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ESSENTIALS Pancreatic neuroendocrine tumours (islet-cell tumours) are rare and usually sporadic, but they may be associated with complex familial endocrine cancer syndromes. Recognized types of pancreatic neuroendocrine tumours are those that are nonfunctioning (often advanced at diagnosis and presenting with mass effects due to the absence of symptoms attributable to hormone

hypersecretion), insulinoma (the most frequent type), and others including: Gastrinoma—90% located in the pancreatic region; present with severe, multiple peptic ulcers that are often associated with complications such as haemorrhage, perforation, and stricture formation (Zollinger-Ellison syndrome); diagnosis requires demonstration of a raised fasting plasma gastrin concentration associated with increased basal gastric acid secretion; symptomatic treatment is with high-dose proton pump inhibitors. VIPoma—90% occur in the pancreas; present with large-volume diarrhoea without steatorrhoea (Verner-Morrison syndrome, pancreatic cholera); hypokalaemia may be profound; diagnosis can be confirmed by finding of an elevated plasma level of peptide histidine-methionine (PHM, produced from the prepro-VIP molecule); diarrhoea responds well to somatostatin analogues (octreotide, lanreotide) and parenteral hydrocortisone treatment. Glucagonoma—rare α -cell tumours of the pancreas; presenting features include weight loss, diarrhoea, anorexia, abdominal discomfort due to hepatomegaly from metastases, and diabetes, also necrolytic migratory erythema; diagnosis is made on the basis of an elevated fasting plasma glucagon in association with characteristic clinical features; skin rash and other symptoms may respond to somatostatin analogues; topical zinc sulphate pastes and oral zinc sulphate supplementation may be of benefit. Management—the following should be considered in addition to the symptomatic treatments for pancreatic neuroendocrine tumours described: (1) surgical resection—the only curative treatment, but not possible in many cases; (2) tyrosine kinase inhibitors which inhibit specific kinases involved in tumour cell proliferation, growth, and

angiogenesis; (3) mammalian Target of Rapamycin (mTOR) inhibitors; (4) peptide-receptor radionuclide therapy (radiolabelled somatostatin analogues). Multiple endocrine neoplasia (MEN) There are two main MEN syndromes, which are rare hereditary conditions characterized by a predisposition to cancer development within two or more endocrine organs. MEN-1—typical features are parathyroid adenomas, pancreatic neuroendocrine tumours (gastrinomas > insulinomas > others) and pituitary adenomas; caused by mutation of the MEN1 gene, which encodes a nuclear protein (menin) that is presumed to be a tumour suppressor gene, with diagnosis confirmed by genetic analysis; following identification of an index case, genetic analysis in first-degree relatives allows identification of affected family members; minimal surveillance programme for individuals with MEN1 syndrome or a family-specific mutation of the MEN1 gene should include annual measurement of serum prolactin (from age 5 years), fasting serum calcium and PTH (from age 8 years), and fasting serum gastrin concentration (from age 20 years), and consideration of serial imaging of the pituitary and pancreas using MRI scanning at 1–3 yearly intervals. MEN-2—there are three variants: (1) MEN-2A (Sipple's syndrome)—medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia/adenomas; (2) MEN-2B—medullary thyroid carcinoma and pheochromocytoma, with other features including marfanoid habitus and mucosal neuromas; (3) familial medullary thyroid carcinoma. These are caused by mutations in the RET oncogene, with diagnosis confirmed by genetic analysis and strong genotype–phenotype correlation. The codon location and type of mutation allows for risk-assessment and informs the management of index cases and affected family members (e.g. prophylactic thyroidectomy is recommended for those possessing mutations conferring the highest risk of aggressive medullary thyroid carcinoma; annual measurement of urinary metanephrines for those with high risk of pheochromocytoma). Other syndromes of MEN include (1) Carney complex, (2) McCune–Albright syndrome, (3) neurofibromatosis type 1, (4) von Hippel–Lindau syndrome, (5) familial paraganglioma syndromes, including Carney–Stratakis syndrome.

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section 13 Endocrine disorders 2450 Pancreatic neuroendocrine tumours Pancreatic neuroendocrine tumours (islet-cell tumours) are rare tumours representing 1 to 2% of all pancreatic neoplasms and have an incidence of approximately 1.8 to 2.6 per million per year. Although pancreatic neuroendocrine tumours may be associated with complex familial endocrine cancer syndromes such as multiple endocrine neoplasia (MEN), the majority are nonfamilial (sporadic) cases. Pancreatic neuroendocrine tumours have a wide range of clinical manifestations. Between 15 and 30% are clinically silent (nonfunctioning) and usually present with mass effect or metastatic disease. However, even so-called nonfunctioning pancreatic neuroendocrine tumours may secrete detectable amounts of tumour markers such as pancreatic polypeptide, chromogranin A, neuron-specific enolase, and human chorionic gonadotrophin subunits. Those pancreatic neuroendocrine tumours associated with a specific endocrine hyperfunction syndrome are termed 'functional', with insulinomas and gastrinomas being the most common. Other types of neuroendocrine or 'carcinoid' tumours are described in Chapter 15.9.2. This section will consider the biochemical confirmation and localization of pancreatic neuroendocrine tumours, specific clinical presentations of functional tumour types, management options, and discussion of the clinical features of MEN types 1 and 2 (MEN-1 and MEN-2). Introduction and definition The gastrointestinal tract is the largest endocrine organ in the body, which includes endocrine cells of the gut and pancreas. Current evidence suggests that these cells are derived from endodermal,

om- nipotent stem cells. Since these enteroendocrine cells share many of the properties exhibited by neural cells, this has led to their de- scription as neuroendocrine cells. Criteria for defining neuroendo- crine cells include production of bioactive substances that provide transmitter functions, release of hormones via exocytosis from dense-core secretory vesicles following an external stimulus, and an absence of axons or synapses. The histopathological hallmark of tumours arising from these cells, so-called neuroendocrine tu- mours, is the expression of neuroendocrine markers, for example, chromogranins A, B, and C, synaptophysin, and neuron-specific enolase. Pancreatic neuroendocrine tumours, the subject of this chapter, are now recognized to be a subtype of neuroendocrine tu- mour, which also include gastrointestinal neuroendocrine tumours (so-called 'carcinoid' tumours), bronchial neuroendocrine tumours, and medullary thyroid carcinoma. Aetiology and genetics Pancreatic neuroendocrine tumours are associated with complex familial endocrine neoplasia syndromes, including MEN-1 and MEN-2, von Hippel-Lindau (VHL) syndrome as well as the phacomatoses neurofibromatosis type 1 (NF-1) and tuberous scler- osis. Nevertheless, most pancreatic neuroendocrine tumours are actually sporadic (i.e. noninherited). Pancreatic neuroendocrine tumours are a principal feature of multiple endocrine neoplasia type 1. Most patients with MEN-1 display germline-inactivating mutations in the MEN1 gene, a tumour suppressor gene located on chromosome 11q13 which encodes the menin protein. Of all these familial endocrine neoplasia syndromes, it is MEN-1 that has the strongest association with pancreatic neuroendocrine tumours and these tumours occur in up to 80% of MEN-1 patients. With regards to sporadic pancreatic neuroendocrine tumours, three pathways have been shown to be associated with the patho- genesis of these tumours. 44% of these tumours possess somatic mu- tations in MEN1, again supporting the significant role of menin in pathogenesis. However, these same studies also show that pathways controlled by DAXX (death-domain associated protein) and ATRX (α -thalassaemia/mental retardation syndrome X-linked) are also aetiologically linked. Mutations in DAXX and ATRX activate the 'al- ternative lengthening of telomeres' (ALT) pathway, which immor- talizes cells. 61% of sporadic pancreatic neuroendocrine tumours show signs of ALT activity, supporting the role of this pathway in pathogenesis. Lastly, 15% of tumours possess mutations in the mam- malian Target of Rapamycin (mTOR) pathway, notably the tumour suppressor gene PTEN, the tuberous sclerosis complex gene TSC2, and the PI3 kinase subunit PIK3CA. The mTOR pathway controls translation, ribosomal assembly, cell growth, and cell proliferation. The clinical implication is that inhibition of this pathway with in- hibitors such as everolimus, and these have found application as tar- geted treatments for pancreatic neuroendocrine tumours (see next). Approximately 14% of patients with VHL have pancreatic neuroendocrine tumours, which are usually nonfunctioning and often multiple. VHL mutations lead to reduced clearance of the hypoxia-induced transcription factor HIF-1 α via ubiquitination and proteasomal degradation, with inappropriate activation under normoxic conditions of the hypoxic response. In turn this induces angiogenesis via vascular endothelial growth factor (VEGF), cel- lular growth via platelet-derived growth factor (PDGF) and trans- forming growth factor (TGF) α , metabolic changes promoting the transport of glucose, and enhanced cell survival. This 'pseudo-hypoxic' response is classically implicated in the pathogenesis of renal cell carcinomas, phaeochromocytomas and paragangliomas, and haemangioblastomas (i.e. the components of VHL syndrome). Although the exact link between activation of this pathway and the development of pancreatic neuroendocrine tumours is also obscure, it is of interest to note that sunitinib and other angiogenesis inhibi- tors are known to be effective against pancreatic NETs (see next). Interestingly, the 'pseudo-hypoxic' pathway does not appear to be involved in the pathogenesis of sporadic pancreatic neuroendocrine tumours, as somatic mutations in the components of this

pathway are not seen in these tumours. Again, the clinical implication is that 'pseudo-hypoxic' pathway inhibitors such as sunitinib have been shown to be useful for treatment of metastatic pancreatic neuro- endocrine tumours. Pancreatic neuroendocrine tumour markers Serum markers The chromogranins are acidic glycoproteins stored in the dense-core secretory granules of neuroendocrine cells. Chromogranin A is re- leased into the circulation by neuroendocrine cells and, to date, is considered to be the most useful nonspecific neuroendocrine tumour marker. Chromogranin A concentrations may correlate with tumour burden and can be also useful in monitoring response to treatment or recurrence of disease. Several commercial immunoassays for the measurement of chromogranin A are available. The standardization of chromogranin A measurement is confounded by the multiplicity

13.8 Pancreatic endocrine disorders and multiple endocrine neoplasia 2451 of methods and by the fact that chromogranin A is processed to multiple post-translational variants, leading to variable perform- ance between assays. Nevertheless, chromogranin A is useful for the following purposes: (1) prognostication, higher levels connoting a worse prognosis; (2) for the longitudinal assessment of tumour burden during treatment, provided the same assay is used for each measurement; (3) for prediction of the response to somatostatin ana- logue treatment. Other conditions that may lead to false-positive ele- vations of chromogranin A include chronic atrophic gastritis leading to achlorhydria, proton pump inhibitor therapy, chronic kidney dis- ease, pregnancy, untreated hypertension, and glucocorticoid treat- ment. The most important practical point concerns proton pump inhibitor therapy, which should be withdrawn for 3–5 days before measurement of chromogranin A. Chromogranin B coexists with chromogranin A, but differs in its amino acid sequence. It has been reported to be less influenced by renal failure and proton pump inhibitors. Immunoassays directed against the 74 amino acid C-terminal fragment of chromogranin B, known as GAWK, possess a better diagnostic accuracy for pancre- atic neuroendocrine tumours than chromogranin A. Pancreatic polypeptide is produced by the pancreatic poly- peptide (PP) or F cells of the normal pancreas. Plasma levels of pancreatic polypeptide are frequently increased in patients with non- functioning pancreatic neuroendocrine tumours. Some of these are explained by PP cell hyperplasia in the normal islets surrounding a pancreatic NET, and some due to incorporation of PP cells within the tumour itself. More rarely, some patients have a primary pan- creatic polypeptide-secreting PNET, a so-called PPoma. Pancreatic polypeptide alone is a less sensitive neuroendocrine tumour marker than chromogranin A, yet its diagnostic sensitivity may be signifi- cantly increased when combined with chromogranin A. Cocaine-amphetamine-regulated transcript (CART) peptide was originally characterized as a transcript up-regulated in neurones in response to cocaine and amphetamines. CART peptide is made in various tissues within the body including endocrine and nervous tis- sues. Plasma CART peptide is elevated in patients with various types of neuroendocrine tumour, and relevantly in pancreatic neuroendo- crine tumours, although its diagnostic performance appears to be similar to that of chromogranin B, and better than chromogranin A. Pancreastatin, a cleavage product of chromogranin A from res- idues 250–301, can also be measured by commercially available immunoassay, although it is unclear whether this has any concrete advantages over chromogranin A assays. 5-hydroxyindole acetic acid (5-HIAA), the principal metabolite of 5-hydroxytryptamine, is not at all useful for the diagnosis and monitoring pancreatic neuroendocrine tumours, and should not be measured. In addition to general pancreatic neuroendocrine tumour markers, specific gut hormones produced by these tumours can be measured by RIA using a single fasting plasma sample, and for certain syndromes a small number of confirmatory tests. As with chromogranins, several nonneoplastic conditions are asso- ciated

with increased levels of specific circulating gut hormones (Table 13.8.1). Gut hormone RIAs are not well standardized, and there is considerable variation between laboratories. However, concentrations are usually of the same order of magnitude in all assays and show a similar percentage increase above normal. Immunohistochemical markers Assessment of pancreatic neuroendocrine tumours using immunohistochemistry involves general neuroendocrine tumour markers derived either from the cytosol such as neuron-specific enolase and the protein gene product 9.5 (PGP9.5), or granular markers such as chromogranin A and synaptophysin. The tumour should be stained for Ki-67 protein, to generate a proliferative index, which is useful for grading tumours (Table 13.8.2) and for prediction of tumour response to treatment. Table 13.8.1 Causes of elevated gut hormones other than pancreatic endocrine tumours All hormones Nonfasting sample Chronic kidney disease Gastrin Hypercalcaemia Achlorhydria (most commonly proton pump inhibitor or other antacid therapy, also chronic atrophic gastritis) Antral gastrin cell hyperfunction Small bowel resection Gastric outlet obstruction VIP Hepatic cirrhosis Bowel ischaemia Glucagon Hepatic failure Oral contraceptives and danazol Stress Prolonged fast Familial hyperglucagonaemia PP Elderly Pernicious anaemia Hypercalcaemia Neurotensin Fibrolamellar hepatoma PP, pancreatic polypeptide; VIP, vasoactive intestinal polypeptide. Table 13.8.2 WHO 2010 and ENETS grading systems for NETs WHO 2010 classification WHO grading criteria ENETS classification ENETS grading criteria NE neoplasm grade 1 <2 mitoses/10 hpf and no necrosis NET grade 1 (G1) <2 mitoses/10 hpf and <3% Ki-67 index NE neoplasm grade 2 <2 mitoses/10 hpf or foci of necrosis NET grade 2 (G2) 2–20 mitoses/10 hpf or <3–20% Ki-67 index Small cell NE carcinoma Large cell NE carcinoma

“ 10 mitoses/10 hpf NE carcinoma grade 3 (G3)—small cell or large cell 20 mitoses/10 hpf or >20% Ki-67 index hpf, high power fields

section 13 Endocrine disorders 2452 Imaging in pancreatic neuroendocrine tumours Investigations used in the radiographic localization of pancreatic neuroendocrine tumours include ultrasonography, CT, and MRI. Transabdominal ultrasonography may have limited use in the detection of small pancreatic neuroendocrine tumours, but can be used to take biopsies from liver metastases for histopathological analysis. In experienced hands, endoscopic ultrasonography may be more sensitive than conventional imaging, with a resolution of 2 mm and a detection rate of over 75% for tumours in the pancreatic head (Fig. 13.8.1). However, visualization using ultrasound is poorer for lesions in the pancreatic tail. Intraoperative ultrasonography may be particularly effective in identifying pancreatic neuroendocrine tumours, especially when it is combined with palpation by the surgeon. Neuroendocrine tumour cells express somatostatin receptors, and hence somatostatin receptor imaging with radiolabelled somatostatin analogues is the mainstay in most neuroendocrine tumours, particularly those arising from the pancreas. Somatostatin receptor imaging is the most sensitive imaging modality for pancreatic neuroendocrine tumours (80–90%). There are five somatostatin receptor subtypes (SSTRs 1–5) which all avidly bind endogenous somatostatin. The clinically used somatostatin analogues, octreotide and lanreotide, used for diagnosis and treatment, bind to SSTR-2 and SSTR-5. DOTATATE binds to SSTR-2 primarily, but also SSTR-4 and -5. In cases of nonfunctioning pancreatic neuroendocrine tumours presenting as otherwise undifferentiated pancreatic masses, somatostatin receptor imaging is helpful in differentiating these from pancreatic adenocarcinomas. Somatostatin receptor imaging is also useful in detecting metastatic disease (Fig. 13.8.2), and is

more sensitive than conventional ^{99}Tc bone scintigraphy in identifying bony metastases. Traditionally, somatostatin receptor imaging has utilized indium-111 octreotide (^{111}In -octreotide), with more than 80% sensitivity for neuroendocrine tumours. This radiotracer is less suitable for detecting small tumours because of the limited spatial resolution of single-photon emission computed tomography (SPECT). This is significant, since 40% of gastrinomas and insulinomas are microadenomas (<1 cm). The recent combination of higher-resolution positron emission tomography (PET)/CT with somatostatin receptor scintigraphy using newer radio-tracers such as gallium-68 (^{68}Ga) DOTATATE, ^{68}Ga DOTANOC and ^{68}Ga DOTATOC has improved tumour detection with improved sensitivities of more than 90% and has the advantage of identifying patients suitable for radionuclide therapy with yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu) labelled somatostatin analogues. ^{18}F fluorodeoxyglucose (FDG) PET imaging is not sensitive for well differentiated neuroendocrine tumours, as they are metabolically relatively inactive, but is better for detecting high-grade tumours, and may well suggest that systemic chemotherapy is an option. ^{11}C 5-hydroxytryptophan imaging shows some promise as a more sensitive marker for pancreatic neuroendocrine tumours but requires further clinical validation. Fig. 13.8.1 Endoscopic ultrasound scan showing a 0.7 cm insulinoma in the head of the pancreas (arrowed). (a) (b) Fig. 13.8.2 (a) Rugal hypertrophy (arrowed) in a patient with Zollinger-Ellison syndrome; (b) gastrinoma with metastatic lymph-node and periduodenal uptake (arrowed) of ^{68}Ga -DOTATATE on PET scanning.

13.8 Pancreatic endocrine disorders and multiple endocrine neoplasia 2453 Even with ^{68}Ga DOTATATE PET scanning, insulinomas remain the most elusive of pancreatic neuroendocrine tumours. Only 50% of nonmetastatic insulinomas express SSTR-2, although insulinomas with metastatic spread are more likely to be positive for these receptors. Therefore, somatostatin receptor imaging's role in detecting nonmetastatic insulinomas is limited. Capitalizing on the fact that these tumours express receptors for glucagon-like peptide-1 (GLP-1), exendin-4 based tracers are emerging as a much more specific and sensitive marker for insulinomas at 95% sensitivity vs. 47% for cross-sectional imaging (Fig. 13.8.3). Small pancreatic neuroendocrine tumours may be detected by arterial stimulation venous sampling (ASVS). This operates on the principle of instilling a secretagogue into the main pancreatic arteries (gastroduodenal, superior mesenteric, inferior pancreaticoduodenal, and splenic) and measuring the secretion of hormonal markers such as insulin and gastrin in the effluent from the hepatic vein. In addition to anatomical localization with the tumour 'blush' (Fig. 13.8.4), this enables biochemical localization. Calcium (chloride or gluconate) is the secretagogue of choice, having replaced secretin for this purpose. Injection of calcium into the artery supplying the tumour causes a marked rise in hormone levels in the hepatic vein, and hence allows equivocal lesions to be verified, particularly in the presence of multiple pancreatic neuroendocrine tumours as occurs in MEN-1. Visualization of a tumour blush on angiography prior to calcium stimulation further increases the sensitivity of this investigation. Furthermore, since the hepatic artery is cannulated at the end of the procedure, the presence of microscopic hepatic metastases may also be detected by measuring rises in hormone levels after secretagogue injection into the hepatic artery. Natural history The spontaneous course of disease in pancreatic neuroendocrine tumours is difficult to ascertain because of their low incidence, heterogeneous behaviour, and a relative absence of controlled prospective clinical trials to assess the efficacy of different therapeutic strategies. Those tumours that secrete functionally active peptides present early with smaller tumours, morbidity and mortality resulting from the effects of peptide hypersecretion rather than tumour bulk. Nonfunctioning pancreatic neuroendocrine tumours are often more advanced at diagnosis because of the absence of symptoms attributable to

hormone hypersecretion. They frequently present with mass effects (e.g. biliary tract obstruction, liver metastases, and local lymphadenopathy). Poorly differentiated, large (>3 cm) tumours associated with metastases are indicators of a poor prognosis. Metastatic spread to liver (in 42% of patients at presentation) and bone (in 8% of patients at presentation) is the major cause of death in patients with pancreatic neuroendocrine tumours. The overall 5-year survival for pancreatic neuroendocrine tumours is 50 to 80%, with insulinomas and gastrinomas having up to 94% 5-year survival, primarily because their obvious clinical presentations prompt early surgical intervention. Pancreatic neuroendocrine tumours associated with familial disease such as MEN-1 may have a less favourable outcome than sporadic tumours, since these are frequently multiple and diffuse, which may limit surgical cure.

Specific tumour syndromes

Insulinomas Insulinomas are the most frequent functional pancreatic neuroendocrine tumours and are discussed in Chapter 13.9.2.

Gastrinoma The gastrinoma syndrome was first described in 1955 by Zollinger and Ellison, who reported the triad of fulminating ulcer diathesis, recurrent ulceration with a poor response to therapy, and pancreatic non- β -cell islet tumours. The syndrome, also known as Zollinger–Ellison syndrome, is the result of excess gastrin-stimulated gastric acid secretion. This causes severe, multiple peptic ulcers, which are usually duodenal, but may occur in the oesophagus and jejunum, and are often associated with complications such as gastric rugal hypertrophy, haemorrhage, perforation, and stricture formation (Fig. 13.8.2). The excess gastric acid secretion inactivates pancreatic enzymes and damages the intestinal mucosa, resulting in diarrhoea and steatorrhoea, which may be prominent features that precede symptoms of peptic ulcer disease. Overall, gastrinomas are the second most frequent functionally active pancreatic neuroendocrine tumour. At the time of diagnosis, 50 to 60% are malignant. Over 90% of gastrinomas are in the pancreatic region of the ‘gastrinoma triangle’, an area bounded by the Fig. 13.8.3 68Ga DOTA-exendin-4 PET scan showing the presence of an insulinoma within the neck/body of pancreas. Fig. 13.8.4 Venous phase of coeliac axis angiogram demonstrating gastrinoma blush in duodenal wall (arrowed).

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junction between the cystic duct and the common bile duct, the junction between the second and third parts of the duodenum, and the junction between the head and neck of pancreas. Those arising in the duodenum (50–88%) are frequently multiple, relatively small, and therefore difficult to localize. Those gastrinomas arising in the pancreas are most frequently situated in the pancreatic head. In MEN-1 patients, gastrinomas are the most common functional pancreatic neuroendocrine tumour. Approximately 25% of gastrinomas are associated with MEN-1, and a higher proportion (70–100%) are situated in the duodenum rather than the pancreas. Gastrinomas are also less commonly found outside the ‘gastrinoma triangle’ in the stomach, liver, bile duct, ovary, heart, and lung. The diagnosis of the gastrinoma syndrome requires the demonstration of a raised fasting plasma gastrin concentration (>40 pmol/litre), associated with increased basal gastric acid secretion. Hypercalcaemia may increase plasma gastrin concentrations, which may be of consequence in patients with MEN-1 and coexistent primary hyperparathyroidism. Since plasma gastrin levels in gastrinomas overlap with those seen with the use of antacids such as proton pump inhibitors, ideally patients should not take H₂-blockers for 3 days or proton pump inhibitors for 2 weeks before gastrin measurement. However, patients with true gastrinomas may be at risk of peptic ulcer perforation if antacids are stopped for plasma gastrin measurements. It is therefore often necessary to wean patients off antacids, for example by switching proton pump inhibitors to H₂-blockers for 2 weeks before switching the H₂-blockers to high-dose calcium/magnesium-based antacids for 3 days, prior to gastrin sampling. Hypergastrinaemia and raised acid output may also arise from other causes (Table 13.8.1). The

intravenous secretin test (2 U/kg body weight) distinguishes these conditions from gastrinoma and can aid diagnosis when other investigations are equivocal. Under normal physiological conditions, secretin inhibits serum gastrin. In contrast, secretin provokes a paradoxical rise in serum gastrin of at least 120 pg/ml in patients with gastrinoma. Alternatively, an intra-venous calcium infusion can be used diagnostically, with a rise in plasma gastrin observed in gastrinoma patients. Since ingestion of food is a stimulus for gastrin secretion from the antral and duodenal mucosa, it has been proposed that a standard test meal may differentiate hypergastrinaemia of antral and tumoural origin. However, more recently the usefulness of this test has been questioned. If gastric acid output studies are not possible, a basal gastric pH above 2 virtually excludes the diagnosis of Zollinger-Ellison syndrome and instead suggests the alternative diagnoses of chronic atrophic gastritis or antacid treatment. Endoscopy may be valuable in demonstrating oesophageal and duodenal ulceration and hypertrophy of the gastric mucosa. Localization of microgastrinomas may be aided preoperatively by endoscopic ultrasound, somatostatin receptor imaging, or selective visceral angiography and venous sampling. Survival depends on the presence of hepatic metastases at presentation, which is more commonly seen with pancreatic rather than duodenal gastrinomas. Overall, the 5-year survival rate is about 65%.

VIPoma Tumours secreting vasoactive intestinal polypeptide (VIP) are termed VIPomas. Ninety per cent of VIPomas occur in the pancreas, most frequently arising from the pancreatic tail. Extrapaneatic VIPomas may be of neural origin, such as gangliomas or ganglioneuroblastomas which arise from the sympathetic chain or adrenal medulla, and these tumours are especially common in children. Most extrapancreatic tumours are benign, but more than 50% of pancreatic VIPomas have metastasized at the time of diagnosis, usually to local lymph nodes and the liver. Approximately 9% of VIPomas are associated with MEN-1. The features of the VIPoma (Verner-Morrison, or 'pancreatic cholera') syndrome reflect the known biological actions of VIP. Large-volume diarrhoea without steatorrhoea is the cardinal symptom, with most patients excreting more than 3 litres per day. It is often intermittent at first, but in severe crises the volume loss coupled with the vasodilatory effects of VIP and the associated hypokalaemia may precipitate cardiovascular collapse. Hypokalaemia in the VIPoma syndrome may be profound, resulting from gastrointestinal losses and activation of the renin-angiotensin system. The loss of bicarbonate in the stool leads to a paradoxical acidosis, which may mask the true potassium deficit. Achlorhydria or hypochlorhydria occurs in more than 50% of patients and distinguishes this diarrhoeal syndrome from that associated with gastrinoma. Nevertheless, the absence of this feature in a significant proportion of VIPoma patients makes the acronym WDHA (watery diarrhoea, hypokalaemia, and achlorhydria) syndrome inappropriate. In up to 50% of cases there is glucose intolerance as a result of the glucagon-like actions of VIP. Other biochemical abnormalities include hypercalcaemia, probably due to secretion of parathyroid hormone-related peptide (PTHrP) and exacerbated by the dehydration and hypomagnesaemia, due to loss in stools. The vasodilatory action of VIP may cause flushing of the head and neck and, particularly on tumour palpation, may be associated with a marked fall in systemic blood pressure. In advanced cases, extreme weight loss may occur. VIPomas are usually associated with markedly raised plasma VIP concentrations (>30 pmol/litre). Since the half-life of circulating VIP is only 2 min it may be difficult to always confirm an elevation. Peptide histidine-methionine (PHM) produced from the prepro-VIP molecule, is more stable in plasma than VIP, and is cosecreted by VIPomas. Therefore, in patients with features consistent with VIPoma syndrome, the finding of an elevated PHM may confirm the diagnosis. Pancreatic polypeptide concentrations are elevated in 75% of cases and neurotensin in 10%. Primary pancreatic VIPomas are usually large (>2 cm) and so localization is rarely a problem. Occasionally, selective visceral angiography and

venous sampling may be necessary to detect small pancreatic lesions. In those with nonmetastatic VIPomas, the 5-year survival rate is more than 90%; when metastases are present it is about 60%.

Glucagonoma Glucagonomas are rare α -cell tumours of the pancreas which secrete various forms of glucagon and other peptides derived from the preproglucagon molecule. Primary glucagonomas most commonly arise in the pancreatic tail and extrapancreatic glucagonomas are rare. Glucagonomas are usually more than 2 cm in diameter at presentation. Smaller glucagonomas tend to be benign and increased tumour size correlates with risk of malignancy. In most cases of sporadic glucagonomas, metastases have occurred at presentation. Up to 17% of glucagonomas are associated with MEN-1 and these patients tend to present at a younger age. Common presenting features of glucagonoma syndrome are weight loss, diarrhoea, anorexia, and abdominal discomfort, with the latter often reflecting tumour bulk from hepatomegaly. Necrolytic migratory erythema is a frequent presenting feature of glucagonoma

13.8 Pancreatic endocrine disorders and multiple endocrine neoplasia 2455 syndrome; it is cyclical in nature, consisting of macules, central bulla formation, and crusted plaques occurring mainly at friction sites such as perineum, buttocks, groin, lower abdomen, and lower extremities. Mucous membranes are also affected, leading to angular cheilitis, stomatitis, glossitis, and blepharitis. The exact pathogenesis of this unusual skin eruption remains unclear and is likely to be multifactorial. Hypoaminoacidaemia, zinc deficiency, hypovitaminosis B, and hepatic dysfunction have all been implicated. Diabetes mellitus is present in approximately two-thirds of those with the glucagonoma syndrome and this may predate necrolytic migratory erythema. Neurological and psychiatric symptoms may also be a presenting feature, including ataxia, dementia, optic atrophy, and proximal muscle weakness. Thromboembolism has been described in up to 30% of all cases of glucagonoma syndrome, which is not a feature of other pancreatic neuroendocrine tumours and is a significant cause of death in glucagonoma syndrome. A normocytic anaemia may also occur. The diagnosis of glucagonoma is made on the basis of an elevated fasting plasma glucagon (>50 pmol/litre), in association with characteristic clinical features and a demonstrable neuroendocrine tumour and/or metastatic deposits. Glucagonomas are usually of significant size at presentation to be identified by contrast-enhanced CT or MRI. Endoscopic ultrasonography may be of limited use in glucagonomas, as these are usually located in the pancreatic tail. Glucagonomas and their metastases are commonly hypervascular, making selective visceral angiography and venous sampling particularly useful in localizing the tumour and identifying small hepatic metastases. Although most patients with glucagonoma syndrome present with evidence of metastases, the slow-growing nature of these tumours can result in a relatively good prognosis. The 5-year survival ranges from 66 to 85%.

Somatostatinoma Somatostatinomas are extremely rare, with an estimated annual incidence of about 1 in 40 million per year. Fifty per cent of these tumours are pancreatic, the remainder arising in the duodenum. Unlike other functional pancreatic neuroendocrine tumours, somatostatinomas are rarely associated with MEN-1. Pancreatic somatostatinomas are usually large, more than 2 cm at diagnosis, and thus present with local symptoms, biliary obstruction, or features relating to excess somatostatin secretion. Somatostatin has pan-inhibitory effects on gut motility, transit and absorption, gallbladder contraction and secretion, and endocrine and exocrine pancreatic functions. The so-called somatostatin syndrome resulting from somatostatin hypersecretion therefore consists of steatorrhoea (due to inhibition of pancreatic exocrine function), cholelithiasis (due to reduction of cholecystokinin secretion and inhibition of gallbladder contraction), hyperglycaemia (due to suppression of insulin secretion), and hypochlorhydria (due to suppression of gastrin secretion). Hypoglycaemia has occasionally been

described, possibly due to larger molecular forms of somatostatin having a greater inhibitory effect on counterregulatory hormones such as glucagon than on insulin. In comparison to pancreatic somatostatinomas, duodenal somatostatinomas are smaller, frequently associated with neurofibromatosis type 1, seldom associated with a recognizable 'somatostatin syndrome' and often containing psammoma bodies (a round concretion of calcium said to originate from the calcification of abnormal collagen produced by the neoplastic cells). Duodenal somatostatinomas usually present with obstructive jaundice, pancreatitis, intestinal obstruction, or gastrointestinal haemorrhage. Diagnosis of a somatostatinoma is secured by demonstrating elevated plasma somatostatin levels (>150 pmol/litre) in the context of a relevant clinical history and the presence of a pancreatic mass. Multiple molecular weight forms of somatostatin may be demonstrated by column chromatography of plasma or tumour extracts, and these may explain unusual clinical features. Localization is rarely a problem due to the large size at presentation. Pancreatic and duodenal somatostatinomas appear to have similar rates of metastases and malignancy. The overall 5-year survival rate is 75%, or 60% if metastases are present. GLP-1omas Neuroendocrine tumours that cosecrete GLP-1 together with other bioactive peptides have been described. In one case, an ovarian neuroendocrine cosecreting GLP-1 and somatostatin was associated with diabetes mellitus during oral and IV glucose tolerance tests followed by a profound reactive hypoglycaemia, due to the subsequent glucose-dependent potentiation of insulin secretion by GLP-1. In a second case, a patient with a pancreatic neuroendocrine tumour cosecreting glucagon and GLP-1 manifested diabetes mellitus (due to the hyperglucagonaemia) together with a fasting hyperinsulinaemic hypoglycaemia, attributed to chronic hypertrophy of β cells and autonomous secretion of insulin. In two other cases, cosecretion of GLP-1 and the related peptide glucagon-like peptide-2 (GLP-2) caused hyperplasia of the small intestinal mucosa (due to the excess GLP-2), prolonged intestinal transit time, intractable constipation, and recurrent vomiting. Other rare pancreatic neuroendocrine tumour syndromes Other functional peptides can present with characteristic syndromes such as:

- Ectopic ACTH production by pancreatic neuroendocrine tumours, resulting in Cushing's syndrome, is well documented in the literature and virtually all cases are highly malignant with a poor prognosis. These patients can develop a pseudo-Nelson's syndrome which is due to the evolution of α -MSH from the tumour, stimulating skin pigmentation.
- Secretion of parathyroid hormone-related peptide (PTHrP) by pancreatic neuroendocrine tumours can manifest with intractable hypercalcaemia.
- Neurotensinomas are rare and truly difficult to separate from the symptom complex produced by VIP excess.
- Patients can present with a secondary acromegaly and gigantism as a result of ectopic GHRH secretion by pancreatic neuroendocrine tumours.
- Arginine vasopressin (AVP) leading to hyponatraemia due to the syndrome of inappropriate antidiuresis.
- Calcitonin, which can be released by neuroendocrine tumours other than medullary thyroid carcinoma, and which leads to a syndrome of flushing and diarrhoea.
- Insulin-like growth factor-II (IGF-2) causing hypoglycaemia. Other peptides produced by islet-cell tumours include neuropeptide Y, neuromedin B, calcitonin gene-related peptide, bombesin, and motilin, but these are not associated with recognized clinical syndromes.

section 13 Endocrine disorders 2456 Pancreatic polypeptide-secreting tumours (PPomas) PP is secreted by up to 75% of pancreatic neuroendocrine tumours, and as noted above PP appears to be secreted in many cases as an epiphenomenon of an otherwise nonfunctioning neuroendocrine tumour. Where the tumour is secreting PP as its primary secretion, PPomas may present with either watery diarrhoea or weight loss, due to the known appetite-suppressive effects of PP. Nonfunctioning pancreatic neuroendocrine tumours Nonfunctional tumours represent 15 to 30% of

pancreatic neuro- endocrine tumours. These most frequently arise in the pancreatic head and are most often diagnosed in the fifth to sixth decades of life. Twenty to thirty per cent (20–30%) of these tumours are associated with MEN-1. They usually present late with symptoms attributable to either tumour bulk, such as anorexia and weight loss, or to effects on local structures, such as obstructive jaundice or intestinal obstruction. The clinical silence of these nonfunctioning pancreatic neuroendocrine tumours may also reflect secretion of neuropeptides at low circulating concentrations, biologically inactive molecular forms, downregulation of peripheral receptors, or simultaneous production of an inhibitor such as somatostatin. Nonfunctioning pancreatic neuroendocrine tumours are often mistakenly diagnosed as adenocarcinomas, but the presence of elevated circulating markers such as chromogranins A and B, CART, pancreatic polypeptide, or neurotensin, uptake on somatostatin receptor imaging and the presence of neuroendocrine markers on biopsy samples can establish the correct diagnosis. The overall 5-year survival is about 50%.

Management of pancreatic neuroendocrine tumours As can be seen from the following sections, the treatment of pancreatic neuroendocrine tumour runs the entire gamut of modalities including gastroenterology, endocrinology, surgery, nuclear medicine, interventional radiology, and oncology. Treatment decisions must essentially be taken in a suitably constituted multidisciplinary meeting so that all suitable modalities are considered.

Surgical treatment Surgery is the only curative treatment for pancreatic neuroendocrine tumours and should be considered for tumours of G1 or G2 grade. Generally, tumours less than 2 cm have a low propensity to metastasize with only 6% being malignant when discovered. These can be surveyed with cross-sectional imaging without the necessity for surgery. Localized pancreatic NETs less than 2 cm, or those causing significant hormonal syndromes may be considered for curative resection, for example, enucleation for lesions close to the surface, pancreaticoduodenectomy for head of pancreas lesions, a distal pancreatectomy ± splenectomy for lesions in the body and head of pancreas. The question as to whether the primary tumour should be resected in the presence of unresectable liver metastases is not yet answered. Although there is some evidence that suggests some improvement in median overall survival with resection of the primary tumour under these circumstances, this should be taken with caution as the quality of evidence in this area is relatively poor. The surgical management of pancreaticoduodenal neuroendocrine tumours in MEN-1 remains controversial because of the multifocal nature of the associated pancreatic disease. In cases where patients present with functional syndromes such as insulinomas or Zollinger-Ellison syndrome, detailed investigation (e.g. with exendin-4 imaging or ASVS) is sometimes necessary to distinguish those tumours which are secretory from those that are nonfunctional, so that the right procedure may be planned. In patients with MEN-1, surgical cure rates are high for insulinomas, but are significantly lower for gastrinomas, as gastrinomas are frequently multifocal and situated in the duodenum. Even so, resection of gastrinomas can reduce the rate of subsequent liver metastases, thus improving their overall prognosis, and this option should be seriously considered where there is no evidence of extrapancreaticoduodenal spread. Some centres advocate an aggressive surgical approach to MEN-1-associated pancreaticoduodenal neuroendocrine tumours, including the choices of total pancreaticoduodenectomy or distal subtotal pancreatectomy combined with preservation of the pancreatic head, enucleation of any neuroendocrine tumours remaining in the pancreatic head and in the duodenal wall. This approach may significantly reduce the morbidity and mortality associated with pancreatic neuroendocrine tumours in MEN-1 patients, but comes at the cost of perioperative morbidity and mortality, as well as the morbidity associated with endocrine and exocrine pancreatic insufficiency, particularly brittle diabetes mellitus.

Somatostatin analogues Somatostatin analogues such as octreotide and lanreotide are the

standard of care in the medical treatment of neuroendocrine tumours. Octreotide and lanreotide bind most avidly to SSTR-2 and -5 with a lower affinity for SSTR-3. A newer SSTA, pasireotide, possesses a different affinity for SSTR-1, -3, and -5 and is still being studied for its effects in neuroendocrine tumour therapy. SSTR-2 is believed to mediate the biochemical responses to somatostatin analogues, whereas both SSTR-2 and -5 subtypes are believed to mediate their antiproliferative effects. Somatostatin analogues have two principal effects: (1) antisecretory, leading to relief of functional syndromes. This is particularly useful for glucagonomas and VIPomas, although analogues are markedly less reliable for suppressing insulinomas (50% effectiveness) and gastrinomas (see next); (2) antiproliferative, supported by the results of the CLARINET study in patients with pancreatic, jejuno-ileal, colonic, and rectal NETs of grades G1 and G2, which demonstrated that lanreotide Autogel therapy was capable of significantly extending progression-free survival. Octreotide has a half-life of several hours in the circulation and requires frequent subcutaneous injected administration three times a day. Depot injection preparations of somatostatin analogues such as octreotide LAR or lanreotide Autogel are more commonly used since these allow sustained release, typically necessitating an intramuscular or deep subcutaneous injection every 4 weeks. Patients are often initially stabilized on short acting subcutaneous octreotide to ensure that treatment is tolerated well and that there are no adverse reactions, before converting to longer acting depot preparations. Tachyphylaxis is said to occur with time, but this is not a frequent issue. Peptide-receptor radionuclide therapy (PRRT) Following the binding of labelled somatostatin analogues to SSTRs, neuroendocrine tumour cells internalize and retain the analogues, leading to the retention of tracer. By binding high-energy β -particle

13.8 Pancreatic endocrine disorders and multiple endocrine neoplasia 2457 emitting radionuclides such as ^{177}Lu and ^{90}Y to somatostatin analogues such as lanreotide and DOTATATE, tumour cells can be selectively exposed to high-energy β -radiation, leading to cell apoptosis. Such PRRT acts systemically and is a particularly useful palliative option for patients with inoperable or multisite disease. A key prerequisite prior to treatment is to demonstrate that there is high tumour uptake of the SSTA relative to nontarget tissues on quantitative somatostatin receptor imaging, preferably with the same peptide (e.g. DOTATATE) that will be used for therapy. Patients must also have stable haematological and renal function. In uncontrolled case series, PRRT is associated with favourable partial responses or tumour stabilization, with relatively mild adverse reactions—acute nausea, bone marrow suppression, and renal toxicity being the chief problems. The results from a randomized controlled trial in mid-gut neuroendocrine tumours (NETTER-1) show that ^{177}Lu DOTATATE therapy is capable of increasing progression-free survival and overall survival compared to treatment with high-dose somatostatin analogue therapy. Definitive randomized controlled trials in patients with pancreatic neuroendocrine tumours are currently lacking, but it should be noted that ^{177}Lu DOTATATE therapy for pancreatic NETs is now approved by cost-effectiveness bodies such as the UK National Institute for Health and Care Excellence based on appraised data from single-arm studies. Systemic chemotherapy Traditional antiproliferative chemotherapy has a relatively limited role in the treatment of neuroendocrine tumours. It is more effective against high-grade G3 tumours, those exhibiting high-grade FDG uptake or biologically aggressive behaviour. Typical chemotherapeutic regimens include combinations of etoposide and cisplatin, fluorouracil with streptozocin, fluorouracil with doxorubicin, or fluorouracil with streptozocin and cisplatin. Temozolomide $\pm$ capecitabine has also been advocated for the treatment of pancreatic NETs. Temozolomide is a cytotoxic alkylating agent, with comparable antitumour activity to streptozotocin, and is particularly effective in neuroendocrine tumours

expressing low levels of the DNA repair enzyme O6- methylguanine DNA methyltransferase (MGMT). Capecitabine with streptozocin has also recently been shown to be reasonably effective in the Phase II NET-01 trial, producing a radiological response or stabilization in 74%, a median progression-free survival of 9.7 months and median overall survival of 27.5 months. The addition of cisplatin to the regimen did not improve outcomes.

Targeted molecular therapy Targeted molecular therapies, for example the tyrosine kinase inhibitor sunitinib (inhibiting VEGFR, PDGFR, c-KIT, and FLT3) and everolimus (inhibiting mTOR), have been shown to be active against pancreatic neuroendocrine tumours in recent Phase III trials. In a placebo-controlled randomized controlled trial in 171 patients with advanced and nonresectable pancreatic neuroendocrine tumours, sunitinib therapy was shown to double median progression-free survival compared to placebo. Overall survival was improved. The main adverse effects were diarrhoea, nausea, and vomiting, tiredness, hypertension, and neutropenia. The RADIANT-3 Phase III randomized controlled trial showed that everolimus was also capable of doubling median progression-free survival in patients with progressive and metastatic pancreatic neuroendocrine tumours. Unlike sunitinib, no benefit on overall survival was noted. The most common adverse effects noted were stomatitis/aphthous ulceration, rash, diarrhoea, fatigue, neutropenia, and an increased rate of infections. The latter side effect is due to its activity as an immunosuppressant. Everolimus also induces some metabolic adverse effects: hypertriglyceridaemia and diabetes mellitus. The metabolic effects are controllable with insulin and hypolipidaemic treatment. Indeed, its hyperglycaemic effect is sometimes advantageous in the case of metastatic insulinomas. The main dose-limiting adverse effect of everolimus is pneumonitis, interstitial lung disease, and sometimes lung fibrosis. This can be potentially very serious and may require steroid treatment and withdrawal or dose reduction of everolimus. Other angiogenesis inhibitors such as sorafenib (a tyrosine kinase inhibitor of VEGFR2, PDGFRB, FGFR1 and FLT3), pazopanib (targeting VEGFR-1, -2 and -3, PDGFR α and β , FGFR-1, -2 and -3, c-Kit, Itk, Lck, c-Fms and B-Raf) and bevacizumab (a monoclonal antibody against VEGF-A) have shown some promising activity in smaller trials but are not currently in routine use. Pazopanib, brivanib, cabozantinib, sulfatinib, famitinib and lenvatinib are newer tyrosine kinase inhibitors also targeting VEGFR which are currently under evaluation.

External beam radiotherapy This may be effective in relieving pain from bone metastases and, in a small number of cases, has been curative in patients with locally unresectable pancreatic neuroendocrine tumours.

Orthotopic liver transplantation Because of the generally less aggressive biological behaviour of neuroendocrine tumours, orthotopic liver transplantation (OLT) is an accepted, if uncommon, treatment of disease limited to liver metastases. The 5-year survival after OLT has been shown in various series to vary between 36% and 90%. Contraindications include high-grade tumours (G3), extrahepatic disease, or disease draining to the systemic circulation. As the experience of OLT for this indication is limited, there remains considerable uncertainty about the true benefit of OLT and this treatment is usually recommended only on a case-by-case basis.

Interferon alpha Interferon alpha (IFN- α) exhibits an antiproliferative activity and has been used for the treatment of gastrointestinal and pancreatic neuroendocrine tumours, with an overall response rate of 20% and a biochemical response rate of 63% (26). However, its adverse effects—flu-like symptoms, myelotoxicity, weight loss, and fatigue, depression, and on occasion, suicidal ideation—limit the dose and duration of treatment, making this usually a third-line therapy.

Local ablation Ablation of liver metastases may be considered if the number of lesions is small (<5) and the lesion size limited (<5 cm). The types of ablative techniques include radiofrequency (most commonly used), microwave, laser, and cryotherapy. The experience with radiofrequency ablation suggests that this is a well-tolerated procedure, although local recurrence is fairly common in

approximately 1 in 5, and the majority of patients go on to develop either new liver metastases or extrahepatic disease at a median time of 30 months or so. Transarterial embolization therapies Hepatic metastases obtain their blood supply from the hepatic artery, and the liver parenchyma is supplied with blood both from the

section 13 Endocrine disorders 2458 hepatic artery and the portal vein. Exploiting this, interventional intra-arterial therapies which serve to block off the hepatic arterial supply to liver metastases (transarterial embolization, TAE), deliver cytotoxic chemotherapeutic agents such as doxorubicin (transarterial chemoembolization, TACE) or radionuclide therapy (selective internal radiotherapy, SIRT) have been employed with some success in the treatment of patients presenting with liver metastases. The most clinical experience has been accumulated with TAE/ TACE, which is successful in reducing syndromic symptoms in the majority of patients, and in reducing the size of metastases in 35–74%. Median progression-free survival is 18 months and 5-year survival of patients undergoing this type of therapy is 40–83%. Many patients experience a postembolization syndrome (fever, abdominal pain, elevated liver transaminases); there is severe morbidity in 10% (acute liver and renal failure, carcinoid crisis, cholecystitis, gastrointestinal bleeding) and an associated mortality of up to 5.6%. Contraindications to embolization therapy include complete portal vein thrombosis, previous pancreaticoduodenectomy, and liver insufficiency. The overall usefulness of embolization therapy lies in the fact that it can be applied repeatedly to control liver metastases and for symptomatic relief. SIRT, in which ^{90}Y is delivered directly to liver metastases either coupled to microspheres or to somatostatin analogues such as lanreotide, is a newer technique which appears to have similar tolerability to conventional TAE/TACE. There appears to be a tumour response in less than 60% of patients and disease stabilization in 35%. Adverse effects and contraindications are similar to TAE/TACE, but the radiation may also cause damage to the liver, the lungs, and the gastrointestinal tract if delivered off-target. Treatment of specific tumour syndromes Insulinomas Treatment of insulinomas is discussed in Chapter 13.9.2.

Gastrinomas Short- or long-term treatment with high-dose proton pump inhibitors, which inhibit gastric acid secretion, is highly effective for symptomatic relief and tachyphylaxis does not occur. Somatostatin analogues may be superfluous if symptomatic relief occurs with high-dose proton pump inhibitors, although these may be used in metastatic disease to limit tumour progression. As hypercalcaemia tends to aggravate gastrin release, consideration should be given to surgical resection of the hyperplastic parathyroid glands in patients with MEN-1 that present with primary hyperparathyroidism and Zollinger-Ellison syndrome. VIPomas VIPomas are usually exquisitely sensitive to SSTA, with small doses often significantly reducing diarrhoeal symptoms. During acute crises, patients require aggressive intravenous rehydration combined with potassium and bicarbonate replacement if necessary. Parenteral hydrocortisone is often useful also to control the diarrhoea in the acute situation. Glucagonomas Octreotide is particularly useful as a prompt and effective treatment of necrolytic migratory erythema, providing improvement within 48 to 72 h of initiating treatment. Similarly, other symptoms such as diarrhoea and weight loss may also improve. Somatostatin analogues have a variable effect on glucose tolerance and adjuvant oral hypoglycaemic agents or insulin may be required. Most patients with glucagonoma syndrome are treated empirically with oral zinc sulphate supplementation, regardless of plasma zinc levels. Topical zinc sulphate paste is also useful for relieving the rash. Patients should be anticoagulated because of the high incidence of thromboembolic disease. Somatostatinomas There are a small number of cases reported demonstrating improvements of symptoms by administration of somatostatin analogues. Pancreatic enzyme supplementation and insulin for diabetes mellitus

may also be necessary. Ectopic ACTH syndrome Pancreatic neuroendocrine tumours secreting ACTH present with a very aggressive Cushing's syndrome with marked oedema, rapid development of diabetes mellitus, and immunosuppression. Bilateral adrenalectomy, followed by steroid replacement therapy, is frequently necessary to control the hypercortisolaemia, and to enable patients to be treated using the other treatment modalities discussed earlier. PTHrP-secreting tumours The humoral hypercalcaemia that follows from PTHrP secretion can be treated with intravenous bisphosphonates. Zoledronic acid is recommended for this purpose as it is markedly more effective and longer-lasting in its effects compared to pamidronate. Where the hypercalcaemia is unresponsive to bisphosphonates, denosumab may be used, with some case studies suggesting that this is effective in controlling calcium levels. Multiple endocrine neoplasia Multiple endocrine neoplasia refers to rare hereditary cancer syndromes characterized by a predisposition to tumour development within two or more endocrine organs. The two major forms of MEN, namely MEN-1 and MEN-2, are caused by germline mutations which display an autosomal dominant pattern of inheritance and a high degree of penetrance. MEN-1 is associated with mutations in the MEN1 gene, whereas MEN-2 results from a RET (REarranged during Transfection) gene mutation. Recent advances in our understanding of the molecular and clinical genetics of these syndromes have significantly altered the approach to diagnosis and management of these patients. Multiple endocrine neoplasia type 1 (MEN-1) Clinical features and classification The major components of MEN-1 are parathyroid adenomas, pancreatic neuroendocrine tumours, and pituitary adenomas (see Table 13.8.3). Underdahl first described the association of these tumours in 1953, and Wermer subsequently proposed their autosomal dominant inheritance in 1954, with the latter providing the eponym for this syndrome. MEN-1 occurs in approximately 1 in

13.8 Pancreatic endocrine disorders and multiple endocrine neoplasia 2459 30 000 individuals, with an equal sex distribution and may be defined as a case in which two of the three main MEN-1-related endocrine tumours occur. Two different forms of MEN-1, sporadic and familial, have been described. Familial MEN-1 (OMIM 131100) is more prevalent, with an autosomal dominant pattern of inheritance, and is defined as an MEN-1 case with at least one first-degree relative with one of these three characteristic endocrine tumours. More than 95% of MEN1 mutation carriers manifest clinical features of the syndrome by the age of 40 years. Parathyroid hyperplasia/adenomas Primary hyperparathyroidism is the most common presenting feature of MEN-1, reaching almost 100% penetrance by age 50 years. The typical age of onset of primary hyperparathyroidism in MEN-1 is 20 to 25 years, which is 30 years earlier than that of sporadic primary hyperparathyroidism. Patients present either with asymptomatic hypercalcaemia on biochemical screening or with features similar to those of sporadic primary hyperparathyroidism (see Chapter 13.4). In MEN-1, hyperparathyroidism reflects hyperplasia of multiple parathyroid glands and supernumerary glands are common. There is a consensus that minimally invasive parathyroidectomy is not advisable, since it prevents the routine identification of all four glands. However, controversy exists regarding the most appropriate surgical approach. Subtotal parathyroidectomy with near total thymectomy (to remove ectopic parathyroid tissue in the thymus) is the most common approach. Some centres advocate total parathyroidectomy with autotransplantation of a fresh parathyroid gland into the forearm to avoid reoperative neck surgery if recurrent primary hyperparathyroidism in the transplanted hyperplastic gland occurs. An alternative approach is a total parathyroidectomy followed by immediate replacement therapy with 1α -hydroxycholecalciferol or calcitriol. Pancreatic neuroendocrine tumours Pancreatic neuroendocrine tumours are the second most common clinical manifestation of MEN-1, occurring in about 30 to

75% of MEN-1 patients, with gastrinomas accounting for 60% of cases. Insulinomas represent about 30% of MEN-1-associated pancreatic neuroendocrine tumours and coexist with gastrinomas in 10% of cases. Other functional tumour types such as VIPomas, glucagonomas, and somatostatinomas are rare. MEN-1 patients with pancreatic neuroendocrine tumours usually manifest with symptoms of hormone hypersecretion by the age of 40 years, although these tumours may be detected earlier if asymptomatic carriers are having routine biochemical or imaging screening. The pancreas characteristically contains numerous microadenomas, the majority of which are harmless but which have the potential to grow to clinically relevant lesions. Tumours arise in any part of the pancreas, although MEN-1 associated gastrinomas frequently arise within the duodenal submucosa. Surgical management of MEN-1 associated pancreatic neuroendocrine tumours is described earlier in this chapter. MEN-1-associated gastrinomas are associated with a high risk of recurrence after surgery and hence some centres advocate medical management with high-dose proton pump inhibitors in preference to surgery. Pancreatic neuroendocrine tumours associated with MEN-1 are less malignant than sporadic tumours and carry a better prognosis, with a median survival of 15 years compared to 5 years in patients with sporadic tumours. This may reflect more indolent disease or—since known MEN-1 patients usually participate in a surveillance programme—earlier diagnosis. Pituitary adenomas The incidence of pituitary adenomas in MEN-1 patients varies from 10 to 60%. These adenomas are detected by screening in 30% of patients, but are found at autopsy in more than 50% of patients. Most these tumours are microadenomas (diameter <1 cm). Prolactinomas are the most common type of pituitary adenoma in MEN-1 (60%), although tumours secreting growth hormone or ACTH are not uncommon. Double and even triple pituitary adenomas, which may secrete different pituitary hormones, have been described in MEN-

1. Imaging and treatment are the same as for sporadic pituitary tumours (see Chapter 13.2.1). Other manifestations of MEN-1 Foregut neuroendocrine tumours occur in 3 to 4% of patients with MEN-1. These are rarely associated with hypersecretion of hormones. MEN-1 thymic neuroendocrine tumour is seen mainly in men, whereas bronchial neuroendocrine tumours are commoner in women. Gastric neuroendocrine tumours in MEN-1 are small and multiple, and their malignant potential remains uncertain. Adrenal cortical adenomas are present in up to 40% of patients with MEN-1. These are often nonfunctioning and bilateral, but can occasionally present with a non-ACTH dependent Cushing's syndrome emanating from the adrenal adenomas. Other forms of adrenal pathology associated with MEN-1 are diffuse adrenal hyperplasia, adrenal nodular hyperplasia, and adrenocortical carcinoma. The presence of multiple facial angiofibromas, which consist of acneiform papules, is highly suggestive of MEN-1. Collagenomas are another common feature and are multiple, skin-coloured, or occasionally hypopigmented cutaneous nodules, on the trunk, neck, and upper limbs. Subcutaneous or, rarely, visceral lipomas occur in 10 to 30% of MEN-1 patients. Furthermore, MEN-1 gene mutations have been demonstrated in individuals with atypical familial endocrine syndromes including pheochromocytoma. Genetics of MEN-1 The MEN1 gene was identified in 1997 by positional cloning and is a putative tumour suppressor gene, in keeping with the 'two-hit' model of hereditary cancer as originally postulated by Knudson for retinoblastoma. Knudson proposed that affected family members inherited a 'first hit' as an inactivating germline mutation in one allele of a tumour suppressor, resulting in a predisposition to tumour development. The 'second hit' is acquired as a stochastic somatic event in a

susceptible cell type. The inactivation of the remaining functional allele results in progression to neoplasia. Therefore, to Table 13.8.3 Clinical features of MEN1 (Wermer's syndrome) with estimated prevalence in parentheses

Endocrine features	Associated nonendocrine features
Parathyroid hyperplasia/adenoma (>95%)	Pancreatic tumour (30–75%) (gastrinoma most common)
Anterior pituitary tumour (30%) (prolactinoma most common)	Adrenal cortical tumour (nonfunctioning) (25%)
Foregut carcinoid (3–4%)	Facial angiofibromas (85%)
Collagenomas (70%)	Lipomas (10–30%)

section 13 Endocrine disorders 2460 explain the apparent paradox of an autosomal dominant disease that is clearly recessive at the cellular level, there must be a relatively high frequency of such stochastic somatic events. Sporadic cases of MEN-1 involve distinct first and second 'hits' in somatic cells. There is an enormous diversity of mutations occurring in the MEN1 gene, with over 400 different germlines or somatic mutations currently reported in MEN-1 families and sporadic cases. These mutations are dispersed throughout the entire coding region. Unlike the RET gene in MEN-2, there is no significant correlation between the nature or position of the mutation in the MEN1 gene and clinical status. Sequencing of the MEN1 gene detects a germline mutation in about 70–80% of index cases for familial MEN-1. The remaining 20–30% are mostly false negatives, reflecting mutations in the MEN1 gene which are not detected by current gene sequencing techniques. More than 10% of MEN1 mutations arise de novo and may be transmitted to subsequent generations. Menin is usually located in the nucleus in nondividing cells but becomes localized in the cytoplasm in dividing cells. It appears to have multiple interacting partners, and has been implicated in the following processes: 1. Transcription regulation (key interactions with JunD, NF- κ B, Smads 1, 3, and 5); 2. DNA replication, recombination and repair, and genomic stability (interactions with RPA2, FANCD2); 3. Cell division (NMMHC II-A, GFAP, vimentin) and cell cycle control (NM23, ASK); 4. Epigenetic control via modulation of chromatin remodelling (MLL histone methyl-transferase complex ER- α , HDAC). Multiple cellular pathways therefore become dysregulated by mutations in MEN1 but the detailed links between MEN1 mutation to the development of its characteristic tumours are still opaque. Certainly, the observation that patients who come from families with the same MEN1 mutation can have widely divergent phenotypes with some showing only hyperparathyroidism, and others showing the full panoply of tumours, suggests again that stochastic somatic events must play an important part in the development of MEN-1 manifestations. Genetic screening and management

Mutational analysis of the MEN1 gene is recommended in an index case with two or more MEN-1-associated endocrine tumours. In addition, mutational analysis should be considered in patients with parathyroid adenomas before the age of 30 years or multigland parathyroid disease; gastrinoma or multiple pancreatic islet-cell tumours at any age; or individuals who have two or more MEN1-associated tumours, which are not part of the classical triad of parathyroid, pancreatic islet and anterior pituitary tumours (e.g. parathyroid tumour plus adrenal tumour). It should be noted that between 5 and 25% patients with manifestations of MEN-1 may not be shown to possess a mutation in MEN1, for various reasons including: (a) alternative causative mutations, for example in CDKN1B (also known as MEN4), CDC73 (associated with the hyperparathyroidism-jaw tumour syndrome), the calcium sensing receptor CaSR (responsible for familial hypocalciuric hypercalcaemia), and the aryl hydrocarbon receptor interacting protein AIP (responsible for familial isolated pituitary adenoma syndrome); (b) genetic analyses that do not include multiplex ligation-dependent amplification for deletions which are found in up to 33% of patients; (c) the occurrence of phenocopies, defined as the coincidental occurrence of MEN-1-associated tumours. Following identification of an MEN1 mutation

in an index case, genetic analysis in first-degree relatives allows identification of affected family members. Such early identification of MEN-1 in asymptomatic carriers is particularly useful to allow subsequent periodic surveillance. This screening may detect the onset of the disease about 10 years before symptoms develop and thus provide an opportunity for earlier treatment. This early detection and treatment of the potential malignant neuroendocrine tumours should reduce the morbidity and mortality associated with MEN-1 syndrome. The manifestation of MEN-1 tumours is rare before the age of 5 years, so screening does not need to occur before that age. Current guidelines suggest that the minimal surveillance programme for individuals known to have MEN-1 syndrome or to have a family-specific mutation of the MEN-1 gene should include annual measurement of: serum prolactin (from age 5 years), fasting serum calcium and PTH (from age 8 years), and fasting gut hormone concentrations (including chromogranin A, gastrin, insulin and glucose, glucagon, VIP, PP— from age 20 years). Patients should undergo a baseline radiological screening (pituitary MRI, pancreatic protocol, and chest CT scan) and periodic rescreening every 1–3 years. Where the screening investigations suggest that the patient has a manifestation of MEN-1, further investigations including dynamic testing for acromegaly and Cushing's syndrome, endoscopic ultrasound, and somatostatin receptor imaging may be appropriate. Multiple endocrine neoplasia type 2 (MEN-2) Clinical features and classification MEN-2 has at least three distinct variants: MEN-2A, MEN-2B and familial medullary thyroid carcinoma, and their clinical features are outlined in Table 13.8.4. Although MEN-2 can arise sporadically, familial cases are more common. Familial MEN-2 is defined as an MEN-2 case with at least one of the characteristic endocrine tumours in a first-degree relative. MEN-2 has an estimated prevalence Table 13.8.4 Clinical features of MEN-2 with estimated prevalence in parentheses MEN-2Aa MTC (99%) Pheochromocytoma (>50%) Parathyroid hyperplasia/adenoma (15–30%) Hirschsprung's disease (aganglionic megacolon—7%) Cutaneous lichen amyloidosis (rare) MEN-2B MTC (100%) Pheochromocytoma (40–50%) Intestinal ganglioneuromatosis and mucosal neuromas (40%) Marfanoid habitus Megacolon Familial MTC Medullary thyroid carcinoma is sole manifestation MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma. a MEN-2A accounts for c.95% of all MEN-2 cases.

13.8 Pancreatic endocrine disorders and multiple endocrine neoplasia 2461 of 1:30 000. Each variant of MEN-2 is caused by germline mutations in the RET proto-oncogene, which is located on chromosome 10. MEN-2A (OMIM 171400) This may also be referred to as Sipple's syndrome and is characterized by medullary thyroid carcinoma, pheochromocytoma and parathyroid hyperplasia/adenomas. MEN-2A accounts for c.95% of MEN-2 cases. Medullary thyroid cancer is usually the first neoplastic manifestation in MEN-2, appearing between the ages of 5 and 25 years. Phenotypic variants of MEN-2A include MEN-2A plus aganglionic megacolon (MEN-2A plus Hirschsprung's disease) and MEN-2A plus cutaneous lichen amyloidosis, a pruritic rash located on the upper back, which usually arises before the onset of the thyroid cancer and which is characteristically relieved by sun exposure. MEN-2B (OMIM 162300) This variant represents about 5% of all cases of MEN-2, and although MEN-2B is often diagnosed earlier than MEN-2A because of the characteristic associated physical features, it exhibits a higher morbidity and mortality than MEN-2A. Approximately 75% of patients with MEN-2B are sporadic cases with de novo RET mutations, 25% cases are familial. The endocrine features of this subtype are medullary thyroid cancer and pheochromocytoma, but not primary hyperparathyroidism. The medullary thyroid cancer associated with MEN-2B occurs about 10 years earlier than MEN-2B. Patients with this syndrome have a marfanoid habitus, skeletal abnormalities (kyphoscoliosis or lordosis), mucosal

neuromas, intestinal ganglioneuromas (which may cause chronic megacolon) and myelinated corneal nerves (Fig. 13.8.5). Familial medullary thyroid carcinoma (OMIM 155240) Familial medullary thyroid carcinoma (FMTC) is considered a variant of MEN-2A where medullary thyroid carcinoma (MTC) is the only clinical feature, although this may sometimes be associated with Hirschprung's disease. Since MTC is usually the first neoplasm to manifest in MEN-2, because of its earlier and overall higher penetrance, it is essential to correctly classify FMTC. Misdiagnosis of familial medullary thyroid carcinoma in situations where the correct diagnosis is actually MEN-2A may unintentionally exclude future screening for pheochromocytoma, which may have catastrophic consequences. FMTC may be diagnosed where there are at least 10 carriers in the kindred, multiple carriers or affected members above the age of 50 years, and a family history adequate to exclude hyperparathyroidism and pheochromocytoma. Clinical features Medullary thyroid carcinoma Medullary thyroid carcinoma originates from the parafollicular cells (C-cells) of the thyroid (see Chapter 13.3.2). These cells secrete calcitonin, which serves as the primary tumour marker, and sometimes carcinoembryonic antigen. In MEN-2, familial medullary thyroid carcinoma behaves in a relatively benign and indolent manner, whereas medullary thyroid carcinoma in association with MEN-2B represents the most malignant form of the disease. C-cell hyperplasia is the precursor to hereditary MTC, with a variable progression to nodular hyperplasia and finally, through clonal progression, to malignancy. MTC occurs at a younger age in patients with MEN-2 than does the sporadic form. Local invasion is common, with metastatic spread to lymph nodes in the neck and mediastinum occurring in up to 50% of cases. Distant metastases to liver, bone, and lung are seen in 15 to 25% of cases. The clinical presentation in MTC may be with a neck mass, or symptoms from metastases (diarrhoea, flushing, weight loss, or bone pain). Rarely, ectopic ACTH secretion from MTC may cause Cushing's syndrome. Calcitonin is elevated in all cases of clinically palpable MTC. In smaller tumours or cases of C-cell hyperplasia, basal calcitonin levels may be normal and stimulation testing with a secretagogue such as pentagastrin or calcium gluconate may be necessary to confirm the diagnosis. Genetic screening in MEN-2-associated MTC has now largely replaced biochemical screening for MTC using the pentagastrin-stimulated calcitonin test. Cytological diagnosis using fine needle aspiration and staining for calcitonin may be useful where MTC manifests in previously unidentified MEN-2 carriers as a neck mass. Cross-sectional imaging of MTC using CT or MRI may be useful when planning surgery, and somatostatin receptor imaging is often valuable in detecting metastatic disease. As the tumour stage at presentation is the major prognostic factor, early diagnosis and surgical intervention before cervical lymph-node metastases appear is necessary to improve survival. Current practice involves total thyroidectomy with central node dissection. Postoperatively, in (a) (b) Fig. 13.8.5 (a) Characteristic phenotype of MEN-2B showing facial appearance. (b) Characteristic phenotype of MEN-2B showing mucosal neuromas on the tongue.

section 13 Endocrine disorders 2462 addition to a diagnostic role, calcitonin is used as a tumour marker for metastases or disease recurrence. Pheochromocytoma Pheochromocytomas are neuroendocrine neoplasms of neural crest origin. These occur in approximately 50% of patients with MEN-2A or MEN-2B, are usually benign, and are invariably confined to the adrenal glands. The penetrance of pheochromocytomas in MEN-2A depends on the exact codon mutated in RET with codon 634 mutations being associated with a high penetrance of 88% by age 77 years, and exon 10 mutations (codons 609, 611, 618, 620) being associated with a lower penetrance of up to 25% or so. Pheochromocytomas associated with MEN-2A or MEN-2B are bilateral in 50 to 80% of cases. The features and management of pheochromocytomas are outlined in Chapter 16.17.3.

Earlier detection and improved management with laparoscopic adrenalectomy have resulted in a significant reduction in the morbidity associated with pheochromocytoma in MEN-2. If MTC and pheochromocytoma are diagnosed simultaneously in MEN-2A or MEN-2B individuals, adrenalectomy should be performed before thyroidectomy. Parathyroid hyperplasia/adenomas

Primary hyperparathyroidism is a feature in 20–30% of MEN-2A patients and is usually asymptomatic. Compared to MEN-1, parathyroid disease in MEN-2A is usually milder and has a later onset. Surgical management of primary hyperparathyroidism in MEN-2A is similar to that in MEN-1. During thyroidectomy in MEN-2A, enlarged parathyroid glands in a normocalcaemic individual should be evaluated and removed if necessary.

Genetics of MEN-2

In contrast to MEN1, which is a tumour suppressor gene, RET is an oncogene. RET has 21 exons and encodes a membrane tyrosine kinase receptor protein called RET. Normal RET is expressed mainly in developing and adult neural ectoderm and comprises extracellular, transmembrane, and intracellular regions. The extracellular region contains four cadherin-like domains and a juxtamembrane cysteine-rich region. Two tyrosine kinase domains located in the intracellular region are involved in the activation of numerous intracellular signal transduction pathways. Mutations involving exons 8, 10, 11, 13, 14, 15, and 16 have been identified in patients with MEN-2A, MEN-2B, and familial medullary thyroid carcinoma. These exons should therefore be routinely screened for RET mutations. MEN-2A and FMTC mutations usually affect the extracellular cysteine-rich domain, whereas those associated with MEN-2B most frequently involve the intracellular tyrosine kinase domains of RET. In less than 95% of cases of MEN-2A, codons 609, 611, 618, 620, 634 are affected. More than 95% of cases of MEN-2B result from the M918T mutation, with less than 5% due to A883F mutations. Generally, mutations associated with FMTC are distributed among the six cysteine codons. In contrast to MEN-1, MEN-2 displays a strong genotype–phenotype correlation and mutations are identified in more than 95% of patients.

Genetic screening and management

Early recognition of carriers of RET mutations can prevent and cure medullary thyroid cancer, by enabling prophylactic thyroidectomy before metastatic spread. Genetic testing for germline RET mutations is performed in blood leucocytes. Since there is a strong correlation between the specific RET codon mutation and the aggressiveness of the tumour, decisions regarding prophylactic thyroidectomy are based on the RET mutation identified. Genetic testing for germline RET mutations is recommended in all children with a parent known to have MEN-2. Based on the location and nature of the mutation, these patients can be triaged into risk categories according to the American Thyroid Association's classification, in order of highest to lowest risks: ATA-HST, ATA-H, ATA-MOD. Those children carrying the most common MEN-2B mutation M918T have the highest risk of aggressive MTC (risk category ATA-HST) and total thyroidectomy with central node dissection is recommended within the first 6 months of life. This surgery should be performed by age 5 years in carriers of RET codon mutations 611, 618, 620, and 634. Those in the ATA-H category (e.g. mutations in codons 634 and 883) should be considered for total thyroidectomy at or before 5 years of age. Those in the ATA-MOD category (e.g. mutations affecting codons 533, 609, 611, 620, 631, 666, 768, 790, 804, 891, and 892) may be considered for prophylactic surgery later on in life or following first detection of abnormal stimulated calcitonin. Genetic screening may also be useful in the management of MEN-2-associated pheochromocytoma. Individuals with RET mutations associated with a high risk of developing pheochromocytoma should have annual measurement of urinary metanephrines or catecholamines.

Other MEN syndromes

In addition to MEN-1 and MEN-2, there are four other MEN syndromes. Carney complex (OMIM 160980) is a rare syndrome characterized by myxomas (cutaneous, mucosal, and cardiac), spotty skin pigmentation (lentiginosis), primary pigmented

adrenocortical disease, and pituitary adenomas. A diagnosis of McCune–Albright syndrome (OMIM 174800) requires at least two features of the triad of polyostotic fibrous dysplasia, café-au-lait skin pigmentation, and autonomous endocrine hyperfunction. Patients with Carney complex or McCune–Albright syndrome have mild hypersomatotropinemia (excess growth hormone secretion) starting in adolescence. In both disorders, pituitary hyperplasia appears to precede tumour development. Patients with neurofibromatosis type 1 (NF1; OMIM 162200) are predisposed to neuroendocrine tumours including pheochromocytomas and duodenal somatostatinomas. As previously described, VHL syndrome (OMIM 193300) is associated with pheochromocytomas and pancreatic neuroendocrine tumours. Finally, familial paraganglioma syndromes (OMIM 168000, 601650, 605373, 115310, 614165) are associated with mutations in the succinate dehydrogenase or SDHAF2 genes, and present with pheochromocytomas, paragangliomas, and occasionally renal cell carcinomas and gastrointestinal stromal tumours. FURTHER READING Herrera MF, et al. (2015). AACE/ACE disease state clinical review: pancreatic neuroendocrine incidentalomas. *Endocr Pract*, 21, 546–53.

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