paroxysm during micturition. The elevations of blood pressure are induced by the sudden release of catecholamines that may acutely precipitate congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation, and cerebrovascular accidents.

The cardiac complications have been attributed to what has been called *catecholamine cardiomyopathy*, or catecholamine-induced myocardial instability and ventricular arrhythmias. Nonspecific myocardial changes, such as focal necrosis, mononuclear infiltrates, and interstitial fibrosis, have been attributed either to ischemic damage secondary to catecholamine-induced constriction of myocardial blood vessels or to direct catecholamine toxicity. In some cases pheochromocytomas secrete other hormones, such as ACTH and somatostatin, and may therefore be associated with clinical features related to the secretion of these or other peptide hormones. The laboratory diagnosis of pheochromocytoma is based on the demonstration of increased urinary excretion of free catecholamines and their metabolites, such as vanillylmandelic acid and metanephrines.

Isolated benign tumors are treated with surgical excision, after preoperative and intraoperative medication of patients with adrenergic-blocking agents to prevent a hypertensive crisis. Multifocal lesions require long-term medical treatment for hypertension.

# MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

**The MEN syndromes are a group of inherited diseases resulting in proliferative lesions (hyperplasia, adenomas, and carcinomas) of multiple endocrine organs.** Like other inherited cancer disorders (Chapter 7), endocrine tumors arising in the context of MEN syndromes have certain distinct features that contrast with their sporadic counterparts.

- Tumors occur at a *younger age* than sporadic tumors.
- They arise in *multiple endocrine organs*, either *synchronously* (at the same time) or *metachronously* (at different times).
- Even in one organ, the tumors are often *multifocal*.
- The tumors are usually preceded by an *asymptomatic stage of hyperplasia* involving the cell of origin. For example, individuals with MEN-2 almost universally demonstrate C-cell hyperplasia in the thyroid parenchyma adjacent to medullary thyroid carcinomas.
- These tumors are usually *more aggressive* and *recur* in a higher proportion of cases than do similar sporadic endocrine tumors.

## Multiple Endocrine Neoplasia, Type 1

MEN-1, or *Wermer syndrome*, is a rare heritable disorder with a prevalence of about 2 per 100,000. MEN-1 is characterized by abnormalities involving the *parathyroid*, *pancreas*, and *pituitary glands*; thus the mnemonic device, the *3Ps*:

- *Parathyroid: Primary hyperparathyroidism* is the most common manifestation of MEN-1 (80% to 95% of patients) and is the initial manifestation of the disorder in most patients, appearing in almost all patients by age 40 to 50. Parathyroid abnormalities include both hyperplasia and adenomas.
- *Pancreas: Endocrine tumors of the pancreas* are a leading cause of morbidity and mortality in persons with MEN-1. These tumors are usually aggressive and often present with metastatic disease. It is not uncommon to find multiple "microadenomas" scattered throughout the pancreas in conjunction with one or two dominant lesions. MEN-1-associated pancreatic endocrine tumors are often functional; however, because pancreatic polypeptide is the most commonly secreted product, many tumors fail to produce an endocrine hypersecretion syndrome. Among those that do, Zollinger-Ellison syndrome (associated with gastrinomas) and hypoglycemia and neurologic manifestations (associated with insulinomas) are most common.
- *Pituitary:* The most frequent anterior pituitary tumor encountered in MEN-1 is a *prolactinoma*; some patients develop acromegaly from somatotrophin-secreting tumors.
- It is now recognized that the spectrum of this disease extends beyond the *3Ps*. The *duodenum is the most common site of gastrinomas in individuals with MEN-1* (far in excess of the frequency of pancreatic gastrinomas), and synchronous duodenal and pancreatic tumors may be present in the same individual. In addition, carcinoid tumors, thyroid and adrenocortical adenomas, and lipomas are more frequent than in the general population.

**MEN-1 syndrome is caused by germline mutations in the *MEN1* tumor suppressor gene, which encodes a protein called menin**. Menin is a component of several different transcription factor complexes, which (depending on the specific binding partner) may either promote or inhibit tumorigenesis. This dichotomy in menin function is best exemplified in the interactions of menin with two oncogenic transcription factors—JunD and the mixed-lineage leukemia (MLL) protein. When menin partners with JunD, it blocks transcriptional activation by JunD; in fact, loss of this tumor suppressor interaction is believed to contribute to the multiple endocrine neoplasia observed in the setting of MEN1 inactivating mutations. On the contrary, the association of wild-type menin with MLL leads to the formation of a tumor promoting transcriptional complex in a subset of leukemias (Chapter 13).

The dominant clinical manifestations of MEN-1 usually result from the peptide hormones that are overproduced and include such abnormalities as recurrent hypoglycemia due to insulinomas, intractable peptic ulcers in persons with Zollinger-Ellison syndrome, nephrolithiasis caused by PTH-induced hypercalcemia, or symptoms of prolactin excess from a pituitary tumor. As expected, malignant behavior by one or more of the endocrine tumors arising in these patients is often the proximate cause of death.