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Parathyroid Hormone-Related Disorders

John P. Bilezikian, MD,* and T.J. Martin, MD†

Pathogenesis of Parathyroid Hypersecretion

The pathogenesis of primary hyperparathyroidism is the subject of several different experimental approaches which were presented in the first part of this session. Genetic control of the hyperparathyroid secretory state could be due to a single lesion in a single cell giving rise to a monoclonal origin of the hyperparathyroidism. Alternatively, the hyperparathyroid gland could have its genetic roots in a multicellular process in which the tissue responds to a variety of more pervasive external influences such as humoral factors, circulating antibodies, or cell-to-cell spread of a tumorigenic virus. Molecular genetics have helped to begin to test further the hypothesis that the single adenomatous parathyroid gland is a monoclonal neoplasm whereas the form of hyperparathyroidism due to four-gland hyperplasia is a polyclonal disorder.

Approaches to the clonality of human tumors and their application to parathyroid adenomas

Arnold and Kronenberg (1) have applied the technique of restriction fragment length polymorphism to examine this issue. Eight of 43 adenomas and five of 23 hyperplastic glands were found to be heterozygous for the BamHI/HPRT polymorphism and thus available for study by this technique. Six of eight adenomas showed clear loss of one allele, consistent with monoclonality, while all five hyperplastic parathyroids showed relative nonpreferential HpaII cleavage consistent with polyclonality. Certain technical limitations of this approach require that these results be confirmed by other molecular tests as well as by more classical genetic approaches. The data, however, do indicate that a majority of parathyroid adenomas are monoclonal neoplasms and suggest a fundamental difference in their pathogenesis as compared to the multiglandular form of primary hyperparathyroidism.

Physiology and pathophysiology of Ca++-regulated parathyroid hormone release

The parathyroid cell is an unusual secretory cell in terms of its relationship to calcium. Whereas most secretory cells are stimulated by cellular calcium (classical stimulus-secretion coupling), the parathyroid cell is inhibited by cellular calcium. In normal parathyroid tissue, the relationship between parathyroid hormone secretion and extracellular calcium is steep with the major element of control by calcium being exerted over the physiological range of calcium (1 to 1.25 mM). In primary hyperparathyroidism, sensitivity to control by calcium is reduced both by virtue of the increased number of parathyroid cells and by an increase in the "set-point" for calcium-regulated parathyroid hormone release. The work presented by Brown et al (2)

Multiple endocrine neoplasia type 1: Role of a circulating growth factor in parathyroid cell hyperplasia

Insight into the pathophysiological disturbance of the primary hyperparathyroidism associated with multiple endocrine neoplasia type 1 (MEN-1) has been made by Brandi et al (3). They hypothesized that a substance stimulating parathyroid cell proliferation is involved in the pathophysiology of the disorder. Plasma from MEN-1 was shown to be selectively mitogenic for parathyroid cells. Plasma from other hyperparathyroid syndromes was considerably less mitogenic. Characterization of the factor shows it to have an apparent molecular weight of 50 kilodaltons and to share certain properties of the fibroblast growth factor-related proteins. Evidence has recently been obtained to suggest that the target cell of this growth factor appears to be the endothelial cell of the parathyroid vasculature. The parathyroid epithelial cell and other endothelial cells do not show reactivity to the parathyroid growth factor. How this factor is released into the circulation, its exact relationship to FGF-like proteins and/or

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Pseudohypoparathyroidism

This classic genetic disorder of calcium metabolism has distinctive characteristics: short stature, round facies, short neck, foreshortened metacarpal and metatarsal bones, a tendency to mental retardation, and calcifications in the basal ganglia (Albright hereditary osteodystrophy or pseudohypoparathyroidism, type Ia). In contrast to true hypoparathyroidism, the hypocalcemia is accompanied by elevated immunoreactive parathyroid hormone levels; hence the designation, pseudohypoparathyroidism. The salient biochemical feature of pseudohypoparathyroidism, Ia, resistance to the actions of parathyroid hormone, is seen by the lack of a phosphaturic and cyclic AMP response to parathyroid hormone. Pseudohypoparathyroidism, type Ib, is identical to type Ia except that Albright hereditary osteodystrophy is not present and other hormone resistant states, typical of the Ia phenotype, are not seen. Patients do have the biochemical abnormalities. After Albright described pseudohypoparathyroidism, he observed a patient with the typical body habitus of pseudohypoparathyroidism but without evidence for hypocalcemia or target organ resistance. In his attempt to distinguish this variant from classical pseudohypoparathyroidism, Albright dubbed it pseudopseudohypoparathyroidism. Pseudohypoparathyroidism and pseudopseudohypoparathyroidism clearly belong to the same genetic family as evidenced by family trees that contain both forms of the disorder, by selected patients whose biochemical profile has been known to cross over to the other, and by the molecular basis of the disorder.

G proteins as signal transducers

Important clues to the defect in pseudohypoparathyroidism were gained by observations of Levine (4) as well as by several other groups. The constellation of hormone resistant states included in the syndrome involves the adenylate cyclase messenger system. A site common to all hormones that utilize adenylate cyclase is the guanine nucleotide binding protein, Gs, that links their different receptors to the catalytic unit of adenylate cyclase. Patients with Albright hereditary osteodystrophy (pseudohypoparathyroidism, type Ia) demonstrate a 50% reduction in the alpha subunit of Gs. There does not appear to be any gross gene deletions or rearrangements of the gene encoding Gs alpha. Levels of the alpha subunit of the inhibitory guanine nucleotide binding protein, Gi, are normal. Despite the enthusiasm generated by this observation, reduced Gs alpha levels do not entirely account for the syndrome. Patients with pseudopseudohypoparathyroidism in which the typical physiognomy is not accompanied by hormone resistance nevertheless do have reduced Gs alpha levels. Only patients with the classical disorder, but not all, have the reduction in Gs alpha. Patients with type Ib and parathyroid resistance in the absence of any other hormone resistance have normal levels of Gs, implicating that this isolated hormone resistant state might be due to a defect in the parathyroid hormone receptor per se. Even within the group of patients who show reductions in Gs alpha, there is heterogeneity. Most, but not all, patients manifesting a reduction in Gs alpha activity show a decrease in messenger RNA by Northern blot analysis.

Pseudohypoparathyroidism: Studies of the pathogenesis of parathyroid hormone resistance

In view of the fact that the G protein abnormality does not appear to account entirely for the syndrome, Goltzman et al (5) as well as others have examined the possibility that characteristics of parathyroid hormone per se might contribute to the manifestations of functional hypoparathyroidism in pseudohypoparathyroidism. Characteristics of circulating parathyroid hormone (PTH) were examined in three patients with the classical syndrome. In the plasma of these patients were elevations in immunoreactive PTH but reductions in biologically active PTH as determined by cytochemical bioassay. In addition, the plasma of these patients appeared to contain an inhibitor of exogenous, biologically active PTH by two in vitro bioassays. The biochemical profile of immunoreactive PTH in patient plasma showed differences from normal plasma in that the bulk of the circulating immunoreactivity in pseudohypoparathyroidism consisted of more hydrophobic moieties. These results are consistent with the presence of an alteration in parathyroid hormone metabolism within the parathyroid gland in pseudohypoparathyroidism. The defect in Gs alpha might accommodate such an hypothesis because the parathyroid cell presumably also is impaired in this regard. Goltzman et al (5) have pursued this possibility further by investigating an experimental model of parathyroid hormone resistance in the vitamin D deficient rat. Elevated levels of parathyroid hormone in this syndrome are associated with post-PTH receptor reductions in Gs alpha that extend to other hormones that utilize the adenylate cyclase system. When these observations are viewed together, they suggest that reduced levels of Gs are not necessarily causally related to hormone resistance in pseudohypoparathyroidism and also that the underlying mechanism for the various forms of pseudohypoparathyroidism are likely to be heterogeneous.

Primary Hyperparathyroidism

Primary hyperparathyroidism: The surgically cured patient

Primary hyperparathyroidism has become a relatively common endocrine disorder due to the widespread use of multichannel autoanalyzers in medicine. The increased incidence has been accompanied by a marked reduction in the presence of obvious signs and symptoms related to the hyperparathyroid state. These observations have led to a change in the therapeutic approach to primary hyperparathyroidism. Patients are not always subjected to parathyroidectomy because many are asymptomatic and do not appear to be suffering adverse consequences of the disease. In an effort to gain greater insight into the modern-day presentation of primary hyperparathyroidism, Ljunghall and associates (6) reviewed an experience of 570 patients who underwent parathyroid exploration between 1965 and 1984. The average postoperative follow-up period was seven years. The average age was 59, with women predominating over men by 3:1. Adenomas were found in 80%. The overwhelming
majority of patients with adenomatous disease became normocalcemic (93%). Recurrences, however, tended to increase with time for both adenomatous and hyperplastic disease. Postoperative results focused on the relatively nonspecific aspects of primary hyperparathyroidism because classical bone and stone disease have become relatively infrequent. A fair number of patients, however, did report postoperative improvement in complaints such as easy fatigability, memory, concentrating ability, depression, and several neuropsychiatric complaints. Ljunghall et al (6) also assessed other disorders believed to be associated with primary hyperparathyroidism such as hypertension and diabetes mellitus. They found little evidence for a pathophysiological association between either disease and primary hyperparathyroidism in that successful parathyroid surgery does not appear to alter the hypertension or the diabetes. They also addressed the epidemiological evidence for increased mortality from cardiovascular and malignant disease in primary hyperparathyroidism.

Primary hyperparathyroidism in the 1980s

In examining the asymptomatic patient with primary hyperparathyroidism in a prospective long-term study, two key questions are being addressed (7): In mild, asymptomatic primary hyperparathyroidism, can other evidence for parathyroid bone disease be discovered upon more detailed evaluation? Which asymptomatic patients are at risk for developing complications of primary hyperparathyroidism? Among the 67 patients evaluated so far, the average age is 55, with women dominating over men by 2.5:1. The biochemical indices are typical with mild hypercalcemia (11.1 ± 0.1 mg/dL) and elevations in parathyroid hormone by radioimmunoassay. “Mid-molecule” radioimmunoassay and “intact” immunoradiometric assays show frankly elevated values in well over 90% of patients. No patient has radiologically overt parathyroid bone disease; 19% of patients had nephrolithiasis. Only one patient showed classical neuromuscular disease of primary hyperparathyroidism.

By bone densitometry, patients showed reductions in bone mineral density that were preferential to cortical bone. The distal radius, consisting of predominantly cortical bone, showed a reduction in bone mineral density to less than 80% of expected in 58% of the patients. In contrast, trabecular bone appeared to be relatively preserved. Only 13% of patients showed a reduction in trabecular bone mineral density to less than 80% of expected. These results were confirmed by results of the percutaneous bone biopsy in which the vast majority of patients (84%) had mean cortical width determinations below expected, whereas an equivalently large number of patients (85%) showed trabecular bone volume greater than average. These early results indicate that the routine assignment of patients with primary hyperparathyroidism to an asymptomatic cohort, if they don’t show clinically apparent complications, should be tempered by the likely possibility of skeletal involvement after more detailed testing. The results raise questions about the definition of asymptomatic primary hyperparathyroidism and call for additional long-term studies in order to define better the risk factors for complications of this disease.

References