PRIMARY hyperparathyroidism

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INTRODUCTION

In the past 3 decades, our views of Primary Hyperparathyroidism have changed in terms of diagnosis, management, and course. These changes in the clinical phenotypes of primary hyperparathyroidism and resultant mofications in guidelines for management are summarized in publications that resulted from The Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism was held in Orlando, Florida on May 13, 2008 (1-6). The syllabus has been updated to include the key features of that Consensus Conference as well as developments in the field over the past several years.

DIAGNOSIS

In the differential diagnosis of hypercalcemia, primary hyperparathyroidism is the most common cause. It is important to distinguish readily between primary hyperparathyroidism and other causes of hypercalcemia. The biochemical distinction between primary hyperparathyroidism and malignancy-asociated hypercalcemia, the second most common cause of hypercalcemia, is firmly established by measuring the PTH level. With the 2-site immunoradiometric or immunochemiluminometric assay for PTH, elevated levels in primary hyperparathyroidism are seen approximately 75%-80% of the time. When the parathyroid hormone level is normal, it tends to be in the upper range of normal and, thus, clearly "abnormal" when hypercalcemia is simultaneously present. In the context of hypercalcemia of malignancy and virtually all other causes of hypercalcemia (with the exceptions being those related to thiazide diuretics, lithium, and Familial Hypocalciuric Hypercalcemia), the parathyroid hormone level will be suppressed. Thus, when the parathyroid hormone level is in the upper range of normal and hypercalcemia is present, abnormal regulation of serum calcium by the parathyroid gland(s) is most likely.

Using the IRMA assay for parathyroid hormone in which the normal range is typically given as 10-65 pg/ml, in individuals under the age of 45, the upper limit of normal for parathyroid hormone should be regarded to be closer to 45 pg/ml. This is because parathyroid hormone levels normally rise with age and the laboratory reference range doesn't make a distinction. For example, in a 32 year old woman with hypercalcemia, a parathyroid hormone level of 50 pg/ml should be regarded as frankly elevated, even though technically it is still within normal limits for the assay.

The most widespread IRMA assay for parathyroid hormone is called "intact", but work by Broussard et al. have demonstrated that in addition to the full length, intact peptide, amino-terminally truncated forms of PTH are also detected by this assay (7). These forms of parathyroid hormone have 100% cross-reactivity with the native full length peptide in this assay. Truncation is due to 3-14 amino acids missing from the amino terminus (8-9). PTH(7-84) is the most prominent of these variants. Together, these forms of PTH may constitute up to 50 percent of the circulating species of PTH in normal subjects. In renal failure they may constitute an even higher percentage. An IRMA assay for PTH includes a recognition site for the first 6 N-terminal amino acids (1-6), thus giving this newer assay rather exclusive specificity for the full-length biologically active PTH molecule (10-11). Silverberg et al. have applied this "whole" assay to a group of subjects with surgically proved primary hyperparathyroidism. In comparison to the intact assay and the older radioimmunoassay for mid-molecule PTH, the whole assay performed somewhat better with respect to a higher percentage of patients with frankly elevated levels (96%) in comparison to the intact (73%) and mid-molecule assays (63%) (12). Subsequent experience, however, has given the

general sense that in subjects without renal failure, the intact assay and the “whole” assay are equivalently useful (13-14). In subjects with renal compromise, however, mid-molecule and the larger aminoterminally truncated forms of PTH do build up. While it may be expected that the “whole” assay would give a more accurate depiction of PTH in these situations, this has not always been appreciated (15).

As noted, exceptions to the rule that patients with hypercalcemia and elevated PTH levels have primary hyperparathyroidism include two medications, lithium (16) and thiazide diuretics. Actually, many of these patients do have primary hyperparathyroidism but the only way to be sure is to withdraw the medication and to monitor the serum calcium over the next 3-6 months. In those who are dependent upon lithium therapy for their mental well-being, withdrawal may be difficult or unwise, although newer psychotropic agents- effective in bipolar disease, can effect this change more safely than in the past. Recent experience has shown that primary hyperparathyroidism should be seriously considered in someone on lithium because it is unlikely that lithium alone would be responsible for the hypercalcemia. Another exception is tertiary hyperparathyroidism, an end result of longstanding, poorly controlled renal insufficiency. Hypercalcemia in this setting usually does not present a problem in differential diagnosis because the advanced renal failure is clearly evident. In these cases, there is a change from mechanisms of parathyroid gland compensation (i.e., to normalize the tendency for hypocalcemia to develop; a secondary hyperparathyroidism) to mechanisms of parathyroid gland autonomy with attendant hypercalcemia. It is of interest that when surgery is performed, some of these patients are actually found to have primary hyperparathyroidism, that is a single adenomatous gland superimposed upon a background of parathyroid hyperplasia (17). Another exception to the rule that patients with elevated levels of calcium and PTH have primary hyperparathyroidism is the rare disorder, Familial Hypocalciuric Hypercalcemia (FHH). It is due to an inactivating mutation of the calcium sensing receptor (CASR) gene resulting in an increase in the set point for serum calcium suppression of PTH secretion (18). These individuals tend to be younger than the average patient with primary hyperparathyroidism. In fact the clinical expression of FHH with mild hypercalcemia typically can be traced to childhood or the young adult years. There is also usually a family history of asymptomatic hypercalcemia. The inactivating mutation of this gene also affects the kidney, enhancing calcium reabsorption, resulting in hypocalciuria, with a calcium to creatinine clearance ratio (Ca/Cr) typically less than 0.01, on a normal calcium diet. It is important to distinguish between primary hyperparathyroidism and FHH because surgery is never indicated in FHH, Because of its high penetrance, FHH becomes a particularly important consideration in children and young adults. When the diagnosis is in doubt, CASR gene sequence testing can be obtained (19)

True ectopic parathyroid hormone production.
Very rarely, non-parathyroid malignancies have been described in which authentic parathyroid hormone is produced (20). In a patient with a known malignancy, hypercalcemia and elevated parathyroid hormone levels, it is actually more common for that patient to have concomitant primary hyperparathyroidism because ectopic parathyroid hormone production by malignant tumors is so rare. Far more common, in the setting of malignancy-associated hypercalcemia, is the production of parathyroid hormone-related protein (PTHrP). This latter situation does not present a problem vis a vis the measurement of parathyroid hormone since the modern immunoassays do not have any cross reactivity between the two molecules.

Normocalcemic Primary Hyperparathyroidism. The diagnosis of primary hyperparathyroidism can be made at times in subjects whose total and ionized serum calcium are completely normal but in whom the parathyroid hormone level is persistently elevated (21). In order to make the diagnosis of normocalcemic primary hyperparathyroidism, all causes for a secondary hyperparathyroid state must be considered and ruled out. It is essential to recognize the presence of coexisting vitamin D insufficiency which may well be the most common cause for an elevated PTH level. Replacing these patients with vitamin D to reach

levels now considered to be normal (i.e., 25-hydroxyvitamin D >30 ng/mL) often returns the PTH to normal. The recent recommendations for a revision downward of the normal range to 20 ng/mL (22) has not changed the opinion of this author that for the diagnosis of normocalcemic primary hyperparathyroidism, levels of 25-hydroxyvitamin D should be > 30 ng/mL Occasionally, however, these patients will become hypercalcemic with vitamin D replacement thus unmasking more typical hypercalcemic PHPT. If the PTH remains elevated and the serum calcium remains normal, following vitamin D repletion, and other causes of an elevated PTH such as renal insufficiency have been excluded, then the diagnosis of normocalcemic PHPT can be considered. Since there are limited data on the natural history of normocalcemic PHPT, it is unclear how these subjects should be regarded vis a vis parathyroid surgery.

A large population based study of over 5,000 postmenopausal women who were screened and then retested 8 yrs later provided evidence for the development of hypercalcemia in some of these subjects (23-24). Two observational studies of normocalcemic PHPT have followed patients longitudinally. In one study (25), 37 patients were followed for a mean of 3 yrs (range 1-9). Typical hypercalcemic PHPT emerged in 7 (19%) individuals. However, 40% developed evidence of disease progression with development of kidney stones, fractures, marked hypercalciuria or >10% decline in BMD. Seven patients had successful parathyroidectomy of whom three were hypercalcemic and the rest met other criteria for surgery.

The cumulative experience with these individuals by us and others has established this variant of primary hyperparathyroidism as a real clinical entity (21, 25-28). At the 3rd International Workshop on the Management of Asymptomatic PHPT, normocalcemic PHPT was recognized, for the first time, as a form of primary hyperparathyroidism.

It might be asked reasonably why would someone measure PTH in a normocalcemic individual? The answer is related, at least in part, to the pro-active approach to individuals who are being evaluated in their early postmenopausal years for parameters of skeletal health as well as for the fact that many specialists are measuring PTH in anyone being evaluated for osteoporosis or osteopenia. In this setting, therefore, the discovery of elevated PTH levels without hypercalcemia can be made.

EPIDEMIOLOGY

Primary hyperparathyroidism has become a common endocrine disorder, due in large part to the widespread use of the multichannel autoanalyzer that was introduced in the early 1970s (29). Prior to that time, however, PHPT was not a common endocrine disease (30). Despite its rarity, as described in older reports, the frequency with which it was diagnosed was, in large measure, a function of one's index of suspicion. For example, Raymond Keating, whose work at the Mayo Clinic helped to establish modern concepts of the disease, began to recognize primary hyperparathyroidism with regularity, only after he was made more acute aware of it by Aub, Bauer and Albright (31). This experience was the clue that primary hyperparathyroidism was much more prevalent in the population at large than its incidence would have suggested it to be. Then, with the advent of the autoanalyzer, in the 1970's, it was rather quickly apparent that there were many individuals with primary hyperparathyroidism whose disease was not being recognized simply because calcium determinations were not being routinely obtained. Incidence figures rose dramatically when calcium determinations were obtained in the context of the multichannel biochemistry profile. Reporting its experience before and after the introduction of the autoanalyzer, the Mayo Clinic saw a 4-5-fold increase in the incidence of primary hyperparathyroidism to approximately 100,000 new cases per year or about 22 cases per 100,000 person years. (29, 32). Apart from these reports, most other population-based studies on the prevalence of primary hyperparathyroidism are Scandinavian (33-34). Epidemiological uncertainties with the extensive Scandinavian databases include the fact that persistent hypercalcemia has been the primary identification marker without clear documentation of parathyroid disease by concomitant parathyroid hormone determinations (35-36). Post-mortem examination of the parathyroid glands does not help to solidify the database because such studies are not accompanied by functional evidence for hyperparathyroidism during life (37). Using serum parathyroid hormone values along with the serum

calcium concentration, Lundgren et al. showed that 2.6% of the postmenopausal population in Sweden had primary hyperparathyroidism (38-39). On follow-up testing, however, only two-thirds had confirmation of the diagnosis. These results, nevertheless, help to underscore the point that primary hyperparathyroidism is a common endocrine disorder. It increases with age and is much more common in women by a ratio of approximately 3:1 (29, 38-39).

Reports from United States and Europe have suggested that the incidence of primary hyperparathyroidism may be declining (40). Although surprising, these reports have not been widely confirmed. In the experience of most endocrinologists, in fact, the incidence of primary hyperparathyroidism would appear to be unchanged. If it is demonstrated that the incidence of primary hyperparathyroidism is declining, this could well be due to efforts on the part of health care insurers to control costs by restricting access to the multichannel screening test. In the sporadic form of primary hyperparathyroidism, by far the most common presentation seen, there are no clearly definable risk factors that can be identified. A history of childhood irradiation to the face or neck is obtained in a small number of individuals (41-42)

Hereditary Hyperparathyroid States

Multiple Endocrine Neoplasia (MEN), both type 1 and type II, is inherited in an autosomal dominant manner. Primary hyperparathyroidism is often the first and is the most common of the endocrinopathies in MEN1, reaching nearly 100% penetrance by the age of 50 (43-44). On the other hand, among subjects with primary hyperparathyroidism, MEN1 is rare accounting for only 2-4% of cases. Recognition of primary hyperparathyroidism in a young adult, nevertheless, can lead to the discovery of a kindred with MEN1. In MEN I, the other tumors, besides the parathyroids, that can develop are those of pancreas and anterior pituitary glands. Involvement of two of the three endocrine glands confirms the presence of MEN I. The presence of a tumor involving one of the three tissues in a first degree family member also confirms the presence of familial MEN I. The tumor suppressor gene which is inactivated in MEN I encodes menin, the gene product of the MENIN gene. Gene testing can be of value if the clinical diagnosis is considered (45-47).

MEN IIa, in which hyperparathyroidism can be associated with medullary thyroid cancer, is due to a germline mutation of the RET proto-oncogene located on chromosome 10. The onco-protein is activated with a gain of function mutation detectable in more than 95% of MEN IIa families. DNA sequencing is of value if prophylactic thyroidectomy is being considered (46). When codon 634 of the RET gene is involved, primary hyperparathyroidism is seen with the highest frequency (48)

Hyperparathyroidism jaw tumor syndrome, transmitted, an autosomal dominant manner, is associated with PHPT and fibromas in the mandible or the maxilla. Tumors can also be present in the kidneys and the uterus. Unlike FHH or the MEN I and II, parathyroid carcinoma is more common in hyperparathyroidism jaw tumor syndrome, occurring with an incidence of up to 15-20% of patients (48-49). The condition is caused by germline mutations of the HRPT2 gene located on chromosome arm 1q. Family members at risk can be identified by DNA analysis of the HRPT2 gene, which is detectable in approximately 70% of the kindreds. These mutations result in inactivation of the gene product, parafibromin (50-51).

Familial isolated hyperparathyroidism (FIH) includes familial syndromes that do not clearly meet the diagnostic classification of the previous genetically transmitted categories. In order to rule out these other genetic forms of primary hyperparathyroidism, DNA testing for the CASR, MEN I or MEN II genes may also assist in establishing a definitive diagnosis. However, the majority of kindreds with only hyperparathyroidism appear to be genetically distinct from the recognized familial hyperparathyroid syndromes (48).

Familial hypocalciuric hypercalcemia (FHH). This presentation that can be confused with the most common form of primary hyperparathyroidism, namely the sporadic isolated disorder, is considered above in the discussion of the differential diagnosis of primary hyperparathyroidism.

Neonatal severe primary hyperparathyroidism (NSHPT). This is a rare but life-threatening presentation in which neonates have marked hypercalcemia, very high levels of parathyroid hormone, hypotonia and respiratory distress. It is due to the presence of two copies of the abnormal calcium receptor gene responsible for FHH (18).

Genetic testing for syndromes associated with primary hyperparathyroidism (52): The recognition of these syndromes, which can alter medical or surgical management, can now be aided by commercially available genetic testing for the MENIN gene (MEN1), the RET protooncogene (MEN 2A), HRPT2 (HPT-JT) and CASR genes (FHH). This is especially important for HRPT2 mutation, which entails a heightened risk for parathyroid malignancy (53-54).

Molecular pathogenesis

In primary hyperparathyroidism, clones of abnormal parathyroid cells emerge that dominate and shift the usual steep inverse relationship between PTH release and calcium ion “to the right”. For a given extracellular calcium concentration, PTH is higher. Although in large measure, the defect is altered sensitivity of a clone of parathyroid cells to calcium, increases in the mass of abnormal parathyroid tissue also contribute to excessive secretion of PTH (20,55). No specific mutations of the calcium sensing receptor have been described in primary hyperparathyroidism. Other genes such as the vitamin D receptor gene, the proto-oncogene RET have also not been demonstrated to be abnormal in primary hyperparathyroidism.

The clonal origin of most parathyroid adenomas implies that defects in specific genes, such as those capable of controlling parathyroid cell growth, were acquired in tumor development and conferred a selective advantage upon an original cell and its progeny. Interestingly, in a model of experimental hyperparathyroidism, the altered sensitivity to calcium, and hypercalcemia, are a secondary consequence of the primary disturbance in parathyroid cell growth (56). The pathogenetic abnormalities in primary hyperparathyroidism involve several genes that have variably been implicated as causal in the disorder. The first gene to be associated with primary hyperparathyroidism is the cyclin D1 oncogene (formerly PRAD 1). Overexpression of cyclin D1, on human chromosome 11q13, is thought to have an important role in the pathogenesis of some sporadic parathyroid adenomas. The rearrangement of the PTH gene locus in proximity to cyclin D1 leads to transcriptional activation and overexpression of structurally normal cyclin D1 (57-58). Thus, when the PTH gene is active or activated, the cyclin D1 gene is also stimulated, leading to growth of the clone that harbors the genetic abnormality. As many as 20-40% of parathyroid adenomas may overexpress cyclin D1, although the exact mechanisms for this overexpression are likely to vary greatly (59-60).

The second genetic abnormality that has been described as etiologically important in primary hyperparathyroidism is the gene associated with multiple endocrine neoplasia, type 1 (MEN1; 61-62). The MEN1 gene product is a tumor suppressor. In primary hyperparathyroidism, or in any mechanism of tumorigenesis due to a tumor suppressor gene, complete inactivation (biallelic dysfunction) is required. Some parathyroid tumors from patients with sporadic primary hyperparathyroidism, that is those who do not have the multiple endocrine neoplasia syndrome, have been shown to harbor biallelic defects in the MEN1 gene (62-63).
The cell division cycle 73 gene (HRPT2, CDC73) shown to be abnormal in parathyroid cancer and in autosomal dominant hyperparathyroidism-jaw tumor syndrome does not seem to be abnormal in benign, sporadic parathyroid adenomas (64-66).

Although, much more information is needed about the molecular pathogenesis of primary hyperparathyroidism, the implication of several genes so far suggests that perhaps most patients with this order will ultimately be shown to have some underlying molecular defect that leads to the abnormal set point for calcium in this disorder. A number of other candidate gene defects have been described (67-70).

PATHOLOGY

By far the most common lesion found in patients with primary hyperparathyroidism is the solitary, benign parathyroid adenoma, occurring in 80% of patients. While in most cases, a single adenoma is found, multiple parathyroid adenomas have been reported in 2-4% of cases (71-73). These may be familial or sporadic. Parathyroid adenomas can be discovered in many unexpected anatomic locations. Embryonal migration patterns of parathyroid tissue account for a plethora of possible sites for ectopic parathyroid adenomas. The most common sites for ectopic adenomas are within the thyroid gland, the superior mediastinum, and within the thymus. Occasionally, the adenoma may ultimately be identified in the retroesophageal space, the pharynx, the lateral neck, and even the alimentary submucosa of the esophagus.

In approximately 15% of patients with primary hyperparathyroidism, all four parathyroid glands are involved. There are no clinical features that differentiate single versus multiglandular disease. The etiology of 4-gland parathyroid hyperplasia is multi-factorial. It may be associated with a familial hereditary syndrome, such as multiple endocrine neoplasia, Types 1 and 2a. As in the case of parathyroid adenomas, underlying molecular mechanisms are heterogeneous. Very rarely, in fewer than 0.5% of patients with primary hyperparathyroidism, the parathyroid disease will be malignant.

BIOCHEMICAL FEATURES

Typical biochemical indices associated with primary hyperparathyroidism are shown in Table 1. The serum calcium determination is generally not greater than 1 mg/dl above the upper limits of normal. The serum phosphorus is in the lower range of normal with only approximately 25% of patients showing phosphorus levels that are frankly low. Total alkaline phosphatase activity is in the high normal range as is the case also for more specific markers of bone turnover, bone-specific alkaline phosphatase activity, osteocalcin, or collagen breakdown products (N-telopeptide, deoxypyridinoline). If the normal concentration of 25-hydroxyvitamin D level is taken to be >30 ng/ml, then most patients with primary hyperparathyroidism will have low levels. In contrast, the 1,25-dihydroxyvitamin D level tends to be in the upper range of normal and, in fact, frankly elevated in 25% of patients with primary hyperparathyroidism (74). The pattern of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in primary hyperparathyroidism is due to the property of parathyroid hormone to facilitate the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Urinary calcium excretion is typically in the upiper range of normal with as many as 40% of individuals showing frank hypercalciuria. Curiously, the presence of hypercalciuria in those without a history of kidney stones does not have predictive value for the development of nephrolithiasis (75).

Table 1. Baseline chemical and hormonal profile in mild primary hyperparathyroidism

Index	Patients	nl range
• Calcium (mg/dl)	10.7±0.1	8.4-10.2
• Phosphorus (mg/dl)	2.9±0.1	2.5-4.5
• Alk Phos (IU/l)	114±4	<100
• PTH (pg/ml)	121±7	10-65
• 25-OH Vit D (ng/ml)	21±1	9-52
• 1,25-OH_2 Vit D (pg/ml)	59±2	15-60
• Urinary calcium (mg)	248 ± 12	100-300
• DPD (nmol/mmol Cr)	17 ± 6	4-21

Table 1. Biochemical indices in primary hyperparathyroidism. The values for this table are obtained from the cohort of patients followed by Silverberg, Bilezikian et al. over the past 15 years.

CLINICAL FEATURES

It is not surprising that with more widespread recognition of primary hyperparathyroidism, the classical signs and symptoms of the disease would change (76-78).

The Skeleton.

The frequency of specific radiological manifestations of primary hyperparathyroidism has fallen from 23% in the Cope Series (30) to less than 2% in the experience of Silverberg et al. (79-82). In fact, overt skeletal disease in primary hyperparathyroidism is so infrequent that skeletal X-rays are rarely indicated. Although *osteitis fibrosa cystica* is distinctly unusual in patients who present with primary hyperparathyroidism in the United States, this does not imply that the skeleton is unaffected in those with asymptomatic disease. The availability of sensitive techniques to monitor the skeleton has given us an opportunity to address these issues in patients who have asymptomatic primary hyperparathyroidism.
*Bone Densitometry***.** The advent of bone mineral densitometry as a major diagnostic tool for osteoporosis occurred at a time when the clinical profile of primary hyperparathyroidism was changing from a symptomatic to an asymptomatic disease. Questions about skeletal involvement in primary hyperparathyroidism could be addressed, therefore, despite the absence of overt radiological features. Bone mass measurement, now an integral element of the evaluation of all patients with primary hyperparathyroidism, typically shows evidence for skeletal involvement (79-80). Parathyroid hormone is known to be catabolic at sites of cortical bone. The distal 1/3 site of the radius provides a convenient cortical site for bone density evaluation in primary hyperparathyroidism to investigate the possibility that this site would be preferentially affected. In primary hyperparathyroidism, as expected from physiological considerations, bone density at the distal radius (1/3 site) is diminished (76,79). The common observation that the cortical compartment is reduced in primary hyperparathyroidism has been seen also with the newer non-invasive technology, high resolution peripheral computed tomography (83-84). Another physiological property of parathyroid hormone is an anabolic one, at cancellous sites, such as the lumbar spine. Bone density at the lumbar spine is only minimally reduced, typically within 5% of age matched mean values. The hip region, containing a relatively equal admixture of cortical and cancellous elements, shows bone density that is intermediate between the cortical and cancellous sites (Figure 1). The results support not only the notion that parathyroid hormone is catabolic in cortical bone, but also the view that parathyroid hormone can be, under certain circumstances, anabolic for cancellous bone (82,85-87). In postmenopausal women, the same pattern is observed (79). Postmenopausal women with primary hyperparathyroidism, therefore, show a reversal of the pattern typically associated with postmenopausal estrogen deficiency, namely preferential loss of cancellous bone. These observations suggest that primary hyperparathyroidism may help to protect postmenopausal women from bone loss due to estrogen deficiency

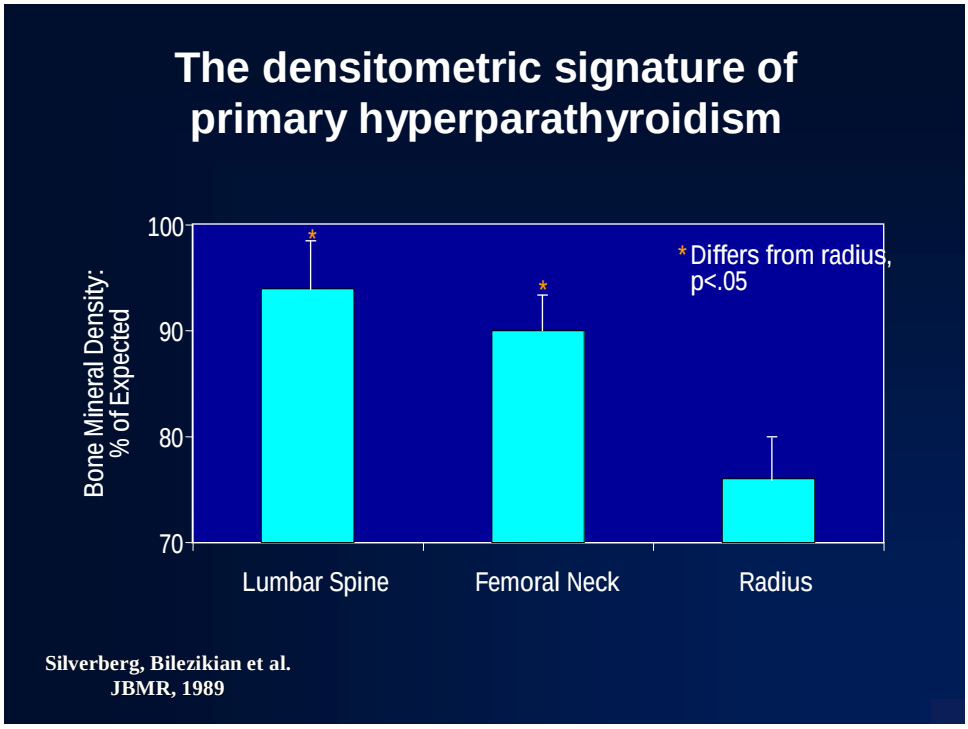

Figure 1. The pattern of bone loss in primary hyperparathyroidism. A typical pattern of bone loss is seen in asymptomatic patients with primary hyperparathyroidism. The lumbar spine is relatively well preserved while the distal radius (1/3 site) is preferentially affected. (Reprinted with permission from reference #79).

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The densitometric profile in which there is relative preservation of skeletal mass at the spine and diminution at the more cortical radial site is not always seen in primary hyperparathyroidism. About 15% of patients with primary hyperparathyroidism will be shown to have evidence of vertebral osteopenia at the time of presentation (88).

Histomorphometric analysis of the bone biopsy specimen in primary hyperparathyroidism demonstrates cortical thinning, maintenance of cancellous bone volume and a very dynamic process associated with high turnover and accelerated bone remodeling. Confirming the results by bone densitometry, cancellous bone volume is clearly well preserved in primary hyperparathyroidism. This is seen in the group of all subjects we studied as well as among the subcohort of postmenopausal women with primary hyperparathyroidism. Several studies have shown that cancellous bone is actually increased in primary hyperparathyroidism as compared to normal subjects (89-91). Preservation of cancellous bone volume even extends to comparisons with the expected losses associated with the effects of aging on cancellous bone physiology. In patients with primary hyperparathyroidism, there is no relationship between trabecular number or separation and age, suggesting that the actual trabecular plates and their connections are maintained over time more effectively than in normal aging individuals. Thus, primary hyperparathyroidism seems to retard the normal age-related processes associated with trabecular loss. One of the mechanisms by which cancellous bone is preserved in primary hyperparathyroidism is

through the maintenance of inter-connected trabecular plates. Further recent studies have confirmed the salutary effects of PTH on cancellous elements in primary hyperparathyroidism (92-93).

Fracture risk. Since bone mineral density is an important predictor of fracture risk, the densitometric data in primary hyperparathyroidism suggest certain expectations about fracture incidence. One would expect, for example, that fracture incidence would be increased in the forearm and reduced in the lumbar spine. Dauphine et al. and Khosla et al. (94-95) reported that vertebral fractures were increased but other observations have failed to confirm these reports (96-98). When vertebral fracture is the starting point for case finding, primary hyperparathyroidism is rarely found, although measurement of the serum calcium is recommended by many as part of the evaluation of all newly diagnosed cases of osteoporosis.
Expectations for increased fracture risk at cortical sites such as the forearm are also not supported by available data although it would seem logical to anticipate more long bone fractures. But, primary hyperparathyroidism is not a dominant feature in most series of hip fracture patients (94). Khosla et al. have analyzed retrospectively the incidence of fractures in primary hyperparathyroidism over a 28-year period, 1965-1992). Fracture rate at the forearm was increased among the 407 cases of primary hyperparathyroidism (95). Vignali has reported an increase in morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism (99). When their cohort was divided into those who did or did not meet criteria for surgery, only those who met criteria for surgery demonstrated the increase in fracture incidence.
Expectations of fracture risk in primary hyperparathyroidism have to take into account other skeletal effects of parathyroid hormone that contribute to bone quality. It is clear that bone density is only one of a number of factors that account for bone strength (100). As noted above, the effects of parathyroid hormone to preserve cancellous microarchitecture may tend to counteract the cortical thinning for which parathyroid hormone is also responsible. Another important point is the effect of parathyroid hormone on bone size. Cortical thinning tends to be compensated by the actions of parathyroid hormone to increase periosteal apposition, thus leading to an increase in cross sectional diameter (101-103). The increase in cross-sectional diameter will tend to increase bone strength independent of the parathyroid hormone effect to thin the cortices. Thus, in primary hyperparathyroidism, certain skeletal features tend to compete with each other: cortical thinning favoring an increase in fracture risk; increased bone size and preserved skeletal microarchitecture favoring a reduction in fracture risk. These considerations suggest the need for prospective studies of site-specific fracture incidence in primary hyperparathyroidism.
After successful parathyroid surgery, increases in BMD are seen at the lumbar spine, hip regions, and, after some delay, at the distal third radius site as well (104-107). In one study (104-105), this global increase in BMD after parathyroidectomy was sustained for as long as 15 years. Sankaran et al confirmed these individual reports in their meta-analysis of post-operative increases in BMD from a number of different studies (108). The effects of surgery on fracture risk was evaluated and compared to controls in a 10-year cohort study (109). Fracture-free survival was significantly improved with surgery in comparison to no surgery.

Renal Involvement

Also noteworthy with regard to the changing clinical profile of the disease is the reduction in the incidence of stone disease from approximately 60% in the preautoanalyzer era to current series in which the incidence is less than 20% (75,110). Still, stone disease is the most common complication of primary hyperparathyroidism. What disposes some individuals to have stone disease is not known but work by Schillitani et al. suggests that specific polymorphisms of the calcium receptor gene might be an important pathogenetic factor (111). Other renal manifestations of primary hyperparathyroidism include hypercalciuria, which is seen in approximately 40 percent of patients, and nephrocalcinosis, the frequency of which is unknown. An unexplained reduction in the creatinine clearance has also been regarded to be a potential renal manifestation of primary hyperparathyroidism.

In order to rule out renal involvement in subjects with no history of kidney stones, renal imaging, with ultrasonography of CT scanning, can be performed. It seems reasonable to consider measuring the urinary calcium, particularly in situations where FHH is a diagnostic possibility. Whether urinary calcium is helpful to assess stone risk in primary hyperparathyroidism has become less clear. Urinary calcium excretion is only 1 of 6 important risk factors for kidney stones, the others being urinary volume, oxalate, uric acid, pH, and citrate excretion. In PHPT, stone formers do have a higher urinary calcium excretion than those who do not form stones (112). However, in patients who have not yet formed stones, a high urinary calcium is not associated with the development of stones (113). Other issues the complicate relying upon the urinary calcium excretion as an index of activity of the disease are the points that urinary calcium excretion has low precision; varies with age, sex, race, dietary calcium intake and vitamin D status as well as with GFR. Thus, the proceedings of the 2008 Workshop on primary hyperparathyroidism no longer recommend marked hypercalciuria as a criterion for parathyroidectomy (2). This recommendation does not mean that a 24-hour urinary calcium is not recommended in the evaluation of PHPT. Most experts do obtain a 24-hour urinary calcium which helps in the differential diagnosis of hypercalcemia (i.e. to rule out FHH) and to gain a sense of the activity of the hypeparathyroid process.

Renal function is another issue that has been revisited. Typically renal function is considered in the evaluation of the patient with primary hyperparathyroidism but how to assess renal function in this or any other state rely on guidelines from The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) and the more recent KIDIGO guidelines (114-115). The 24-hour urinary collection for creatinine is not recommended to estimate creatinine clearance. Rather, glomerular filtration rate (eGFR) is estimated from equations based on anthropomorphic criteria (age, gender, race, weight) and serum measurements (creatinine, albumin, urea, nitrogen:116-117).
The value set by the Hyperparathyroidism Workshop Panel is a GFR of 60 ml/min/1.73 m^2 below which it is thought that PTH levels begin to rise in individuals with chronic kidney disease in the absence of PHPT. However, recent work by Walker et al. has indicated that PTH levels are not higher among individuals whose creatinine clearance is 30-60 cc/min when compared to those with clearances greater than 60 cc/min (118)

Gastrointestinal Manifestations

Glucose Tolerance: Attempts to link carbohydrate intolerance and frank diabetes mellitus to primary hyperparathyroidism have been made (119-121), but the association is even more tenuous than other associations that have been proposed (see below). Whether there is a true increase in the prevalence of Type 2 diabetes mellitus among subjects with asymptomatic primary hyperparathyroidism is not established.
Peptic ulcer disease. Most studies place the incidence of peptic ulcer disease in primary hyperparathyroidism to be 10%, about the same percentage as in the general population. On the other hand, in genetic syndromes such as MEN1, in which 40% of patients have clinically apparent gastrinomas, one does see more peptic ulcer disease. In these patients, improvement in the gastrointestinal symptomatology after parathyroidectomy has been reported (122). Despite this, current recommendations state that the coexistence of Zollinger-Ellison syndrome does not represent sufficient indication for parathyroidectomy because medical therapy of the ulcer diathesis is so successful (123)

Pancreatitis. Although hypercalcemia can underlie pancreatitis, most large series have not reported an increased incidence of pancreatitis in primary hyperparathyroidism (124-126). The Mayo Clinic experience reported only 1.5% of those with primary hyperparathyroidism had coexistent pancreatitis (127)

Neurological manifestations

*Neuromuscular***.** The classical neuromuscular dysfunction that used to be associated with primary hyperparathyroidism (128) is virtually never seen anymore. In a detailed neurologic study of 42 patients with a mean serum calcium concentration of 11.1 ± 0.1 mg/dl, Turken et al. (129) found no consistent pattern of abnormalities either on physical examination or on electromyography.
Neurobehavioral and Neurocognitive Features. Quite apart from the potential for specific neuromuscular involvement in primary hyperparathyroidism, neuropsychiatric and cognitive complaints are common and remain an area of active interest (130-133). Many patients, families, and physicians note features of depression, cognitive difficulties and anxiety in those with the disease. One of the issues related to this set of complaints is that they are non-specific and are found in many chronic disorders. Furthermore, it is very hard to quantitate these features on a verifiable scale that can be tested both before and after parathyroid surgery. Some, but by no means all, studies that have attempted to associate neuropsychiatric elements with PHPT (132, 134-140), suggest that there are psychological features of the disease that improve with surgery. Review of this literature underscores confounders among them such as variability in their observational design, small sample sizes, inclusion of subjects with symptomatic PHPT, lack of appropriate control groups, and short testing intervals following parathyroidectomy. Nevertheless, the more recent literature has added to our knowledge in this area.

Using newer instruments to test quality of life measures, a significant improvement in some aspects of well being and energy, as well as in the perception of health status have beenreported (141-143). Several observational studies of cognitive function (138-139, 143) have been inconsistent with some reports suggesting improvement after parathyroidectomy, and others not showing any changes (131,134,145-146).

The 2008 Workshop reviewed the first randomized studies of neurocognition and quality of life measures after parathyroid surgery in subjects with mild hypercalcemia. Rao et al. found no difference in baseline SF-36 scores between PHPT patients and normal subjects (147). They did show significant improvements after surgery in social functioning and emotional role function, but no differences were reported in other measures such as depression, somatization, aggression, obsessive-compulsive, interpersonal sensitivity, paranoid ideation and psychoticism. No significant differences between groups were noted in the 3 composite scores (Global Severity Index, Positive Symptom Distress Index, Positive Symptom Total), or in any or the 9 individual or 3 composite scores in the observational group alone over time.

Bolleslev et al reported that the parathyroid patient population scored lower in all psychological domains and the mental component summary of the SF-36 (148). PHPT was associated with more psychiatric symptoms than controls. Two years after parathyroidectomy, there were no improvement in SF-36-assessed physical function, psychological domans of functioning or in psychiatric symptoms. In some of these domains, however, the control group was shown to have deteriorated.

Ambrogini et al. studied 50 patients with asymptomatic PHPT (149) showed minimal but significant baseline differences between PHPT and normal subjects in emotional role function score that improved following surgery. Between-group analysis demonstrated a benefit of parathyroidectomy in bodily pain, general health, vitality and mental health. No differences were noted in any of the other SF-36 or SCL-90 domains between the two groups, and no worsening in the non-operated group was noted.
Walker et al. (150-151) have published their experience and commented on the neurocognitive domains after successful parathyroid surgery. In some, but not in all domains, improvement was seen, with the control population being individuals without primary hyperparathyroidism who had the same test 6 months apart and did not change.

In the study of Roman et al (152), successful parathyroidectomy was associated with improvements in depressive and anxiety symptoms as well as visuospatial and verbal memory.
It is noteworthy that although these 5 studies in which neurocognitive changes were monitoried after successful parathyroidectomy, improvement in certain domains is not consistent from study to study. Although these recent studies are helpful in the overall assessment of this putative extraskeletal manifestation of PHPT, much more work will be needed before one can be sure about the extent to which the neurocognitive functioning is altered at baseline and subsequently improved following successful parathyroidectomy. For this reason, the Workshop Panel does not recommend that neurocognitive function be used as a criterion for decision-making in asymptomatic PHPT.

Vitamin D deficiency

An interesting association has been made between the presence of overt vitamin D deficiency and clinical manifestations of primary hyperparathyroidism (153-154). Years ago, Lumb and Stanbury suggested that primary hyperparathyroidism is worse in the presence of vitamin D deficiency (155). This hypothesis has been extended even to mild asymptomatic primary hyperparathyroidism in which low 25-hydroxyvitamin D levels are associated with increased indices of disease activity (156). The idea is that even in primary hyperparathyroidism, where usual controls of parathyroid hormone secretion are deficient, vitamin D deficiency further fuels the hyperparathyroid state. The logic follows that vitamin D replacement should be associated with better control of the hyperparathyroidism. To address this question, Grey et al. (157) administered vitamin D3 (cholecalciferol) to 21 patients with mild primary hyperparathyroidism whose 25-hydroxyvitamin D levels averaged 20 ng/ml. Repletion consisted of a 50,000 International Unit (IU) capsule weekly for the first month and then 50,000 IU monthly for the next 12 months. Mean 25-hydroxyvitamin D levels after 12 months of vitamin D repletion rose to 31 ng/ml. Serum parathyroid hormone levels fell by an average of 25% but the serum calcium did not change. Although urinary calcium excretion did not change significantly in most individuals, three subjects did develop marked hypercalciuria (.>400 mg/day). There was a tendency for bone turnover markers to fall but only the total alkaline phosphatase activity fell significantly. This report provides evidence for the hypothesis that vitamin D deficiency makes the biochemical features of primary hyperparathyroidism worse but does not give clear guidelines as to how vitamin D should be replaced in these subjects. Most experts would not advocate giving such high doses of Vitamin D3 to these individuals but rather would start with much lower doses, such as 400-1000 IU daily with close monitoring of the serum calcium level. Amstrup et al have reported a relationship between vitamin D deficiency and muscle strength in primary hyperparathyroidism (158). A histomorphometric analysis from bone biopsies of subjects with primary hyperparathyroidism, conducted by Stein et al., showed that the activity of the disease was related to the vitamin D status of the patients (159). Those in the lowest tertile of 25-hydroxyvitamin D demonstrated the most pronounces changes in cortical (reduced) and trabecular (maintained) skeletal compartments. This observation is consistent with other observations that patients with more severe disease have exaggerated characteristics of preserved cancellous bone and reduced cortical bone.

Cardiovascular manifestations

Hypertension has long been regarded to be associated with PHPT. Although older studies have shown a reduction in blood pressure immediately after parathyroidectomy (160-161), the much more common outcome as documented in most studies is that hypertension is not reversible with surgical cure (162). For this reason, hypertension continues to be excluded as an indication for surgery.
There are very limited data regarding coronary artery disease in PHPT and the published studies have been confounded by very high serum calcium level in some cases (163), and/or the presence of traditional cardiovascular risk factures. Similarly, myocardial and valvular calcifications, while clearly demonstrated

in PHPT patients with marked hypercalcemia are less likely to be seen in those with only mildly elevated serum calcium (164-165).

Left ventricular hypertrophy (LVH) has been associated with PHPT in most, but not all (166-167), studies across a wide range of calcium levels. Data suggest that LVH is independent of hypertension, and is instead, associated with the PTH level (165,165-169). Whether or not LVH is reversible in PHPT is key to determining the management implications of these findings. LVH has been found to regress following parathyroidectomy in some, but not all, studies (166-171). Other cardiovascular features which have been monitored such as the metabolic syndrome are not clearly improved after successful parathyroid surgery (172).

Population-based evidence from Rubin et al. supports an association between serum calcium concentration and carotid plaque thickness (173). In the recent study of Walker et al (174), left ventricular mass index was inversely associated with 25-hydroxyvitamin D levels with lower levels associated with worsening function. Carotid intima-medial thickness (IMT), a strong predictor of systemic atherosclerosis and cerebrovascular events, has been studied in patients with severe PHPT. Studies in mild disease show no effect on carotid IMT by the presence of PHPT or its cure. These studies have been limited by small sample sizes and by technical difficulties (175-177).

Vascular dysfunction in patients with severe PHPT has occasionally been shown (176-177), an observation that has also been made, at times, even in those with lower calcium levels [10.7-10.9 mg/dl (2.68-2.73)] (178). In mild PHPT, 2 studies have reported increased vascular stiffness (179-180).

Malignancy

There are several reports of more cancers in patients with primary hyperparathyroidism (181-182). Many of these reports, however, are subject to selection bias. In patients with hypercalcemia detected unexpectedly on a biochemical profile, the most important cause to exclude is hypercalcemia associated with malignancy. Thus, the association between primary hyperparathyroidism and malignancy may be due simply to a more diligent search for cancer in patients with hypercalcemia. Another possible mechanism for a chance association between primary hyperparathyroidism and cancer results from the frequency with which clinically silent thyroid malignancies are found during neck exploration for parathyroid disease (183-184). Wermers et al. have reported, on the other hand, that following the diagnosis of primary hyperparathyroidism, there is no increase in the incidence of malignancy (185).

Mortality

Mortality does not seem to be increased in primary hyperparathyroidism, according to the epidemiology data from the Mayo Clinic experience (185). On the other hand, the Scandinavian and German literature do report increased mortality (186-187). The reason for this difference in mortality figures may again be explained by the extent of disease. Mortality figure from the Scandinavian experience did correlate with the extent of hypercalcemia and the weight of the parathyroid adenoma (188). Also consistent with this idea is the Mayo Clinic experience in which those whose serum calcium was in the highest quartile did have an increased mortality (185). A recent epidemiologica study reported increased mortality and morbidity in “mild hyperparathyroidism” (189) On the whole, these observations suggest that mild, asymptomatic primary hyperparathyroidism is not associated with increased mortality rates. On the other hand, when the disease presents in more symptomatic forms, mortality may be increased.

ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

Although the discussion above covers a host of potential classical and non-classical target organs that can lead to symptomatology, most patients with primary hyperparathyroidism are asymptomatic. They have neither symptoms nor complications that are clearly and commonly associated with hypercalcemia or excessive parathyroid hormone. The preponderance of asymptomatic individuals raises important questions as to how to manage such individuals once the diagnosis is made. There is no controversy about the appropriate decision in individuals who are symptomatic. Surgery is clearly the right choice, unless extenuating medical conditions preclude the surgery. Whether all patients, including those who are asymptomatic and whose hyperparathyroidism was discovered by accident, should have parathyroid surgery is a much more difficult question to address.

INDICATIONS FOR SURGERY IN ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is cured when abnormal parathyroid tissue is removed. Since this is the only definitive approach to primary hyperparathyroidism, surgery is an acceptable approach to this disease even if patients are completely asymptomatic. However, the decision to recommend surgery is tempered by the fact that most patients with primary hyperparathyroidism are asymptomatic. In patients who are asymptomatic, a recommendation for an invasive procedure like surgery is not always met with ready acceptance on the part of the patient or the physician. On the other hand, the alternative, namely to recommend a conservative, non-surgical course, is tempered by the realization that there are few indices that predict who among the asymptomatic are at risk for experiencing complications of this disease (131,190-194) .

The Third International Workshop has led to a revision of the guidelines for surgery in PHPT (2), since the previous two Workshops (195-196). Among those with asymptomatic primary hyperparathyroidism, the following guidelines for surgery are shown in Table 2 and listed here: 1. Serum calcium concentration greater than 1 mg/dl above the upper limit of normal; 2 Creatinine Clearance below 60 mL/min 3. Bone density more than 2.5 standard deviations below standard referent values for sex-matched peak bone mass at any site (T-score <-2.5); 4. Age < 50 years old; 5. Inability or unwillingness to be followed without surgery.

Measurement	**Surgery Recommended[2]**
Serum Calcium	>1.0 mg/dl (0.25 mmol/L) above normal
Creatinine Clearance (calculated)	Below 60m1/min /1.73 m^2)
Bone Mineral Density	T score < -2.5 SD at spine, hip (total or femoral neck) or radius (distal 1/3 site) or presence of fragility fracture
Age	Age < 50 years

4

[1] Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.
[2] If any one of these criteria are met, the patient is considered to be a candidate for parathyroid surgery.

Table 2. Guidelines for parathyroid surgery in asymptomatic primary hyperparathyroidism from the NIH Workshop of 2008[1].Reference #2

It should be emphasized that these are guidelines, not rules. They are subject to modification by the physician and the patient. Some physicians will recommend surgery for all patients with asymptomatic primary hyperparathyroidism; other physicians will not recommend surgery unless clear-cut complications of primary hyperparathyroidism are present. Still others will use other criteria. The patient enters into this therapeutic dialogue as well. Some patients cannot tolerate the idea of living with a curable disease and will seek surgery in the absence of any of the aforementioned criteria. Other patients with coexisting medical problems may not wish to face the risks of surgery even though surgical indications are present.

The 2008 Workshop on Asymptomatic Primary Hyperparathyroidism recognized that some patients who do not meet any guidelines for surgery progress over time to develop one or more criteria More recent data, since the time of the 2002 Workshop confirm this impression (197) . Particularly noteworthy is the natural history study of Silverberg and Bilezikian that extend now to over 15 years (104-105). In this study, the years 10-15 were associated with reductions in cortical bone density and slight increases in the serum calcium concentration. Thus, monitoring is essential if patients are not to have parathyroidectomy. If a patient with asymptomatic primary hyperparathyroidism cannot be followed for any reason, therefore, surgery would seem to be the preferred option.

Monitoring patients with primary hyperpararathyroidism who do not undergo parathyroid surgery.

Currently guidelines for monitoring are shown in Table 3. The serum calcium should be measured, annually. Aso an annual creatinine clearance should be assessed. Bone mineral densitometry should be performed every 1 or 2 years.

Measurement	**Frequency**
Serum calcium	Annually
Crreatinine clearance (calculated)	Annually
Bone Mineral Density	Every 1 – 2 years

Table 3: Management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroid surgery, according to the 2008 NIH Workshop. Reference #2

SURGERY FOR PRIMARY HYPERPARATHYROIDISM.

In some respects the basic principles upon which surgery for primary hyperparathyroidism are based have not changed very much over the years. For example, it is as important now as it was in the past for parathyroidectomy to be performed by surgeons who are highly experienced and skilled in the operation (5,198-199). What has changed over the past decade is the operation itself. The standard operation for parathyroidectomy used to be a full exploration of the neck with identification of all 4 parathyroid glands. The rationale for identifying all four glands is that in 15-20% of patients with sporadic primary hyperparathyroidism, enlargement of more than one gland with four-gland hyperplasia will be present. Recent advances in preoperative imaging modalities by which the most likely cause of primary hyperparathyroidism, namely the single parathyroid adenoma, can be identified as well as the intraoperative use of the rapid immunoassay for parathyroid hormone has changed the way most parathyroid surgeons perform the operation. The minimally invasive parathyroidectomy (MIP) under local anesthesia with intraoperative monitoring of parathyroid hormone before and after removal is the preferred approach of most experts, although there is still debate on this issue (200-203).

MIP is absolutely dependent upon successful preoperative identification of the parathyroid adenoma. The operation consists of identification and removal, under local anesthesia and conscious sedation, of the abnormal tissue without visualization of other glands by the surgeon. Before and after the adenoma is removed, an intraoperative PTH level is obtained to ascertain that the gland removed is the only source of excess PTH (204-205). Such intraoperative PTH assays can be done literally within minutes, in the operating room, and thereby do not extend significantly the duration of the operation. If, within minutes after removal of the adenoma, the intraoperative PTH level falls by greater than 50%, into the normal range, the operation is terminated. If the intraoperative PTH level does not fall by greater than 50% and/or remains above normal, the operation is extended and, if necessary, a full neck exploration is performed to seek other overactive glands (206-207). Success rates for parathyroid surgery with the MIP procedure are just as great as success rates with the classical 4-gland exploration, namely greater than 90% (203,208). The advantages of the MIP procedure relate to the speed of the operation and the much more rapid recovery time in comparison to general anesthesia (201-202). In many centers, the patients is admitted to and discharged from the hospital on the same day.
In the case of parathyroid hyperplasia, options include subtotal parathyroidectomy with removal of 3.5 glands or total parathyroidectomy with immediate autotransplantation of parathyroid tissue into the forearm. If successful, the forearm site provides easy access to the transplanted tissue, should hyperparathyroidism recur. Cryopreservation facilities are necessary for autotransplantation in case the initial graft does not take. This approach is often used in cases of familial hyperparathyroidism in which 4-gland disease is generally the rule (209-211)

PARATHYROID GLAND IMAGING

Pre- operative imaging is of value prior to surgery in the localization of abnormal parathyroid tissue (212-213). The diagnosis of PHPT is based on the biochemical findings and is not affected by the results of the imaging studies. Sestamibi imaging is of value in localizing abnormal parathyroid tissue. The sensitivity and specificity varies among institutions and should be considered in evaluating the results of a study. Civelek et al. evaluated 387 patients prospectively and confirmed a sensitivity of 90% for single adenomas (214). The sensitivity for small adenomas or double adenomas or hyperplasia is much lower. Sestamibi scans are helpful in identifying ectopic tissue, particularly in the mediastinum and can be a useful tool in guiding the surgical approach to parathyroidectomy.

Ultrasound is a non-invasive modality which is easily available at low cost. Co-existing thyroid pathology can be assessed and these results integrated with sestamibi imaging. Sensitivity can range from 42–82% with specificity of approximately 90% (215).

CT scanning of the neck and mediastinum is a valuable tool in assessing the parathyroid anatomy. Four dimensional CT Scans (4DCT) provide additional information of value, in guiding the surgical approach (216). MRI with contrast can be of value for lesions in the mediastium and for those individuals who have persistent disease following parathyroidectomy (217).

Arteriography and selective venous sampling can be of value in those individuals with persistent or recurrent disease and in whom other imaging modalities have not been fruitful in indentifying the abnormal parathyroid tissue (218).

CLINICAL COURSE OF PRIMARY HYPERPARATHYROIDISM

The change in clinical presentation of primary hyperparathyroidism from a symptomatic to an asymptomatic disease has required longitudinal studies to assess the extent to which any features progress or complications appear over time. Attempts to document the natural history of primary hyperparathyroidism extend back to an earlier generation through the work of Sholtz and Purnell (219). With allowance for confounders that weakened conclusions that could be drawn from their longitudinal study, nevertheless, they did demonstrate that primary hyperparathyroidism is not necessarily a progressive disease. The first truly long-term prospective study of the natural history of primary hyperparathyroidism with or without surgery has been provided by Silverberg and her colleagues over a 10-15 period of surveillance (104-105).

Natural History Without Surgery

About 40-50% of patients with asymptomatic primary hyperparathyroidism will not meet any guidelines for surgery. Although one could justify the recommendation for surgery, even without any guidelines being met, many of these subjects and their physicians are reluctant to recommend the surgical approach. Data are now available on these patients with mild, asymptomatic primary hyperparathyroidism who have been followed for up to 15 years without surgery or specific medical therapy (104-105). Biochemical abnormalities associated with primary hyperparathyroidism are stable during long-term follow-up of mild, asymptomatic patients over the first 10 years. The serum calcium, however, does tend to increase slightly during the years 10-15. There is no evidence that mild primary hyperparathyroidism is associated with progressive renal impairment, at least as measured by the serum creatinine, blood urea nitrogen, or creatinine clearance. Over a 10-year period, yearly bone mass measurements did not reveal that the group as a whole showed any declines at the lumbar spine, hip, or distal radius (Figure 2). The individual data from the 10-follow up study however do indicate that about 25% of subjects show evidence of progressive disease. Four percent of patients developed substantial worsening of their hypercalcemia (serum calcium > 12 mg/dl) and 15% developed marked hypercalciuria (urinary calcium excretion > 400 mg/day). Approximately 12% of patients demonstrated declines in bone mineral density to the point where they met NIH guidelines for surgery. A total of 37% of subjects followed for up to 15 years met one or more indications for parathyroid surgery. There were no clinical, biochemical, or densitometric predictors of disease progression that could be identified, except for the observation that patients at risk were younger, on average, than those who did not progress over time (52 vs. 60 years old).

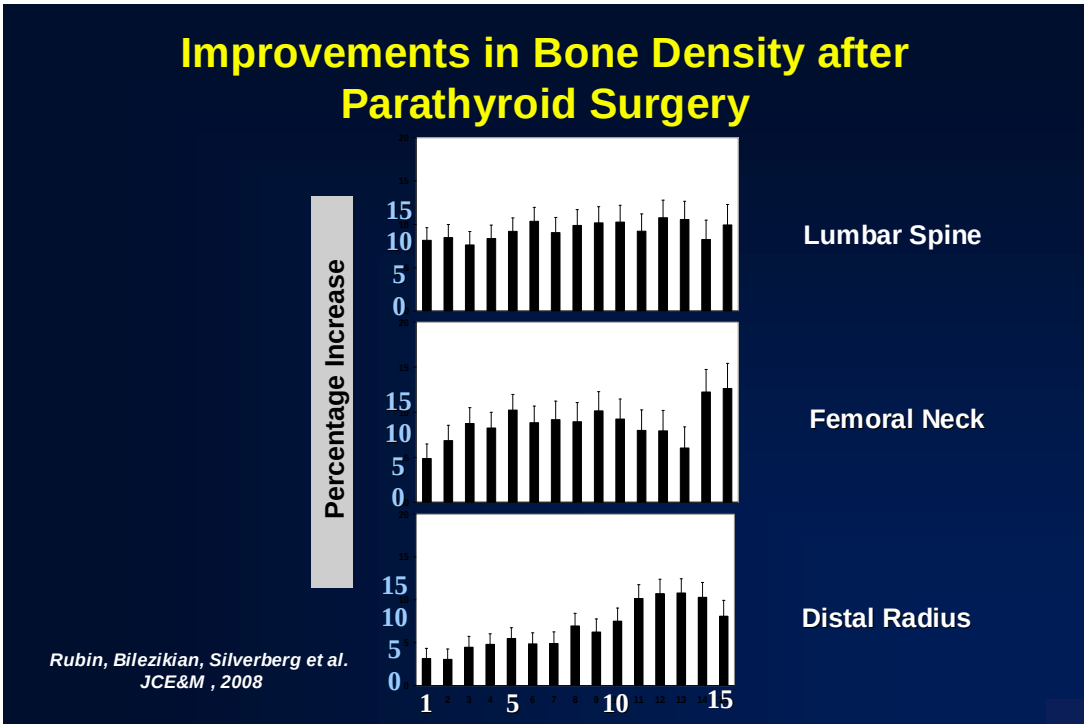

Figure 2. Conservative vs Surgical Management of Primary Hyperparathyroidism: changes in bone mineral density. Data shown are the cumulative percentage changes from baseline over 15 years of follow-up in patients who did not undergo parathyroidectomy and in those who underwent parathyroidectomy. (Reprinted with permission from reference #105)

More recent data extending these results to 15 years indicate that bone mineral density at the hip and distal radius eventually does decline as a group (105). The lumbar spine bone density remains stable. These recent observations suggest that over time the proclivity of parathyroid hormone to be catabolic at cortical sites eventually surface in some patients. Alternatively, the need for such long term surveillance may highlight the slow but progressive nature of the bone disease in this disorder. The relative stability of bone mineral density at the lumbar spine is supported by histomorphometric data from bone biopsies showing in primary hyperparathyroidism that age-related declines in indices of trabecular connectivity are not evident (220). Thus, despite advancing age, patients with primary hyperparathyroidism maintain microarchitecture of cancellous elements.
In all patients who met surgical guidelines, such as nephrolithiasis, and chose not to undergo parathyroid surgery, the disease clearly continued to progress as demonstrated by recurrent nephrolithiasis or other complication of primary hyperparathyroidism. Although only few patients in this category were followed without surgery, the fact that all of them showed evidence for progression argues that these patients are best advised to under parathyoidectomy.

Natural History With Surgery

Following parathyroid surgery, there is a prompt return to normal of serum and urinary calcium levels along with the parathyroid hormone level per se. Studies of bone markers are limited but indicate a

reduction in these markers of bone turnover following successful surgery. Although the choice of markers in individual studies varied, our group (221), Guo et al. (222) and Tanaka et al. (223) all report declining levels of bone markers following surgery. Data are also available concerning the kinetics of change in bone resorption versus bone formation following parathyroidectomy. Markers of bone resorption decline rapidly following successful parathyroid surgery, but indices of bone formation decline more gradually (221). Urinary pyridinoline and deoxypyridinoline fell as early as two weeks post-operatively, preceding reductions in alkaline phosphatase. Similar data were reported by Tanaka et al. (223), who demonstrated a difference beween changes in osteocalcin and urinary N-telopeptide following parathyroid surgery; and Minisola et al. who reported a decrease in bone resorption markers without any significant change in alkaline phosphatase or in osteocalcin (224). The persistence of elevated bone formation markers coupled with rapid declines in bone resorption markers indicates a shift in the coupling between bone formation and bone resorption toward an anabolic accrual of bone mineral after surgery.

In fact, bone density does increase following parathyroid surgery (104-105,148-149,225-226). Parathyroid surgery leads to a 10-12% increase in bone density at the lumbar spine and hip (Figure 2). The increase at the lumbar spine and femoral neck is prompt, with the greatest increment in the first postoperative year. Increases at the lumbar spine, hip and distal radius are sustained over 10-15 years following surgery, despite the tendency of advancing age to be associated with a decline in bone mass over time. Lumbar spine and femoral neck bone density increase to the same extent in a subgroup of postmenopausal women with primary hyperparathyroidism who underwent parathyroid surgery. Part of increase in bone density at these sites is related to remineralization of the enlarged remodeling space. Other potential explanations for the postoperative increase in bone density include the possibilities that normal pulsatility and amplitude of the secretory patterns of parathyroid hormone are restored. In patients who have vertebral osteopenia or frank osteoporosis (15% of the population of our hyperparathyroid subjects), the postoperative increase in bone density is even greater than the group as a whole, reaching an average of 20% higher after surgery (88).

The capacity of the skeleton to restore itself is seen dramatically in young patients with severe primary hyperparathyroidism. Kulak et al. (227) reported 2 patients with osteitis fibros cystica who experienced increases in bone density that ranged from 260 to 430%, 3-4 years after successful surgery.

An important question yet to be resolved is whether the postoperative improvement in bone mineral density is associated with an increase in bone strength and a reduction in fracture incidence. The complex relationship between bone strength and bone density in primary hyperparathyroidism, as already noted, involves other skeletal properties besides bone mineral density, such as microarchitecture and bone size. It is clear that parathyroid hormone is affecting these properties of bone in the disease that may well tend to counteract the impression that fracture risk is increased in primary hyperparathyroidism. On the other hand, after parathyroid surgery, it is not known to what extent these other properties of bone may also change and conceivably mitigate or augment the salutary effects of bone mineral density. Moreover, since it is now clear that changes in bone mineral density in the context of therapeutics for osteoporosis do not account for more than a small component of the reduction in fracture incidence, a similar loose relationship could exist in terms of bone mineral density and fracture risk after successful parathyroidectomy.
In patients who underwent parathyroid surgery because of their renal stone disease, there were no recurrences of nephrolithiasis over a decade. These observations are consistent with other published reports in which a reduction in stone incidence of 90% is typically seen after successful surgery. The 5-10% of patients who continue to form stones after parathyroidectomy may well have a non-parathyroid cause for their stone disease, which persists despite cure of their primary hyperparathyroidism (228-229). Alternatively, previous stone disease could have damaged the kidney such that the local environment continues to be hospitable for recurrent stones even after successful surgery.

The course of neurocognitive and cardiovascular aspects of primary hyperparathyroidism have been covered earlier.

NON-SURGICAL APPROACHES TO PRIMARY HYPERPARATHYROIDISM

Many patients who not meet guidelines for surgery are followed conservatively (230). General management principles as well as specific pharmacologic approaches are covered in this section. Patients should be encouraged to maintain a normal intake of calcium, despite the temptation place constraints on dietary calcium. Calcium excretion is not different when individuals on high or low calcium intakes are compared (231). On the other hand, in those with elevated levels of 1,25-dihydroxyvitamin D3, high calcium diets can be associated with worsening hypercalciuria (232). This observation suggests that dietary calcium intake in primary hyperparathyroidism can be liberalized to 1000 mg/day if 1,25-dihydroxyvitamin D3 levels are not increased, but should be more tightly controlled if 1,25-dihydroxyvitamin D levels are elevated. However, there is no evidence in individuals without a history of nephrolithiasis, that they are more at risk for a kidney stone if hypercalciuria is present.

Phosphate

Oral phosphate can lower the serum calcium by up to 1 mg/dl (231). Problems with oral phosphate included limited GI tolerance, possible further increase in parathyroid hormone levels, and the possibility of soft tissue calcifications, after long term use (231). This agent is no longer advisable as a chronic treatment for primary hyperparathyroidism.

Estrogen

Although the beneficial effects of estrogen therapy in primary hyperparathyroidism are well documented in the literature (233-235**),** risks associated with estrogen use have also been well publicized (236**).** In addition, the amount of estrogen required to reduce the serum calcium in primary hyperparathyroidism is higher than most tolerate, although some positive results have been observed with lower doses (237). Nevertheless, among postmenopausal women who are not candidates for parathyroid surgery or refuse this option, and will agree to take estrogen, it remains a reasonable alternative. Estrogen use is associated with a 0.5 to 1.0 mg/dl reduction in total serum calcium levels in postmenopausal women. Parathyroid hormone levels do not change. Estrogen-treated patients also show a salutary effect on BMD at the femoral neck and lumbar spine (235). This makes estrogen replacement therapy an attractive approach in the postmenopausal woman with very mild primary hyperparathyroidism, who do not have any contraindications to such therapy.

Selective Estrogen Receptor Modulator (SERM).

The SERM, raloxifene is a potential alternative to estrogen. Rubin et al. (238) studied 18 postmenopausal women with primary hyperparathyroidism. They were randomly allocated to an 8-week course of raloxifene (60 mg/day) or placebo. There was a 4-week follow up period off therapy. In the raloxifene group, the average serum calcium fell significantly by about 0.5 mg/dL. The placebo group did not show any change in serum calcium over this period of time. Along with the reduction in the serum calcium concentration, bone turnover markers, osteocalcin and N-telopeptide, significantly fell. During the 4-week wash out period when the subjects on raloxifene were withdrawn, serum calcium concentration and bone turnover markers returned to baseline values. Raloxifene administration was not associated with any changes in serum parathyroid hormone or in urinary calcium excretion. In an open pilot study of only 3 patients, Zanchetta and Bogado (239) showed a similar reduction in serum calcium with raloxifene. They also were able to show increases in bone mineral density in their subjects. Clearly, these are promising data but more extensive, controlled studies are needed.

Bisphosphonates.

The conceptual basis for expecting that bisphosphonates have potential as a medical approach to primary hyperparathyroidism is due to their antiresorptive properties. In primary hyperparathyroidism, even when completely asymptomatic, bone turnover is increased (240)**.** Although they do not affect parathyroid hormone secretion directly, bisphosphonates could reduce serum and urinary calcium levels. An additional benefit would be to increase bone mineral density. Early studies with the first generation bisphosphonates (etidronate aand clodronate) were disappointing (241-242). The aminosubstituted bisphosphonates have been studied more extensively. In a very short 7-day study of 19 patients with primary hyperparathyroidism, risedronate lowered the serum and urinary calcium as well as hydroxyproline excretion significantly while the parathyroid hormone concentration rose (243). More extensive studies have been conducted with alendronate. A randomized, controlled study of 26 patients with primary hyperparathyroidism (244) evaluated effects on bone mineral density after a two-year study with 10 mg every other day (5mg/d) of alendronate. Alendronate was associated with a reduction in bone turnover and an increase in bone mineral density over baseline by 8.6+/-3.0%, in the hip by 4.8+/-3.9% and in the total body by 1.2+/-1.4%. The control group that did not received alendronate lost about 1.5% BMD in the femoral neck. Hassani et al. investigated 45 patients with asymptomatic primary hyperparathyroidism with alendronate, 10 mg daily in a study that was not randomized (245). Nevertheless, the results also showed that alendronate was associated with increases in bone mineral density of the lumbar spine and femoral neck. Three well-controlled studies following up on these experiences with alendronate have been even more impressive (246-248). The study by Khan et al. (248) was a randomized, double-blinded study of daily alendronate versus placebo in 44 patients with mild, asymptomatic primary hyperparathyroidism. After 1 year, the placebo group was crossed over to alendronate treatment while the group initially assigned to alendronate continued on the bisphosphonate for another year. After 1 year of alendronate, there was a significant 5.3% increase in lumbar spine, increasing further to 6.85 % by year 2. Total hip bone mineral density increased by 3.7% in year 1 and by 4.01 % in year 2. There was no significant change in distal radius bone mineral density. When the placebo group, that did not show any change in bone density at any site after the first year, was crossed over to alendronate in year 2, the increase in bone mineral density matched the increase after 1 year in the group that was initially assigned to drug (Figure 3). The bone turnover markers, N-telopeptide and bone-specific alkaline phosphatase activity fell by over 50%. There were no changes in ionized calcium, phosphorus or PTH. The results from the subgroup of men treated with alendronate were similar (249-250). The experience of Chow et al. (249) in their 1-year randomized, placebo-controlled study is remarkably similar to the experience of Khan et al. except that there was a significant alendronate-associated reduction in the serum calcium concentration, by 0.34 mg/dL.

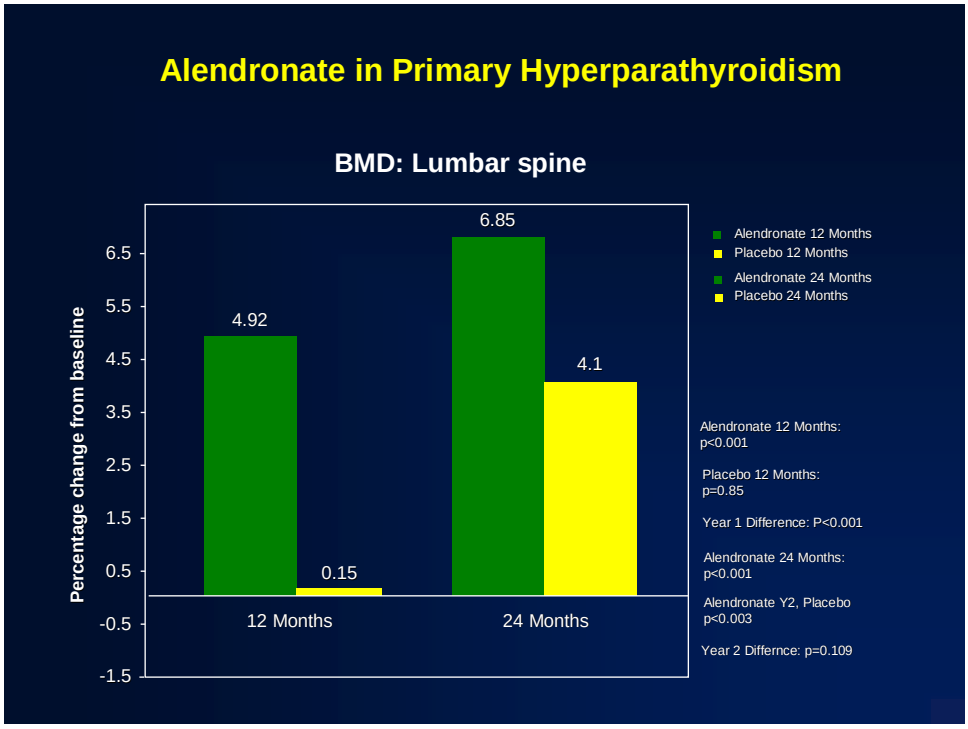

Figure 3. The effect of Alendronate on bone mineral density in primary hyperparathyroidism. With alendronate, bone mineral density increases significantly after 1 year, while the placebo group shows no change until it is crossed over to alendronate in year 2.
(Modified from reference #248).

The cumulative investigative experience with alendronate in primary hyperparathyroidism suggests a use for this drug in subjects whose bone density is low, but not in the osteoporotic range. Such individuals might be at substantial risk for fracture because they have other risk factors. If these individuals do not meet any criteria for parathyroid surgery, it would seem reasonable to consider alendronate. This decision should be made with the full realization that no bisphosphonate has received yet an indication for use in primary hyperparathyroidism by the FDA.

Calcimimetics.

A more targeted approach to the medical therapy of primary hyperparathyroidism is to interfere specifically with the production of parathyroid hormone. A new class of agents that alters the function of the plasma membrane cellular calcium sensing receptor exemplifies this concept. By binding to a site different from the calcium binding site per se, these agents increase the affinity of the receptor for extracellular calcium. These calcimimetics.would be expected to increase the signal generated by the calcium-calcium receptor complex and lead to an increase in intraceullar calcium. An increase in the intracellular calcium should inhibit the synthesis and secretion of parathyroid hormone from the parathyroid cell. The phenylalkylamine (R)-N-(3-methoxy-alpha-phenylethyl)-3-(2-chlorophenyl)-1-propylamine [R-568], was the first such calcimimetic compounds to be tested clinically (251). In a pilot study by Silverberg et al., it was shown to reduce serum calcium concentration and parathyroid hormone

in a dose-related fashion among postmenopausal women with primary hyperparathyroidism (252). A more potent calcimimetic, cinacalcet hydrochloride has replaced R-568 and has been the subject of a more extensive series of human studies. Cinacalcet hydrochloride has been approved by the FDA in the management of the hyperparathyroidism associated with renal failure and parathyroid cancer (253) with mounting evidence for its utility in primary hyperparathyroidism (254). In fact, it has been approved for use in primary hyperparathyroidism in Europe and, more recently, in the United States. Shoback et al. (255) studied cinacalcet hydrochloride in 22 patients with primary hyperparathyroidism. In this dose-ranging study, patients were given placebo or drug in amounts of 30, 40, or 50 mg twice daily for 15 days. In all dose groups, except placebo, cinacalcet hydrochloride was associated with a normalization of the serum calcium after the second dose and remained normal values for the entire 2-week period. Maximal reductions in parathyroid hormone, over 50%, occurred 2-4 hours after dosing. There were no significant changes in urinary calcium excretion. Peacock et al. have followed this pilot study with a longer trial in which subjects were treated for 3 years (256). Most patients treated with cinacalcet hydrochloride achieved the primary endpoint, namely normocalcemia (Figure 4). The serum calcium remained normal for the entire duration of the study. This experience has now been extended to 5 years, again with maintenance of normal calcium levels throughout (257). Cinacalcet has been shown to be effective in primary hyperparathyroidism across a spectrum of severity (258) as well as in intractable disease (259).

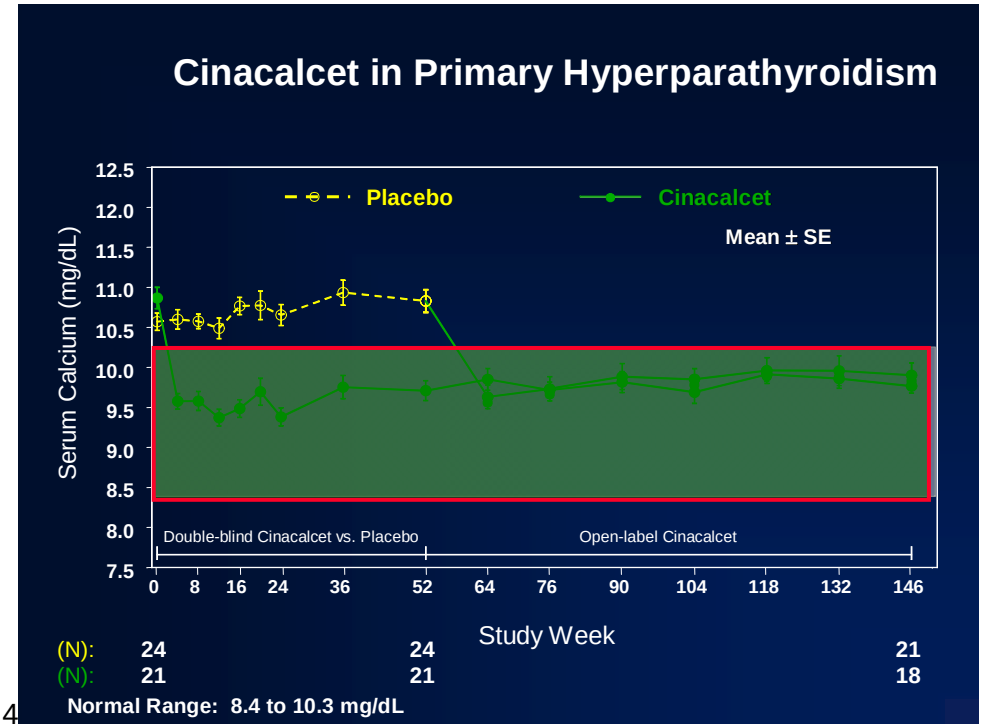

Figure 4. Cinacalcet in primary hyperparathyroidism. Cinacalcet is associated with a rapid and sustained normalization of the serum calcium concentration. (from reference #256 with permission).

Of particular interest is the idea that if the neuropsychological and cognitive abnormalities associated with primary hyperparathyroidism are truly related to the disease, then normalization of these indices could conceivably lead to improvement in such symptoms. If a rigorous study conducted to test for this possibility is positive, then cinacalcet hydrochloride could conceivably be used to control such symptomatology. It could even be used as a trial to forecast whether after successful parathyroid surgery, such symptoms would remit.
The calcimimetics have also been studied in parathyroid cancer, a rare but often fatal disorder in which the hyperparathyroidism, and not the tumor per se, is the major problem. The first experience with a patient with end-stage parathyroid cancer and intractable hypercalcemia was with the first generation calcimimetic, R568 (260). On R568, the patient's hypercalcemia remitted from 17 mg/dL to 11-12 mg/dL and was controlled at this level for 2 years. A much larger experience with cinacalcet hydrochloride has been gained in parathyroid cancer by Rubin et al. (261). In a study of 21 patients with parathyroid cancer, she showed that the serum calcium could be controlled in most patients although doses up to 90 mg four times daily were needed. The parathyroid hormone did not uniformly fall; in some patients, there was even an increase in parathyroid hormone, despite the reduction in the serum calcium. Additional studies have provided further evidence for the effectiveness of cinacalcet hydrochloride in parathyroid cancer and in severe primary hyperparathyroidism (262-263).

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