phenotypic expression/penetrance indicate the multiplicity of the genetic factors responsible. Nonetheless, the ability to detect the presence of the major genetic contributors has greatly aided a more informed management of family members of patients identified in the hereditary syndromes such as MEN 1, MEN 2, and HPT-JT.

An important contribution from studies on the genetic origin of parathyroid carcinoma has been the realization that the mutations involve a different pathway than that involved with the benign gland enlargements. Unlike the pathogenesis of genetic alterations seen in colon cancer, where lesions evolve from benign adenomas to malignant disease by progressive genetic changes, the alterations commonly seen in most parathyroid cancers (*HRPT2* mutations) are infrequently seen in sporadic parathyroid adenomas.

Abnormalities at the *Rb* gene were the first to be noted in parathyroid cancer. The *Rb* gene, a tumor-suppressor gene located on chromosome 13q14, was initially associated with retinoblastoma but has since been implicated in other neoplasias, including parathyroid carcinoma. Early studies implicated allelic deletions of the *Rb* gene in many parathyroid carcinomas and decreased or absent expression of the Rb protein. However, because there are often large deletions in chromosome 13 that include many genes in addition to the *Rb* locus (with similar findings in some pituitary carcinomas), it remains possible that other tumor-suppressor genes on chromosome 13 may be playing a role in parathyroid carcinoma.

Study of the parathyroid cancers found in some patients with the HPT-JT syndrome has led to identification of a much larger role for mutations in the *HRPT2* gene in most parathyroid carcinomas, including those that arise sporadically, without apparent association with the HPT-JT syndrome. Mutations in the coding region have been identified in 75–80% of all parathyroid cancers analyzed, leading to the conclusion that, with addition of presumed mutations in the noncoding regions, this genetic defect may be seen in essentially all parathyroid carcinomas. Of special importance was the discovery that, in some sporadic parathyroid cancers, germline mutations have been found; this, in turn, has led to careful investigation of the families of these patients and a new clinical indication for genetic testing in this setting.

Hypercalcemia occurring in family members (who are also found to have the germline mutations) can lead to the finding, at parathyroid surgery, of premalignant parathyroid tumors.

Overall, it seems there are multiple factors in parathyroid cancer, in addition to the *HRPT2* and *Rb* gene, although the *HRPT2* gene mutation is the most invariant abnormality. *RET* encodes a tyrosine kinase type receptor; specific inherited germline mutations lead to a constitutive activation of the receptor, thereby explaining the autosomal dominant mode of transmission and the relatively early onset of neoplasia. In the MEN 2 syndrome, the *RET* protooncogene may be responsible for the earliest disorder detected, the polyclonal disorder (C cell hyperplasia, which then is transformed into a clonal outgrowth—a medullary carcinoma with the participation of other, still uncharacterized genetic defects).

In some parathyroid adenomas, activation of a protooncogene has been identified (Fig. 424-3*B*). A reciprocal translocation involving chromosome 11 has been identified that juxtaposes the *PTH* gene promoter upstream of a gene product termed *PRAD-1*, encoding a cyclin D protein that plays a key role in normal cell division. This translocation plus other mechanisms that cause an equivalent overexpression of cyclin D1 are found in 20–40% of parathyroid adenomas.

Mouse models have confirmed the role of several of the major identified genetic defects in parathyroid disease and the MEN syndromes. Loss of the *MEN1* gene locus or overexpression of the *PRAD-1* protooncogene or the mutated *RET* protooncogene have been analyzed by genetic manipulation in mice, with the expected onset of parathyroid tumors or medullary carcinoma, respectively.

**Signs and Symptoms** Many patients with hyperparathyroidism are asymptomatic. Manifestations of hyperparathyroidism involve primarily the kidneys and the skeletal system. Kidney involvement, due either to deposition of calcium in the renal parenchyma or to recurrent nephrolithiasis, was present in 60–70% of patients prior to 1970. With earlier detection, renal complications occur in <20% of patients in many large series. Renal stones are usually composed of either calcium oxalate or calcium phosphate. In occasional patients, repeated episodes of nephrolithiasis or the formation of large calculi may lead to urinary tract obstruction, infection, and loss of renal function. Nephrocalcinosis may also cause decreased renal function and phosphate retention.

The distinctive bone manifestation of hyperparathyroidism is *osteitis fibrosa cystica*, which occurred in 10–25% of patients in series reported 50 years ago. Histologically, the pathognomonic features are an increase in the giant multinucleated osteoclasts in scalloped areas on the surface of the bone (Howship's lacunae) and a replacement of the normal cellular and marrow elements by fibrous tissue. X-ray changes include resorption of the phalangeal tufts and replacement of the usually sharp cortical outline of the bone in the digits by an irregular outline (subperiosteal resorption). In recent years, osteitis fibrosa cystica is very rare in primary hyperparathyroidism, probably due to the earlier detection of the disease.

Dual-energy x-ray absorptiometry (DEXA) of the spine provides reproducible quantitative estimates (within a few percent) of spinal bone density. Similarly, bone density in the extremities can be quantified by densitometry of the hip or of the distal radius at a site chosen to be primarily cortical. Computed tomography (CT) is a very sensitive technique for estimating spinal bone density, but reproducibility of standard CT is no better than 5%. Newer CT techniques (spiral, "extreme" CT) are more reproducible but are currently available in a limited number of medical centers. Cortical bone density is reduced while cancellous bone density, especially in the spine, is relatively preserved. In symptomatic patients, dysfunctions of the CNS, peripheral nerve and muscle, gastrointestinal tract, and joints also occur. It has been reported that severe neuropsychiatric manifestations may be reversed by parathyroidectomy. When present in symptomatic patients, neuromuscular manifestations may include proximal muscle weakness, easy fatigability, and atrophy of muscles and may be so striking as to suggest a primary neuromuscular disorder. The distinguishing feature is the complete regression of neuromuscular disease after surgical correction of the hyperparathyroidism.

Gastrointestinal manifestations are sometimes subtle and include vague abdominal complaints and disorders of the stomach and pancreas. Again, cause and effect are unclear. In MEN 1 patients with hyperparathyroidism, duodenal ulcer may be the result of associated pancreatic tumors that secrete excessive quantities of gastrin (Zollinger-Ellison syndrome). Pancreatitis has been reported in association with hyperparathyroidism, but the incidence and the mechanism are not established.

Much attention has been paid in recent years to the manifestations of and optimum management strategies for asymptomatic hyperparathyroidism. This is now the most prevalent form of the disease. *Asymptomatic primary hyperparathyroidism* is defined as biochemically confirmed hyperparathyroidism (elevated or inappropriately normal PTH levels despite hypercalcemia) with the absence of signs and symptoms typically associated with more severe hyperparathyroidism such as features of renal or bone disease.

Three conferences on the topic have been held in the United States over the past two decades, with the most recent in 2008. The published proceedings include discussion of more subtle manifestations of disease, its natural history (without parathyroidectomy), and guidelines both for indications for surgery and medical monitoring in nonoperated patients.

Issues of concern include the potential for cardiovascular deterioration, the presence of subtle neuropsychiatric symptoms, and the longer-term status of skeletal integrity in patients not treated surgically. The current consensus is that medical monitoring rather than surgical correction of hyperparathyroidism may be justified in certain patients. The current recommendation is that patients who show mild disease, as defined by specific criteria (Table 424-2), can be safely followed under management guidelines (Table 424-3). There is, however, growing uncertainty about subtle disease manifestations and whether surgery is therefore indicated in most patients. Among the issues is the evidence of eventual (>8 years) deterioration in bone mineral density after a decade