the value of undertaking a central neck dissection has been subject to debate. Prophylactic thyroidectomy, with life-long thyroxine replacement, has dramatically improved outcomes in patients with MEN 2 and MEN 3, such that ~90% of young patients with *RET* mutations who had a prophylactic thyroidectomy have no evidence of persistent or recurrent MTC at 7 years after surgery. In patients with clinically evident MTC, a total thyroidectomy with bilateral central resection is recommended, and an ipsilateral lateral neck dissection should be undertaken if the primary tumor is >1 cm in size or there is evidence of nodal metastasis in the central neck. Surgery is the only curative therapy for MTC. The 10-year survival in patients with metastatic MTC is ~20%. For inoperable MTC or metastatic disease, the tyrosine kinase inhibitors, vandetanib and cabozantinib, have improved the progression-free survival times. Other types of chemotherapy are of limited efficacy, but radiotherapy may help to palliate local disease.

Pheochromocytoma (See also Chap. 407) These noradrenaline- and adrenaline-secreting tumors occur in >50% of patients with MEN 2A and MEN 2B and are a major cause of morbidity and mortality. Patients may have symptoms and signs of catecholamine secretion (e.g., headaches, palpitations, sweating, poorly controlled hypertension), or they may be asymptomatic with detection through biochemical screening based on a history of familial MEN 2A, MEN 2B, or MTC. Pheochromocytomas in patients with MEN 2A and MEN 2B differ significantly in distribution when compared with patients without MEN 2A and MEN 2B. Extra-adrenal pheochromocytomas, which occur in 10% of patients without MEN 2A and MEN 2B, are observed rarely in patients with MEN 2A and MEN 2B. Malignant pheochromocytomas are much less common in patients with MEN 2A and MEN 2B. The biochemical and radiologic investigation of pheochromocytoma in patients with MEN 2A and MEN 2B is similar to that in non–MEN 2 patients and includes the measurement of plasma (obtained from supine patients) and urinary free fractionated metanephrines (e.g., normetanephrine and metanephrines measured separately), CT or MRI scanning, radionuclide scanning with meta-iodo-(^{123}I or ^{131}I)-benzyl guanidine (MIBG), and PET using (^{18}F)-fluorodopamine or (^{18}F)-fluoro-2-dexoxy-D-glucose (Fig. 408-2).

TREATMENT **PHEOCHROMOCYTOMA**

Surgical removal of pheochromocytoma, using α and β adrenoreceptor blockade before and during the operation, is the recommended treatment. Endoscopic adrenal-sparing surgery, which decreases postoperative morbidity, hospital stay, and expense, as opposed to open surgery, has become the method of choice.

Parathyroid Tumors (See also Chap. 424) Parathyroid tumors occur in 10–25% of patients with MEN 2A. However, >50% of these patients do not have hypercalcemia. The presence of abnormally enlarged parathyroids, which are unusually hyperplastic, is often seen in the normocalcemic patient undergoing thyroidectomy for MTC. The biochemical investigation and treatment of hypercalcemic patients with MEN 2A is similar to that of patients with MEN 1.

Genetics and Screening To date, approximately 50 different *RET* mutations have been reported, and these are located in exons 5, 8, 10, 11, 13, 14, 15, and 16. *RET* germline mutations are detected in >95% of MEN 2A, FMTC, and MEN 2B families, with Cys634Arg being most common in MEN 2A, Cys618Arg being most common in FMTC, and Met918Thr being most common in MEN 2B (Tables 408-1 and 408-4). Between 5 and 10% of patients with MTC or MEN 2A–associated tumors have de novo *RET* germline mutations, and ~50% of patients with MEN 2B have de novo *RET* germline mutations. These de novo *RET* germline mutations always occur on the paternal allele. Approximately 5% of patients with sporadic pheochromocytoma have a germline *RET* mutation, but such germline *RET* mutations do not appear to be associated with sporadic primary hyperparathyroidism. Thus, *RET* mutational analysis should be performed in: (1) all patients with MTC who have a family history of tumors associated with MEN 2, FMTC, or MEN 3, such that the diagnosis can be confirmed and genetic testing offered to asymptomatic relatives; (2) all patients with MTC and pheochromocytoma without a known family history of MEN 2 or MEN 3; (3) all patients with MTC, but without a family history of MEN 2, FMTC, or MEN 3, because these patients may have a de novo germline *RET* mutations; (4) all patients with bilateral pheochromocytoma; and (5) patients with unilateral pheochromocytoma, particularly if this occurs with increased calcitonin levels.

Screening for MEN 2/MEN 3–associated tumors in patients with *RET* germline mutations should be undertaken annually and include serum calcitonin measurements, a neck ultrasound for MTC, plasma and 24-h urinary fractionated metanephrines for pheochromocytoma, and albumin-corrected serum calcium or ionized calcium with PTH for primary hyperparathyroidism. In patients with MEN 2–associated *RET* mutations, screening for MTC should begin by 3 to 5 years; for pheochromocytoma by 20 years; and for primary hyperparathyroidism by 20 years of age (Table 408-4).

MULTIPLE ENDOCRINE NEOPLASIA TYPE 4

Clinical Manifestations Patients with MEN 1–associated tumors, such as parathyroid adenomas, pituitary adenomas, and pancreatic NETs, occurring in association with gonadal, adrenal, renal, and thyroid tumors have been reported to have mutations of the gene encoding the 196–amino acid cyclin-dependent kinase inhibitor (CK1) p27 kip1 (*CDNKIB*). Such families with MEN 1–associated tumors and *CDNKIB* mutations are designated to have MEN 4 (Table 408-1). The investigations and treatments for the MEN 4–associated tumors are similar to those for MEN 1 and non–MEN 1 tumors.

Genetics and Screening To date, eight different MEN 4–associated mutations of *CDNKIB*, which is located on chromosome 12p13, have been reported, and all of these are associated with a loss of function. These MEN 4 patients may represent ~3% of the 5–10% of patients with MEN 1 who do not have mutations of the *MEN1* gene. Germline *CDNKIB* mutations may rarely be found in patients with sporadic (i.e., nonfamilial) forms of primary hyperparathyroidism.

HYPERPARATHYROIDISM-JAW TUMOR SYNDROME (SEE ALSO CHAP. 424)

Clinical Manifestations Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is an autosomal dominant disorder characterized by the development of parathyroid tumors (15% are carcinomas) and fibro-osseous jaw tumors. In addition, some patients may also develop Wilms' tumors, renal cysts, renal hematomas, renal cortical adenomas, papillary renal cell carcinomas, pancreatic adenocarcinomas, uterine tumors, testicular mixed germ cell tumors with a major seminoma component, and Hürthle cell thyroid adenomas. The parathyroid tumors may occur in isolation and without any evidence of jaw tumors, and this may cause confusion with other hereditary hypercalcemic disorders, such as MEN 1. However, genetic testing to identify the causative mutation will help to establish the correct diagnosis. The investigation and treatment for HPT-JT-associated tumors are similar to those in non-HPT-JT patients, except that early parathyroidectomy is advisable because of the increased frequency of parathyroid carcinoma.

Genetics and Screening The gene that causes HPT-JT is located on chromosome 1q31.2 and encodes a 531–amino acid protein, parafibromin (Table 408-2). Parafibromin is also referred to as cell division cycle protein 73 (CDC73) and has a role in transcription. Genetic testing in families helps to identify mutation carriers who should be periodically screened for the development of tumors (Table 408-5).

VON HIPPEL-LINDAU DISEASE (SEE ALSO CHAP. 407)

Clinical Manifestations von Hippel-Lindau (VHL) disease is an autosomal dominant disorder characterized by hemangioblastomas of the retina and CNS; cysts involving the kidneys, pancreas, and epididymis; renal cell carcinomas; pheochromocytomas; and pancreatic islet cell tumors. The retinal and CNS hemangioblastomas are benign vascular tumors that may be multiple; those in the CNS may cause symptoms