Loss of heterozygosity or a somatic mutation of the remaining normal *MENIN* allele leads to tumorigenesis. About half of affected patients develop prolactinomas; acromegaly and Cushing's syndrome are less commonly encountered.

Carney's syndrome is characterized by spotty skin pigmentation, myxomas, and endocrine tumors, including testicular, adrenal, and pituitary adenomas. Acromegaly occurs in about 20% of these patients. A subset of patients have mutations in the R1α regulatory subunit of protein kinase A (*PRKAR1A*).

McCune-Albright syndrome consists of polyostotic fibrous dysplasia, pigmented skin patches, and a variety of endocrine disorders, including acromegaly, adrenal adenomas, and autonomous ovarian function (Chap. 426e). Hormonal hypersecretion results from constitutive cyclic AMP production caused by inactivation of the GTPase activity of Gsα. The Gsα mutations occur postzygotically, leading to a mosaic pattern of mutant expression.

Familial acromegaly is a rare disorder in which family members may manifest either acromegaly or gigantism. A subset of families with a predisposition for familial pituitary tumors, especially acromegaly, have been found to harbor germline mutations in the *AIP* gene, which encodes the aryl hydrocarbon receptor interacting protein.

HYPERPROLACTINEMIA

Etiology Hyperprolactinemia is the most common pituitary hormone hypersecretion syndrome in both men and women. PRL-secreting pituitary adenomas (prolactinomas) are the most common cause of PRL levels >200 μg/L (see below). Less pronounced PRL elevation can also be seen with microprolactinomas but is more commonly caused by drugs, pituitary stalk compression, hypothyroidism, or renal failure (Table 403-5).

Pregnancy and lactation are the important physiologic causes of hyperprolactinemia. Sleep-associated hyperprolactinemia reverts to normal within an hour of awakening. Nipple stimulation and sexual orgasm also may increase PRL. Chest wall stimulation or trauma (including chest surgery and herpes zoster) invoke the reflex suckling arc with resultant hyperprolactinemia. Chronic renal failure elevates PRL by decreasing peripheral clearance. Primary hypothyroidism is associated with mild hyperprolactinemia, probably because of compensatory TRH secretion.

Lesions of the hypothalamic-pituitary region that disrupt hypothalamic dopamine synthesis, portal vessel delivery, or lactotrope responses are associated with hyperprolactinemia. Thus, hypothalamic tumors, cysts, infiltrative disorders, and radiation-induced damage cause elevated PRL levels, usually in the range of 30–100 μg/L. Plurihormonal adenomas (including GH and ACTH tumors) may hypersecrete PRL directly. Pituitary masses, including clinically nonfunctioning pituitary tumors, may compress the pituitary stalk to cause hyperprolactinemia.

Drug-induced inhibition or disruption of dopaminergic receptor function is a common cause of hyperprolactinemia (Table 403-5). Thus, antipsychotics and antidepressants are a relatively common cause of mild hyperprolactinemia. Most patients receiving risperidone have elevated prolactin levels, sometimes exceeding 200 μg/L. Methyldopa inhibits dopamine synthesis, and verapamil blocks dopamine release, also leading to hyperprolactinemia. Hormonal agents that induce PRL include estrogens and thyrotropin-releasing hormone (TRH).

Presentation and Diagnosis Amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia in women. If hyperprolactinemia develops before menarche, primary amenorrhea results. More commonly, hyperprolactinemia develops later in life and leads to oligomenorrhea and ultimately to amenorrhea. If hyperprolactinemia is sustained, vertebral bone mineral density can be reduced compared with age-matched controls, particularly when it is associated with pronounced hypoestrogenemia. Galactorrhea is present in up to 80% of hyperprolactinemic women. Although usually bilateral and spontaneous, it may be unilateral or expressed only manually. Patients also may complain of decreased libido, weight gain, and mild hirsutism.

In men with hyperprolactinemia, diminished libido, infertility, and visual loss (from optic nerve compression) are the usual presenting symptoms. Gonadotropin suppression leads to reduced testosterone,

TABLE 403-5 ETIOLOGY OF HYPERPROLACTINEMIA

- **I. Physiologic hypersecretion**
  - Pregnancy
  - Lactation
  - Chest wall stimulation
  - Sleep
  - Stress
- **II. Hypothalamic–pituitary stalk damage**
  - Tumors
    - Craniopharyngioma
    - Suprasellar pituitary mass
    - Meningioma
    - Dysgerminoma
    - Metastases
  - Empty sella
  - Lymphocytic hypophysitis
  - Adenoma with stalk compression
  - Granulomas
  - Rathke's cyst
  - Irradiation
  - Trauma
    - Pituitary stalk section
    - Suprasellar surgery
- **III. Pituitary hypersecretion**
  - Prolactinoma
  - Acromegaly
- **IV. Systemic disorders**
  - Chronic renal failure
  - Hypothyroidism
  - Cirrhosis
  - Pseudocyesis
  - Epileptic seizures
- **V. Drug-induced hypersecretion**
  - Dopamine receptor blockers
    - Atypical antipsychotics: risperidone
    - Phenothiazines: chlorpromazine, perphenazine
    - Butyrophenones: haloperidol
    - Thioxanthenes
    - Metoclopramide
  - Dopamine synthesis inhibitors
    - α-Methyldopa
  - Catecholamine depletors
    - Reserpine
  - Opiates
  - H_2 antagonists
    - Cimetidine, ranitidine
  - Imipramines
    - Amitriptyline, amoxapine
  - Serotonin reuptake inhibitors
    - Fluoxetine
  - Calcium channel blockers
    - Verapamil
    - Estrogens
    - Thyrotropin-releasing hormone

Note: Hyperprolactinemia >200 μg/L almost invariably is indicative of a prolactin-secreting pituitary adenoma. Physiologic causes, hypothyroidism, and drug-induced hyperprolactinemia should be excluded before extensive evaluation.