result from a different processing of pro-piomelanocortin with the release of high amounts of ACTH precursors and less intact ACTH in the circulation in patients with ectopic hormone production. However, symptoms may overlap those seen in pituitary dependent Cushing's disease. Ectopic ACTH-producing endocrine tumors are more resistant to chemotherapy and the severe hypercortisolism is responsible for a high rate of life-threatening complications.

Treatment is frequently difficult since only few tumors respond to long-acting somatostatin analogs. If ketoconazoles, animogluthetimide or mifepristone do not control hypercortisolism and curative or palliative resection of the primary tumor and its metastases is not possible, patients are likely to benefit from bilateral adrenalectomy. For additional antiproliferative measures see "general aspects of management" (below).

PTH-RP-Producing Tumors. Few endocrine pancreatic tumors present with hypercalcemia and secret parathyroid hormone-related peptide (PTH-RP) or not identified hypercalcemic substances mimicking the action PTH. According to a recent review of 19 patients common features were hypercalcemia, normal or low PTH levels associated with extremely vascular, large and usually malignant tumors (17 of 18) displaing positive stains for PTH-RP. Some patients respond favourably to long-acting somatostatin analogs and to streptozotocin combinations if tumor resection is not possible.

Nonfunctioning Endocrine Pancreatic Tumors

Epidemiology, Classification and Prognosis

Nonfunctioning endocrine pancreatic tumors can be subdivided into benign and small tumors as part of the MEN-1 syndrome and large, malignant tumors which mostly spread into lymph nodes, liver, bones, and elsewhere. The latter can or cannot secret hormonal products into the circulation. Pancreatic polypeptide or neurotensin are released by some tumors but do not produce a clinical syndrome. Other functionally inactive tumors do not secret any products with hormonal activity. However, they release chromogranin A, a constituent of the secretory machinery of endocrine cells. Exact incidence rates for malignant non-functioning tumors are missing but according to own experiences they are at least as frequent as all functionally active endocrine pancreatic tumor together. By histology and immunohistology functioning PETs cannot be distinguished from nonfunctioning tumors.

Clinically, tumors and their metastases are either found incidentally at routine abdominal check-up, by the patient itself who realizes the presence of an upper abdominal mass or by obstructive jaundice due to a pancreatic head tumor. Most patients report no or only little upper abdominal discomfort and few present with more severe abdominal pain and weight loss. Frequently, tumors are misdiagnosed as endocrine pancreatic carcinomas but the unrestricted life quality of patients and hypervascular lesions identified by imaging procedures lead the correct diagnosis. Other patients present during routine US investigations with cystic liver lesions misdiagnosed as benign liver cysts. Prognosis of patients with non-functioning malignant tumors depends on the aggressiveness of tumor growth which can vary considerably from exploding tumor growth to long intervals of stable disease even in the absence of any treatment.

Diagnosis

The correct diagnosis requires histology which can mostly be obtained by ultrasound or CT-guided fine-needle biopsy. If the endocrine nature of the primary tumor or of its metastases is ascertained, OctreoScan should be performed to identify tumor load and the presence of distant metastases as in bones. If the primary is not identified within the pancreas upper and lower endoscopy and careful CT/MRT examinations of the chest should be performed to localize the primary within the fore-, mid- and hindgut (Fig. 6d). Because tumors do not produce a hormone-mediated syndrome, expensive hormone analyses are not helpful and should be avoided. However, chromogranine A should be estimated which is elevated in most metastatic tumors and serves as tumor marker. Some tumors produce, in addition, pancreatic polypeptide which serves as tumor marker as well.

Treatment

Treatment should follow the principles of other endocrine pancreatic malignancies. If resectable, non-metastatic primaries should be removed either by Whipple's procedure or partial pancreatectomy. In metastatic diseases several antiproliferative measures are available which are summarized under "general aspect of management".

Endocrine Tumors of the Stomach and Gut

Gastric Carcinoids

Epidemiology, Classification. Endocrine tumors of the stomach are nonfunctioning. As shown in table 8 there are 4 types of tumors:
- ECL-cell carcinoids;
- EC-cell carcinoids;
- Gastrin-cell tumors;
- poorly differentiated or small cell endocrine carcinomas [9, 10].

With the exception of the latter tumor most endocrine tumors of the stomach are well differentiated. Gastric carcinoids have been reported to occur with an inci-

dence of 0,002–0,1 per 100.000 population per year and account for 11–41% of all gastrointestinal carcinoids from the esophagus to the rectum. The most frequent endocrine tumors of the stomach are gastric ECL-cell carcinoids representing 74% of gastric endocrine tumors and occuring more frequently in females. The mean age of detection is 63 years. Small cell undifferentiated carcinomas represent 6% of endocrine tumors of the stomach. EC-cell and Gastrin-cell carcinoids are extremely rare.

ECL-Cell Carcinoids. *Clinical and histopathological aspects and prognosis:* ECL-cell carcinoids can be subdivided into three entities:

▸ type I ECL-cell carcinoids are associated with type A-gastritis (autoimmune chronic atrophic gastritis) present in the oxyntic and fundic part of the gastric mucosa. Due to the loss of parietal cells type I ECL-cell carcinoids are always associated with achlorhydria and – as a consequence of achlorhydria – with massive hypergastrinemia of antral origin achieving levels comparable to that observed in Zollinger-Ellison syndrome. Carcinoids in type A-gastritis are usually small and multiple.

▸ type II ECL-cell carcinoids arise in patients with hypergastrinemia due to a Zollinger-Ellison syndrome, mostly as part of MEN-1 syndrome. In contrast to type I carcinoids oxyntic mucosa is hyperplastic due to the trophic action of gastrin but without any atrophic changes.

▸ type III (sporadic) ECL-cell carcinoids are neither associated with type- A atrophic gastritis although gastritis is present nor with hypergastrinemia. They arise in areas without ECL-cell hyperplasia which is a prerequisite for the formation of type-I and type-II ECL-cell carcinoids. Clinically, type III tumors present with relatively large (1–3 cm) tumors that are usually aggressive with local invasion and the formation of metastases to adjacent lymphnodes and the liver. They are mostly non-functioning but can be the source of gastric hemorrhage and obstruction. In rare cases they can be associated with an atypical carcinoid syndrome with red long-lasting flushing episodes but without diarrhea. These tumors secrete histamine and 5-hydroxytryptophane.

ECL-cell carcinoids arise from ECL-cells that are physiologically present in the oxyntic and fundic mucosa and contain histamine which stimulates gastric acid secretion via specific receptors on the parietal cells. They can proliferate by two mechanisms: both chronic atrophic gastritis and the trophic action of hypergastrinemia lead to ECL-cell hyperplasia which can further proliferate to type I ECL-cell carcinoids. Histologically ECL-cell hyperplasia consists of linear, diffuse, micronodular and adenomatoid ECL-cell hyperplasia (Fig. 11). The next step in tumor formation is dysplasia with enlarging and fusing micronodules, microinvasion and newly formed stroma. Nodules greater than 0.5 mm and invading into submucosa are called carcinoids. Smaller and multiple
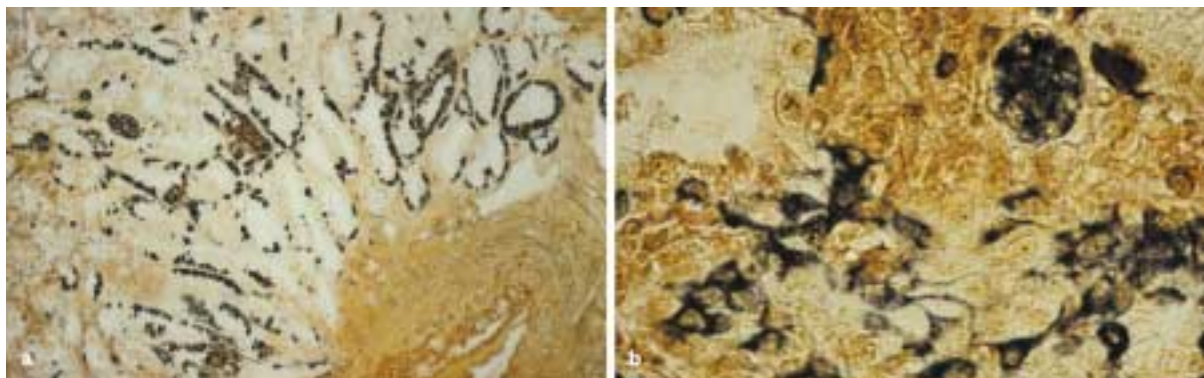
Figure 11
Histology of ECL-cell hyperplasia

nodules together with linear and diffuse ECL-cell hyperplasia a constituents of microcarcinoidosis. All these events are found in type A chronic atrophic gastritis and the ultimate step is the formation of type I carcinoids.

An identical spectrum of ECL-cell growth from ECL-cell hyperplasia to carcinoid formation is present in gastrinoma patients as part of MEN-1 syndrome. In contrast, sporadic gastrinoma patients develop ECL-cell hyperplasia but likely not ECL-cell carcinoids. This indicates the importance of a genetic trait (MEN-1) essential for the formation of type II carcinoids or the presence of severe atrophic gastritis as prerequisit for type I carcinoid formation through the trophic action of hypergastrinemia present in both.

Prognosis of type I and II ECL-cell carcinoids is excellent and favourable prognostic factors are: tumors confined to mucosa and submucosa, size <1 cm, low mitotic activity (Ki-67) and lack of angioinvasiveness. In contrast, angioinvasion, a size >1 cm, invasion of muscularis propria and beyond and high mitotic activity indicate a more aggressive behaviour. Metastatic spread into lymph nodes and to the liver is rare (5% rsp. 2.5% in type-I carcinoids) and slightly greater in type-II carcinoids.

Treatment: ECL-cell carcinoids (type I) in type-A chronic atrophic gastritis are mostly small and should be endoscopically excised. Yearly controls are recommended for further surveillance. If carcinoids are larger than 1 cm endoscopic US should estimate whether or not invasion of muscularis propria is present. In case of invasion local surgical excision is recommended. No agreement exists between experts whether or not antrectomy should be offered to remove the gastrin source as the trophic principle responsible for carcinoid formation.

Type II ECL-cell carcinoids should be handled as type I tumors but patients' prognosis depends mostly on the aggressiveness of underlying Zollinger-Ellison and MEN-I syndrome.

Type III ECL-cell tumors (sporadic carcinoids) should be removed according to the principles for non-endocrine gastric adenocarcinomas. No proven strategy exists if metastatic spread occurred. Tumors are mostly insensitive to available chemotherapeutic strategies.

EC-Cell Carcinoid. EC-cell carcinoids are very rare and always malignant. They present with rapid growth and are functionally inactive.

Gastrin-Cell Tumor. These very rare tumors are mostly well differentiated and small. They are found incidentally at endoscopy as small muscosal/submucosal nodules. They can and can't present with Zollinger-Ellison syndrome.

Small Cell Carcinoma (Poorly Differentiated Endocrine Neoplasm). These very rare tumors display exploding tumor growth similar to small cell carcinomas of the lung and of other origin.

Endocrine Tumors of the Duodenum and Proximal Jejunum

Epidemiology, Classification and Prognosis

Duodenal carcinoids account to 22% of all gastrointestinal carcinoids (see Table 9). In contrast, jejunal carcinoids are very rare. Most endocrine tumors of the duodenum are gastrinomas which in 7–21% are part of MEN-1 syndrome. Not all gastrinomas are cause for a Zollinger-Ellison syndrome and present as non-functional tumors. Gastrinomas can arise at multiple sites (15%) and are mostly small (<1 cm). Non-functioning gastrinomas have a more favourable prognosis as tumors associated with Zollinger-Ellison syndrome that have a higher incidence of metastases. However, compared to pancreatic gastrinomas duodenal gastrinomas have significantly less frequent metastases to the liver (5% versus 52%). Ten years survival of patients with duodenal gastrinoma is significantly better then those of pancreatic origin (59% versus 9%).

Somatostatinomas account for 21% of endocrine tumors in the upper small intestine and are located at, or very close to, the ampulla of vater. They are larger as gastrinomas (>2 cm) and can cause obstructive jaundice, pancreatitis and intestinal obstruction. Histologically, tumors contain characteristic concentrically laminated psammoma bodies. They are mostly malignant, with local invasion into surrounding tissues (sphincter of Oddi, head of the pancreas) and spread into paraduodenal lymph nodes and to the liver. Duodenal somatostatinomas are mostly non-functioning and genetically associated with neurofibromatosis von Recklinghausen.

Gangliocytic paragangliomas are very rare events characterized by an admixture of three cell types: spindle cells, epithelial cells and ganglionic cells. The spindle cells are neural in nature. They are usually benign but can be larger then 2 cm in size.

Treatment

Duodenal gastrinomas should be surgically removed either by local excision or Whipple's procedure. In cased of metastatic spread surgery should be avoided. The place of radical surgery in patients with duodenal and/or pancreatic endocrine tumors as part of MEN-1 syndrome is controversial even between experienced surgeons. Somatostatinomas and gangliocytic paragangliomas should be resected if possible. In case of metastatic spread, see "General aspect of management" under "Control of tumor growth in malignant and metastatic tumors".

Endocrine Tumors of the Distal Small Intestine (Jejunum, Ileum)

Epidemiology, Classification and Prognosis

The incidence of carcinoids arising in the distal small bowel has been reported to be 0,28–0,89 per 100.000 population and year. Most gastrointestinal carcinoids are localized in this area (see Table 10). Carcinoids of this site have been observed in equal proportion in males and females with and age peak in the 6th and 7th decade. Histologically, tumors are EC (enterochromaffine)- cell carcinoids containing serotonin. A minority of carcinoids consists of glucagon-like peptides- or pancreatic polypeptide- and peptide YY producing cells. EC-cell carcinoids can be multiple and are in 15% associated with other malignancies as gastrointestinal adenocarcinoma, breast cancer and others. The majority of tumors is located in the distal ileum close to the ileocecal valve. Only 5–7% of EC-cell carcinoids are functionally active and cause of the carcinoid syndrome. The primary is mostly situated in the ileum. Despite most EC-cell carcinoids are functionally inactive patients present with intermittent lower abdominal cramps due to incomplete intestinal obstruction and desmoplastic reaction of the mesenterium. Occasionally, small ileal carcinoids are incidentally detected during routine colonoscopy.

Prognosis of carcinoids arising in the distal jejunum and ileum is generally unfavourable if compared to that for duodenal, gastric (ECL-cell carcinoids) and rectal carcinoids since endocrine tumors arising in the distal small intestine frequently lead to metastases. 10 year survival is approximately 43% and more favourable if the primary tumor is removed and liver metastases absent. Therefore, patients with even small ileal carcinoids found incidentally during routine colonoscopy should be recommended right-sided hemicolectomy since metastatic spread into regional lymph nodes occurs early and is independent on the size of the primary.

Pathophysiology and Symptoms

Non-Functioning EC-Cell Tumors. Even tumors less than 1 cm, confined to the mucosa and submucosa discovered incidentally during colonoscopy and intubation of the terminal ileum are frequently malignant with metastatic spread to regional lymph nodes (see Table 10). They present very rarely with gastrointestinal bleeding.

Tumors measuring >1 cm in diameter are mostly malignant with metastases to the regional lymph nodes and later to the liver, bone and elsewhere. Patients frequently report on intermittent abdominal discomfort existing sometimes for years. Later, complaints worsen and diagnosis will be made if intermittent intestinal obstruction occurs. The latter is assigned to the role of growth factors secreted by the tumor cell as PDGF, TGFα, bFGF and others which stimulate neighburing fibroblasts which lead to new stroma formation and later to the typical desmoplastic reaction of the mesenterium. The consequence is angulation of the bowel with subsequent obstruction. Since also vasculature is affected by the stroma formation, ischemia develops in the involved segment and surgeons find the respective bowel dark-blue. Gastrointestinal bleeding is also in larger EC-cell tumors rare. Desmoplastic reaction can easily be detected by high-resolution MRT.

Functioning EC-Cell Tumors and Carcinoid Syndrome. EC-cell tumors responsible for the carcinoid syndrome do not different histologically from non-functioning tumors. However, carcinoid syndrome apperars only in patients with metastases to the liver. The symptoms are the consequence of unrestrained release of hormones and other mediators [11]. Flushing is present in up to 94% of patients and is characterized by red to purple discoloration of face, neck and upper chest. Duration of episodes is mostly short (few minutes) but can continue for hours. Frequently, patients themselves do not notice flushing and their attention will be drawn by others. Occasionally, flushing is associated with unpleasant sensations of lacrimation, warmth, facial and conjunctival edema. The hormonal mediator of flushing has not been identified with certainty. The elevation of blood serotonin during flush-

ing does not prove its causal relationship. In addition, serotonin antagonist as methysergide and odansetone have only little effect. A more likely mediator are tachykinins as substance P and related peptides as neurokinins.

Serotonin is synthesized and secreted from carcinoid tumor cells. It arises from the amino acid tryptophan which is hydroxylated to 5-hydroxytryptophan and decarboxilated to 5-hydroxytryptamin (serotonin). Through several enzymes as monoamine oxidase and aldehyde dehydrogenase sterotonin is converted to 5-hydroxy-indolacetic acid (5-HIAA) and excreted into urine.

Diarrhea with watery bowel movements is a common symptom and present in up to 85% of patients. It is possibly related to serotonin production but other mediators as prostaglandins have been suggested to contribute to diarrhea as well. Diarrhea responds better to serotonin antagonists then flushing.

The most important consequence of long-standing carcinoid syndrome is carcinoid heart disease, present in 45–77% of patients. Heart disease threatens patients with carcinoid syndrome at least by the same extent then the tumor itself and patients can die from carcinoid heart disease despite tumor growth is well controlled. Carcinoid heart disease involves mostly tricuspidic valve, pulmonary valve and rarely mitral and aortic valve. The mediator responsible for carcinoid heart disease is unknown. Several studies suggest the concept that serotonin is involved by reporting higher serotinin levels in plasma and 5-HIAA levels in urine in patients with compared to those without heart involvement. However, anorectic factors as well are discussed to be involved. Typically, the affected valves are thickened, shortened and retracted by fibrous transformation leading to tricuspid and pulmonary valve insufficiency which can be easly visualized by two-dimensional echocardiography.

Additional symptoms in carcinoid syndrome encompass bronchoconstriction, Pellegra-like skin changes and abdominal pain. The latter can result from diffuse liver enlargement or desmoplastic mesenterial reaction (see Fig. 7b). Pellegra-like skin reactions are the consequence of niacin deficiency which is due to the formation of serotonin from 5-hydroxytryptophan.

Carcinoid crisis is a rare exacerbation in patients with carcinoid syndrome mostly arising during anesthesia or surgery if patients are not under continuous somatostatin treatment. Flushing, hyper- and hypotension, severe bronchospasm and cardiac arrhythmias are the main features and subsequent death is not uncommon.

Diagnosis

In non-functional tumors, incidental detection of an ileal carcinoid during colonoscopy and in case of intestinal obstruction surgery uncovers the responsible carcinoid, which, in the latter situation, has mostly metastasized into regional lymphnodes. Non-functioning liver metastases from an ileal carcinoid are frequently detected by US during routine check-up. Most sensitive measures to estimate total tumor burden are Octreo Scan, CT and MRT. Biochemically, chromogranin A serves as most reliable tumor marker. Diagnosis of carcinoid syndrome is based on the demonstration of high 5-HIAA levels in the urine and elevated plasma serotonin and chromogranin A levels in the presence of liver metastases from an neuroendocrine tumor. CT, MRT and OctreoScan define total tumor burden and mostly the site of the primary. All patients deserve careful cardiologic diagnosis with two-dimensional echocardiography to prove or disprove cardiac involvement.

Differential Diagnosis

Some patients with non-functional ileal carcinoids develop diarrhea after right-sided hemicolectomy. They are later misdiagnosed as having carcinoid syndrome and somatostatin treatment will be started to prevent diarrhea. However, somatostatin treatment can even worsen diarrhea which is not hormone mediated but the consequence of bile acid loss into colon or bacterial overgrowth.

Treatment

Surgery is the treatment of choice to remove the primary and its local metastases reponsible for the desmoplastic reaction and subsequent abdominal pain. Surgery should further be considered in case of few and large liver metastases. In addition, right-sided hemicolectomy should be offered to patients with small ileal carcinoids detected incidentally during routine colonoscopy. Symptom control in patients with carcinoid syndrome was difficult before the availability of long-acting somatostatin analogs which are currently the principle or first choice to control flushing and diarrhea. They are indispensable in the treatment and prevention of bronchial obstruction and carcinoid crisis. They have, therefore, to be administered perioperatively and during laparotomy.

Their effects on carcinoid heart disease and its progression have not yet been demonstrated. Octreotide should be started at doses of 2–3×50 µg, but higher doses up to 3×500 µg may be necessary in some patients. If effective, LAR formulations should be offered (Octreotide-LAR 20 mg every 28 days). Long-acting somatostatin analogs are safe. One of the most frequent side effects is the formation of gall stones since somatostatin inhibits the release of CCK and by this mechanism gallbladder contraction. In few patients, somatostatin analogs induce diarrhea which can be as severe as diarrhea restulting from carcinoid syndrome. In these patients and those with tachyphylaxis to long-acting somatostatin analogs diarrhea should be controlled by serotonin receptor blockade. 5-HT_1 (methysergide)-, 5-HT_{1+2} (cyproheptadine)-, 5-HT_2 (ketanserin)- and 5-HT_3 (ondansetron)-receptor antagonists have been recommended. But they do not completely stop diarrhea. To substitute niacin deficiency, patients should be offered niacin orally. Cardiac failure should be treated by conventional pharmacologic therapy.

Endocrine Tumors of the Appendix

Incidence rates of appendiceal carcinoids account for 0.075 new cases per 100.000 population and year. 19% of all gastrointestinal carcinoids have been reported to be localized in the appendix. Mean age of presentation is 32–43 years and females are more frequently affected.

Appendiceal carcinoids are mostly detected incidentally during appendectomy or described by pathologists in the resected appendix. They are mostly situated in the distal third of the appendix. By obstructing the lumen they can produce appendicitis. Clinicopathologic staging is summarized in Table 11. Most appendiceal carcinoids are well-differentiated tumors consisting of EC-cells but some contain glucagon-like peptides and PP/PYY-producing cells.

Most patients with appendiceal carcinoids have a favourable prognosis. Several well conducted studies demonstrate that carcinoids of less then 2 cm size confined to the appendiceal wall and not angioinvasive are completely cured by appendectomy. Invasion of the mesoappendix, a size >2 cm and angioinvasion carry an uncertain malignant potential and right sided hemicoletomy should, therefore, be performed as in patients with metastatic spread into regional lymph nodes. Also location of a carcinoid at the base of the appendix with involvement of the cecum has a more unfavourable prognosis requiring right sided hemicolectomy.

Goblet cell carcinoids are more aggressive tumors and should be treated by right sided hemicolectomy since these carcinoids frequently invade the wall of the appendix.

Endocrine Tumors of the Colon and Rectum

With an incidence of up to 0.21 cases per 100.000 population per year hindgut carcinoids (left sided colon, rectosigmoid) are less frequent then midgut carcinoids (see Fig. 7f) (jejunum, ileum, appendix). They account for 20% of all gastrointestinal carcinoids. Within the hindgut most carcinoids are situated in the rectum (54%). Average age for colonic carcinoids is 66 years and for rectal carcinoids 58 years. Histologically, colonic carcinoids consist of EC-cells or L-cells (glucagon-like peptides and PP/PYY-producing carcinoids) and rectal carcinoids mainly of L-cells. Most colonic carcinoids are found in the right colon with an average size of 4,9 cm. Rectal carcinoids represent as submucosal nodules or yellow polypoid lesions situated mostly 4 cm proximal the dentate line. Mostly, they are less then 1 cm in diameter and only in 13% greater then 2 cm (see Table 10). Carcinoids of the colon/rectum are generally non-functioning and present with abdominal pain due to bowel obstruction, bleeding or are detected incidentally during screening colonoscopy or in case of carcinoids >2 cm with liver metastases. Very few colonic carcinoids are associated with a carcinoid syndrome. Few hindgut carcinoids are poorly differentiated and aggressively growing. Their prognosis is poor. Carcinoids >2 cm have a higher malignancy rate with metastases mostly to the liver.

Established malignancy criteria of rectal carcinoids are a size >2 cm, invasion of the muscularis propria, DNA aneuploidy and the presence of 2 mitosis and more per 10 high power microscopic fields (magnification: ×400). The prognosis is in general more favourable then the prognosis of patients with carcinoids situated in the jejunum and ileum.

General Aspect of Management

Surgery

Surgery and endoscopic resection is the only available curative treatment and should always be considered. Solitary tumors (insulinomas, gastrinomas, gastrointestinal carcinoids) should be resected by laparotomy or endoscopy. Surgical management in patients with metastatic spread is not very well defined but should be an important treatment module of a multidisciplinary approach. Single and few liver metastases are exepted examples for palliative surgery. Many patients with slowly growing metastatic GEP tumors whether functionally active as some malignant insulinoma or functionally inactive have a benefit from this approach. Not well established is the place of surgery in patients with multiple, non-functioning endocrine pancreatic tumor as part of MEN-1 syndrome.

Liver transplantation should be considered in patients with resected primary tumorbut metastases only to the liver as shown by Octreoscan and other sensitive imaging methods and unresponsive to established medical and interventional treatment. However, reoccurrence of metastases in the transplanted liver has been observed as well as newly formed extra-hepatic metastases. Nevertheless, some patients have a significant benefitfrom liver transplantation with prolonged survival and quality of life.

Medical Treatment of Symptoms

The respective pharmaceutical principles have been in detail discussed elsewhere in this chapter.

Control of Tumor Growth in Malignant and Metastatic Tumors

Non-surgical control of tumor growth includes biotherapy with long-acting somatostatin analogues and α-interferon, systemic chemotherapy, ablative methods including chemoembolizaton, thermo- and alcohol treatment of liver lesions and tumor targeted radiotherapy.

Every therapeutic modality should recognize that well-differentiated endocrine GEP tumors are mostly slow growing and often exhibit phases of stable disease or such a slow growth that a significant increase in tumor size can only be substantiated with CT- or MRI scans performed in 6–12 months intervals. Therefore, non-surgical treatment options should not be considered in patients with stable disease and uncompromised life quality. Such patients should be offered regular control visits in 6 months intervals and treatment only offered in case of significant tumor growth (>20–25% increase in 3–6 months). Therefore, patients with newly-diagnosed metastatic disease from well-differentiated endocrine GEP-tumors and low mitotic activity should not be offered a specific treatment immediately.

Long Acting Somatostatin Analogs

Evidence for antiproliferative properties of somatostatin and its analogs derives from in vitro and in vivo studies. As discussed earlier, currently available somatostatin analogues bind preferentially to sst2 and sst5 receptors which mediate antimitogenic, antiproliferative and anti-apoptotic signals. Besides these receptor-dependent effects, somatostatin controls cell growth via receptor-independent effects. These include endocrine effects with inhibition of the release of circulating or paracrine tumor growth promoting factors, vascular antiangiogenetic effects and effects on the immune system.

Anecdotal reports of tumor regression in patients with metastatic endocrine tumors of the GI tract and of stable disease over a period of 4 years in two patients with carcinoid syndrome due to malignant metastatic neuroendocrine tumors of the lung are consistent with the above mentioned experimental data.

A retrospective report of the National Institute of Health on 96 patients with metastatic endocrine tumors showed a partial tumor response in 13%, stable disease in 63% and tumor progression in only 24%. However, partial tumor response was a very rare event in prospective studies and disease stabilization occurred in 36–70% of patients. However, even stable disease was short-lasting for a minimum of 2 months and a maximum of 60 months. In one study, patients were classified into those with rapidly-progressing tumors (increase >50% in 3 months) and slowly progressing tumors (increase >50% in 3 months). Inhibition of tumor growth occurred predominantly in slow-growing tumors [27]. All trials were uncontrolled. Regarding the unpredictable course of the disease and the moderate response to treatment for a relatively short period of time, it cannot be excluded that

the phases of stable disease and even partial response observed in a few patients reflect the natural course of the disease. Since long-term treatment with somatostatin analogs is expensive, placebo-controlled studies are now necessary to prove or to disprove the antiproliferative potency of long-acting somatostatin analogs in patients with metastatic endocrine GEP-tumors. Unresolved issues include the therapeutic dose, the equipotency of octreotide and lanreotide versus the longer acting release formulations and the treatment effect with regard to prolongation of live.

α-Interferon

Interferons affect tumor growth by blocking the cell cycle during the G_0-G_1 phase with prolongation of the S-phase. Experimental data suggest that α-interferon induce apoptosis and that tumor cells are replaced by fibrotic tissue. α-interferon, in addition, induces increased expression of class I antigens on the tumor cell surface which renders cells as targets for cytotoxic T-lymphocytes.

Several studies in metastatic endocrine GEP-tumors demonstrate both a symptomatic effect with improvement of flushing and diarrhea in patients with carcinoid syndrome, a concomitant decrease of biochemical markers and a stabilization of tumor growth in 20–40% and a reduction in tumor size in 12–20% of patients. As shown for long-acting somatostatin analogues, these effects are transient (6–20 months). Side effects of α-interferon treatment have a much greater impact on patients well-being and include flu-like symptoms, weight loss, fatigue, anemia, leukopenia, thrombocytopenia, autoimmune manifestations and psychiatric disturbances.

Combination Treatment with Octreotide and α-Interferon

In a prospective trial inhibition of tumor growth was observed in 67% of 21 patients with metastatic endocrine tumors of the GI-tract who were unresponsive to prior octreotide monotherapy. Responders to combined treatment had a significant survival benefit. However, these data could not be confirmed by a prospective two arm study, comparing octreotide versus octreotide plus α-interferon in 105 patients performed by the authors of this chapter demonstrating the need for well-controlled and prospective trials in well-defined subgroups of patients with endocrine GEP-tumors.

Chemotherapy

Several chemotherapeutic agents have been used as single agents and as combinations in metastatic endocrine GEP tumors. The respective original data demonstate that chemotherapy is indicated only in patients with well-differentiated endocrine carcinomas of pancreatic origin and in rapidly growing undifferentiated and small cell endocrine carcinomas [8]. According to a 20 years old prospective study from the Eastern Cooperative Oncology Group (ECOG) which enrolled 125 patients with histologically proven unresectable islet-cell carcinomas streptozotocin plus doxorubicin was found superior to streptozotocin plus 5-fluouracil (5-FU) and to chlorozotocin. Tumor regression occurred in 69% of patients treated with streptozotocin plus doxorubicin and in 45% of patients treated with the combination of streptozotocin and 5-FU. Median duration of regression was 18 months for the doxorubicin combination and 14 months for the 5-FU combination. These beneficial effects influenced also survival. These favourable effects of tumor growth are contrasted by toxic reactions to treatment as nausea, vomiting, alopecia, hematologic and kidney toxicity. Heart failure has been observed in patients receiving the doxorubicin regimen and a cumulative dose of 400–500 mg/m^2 should, therefore, not be exceeded. In the institution of the authors patients are treated with the streptozotocin/doxorubicin combination. In case of response, treatment is changed to streptozotocin plus 5-FU if the limiting doxorubicin dose is reached. The dosages are summarized in table 16. Unfortunately it is impossible to identify patients responding to this treatment and patients not responding. In the latter situation one should try dacarbacine (150 mg/m^2) as short infusion and repeat it every 28 days. At least 3 courses of treatment should be performed to prove or disprove success.

Importantly, streptozotocin combinations and dacarbacine are only effective in tumors of pancreatic origin. There is no established chemotherapy for malignant carcinoids of the stomach, small and large intestine. In patients with exploding undifferentiated tumors the fol-

lowing chemotherapeutic strategy should be offered: 130 mg/m² and day etoposide for 3 days plus 45 mg/m² and day cisplatin on days 2 and 3. Each agent is given by 24 hours infusion and cycles repeated every 6 weeks. These tumors may originate from the pancreas, stomach, small and large bowel and most patients with these rare undiffentiated tumors will respond at least for 2 to 3 cycles. Drug toxicity is a significant problem of these formulations requiring dosage reduction or cessation of treatment in some patients.

Ablative Measures

Ablative measures include transarterial chemoembolization and radio-frequency tissue or alcohol ablation. Transarterial chemoembolization [8] is based on the concept that arterial blood supply of metastases (via hepatic artery) from endocrine GEP tumors is more intense then that of other malignancies except primary hepatocellular carcinoma and that local ischemia induces cell necrosis. Unproven is the concept that the combination of desarterialization vial embolization and local cytotoxic chemotherapy increases response rates. Embolization is performed by selective injection of a mixture of iodinized oil plus doxorubicin followed by injection of gelatine sponge particles. Response rates with a decrease of symptoms in patients with carcinoid syndrome of 68–100%, decreases of hormone levels in 80% and a decrease in size of liver metastases in 37–100% of patients have been described by several institutions. Mean duration of response is approximately 24 months. In the own institution it has been shown that patients with a tumor burden >75% of the liver have not benefit from chemoembolization. Increased survival has been observed in patients with a tumor burden <50% and an accumulation of lipiodol in more then 50% of the tumor mass. Side effects include abdominal pain, nausea, vomiting and fever. Fatal complications are infection and sepsis and hepatic failure.

Radiofrequency treatment [33] is a novel advice to destroy liver metastases and can be performed percutaneously and intraoperatively using a cooled-tip needly applying 50 to 90 watts over 10–12 minutes under ultrasound control. This experimental procedure as well as ablation by injection of alcohol can be considered in case of few and small liver metastases.

Table 16

Chemotherapeutic protocols for well differentiated metastatic islet cell carcinoms

Streptozotocin plus 5-fluorouracil	500 mg/m² streptozotocin/day as intravenous injection for 5 consecutive days; *plus* 400 mg/m² 5-fluorouracil/day as intravenous injection for 5 consecutive days, repeated every 6 weeks
Streptozotocin plus doxorubcin	500 mg/m² streptozotocin/day as intravenous injection for 5 consecutive days; *plus* 50 mg/m² doxorubicin as intravenous injection on days 1 and 22; repeated every 6 weeks

Maximal dose of doxorubicin: 4500 mg/m². Reduced dosages of every drug in case of severe nausea, vomiting, stomatitis, diarrhea, leukopenia, thrombozytopenia. Reduced dosages of streptozotocin in case of elevated creatinine or proteinuria and discontinuation if abnormalities persist.

Radioligand Therapy

Tumor-targeted metabolic endo-radiotherapy using specific receptor ligands such as octreotide or lanreotide coupled to beta-emitting radionuclides is of special interest in endocrine malignancies since biotherapy is only effective in slow growing tumors and systemic chemotherapy in a subpopulation of patients with pancreatic tumors. Almost no treatment modality has been shown to affect bone metastases. Whereas radioiodinated somatostatin analogues usually show target-to-background ratios not high enough for therapeutic applications, which is mainly due to their lipophilicity and rapid intracellular degradability, radiometal-labelled analogues display excellent biodistribution properties. To bind radioisotopes such as [111]Indium, [90]Yttrium and [177]Lutetium tightly to somatostatin analogs, mono- and bifunctional chelators have been developed consisting of polyaminopolycarboxylic acids or their macrocyclic derivatives such as DTPA, TTHA, DFO, DOTA or TETA. To reach biofunctionality, aliphatic side chain, thiourona-tobenzyl,-, acetamidobenzyl- or succinylbenzyl linkers connect the chelators with octreotide and related peptides. ^{111}In-labelled [DTPA]-octreotide has been shown to display an appropriate biodistribution profile in man.

Although generally regarded as mainly diagnostic, [111]-Indium emits Auger and conversion electrons, which display a tissue penetration of 0.02–10 μm and 200–500 μm respectively, and which can be used therapeutically. More therapeutic experience has been gained with [90]Yttrium, which is a classical β-particle emitter. To avoid dissociation of [90]Yttrium with a maximum path length of 9 mm from the chelated somatostatin analog, a stable [DOTA[0], Tyr[3]]-octreotide complex has been developed. Replacement of phenylalanine at the 3-position of octreotide by tyrosine has been shown to even increase the affinity of this compound for the sst2 receptors. The effect of endo-radiotherapy depends on binding to the sst2 receptor and requires internalization of the radio-ligand. Therefore, a sufficient number of sst2 binding sites and rapid internalization are prerequisits for successful therapy. The principal efficacy of somatostatin receptor-mediated radiotherapy has been demonstrated in animal models. Recently, several studies including a limited number of patients with malignant endocrine tumors have been published, suggesting that radio-therapy with [111]In- and [90]-Y-labelled octreotide analogs is able to control symptoms in patients with functionally active endocrine tumors and to inhibit or even significantly decrease tumor load. Whether or not [^{177}Lu-DOTA, Typ[3]]-Octreotate with a tissue penetration of 2 mm is superior to [111]Indium and [90]Yttrium labelled octreotide in the treatment of endocrine GEP tumors is currently under investigation.

How Should we Proceed in Patients with Metastatic Neuroendocrine GEP-Tumors?

Despite the availability of several antiproliferative strategies that can be offered to patients with metastatic disease, current recommendations how to start with non-surgical modalities are controversial and not supported by prospective and controlled studies. Therefore, therapeutic strategies for a single patient are based frequently on personal experiences of expert centers and vary, therefore, from center to center. To harmonize therapeutic ways of proceeding European experts in the field have founded the Eureopean Network for the Study of Endocrine GEP Tumors (ENET) to define the place of currently available and future diagnostic and therapeutic principles. According to the experiences of the authors of this chapter the following recommendations can be applied to patients with metastatic GEP tumors:

1. Surgery with curative resection of the primary in the absence of metastatic spread and tumor debulking in metastatic disease should be intended where ever possible.

2. Antiproliferative strategies should consider the growth characteristics and biology of a given tumor. Do not treat non-growing metastases which are stable by CT for 6 months and longer! It is questionable whether these patients have any benefit from anti-proliferative measures. Consider surgery or local ablative measures (radiofrequence ablation) in these patients.

3. In the case of moderately rapid progression chemotherapy should be offered in patients with tumors of pancreatic origin (streptozotocin combinations, dacarbazine). Chemotherapy should not be offered to patients with well-differentiated non-functional or functional tumors arising from the intestine (from stomach to rectum).

4. Offer chemotherapy (etoposid + cisplatin) in exploding tumors as small cell and undifferentiated neuroendocrine carcinomas.

5. Offer local irradiation in case of pain in patients with bone metastases since bone metastases do not respond to chemotherapy and biotherapy.

6. Offer octreotide to patients with well-differentiated slowly growing neuroendocrine tumors. In case of further growth add α-interferon.

7. Consider chemoembolization primarily in patients with liver metastases due to mid- and hindgut tumors since this group of patients does not respond to chemotherapy.

8. Consider radioligand therapy only within controlled and prospective studies since it is unsettled whether this modality should be offered to patients as first-line treatment or to patients unresponsive to other therapeutic alternatives.

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