tumors of the cerebellum, kidney, brainstem, or spinal cord suggests the possibility of VHL. A personal and/or family history of head and neck paraganglioma suggests PGL1 or PGL4.

A single adrenal pheochromocytoma in a patient with an otherwise unremarkable history may still be associated with mutations of *VHL, RET, SDHB*, or *SDHD* (in decreasing order of frequency). Two-thirds of extra-adrenal tumors are associated with one of these syndromes, and multifocal tumors occur with decreasing frequency in carriers of *RET, SDHD, VHL*, and *SDHB* mutations. About 30% of head and neck paragangliomas are associated with germ-line mutations of one of the SDH subunit genes (most often *SDHD*) and are rare in carriers of *VHL, RET*, and *TMEM127* mutations **(Fig. 407-6*F*)**.

Immunohistochemistry is helpful in the preselection of hereditary pheochromocytoma. Negative immunostaining with antibodies to SDHB, TMEM127, and MAX may predict mutations of the *SDH*, *TMEM127*, and *MAX* genes, respectively.

Once the underlying syndrome is diagnosed, the benefit of genetic testing can be extended to relatives. For this purpose, it is necessary to identify the germ-line mutation in the proband and, after genetic counseling, to perform DNA sequence analyses of the responsible gene in relatives to determine whether they are affected **(Chap. 84)**. Other family members may benefit when individuals who carry a germ-line mutation are biochemically screened for paraganglial tumors.

Asymptomatic paraganglial tumors, now often detected in patients with hereditary tumors and their relatives, are challenging to manage. Watchful waiting strategies have been introduced. Head and neck paragangliomas—mainly carotid body, jugular, and vagal tumors—are increasingly treated by radiation, since surgery is frequently associated with permanent palsy of cranial nerves II, VII, IX, X, XI, and XII. Nevertheless, tympanic paragangliomas are symptomatic early, and most of these tumors can easily be resected, with subsequent improvement of hearing and alleviation of tinnitus.

408 Multiple Endocrine Neoplasia

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Multiple endocrine neoplasia (MEN) is characterized by a predilection for tumors involving two or more endocrine glands. Four major forms of MEN are recognized and referred to as MEN types 1–4 (MEN 1–4) **(Table 408-1)**. Each type of MEN is inherited as an autosomal dominant syndrome or may occur sporadically; that is, without a family history. However, this distinction between familial and sporadic forms is often difficult because family members with the disease may have died before symptoms developed. In addition to MEN 1–4, at least six other syndromes are associated with multiple endocrine and other organ neoplasias (MEONs) **(Table 408-2)**. These MEONs include the hyperparathyroidism-jaw tumor syndrome, Carney complex, von Hippel-Lindau disease **(Chap. 407)**, neurofibromatosis type 1 **(Chap. 118)**, Cowden's syndrome, and McCune-Albright syndrome **(Chap. 426e)**; all of these are inherited as autosomal dominant disorders, except for McCune-Albright syndrome, which is caused by mosaic expression of a postzygotic somatic cell mutation (Table 408-2).

A diagnosis of a MEN or MEON syndrome may be established in an individual by one of three criteria: (1) clinical features (two or more of the associated tumors [or lesions] in an individual); (2) familial pattern (one of the associated tumors [or lesions] in a first-degree relative of a patient with a clinical diagnosis of the syndrome); and (3) genetic analysis (a germline mutation in the associated gene in an individual, who may be clinically affected or asymptomatic). Mutational analysis in MEN and MEON syndromes is helpful in clinical practice to: (1) confirm the clinical diagnosis; (2) identify family members who harbor the mutation and require screening for relevant tumor detection and early/appropriate treatment; and (3) identify the ~50% of family members who do not harbor the germline mutation and can, therefore, be alleviated of the anxiety of developing associated tumors. This latter aspect also helps to reduce health care costs by reducing the need for unnecessary biochemical and radiologic investigations.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Clinical Manifestations MEN type 1 (MEN 1), which is also referred to as Wermer's syndrome, is characterized by the triad of tumors involving the parathyroids, pancreatic islets, and anterior pituitary. In addition, adrenal cortical tumors, carcinoid tumors usually of the foregut, meningiomas, facial angiofibromas, collagenomas, and lipomas may also occur in some patients with MEN 1. Combinations of the affected glands and their pathologic features (e.g., hyperplastic adenomas of the parathyroid glands) may differ in members of the same family and even between identical twins. In addition, a nonfamilial (e.g., sporadic) form occurs in 8–14% of patients with MEN 1, and molecular genetic studies have confirmed the occurrence of de novo mutations of the *MEN1* gene in approximately 10% of patients with MEN 1. The prevalence of MEN 1 is approximately 0.25% based on randomly chosen postmortem studies but is 1–18% among patients with primary hyperparathyroidism, 16–38% among patients with pancreatic islet tumors, and <3% among patients with pituitary tumors. The disorder affects all age groups, with a reported age range of 5 to 81 years, with clinical and biochemical manifestations developing in the vast majority by the fifth decade. The clinical manifestations of MEN 1 are related to the sites of tumors and their hormonal products. In the absence of treatment, endocrine tumors are associated with an earlier mortality in patients with MEN 1, with a 50% probability of death by the age of 50 years. The cause of death is usually a malignant tumor, often from a pancreatic neuroendocrine tumor (NET) or foregut carcinoid. In addition, the treatment outcomes of patients with MEN 1–associated tumors are not as successful as those in patients with non–MEN 1 tumors. This is because MEN 1–associated tumors, with the exception of pituitary NETs, are usually multiple, making it difficult to achieve a successful surgical cure. Occult metastatic disease is also more prevalent in MEN 1, and the tumors may be larger, more aggressive, and resistant to treatment.

Parathyroid Tumors **(See also Chap. 424)** Primary hyperparathyroidism occurs in approximately 90% of patients and is the most common feature of MEN 1. Patients may have asymptomatic hypercalcemia or vague symptoms associated with hypercalcemia (e.g., polyuria, polydipsia, constipation, malaise, or dyspepsia). Nephrolithiasis and osteitis fibrosa cystica (less commonly) may also occur. Biochemical investigations reveal hypercalcemia, usually in association with elevated circulating parathyroid hormone (PTH) **(Table 408-3)**. The hypercalcemia is usually mild, and severe hypercalcemia or parathyroid cancer is a rare occurrence. Additional differences in the primary hyperparathyroidism of patients with MEN 1, as opposed to those without MEN 1, include an earlier age at onset (20–25 years vs 55 years) and an equal male-to-female ratio (1:1 vs 1:3). Preoperative imaging (e.g., neck ultrasound with ^{99m}Tc-sestamibi parathyroid scintigraphy) is of limited benefit because all parathyroid glands may be affected, and neck exploration may be required irrespective of preoperative localization studies.

TREATMENT PARATHYROID TUMORS

Surgical removal of the abnormally overactive parathyroids in patients with MEN 1 is the definitive treatment. However, it is controversial whether to perform subtotal (e.g., removal of 3.5 glands) or total parathyroidectomy with or without autotransplantation of parathyroid tissue in the forearm, and whether surgery should be performed at an early or late stage. Minimally invasive parathyroidectomy is not recommended because all four parathyroid glands are usually affected with multiple adenomas or hyperplasia. Surgical experience should be taken into account given the variability in pathology in MEN 1. Calcimimetics (e.g., cinacalcet), which act via