Therapeutic Controversies in Primary Hyperparathyroidism

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To Treat or Not To Treat: Conclusions from the NIH Consensus Conference

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Parathyroidectomy remains the appropriate therapy for primary hyperparathyroidism when it presents as the symptomatic disease first described in the 1930’s. In the United States today, however, this classical form of primary hyperparathyroidism is rarely seen. Instead, we typically see a disorder that is asymptomatic in 80% of cases. Even in patients with “symptomatic” primary hyperparathyroidism (most often characterized by nephrolithiasis), marked hypercalcemia and overt skeletal involvement (osteitis fibrosa cystica) are uncommon. The evolution of primary hyperparathyroidism from a disabling disease to a largely asymptomatic one has led to uncertainty regarding appropriate therapy for this disorder. This, in turn, led in 1990 to a National Institutes of Health-sponsored Consensus Development Conference, which concluded that there were categories of patients over the age of 50 yr who can be safely followed without surgery. Since then, that view has been challenged and reports favoring surgery in all patients have appeared. We present the view, held by many, that although parathyroidectomy remains the only definitive therapy for primary hyperparathyroidism, surgical intervention is not necessary in all patients. The reasons for this view will be summarized.

Clinical Presentation of Primary Hyperparathyroidism

Classical primary hyperparathyroidism was formerly associated with nephrolithiasis in over one half of cases, and the bone disease, osteitis fibrosa cystica, in approximately one quarter. The latter, characterized by bone cysts and brown tumors of the long bones, subperiosteal resorption of the distal phalanges and clavicles, and “salt and pepper” demineralization of the skull, was easily detected by x-ray. Today, kidney stones are seen in fewer than 20% of patients with primary hyperparathyroidism. Even more drastic reductions have been noted in the incidence of osteitis fibrosa cystica, which is seen in less than 5% of patients. The clinical presentation of primary hyperparathyroidism has evolved from a symptomatic to an asymptomatic disorder.

Patients with primary hyperparathyroidism today present most commonly with mild elevations of the serum calcium concentration along with increased parathyroid hormone levels. With the more sensitive assays based on double antibody methods (immunoradiometric [IRMA] and immunoluminometric [ICMA] assays), parathyroid hormone levels are frankly elevated in 85–90% of patients with primary hyperparathyroidism. Even in patients whose parathyroid hormone levels are “normal,” they are clearly inappropriate to the setting of hypercalcemia in which the parathyroid glands should be suppressed. In this era of cost consciousness, the immunoassay for parathyroid hormone is the standard diagnostic test in this disorder. Other biochemical characteristics are less important for their diagnostic value. Serum phosphorus concentration is generally in the lower range of normal (frankly low in only one quarter of all patients); urinary calcium excretion is in the higher range of normal (elevated in approximately 40%). Vitamin D concentrations tend to reflect the physiological actions of parathyroid hormone, which is to facilitate the renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. 25-hydroxyvitamin D levels tend to be in the lower end of the normal range, while 1,25-dihydroxyvitamin D levels are in the higher range of normal. Frank elevations of 1,25-dihydroxyvitamin D are found in only one third of patients.

While osteitis fibrosa cystica is a rarity, there is ample evidence of skeletal involvement in patients with modern primary hyperparathyroidism. Biochemical markers of bone formation such as serum alkaline phosphatase activity and osteocalcin, and urinary markers of bone re-

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Hyperparathyroidism, parathyroidectomy is indicated. 25% of patients who exhibit signs or symptoms of primary hyperparathyroidism more often than one would expect surgery. Identified as important risk factors for progressive disease were: significant hypercalcemia (>12 mg/dL), marked hypercalciuria (>400 mg/day) or unexplained renal insufficiency, or an episode of acute primary hyperparathyroidism. Included also on this list of recommendations for surgery were reduced cortical bone density (>2 sd below age-matched norms, as measured at the distal forearm, 1/3 site). Also those who are relatively young (less than 50 yr) were considered candidates for parathyroidectomy.

To Treat Not To Treat: New Data 1990–1998. Persistent Controversy

Recent interest has focused on identifying which patients with asymptomatic primary hyperparathyroidism can be safely followed without surgery. It is important to identify two groups of asymptomatic patients in this regard. First, there are patients who are at risk for complications of the disease and who thus would benefit from surgical intervention and cure. Second, there are patients with few or no risk factors for progression of their disease. This second group might be expected to do well with long-term conservative management without surgery. Much of the available information that addresses these questions is from an ongoing longitudinal study led by two of us (J.P.B., S.J.S.), sponsored by the National Institutes of Health.

If one applies National Institutes of Health Consensus Conference guidelines, as we have to our patients with primary hyperparathyroidism, the percentage of patients who are surgical candidates increases from the 20% who are symptomatic, to approximately one half of all patients with the diagnosis of primary hyperparathyroidism. Thus, about two-thirds of patients who are surgical candidates are asymptomatic. Surgery leads to restoration of normal serum calcium, as well as to normalization of all other biochemical indices, including parathyroid hormone levels and markers of bone turnover. In addition, bone mineral density increases, particularly at the lumbar spine and femoral neck, where a mean rise of 12% in bone mass is seen after parathyroidectomy.

Over the past decade we have recognized several additional groups of patients who may benefit from parathyroidectomy. Individuals who have vertebral osteopenia at the time of presentation constitute one such group. This is an unusual presentation because of the tendency of parathyroid hormone to preserve cancellous bone. Nevertheless, primary hyperparathyroidism can affect cancellous sites as well as cortical sites. In addition, menopausal women can have other reasons for experiencing vertebral bone loss. Longitudinal follow-up of these patients with vertebral osteopenia reveals dramatic improvement (up to 20%) in bone density after parathyroidectomy.

This figure includes those with nephrolithiasis, as well as the unusual patient with osteitis fibrosa cystica, or classical neuromuscular symptoms of primary hyperparathyroidism. The National Institutes of Health Consensus Conference on the management of asymptomatic primary hyperparathyroidism addressed issues related to who among the asymptomatic should undergo parathyroid surgery. Identified as important risk factors for progressive disease were: significant hypercalcemia (>12 mg/dL), marked hypercalciuria (>400 mg/day) or unexplained renal insufficiency, or an episode of acute primary hyperparathyroidism. Included also on this list of recommendations for surgery were reduced cortical bone density (>2 sd below age-matched norms, as measured at the distal forearm, 1/3 site). Also those who are relatively young (less than 50 yr) were considered candidates for parathyroidectomy.
Consideration of parathyroidectomy should also be given to patients with primary hyperparathyroidism who are vitamin D deficient. Vitamin D deficiency is associated with a worsening of primary hyperparathyroidism due to loss of the regulatory effects of 1,25-dihydroxyvitamin D on the parathyroid hormone gene. Efforts to correct this deficiency by vitamin D replacement in the face of hypercalcemia and/or hypercalciuria can be risky. Parathyroidectomy becomes a more attractive option in such cases. Finally, preliminary data indicate that parathyroidectomy may protect women from perimenopausal bone loss that seems to accelerate, despite the presence of parathyroid hormone, at this time. If confirmed, this would support consideration of surgery in perimenopausal women with primary hyperparathyroidism.

The clear benefit derived by patients who undergo parathyroidectomy raises some important questions. Can one be sure that patients who do not meet surgical guidelines are unharmed without surgery? Earlier data supporting an increase in cardiovascular mortality and recent reports from Steffenelli et al. on cardiac calcification in primary hyperparathyroidism must be considered. The increase in valvular and left ventricular calcification, along with septal and left ventricular hypertrophy seen in these patients, is not applicable to patients typically seen in the United States, where the disease is less severe than in those patients reported by Steffenelli et al. With regard to reports of increased overall mortality with cardiovascular etiologies assuming a prominent role, the recent study of Wermers et al. clearly dispels that notion. In this study of all residents of Rochester, Minnesota diagnosed with primary hyperparathyroidism between 1965 and 1992, many patients with mild hypercalcemia were observed with no intervention, thus allowing an assessment of risk of death. In this cohort, there was no evidence that primary hyperparathyroidism had any adverse effect on survival.

Data from our group and others show that biochemical and bone densitometric indices of primary hyperparathyroidism in asymptomatic patients who do not meet any guidelines for surgery are stable, in general, with up to a decade of observation. This suggests that those with very mild disease (i.e., serum calcium <1 mg/dL above normal, normal urinary calcium, and adequate bone density) can be followed safely.

While the population of patients with mild asymptomatic primary hyperparathyroidism can be safely followed without intervention, close follow-up is essential. Individual patients can have worsening hypercalciuria, and in a small percentage of patients, bone density may decrease over time. All patients should be evaluated at least twice yearly, including serum calcium levels. Urinary calcium excretion and bone mineral density should be assessed annually.

Patients who are followed without parathyroidectomy should also adhere to certain general medical principles. They must remain well hydrated and avoid immobilization. They should avoid thiazide diuretics, which can lead to further increases in serum calcium. There is no evidence that restricting dietary calcium intake has any effect on serum calcium levels in patients with primary hyperparathyroidism. Indeed, there is concern that low dietary calcium intake can be associated with further stimulation of the hyperparathyroid state. In a study of 71 patients with primary hyperparathyroidism, dietary calcium had no effect on serum calcium or parathyroid hormone levels, urinary calcium excretion, or bone mineral density at any site. However, concern about hypercalciuria in the subset of patients with frankly elevated levels of 1,25-dihydroxyvitamin D has led to the recommendation that standard recommendations for calcium intake (1200 mg daily in postmenopausal women) be reserved for patients with primary hyperparathyroidism whose levels of 1,25-dihydroxyvitamin D are normal.

At this time, options for management have been surgery or no surgery. Are there pharmacological approaches to patients with primary hyperparathyroidism? The use of oral phosphate has been limited by its lack of efficacy, risk of metastatic calcification, and gastrointestinal intolerance. Estrogen is useful in postmenopausal women with very mild primary hyperparathyroidism by lowering serum calcium by approximately 0.5 mg/dL, but estrogen has no effect on parathyroid hormone levels. There are no data on the effectiveness of Selective Estrogen Receptor Modulators (such as raloxifene) on serum calcium or parathyroid hormone levels in this disorder. Bisphosphonates, such as etidronate and dichloromethylene diphosphonate, have not been useful in this disorder, and alendronate has not yet been evaluated systematically.

To date, there is no available medical therapy that specifically targets the abnormality in primary hyperparathyroidism, namely, hypersecretion of parathyroid hormone. The identification of molecules that act as calcium receptor-agonists in parathyroid cells has led to the development of a means of regulating hormone secretion from these cells. By mimicking the effect of extracellular calcium, these agents inhibit the secretion of parathyroid hormone. One such calcimimetic agent, R-568, has been studied in postmenopausal women with primary hyperparathyroidism. Administration of R-568 led to a decrease in both parathyroid hormone and serum calcium levels. This class of compounds holds significant promise for the future.

The Future

When asymptomatic primary hyperparathyroidism was first recognized as a common condition nearly three decades ago, there was speculation, but no data, about the need for parathyroidectomy in this group. Although we now feel that it is safe to follow certain patients with mild disease, our knowledge remains incomplete. Longitudinal data are needed to allow a more complete understanding of which patients do or do not benefit from parathyroidectomy. Finally, the emerging importance of targeted and specific therapeutic agents for the treatment of primary hyperparathyroidism will raise new questions about the exclusive role of surgery as the only definitive way to treat this common endocrine disorder.
The changing spectrum of PHPT: Earlier detection vs. milder disease

Our perception of PHPT has been radically altered by the development of automated chemistry panels, including serum Ca measurements and modern serum PTH assays. What amounts to an unintentional national screening program has detected many cases of hypercalcemia. Most are due to primary hyperparathyroidism, confirmed by elevated or non-suppressed serum PTH levels. The prevalence of PHPT in the general population is now estimated to be 1 or more per thousand (1–4), and among older women it appears to exceed 1% (3–6). However, the number of patients presenting with classical symptoms has not increased in proportion to the total. Instead, the spectrum of PHPT has greatly expanded, encompassing patients with classical features who are detected by screening rather than clinical presentation, patients with nonclassical symptoms, or physiological sequelae detectable only by biochemical measurements and bone densitometry, and patients in whom clinical consequences are minimal or not demonstrable. As this phenomenon began, it was unclear how many patients would progress to classical features and how many had intrinsically less aggressive disease. It was also unclear whether nonclassical or “asymptomatic” PHPT would impose additional health risks with less apparent relationship to known PTH effects. Interestingly, a recent study suggests that the apparent incidence of PHPT, having risen sharply, has subsequently declined. This may be the result of “sweeping” the population of prevalent but previously unrecognized cases, but the authors raise the possibility of a decline in the true incidence (7). Looking forward, it may be that efforts to reduce the use of automated chemistry panels will tend to decrease ascertainment of cases in which overt symptoms are not prominent.

Is there progression of nonclassical PHPT? the challenge of follow-up

Can we assess the risk of progression of unoperated mild asymptomatic PHPT to more classical disease, or perhaps to a decision point for surgery, without development of overt complications? Although patients had somewhat reduced initial bone mass (8–11), and up to 20% of subjects in some

Classical PHPT

Primary hyperparathyroidism is a classical endocrine disorder resulting from adenomatous or hyperplastic glands, which secrete excess hormone, producing clinical signs and symptoms. For many years, the diagnosis of primary hyperparathyroidism typically resulted from the investigation of a symptomatic patient. Classical PHPT is characterized by frank hypercalcemia and hypercalciuria, often with phosphate depletion, as well as clinical features such as urolithiasis, renal injury, and skeletal effects ranging from osteoporosis to osteitis fibrosa. Gastric hypersecretion with peptic ulcer disease, pancreatitis, and severe constipation are described, as are psychiatric disturbances. Surgical cure generally produces gratifying results, leading to the general recommendation of parathyroidectomy in such cases of “kidney stones, aching bones, abdominal groans, and psychic moans.”

Who needs parathyroid surgery? the case for parathyroidectomy in nonclassical primary hyperparathyroidism

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The clinical spectrum of primary hyperparathyroidism (PHPT) includes not only patients with the classical clinical presentation, but also many with nonclassical symptoms, or adverse metabolic effects without overt symptoms, as well as those with minimal clinical manifestations. Apart from the direct effects of PHPT on health, even mildly affected patients may be at increased risk of mortality associated with cardiovascular disease and malignancies. Parathyroidectomy is the only effective treatment for this condition and is generally recommended when clinical sequelae are apparent. Taking into account the subtle adverse effects of PHPT, the excellent surgical results in experienced hands, and the difficulty of maintaining follow-up, the weight of evidence generally favors parathyroidectomy by a skilled surgeon even in nonclassical cases. If surgery is deferred, vigilant follow-up is mandatory.

General references

studies had urolithiasis (8, 11), a number of authors have reported a relatively benign course for most unoperated nonclassical patients over observation periods of several years (9, 10). In view of the expected lifelong exposure of unoperated patients, an extremely long observation period would be required to detect low rates of progression to a more classical clinical profile or gradual effects on organ function. In some reports of adverse outcomes it is difficult to isolate the results for those patients with relatively benign initial presentations (12). Some authors have reported substantial rates of subtle symptoms and/or incident complications (13, 14). Although overt complications occasionally occur (13), renal failure and progressively increasing hypercalcemia are infrequent. Controlled studies describe progressive decreases in bone mineral density, although results of uncontrolled studies have varied (see Bone Metabolism below).

An important prospective study of patients with well-defined mild PHPT conducted at the Mayo Clinic (14) illustrates many of the challenges of nonoperative management of this condition. Of 147 patients entered into the study, 5 actually exceeded the severity criteria at entry, 16 had undergone unsuccessful prior surgery, including 1 who had familial benign hypercalcemia, and in 12 the diagnosis of PHPT was doubtful, as their abnormal findings resolved without intervention. Thirty-two died, and 19 were lost or refused follow-up. Of the 63 previously unoperated subjects with definite PHPT and known outcomes after 10 yr, 33 had undergone surgery, and 3 more had reached criteria for referral. Of the remaining 27 patients, 6 had not completed all the testing specified by the protocol. Another study followed 174 patients who met the authors’ criteria for asymptomatic disease (10). The authors did not find evidence of progressive disease, but stated that only 80 patients had adequate follow-up. Both studies exemplify the difficulties of long-term monitoring, and the Mayo study demonstrated a relatively high rate of eventual surgery in those patients whose follow-up was complete.

**PHPT with Adverse Metabolic Effects in Asymptomatic Patients**

**Bone metabolism.** Patients without classical symptoms may well have adverse metabolic effects of PHPT. Among the best characterized of these is loss of bone mass. Osteopenia is well-described in studies of “asymptomatic” PHPT (8–11). Typically, patients with definite osteoporosis (defined by clinical fractures or very low bone mineral density) are excluded from such studies, but most of the included patients’ bone density measurements nevertheless fall into the lower half of the pertinent reference ranges. In controlled studies, patients with PHPT lost bone mass more rapidly than normal subjects (15, 16), whereas the results of uncontrolled studies have varied (10, 17, 18). Several groups (9, 19–22) have found that bone mineral density increases substantially after parathyroidectomy, although the entire deficit is generally not repaired. In a small but meticulous investigation of patients who met strict criteria for asymptomatic PHPT, Kaplan et al. (21) found subtle but potentially deleterious abnormalities, correctable by surgery, in all patients studied. On the whole, the available data indicate unfavorable effects of expectant management and beneficial effects of surgery on bone mass.

**Renal Effects.** Hypercalciuria in PHPT results from the increased renal filtered load and is corrected by successful surgery, reducing the risk of urolithiasis and renal injury. The magnitude of this risk is related to the severity of the hypercalcemia and hypercalciuria, and would be minimized by the application of strict criteria for the deferral of surgery. While classical PHPT is clearly associated with risk of renal failure, impairment of both creatinine clearance and renal concentrating ability have been well described, even in patients with relatively mild PHPT and normal serum creatinine levels (8).

**Other Effects.** The association of PHPT with hypertension has been well documented but poorly understood (23–25). Parathyroidectomy does not reliably improve hypertension in these patients. It is not clear whether surgery alters the long-term course of their hypertension. Must we identify them at an even earlier stage? There is evidence of impairment of glucose tolerance by PTH. While there is no well-established link between PHPT and clinical diabetes mellitus (26), there is evidence of an interaction between serum glucose and calcium levels and mortality (27). Effects on cardiac function associated with PHPT have improved after surgery (28–31), although it may be difficult to preoperatively estimate the role of PHPT in a particular individual. Adverse effects on hematopoiesis have been reversed by surgery (32).

Taken together, the pathophysiologic effects of PHPT generally favor parathyroidectomy in patients with nonclassical disease, although the impact in an individual case may be difficult to predict.

**PHPT with non-classical symptoms**

There is considerable evidence that many patients with nonclassical PHPT have less specific but nonetheless real symptoms. Such reversible symptoms as lassitude, difficulty with mental concentration, and mild weakness are well described in classical PHPT. Similar though more subtle symptoms were detected with symptom questionnaires in over 90% of patients in a group with predominately mild to moderate hypercalcemia studied before and after surgery (33). Most of these patients demonstrated symptomatic improvement after parathyroidectomy, in contrast to control patients who underwent thyroidectomy for benign nontoxic disease. These results are similar to those seen using the SF 36 Health Status Questionnaire pre- and postoperatively in PHPT patients with mild as well as more severe hypercalcemia (34). Similarly, psychological symptom distress can be detected by formal testing and is reduced by surgery (36, 37). In a small study, post-parathyroidectomy improvement of neuromuscular function was objectively demonstrated in patients with mild preoperative hypercalcemia (35). By their very nature it is quite difficult to predict which less specific symptoms will improve and to what extent. This makes individual risk-benefit assessments difficult, but there does appear to be an advantage for surgery for patients as a group.
Association of Excess Mortality with PHPT

An increased risk of death is described in patients with PHPT, mainly due to cardiovascular disease and cancer. Most studies have suggested that even after parathyroidectomy, there is a residual excess risk of mortality (12, 38, 39). Failure to observe this effect in one large series was attributed by the authors to early surgical intervention (40). Two population-based Swedish studies have demonstrated excess long-term mortality in relatively mildly affected unoperated patients (27, 37, 41). In a large cohort of individuals identified by population screening for hypercalcemia in Gävle, Sweden (27, 37), the risk of death for those under 70 yr of age was about 1.5 times that of matched controls from the same screening group. Nearly half the survivors failed to remain consistently hypercalcemic over the 15-yr follow-up period, suggesting that many of the milder cases may have been over-diagnosed. If so, the relative mortality risk may actually have been underestimated. This study of unoperated patients could not evaluate the effect of surgery on mortality. Another study, following a large group of operated patients (42) with nearly 100% follow-up over an average of 12 yr, found that an excess mortality rate gradually declined after parathyroidectomy, to about that of the general population, indicating that successful surgery eventually ameliorated the excess risk of death in PHPT patients. Strikingly, this study found a statistically significant mortality advantage only for the mildly hypercalcemic patients, suggesting that the greatest benefit might be in those patients for whom surgery is most likely to be deferred. Based on these studies, it appears that the magnitude of the potential reduction of long-term mortality by surgery probably substantially exceeds the extremely low mortality of parathyroidectomy.

Although American observational/natural history studies have generally not reported excess mortality, they have not included concurrent control groups of normal subjects or operated patients. A study of the Rochester, Minnesota population (43) compared outcomes in patients with incidentally discovered hypercalcemia with statistics for white Minnesota residents, adjusted for age and gender. The authors found an increase in mortality only in the top quartile of patients ranked by serum calcium. In this quartile 75% of individuals had serum calcium levels between 11.2 and 11.8 mg/dL, while only 25% were over 11.8 mg/dL. The authors could not demonstrate a clear separation between higher and lower calcium values as predictors of mortality. Many clinicians would regard an uncomplaining patient whose serum calcium level was between 11.2 and 11.8 mg/dL as “asymptomatic” or “mildly affected”. How such patients are classified and treated may have important implications for outcome.

Over-Diagnosis and Misdiagnosis

In clinical practice, over-diagnosis and misdiagnosis of PHPT are especially problematic in mildly hypercalcemic patients. Even in the expertly conducted Mayo Clinic prospective study (14), 13 patients’ diagnoses were ultimately regarded as doubtful or incorrect, leading to the authors’ sensible suggestion that very mildly affected patients should be followed for at least a year before surgery. It is increasingly common for patients to be referred for parathyroid surgery without an endocrinologist’s consultation, often on the basis of a marginally abnormal serum Ca concentration with an elevated or nonsuppressed PTH level. If these patients are systematically evaluated, they are sometimes found to have secondary rather than primary hyperparathyroidism, and correction of the underlying condition may result in correction of the calcium and PTH. As described in the Mayo and Gävle studies, some patients’ laboratory abnormalities appear to resolve spontaneously. Thus, in patients without demonstrable symptoms or adverse metabolic effects, it is essential that confounding diagnoses be excluded, and it may be prudent for surgery to be recommended only after an adequate observation period.

Of course, any long-term prospective study of PHPT should be restricted to patients with unambiguous diagnoses, based on persistent hypercalcemia with normal or nonsuppressed PTH levels, despite correction of all discernible contributory conditions.

Surgical Results and Challenges

Because the surgical trauma is minimal, parathyroidectomy is generally well tolerated, even by frail elderly patients, and the operative mortality is extremely low (5, 44–47). However, the operation is one of considerable delicacy. Injury to the recurrent laryngeal nerve may result in transient or even permanent vocal fold paralysis, but is rare in experienced hands. The variable location of the parathyroid glands, their small size and inconspicuous appearance all contribute to the difficulty that may be experienced locating an adenoma or hyperplastic gland, or especially an ectopic normal gland, and contribute to the occasional problem of missing glands or (rarely) inadvertent surgical hypoparathyroidism. The challenge of locating all abnormal parathyroid glands may be greater in the more subtle cases.

Preoperative localization procedures using isotopic scanning, ultrasound, and CT, as well as selective venous sampling, have been evaluated as aids to the surgeon. Although it is not yet clear that they have actually improved primary surgical results, the use of these techniques is increasing, particularly Tc-sestamibi scans (48). Although results have been impressive in some series, even this technique has yet to consistently demonstrate reliability equal to the best surgeons. Unfortunately, such localizing procedures are most likely to miss exactly those adenomas that are difficult for the surgeon to find. Their value is most apparent before reoperation for persistent or recurrent PHPT, when their use is nearly universal (48), whereas for first operations, the essential localization procedure is still the identification of an expert surgeon (49).

The probability of surgical success and the risk of surgical morbidity depend heavily on the surgeon. There are numerous reports of results from endocrine surgical specialists, but information is more limited from surgeons who perform parathyroidectomies less frequently. Expert
surgeons generally have performed 100 or more parathyroidectomies, often performing 25–50 per year. They should have extremely low operative mortality rates in spite of operating on a fair proportion of frail patients. They consistently identify and remove adenomatous or hyperplastic tissue in perhaps 98% of cases and achieve normal postoperative parathyroid function in about 95% or more. Persistent disease may be related to fifth glands, inadequate resection for hyperplasia, or an ectopic adenoma that is not found. Permanent hypoparathyroidism should occur in no more than 1–2% of patients, and serious complications such as permanent vocal-fold paralysis are rare. For less experienced surgeons, the likelihood of persistent disease or complications would be expected to increase in an inverse relationship to training and experience. Generally, parathyroidectomies should be referred to surgeons who perform the procedure with sufficient frequency to maintain a high level of competence.

**Medical Treatment of PHPT**

We have shown that a medication acting on the calcium receptor can experimentally depress PTH levels in patients with PHPT (50). However, such therapy has no immediate prospect of clinical availability. No other medical treatment controls the underlying condition. Estrogen can reduce the rate of bone resorption, with a favorable effect on bone mass, in postmenopausal women with PHPT (51–54). However, the available studies have not demonstrated a long-term overall benefit for estrogen as an alternative to parathyroidectomy or expectant management. The long-term use of other potent antiresorptive agents to protect the skeleton in PHPT has not been adequately evaluated.

**Risks vs. Benefits**

Parathyroidectomy remains the only cure for PHPT. When performed by an expert surgeon, the risks are minimal and the probability of success is excellent. The anticipated benefits may be either improvement of the present condition, prevention of future complications or both. Surgery is favored without controversy when the patient is symptomatic or has clinical adverse effects. For patients who would otherwise develop complications of PHPT, the benefits of earlier detection and surgical cure surely outweigh operative risks and morbidity. When the patient is young or has another condition that may have additive adverse effects, the advantages of surgery have long been apparent. In nonclassical cases, there is now good evidence for progressive bone loss without surgery and for improved bone mass after parathyroidectomy. The evidence indicates that subtle symptoms are very common in nonclassical patients and are improved by surgery, as are the adverse physiological effects, which are also common in such patients. These considerations, together with the evidence for excess long-term mortality risk even in rather mildly affected unoperated patients, produce a persuasive argument that the benefits of surgery in expert hands generally outweigh the risks, even in nonclassical cases. The risk-benefit balance is harder to estimate when access to surgery at a high level of skill is not immediate. Obviously, individual considerations must always be taken into account, but the remoteness of the benefits and the immediacy of the risks may result in deferral of surgery in practice to a greater extent than objective analysis would justify.

**Deferral of Surgery**

It should be understood that deferral of surgery is not a one-time decision, but rather one that is reviewed and reconsidered regularly in conjunction with meticulous monitoring. It is only acceptable in patients without complications, who are carefully followed to assure that any progression of end-organ effects or development of a complicating condition is promptly detected. The difficulties of nonoperation are illustrated by the high rate of patients lost to follow-up or incompletely evaluated even by conscientious investigators. These difficulties are further compounded by patients’ mobility, both geographical and between insurance plans and health care systems. Depending on the age of the patient, the cost in time and money for nonoperative follow-up may eventually equal or exceed that required for surgery. Furthermore, deferral may result in surgery being performed when a patient is older and in less favorable general health, after suffering a complication of PHPT, or a complicating intercurrent condition. These considerations must be regarded as costs and risks of deferral.

**Summary and Conclusions**

There is little debate about the primacy of surgery in the management of classical PHPT. Rather, the question has been what to do about the many patients with nonclassical disease. A 1990 NIH consensus conference (55) clearly recommended surgery for patients with significant adverse effects of PHPT, for patients with complicating coexistent illnesses, for younger patients, and for those in whom consistent long-term follow-up could not be assured. It allowed that conscientious surveillance may be justified in patients with minimal hypercalcemia and no adverse effects, but it recognized that for many patients, the time and expense involved in rigorous follow-up would outweigh the burden of surgery. Nine years later, the demonstrated prevalence of nonclassical symptoms and their reversibility, the evidence of “asymptomatic” but harmful effects reversible by surgery, and the accumulating evidence for surgical reduction of increased long-term mortality risk substantially strengthen the argument for surgery in such patients. For these reasons, parathyroidectomy should generally be recommended for patients with a secure diagnosis of PHPT, even in the absence of classical symptoms.

**References**

Overview and Summary*

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The more one learns, the more questions arise. The greater the precision with which one can ask questions, the more numerous and more subtle the questions become. The greater the amount of information accrued, the less useful are the broad guidelines to which we have adhered in the past. Or are they? These are the issues raised in the two position papers in this “Therapeutic Controversy” section of JCE&M.

It is now almost a full decade since the 1990 National Institutes of Health Consensus Conference on the evaluation and management of primary hyperparathyroidism. Those of us “in the trenches” trying to formulate optimal recommendations and treatment plans for our patients with primary hyperparathyroidism were never particularly satisfied with the Consensus Statement recommendations. Perhaps most disconcerting was the recommendation that the primary physician should use his or her own discretion in the most difficult patients who, of course, comprise the majority of affected patients we encounter. To be fair to the Consensus conference, the Conference was held at the dawn of evidence-based or outcome-based medicine, and many of the important questions that needed to be answered simply could not be answered on the basis of data available in 1990. Moreover, many of the sensitive and reliable tools that were needed to fully and unequivocally evaluate patients with primary hyperparathyroidism were not available. During the decades of the 70’s and 80’s, we did not have access to sensitive and specific tools for investigating mineral metabolism that we now take for granted.

We don’t often reflect on the events that have overtaken a field over the course of a given decade. In the case of primary hyperparathyroidism, investigators and clinicians in this field might be rather astonished by the list of cumulative advances in the field over the past ten years. This remarkable decade has seen widespread application of sensitive and specific two-site PTH immunoassays, widespread use of high-precision bone densitometry techniques, and the unfolding of large scale clinical trials using vertebral and hip fractures as primary endpoints (in osteoporosis, not hyperparathyroidism). We have seen the cloning of the PTH/PTHrP receptor, and we have learned that it is expressed in almost every organ. We have seen the consequences of ablation of the PTH receptor (horrrendous) or of PTH itself (not so bad) in gene “knockout” mice. Transgenic models of parathyroid adenoma/hyperplasia in mice have been developed and studied. We have seen the identification of a series of parathyroid adenoma/hyperplasia/carcinoma-associated oncogenes and tumor suppressor genes such as PRAD, ret, menin, p53, and Rb, and others. This decade has seen the cloning and characterization of the calcium-sensing receptor, the cell surface receptor that recognizes ambient calcium concentrations and thereby modulates parathyroid hormone secretion. We have learned an immense amount about parathyroid regulation and function at the cellular level.

There have been impressive accomplishments in the pharmaceutical arena over the past decade. New pharmaceuticals that may impact heavily on the management of primary hyperparathyroidism have been developed and are now widely available. These include the newer generation bisphosphonates, such as alendronate, and the selective estrogen receptor modifiers (SERMs), such as raloxifene, with others to come. The discovery of the calcium sensor or receptor coincided with the unveiling of a new class of calcium receptor-targeted drugs that can either increase or decrease PTH secretion. Perhaps most surprisingly, after we had all learned that excessive concentrations of parathyroid hormone were bad for your skeleton, this decade has seen the rebirth of PTH as a therapeutic agent in osteoporosis: many companies currently have PTH or closely related compounds in late-phase clinical trials, and the results are impressive: one recent study reveals a near 35% increase in vertebral bone density after treatment with PTH for glucocorticoid-induced osteoporosis. We still have no clear idea at the cellular level as to how PTH can be at once both harmful and beneficial for the skeleton.

We have learned much in the areas of diagnostic imaging, bone histomorphometry, and epidemiology as they relate to primary hyperparathyroidism. Studies reported recently have shown that parathyroid adenomas can be readily localized using technetium-sestamibi imaging. Other studies have shown that parathyroidectomy in patients with hyperparathyroidism results in very substantial increases in bone density. On the other hand, other studies show that not operating on patients with mild hyperparathyroidism results in stable bone density. It is not clear which of these two outcomes will prove to be superior over the long term. Moreover, even if bone density declines at cortical sites with PTH treatment for osteoporosis, it is not a forgone conclusion that this is a negative outcome: PTH treatment in laboratory animals increases the number of struts and connections among trabeculae in bone and has been associated with increased bone tensile strength. Thus, even if bone density declines in trabecular or cortical sites, this is not necessarily an adverse outcome if the residual bone is of higher tensile strength. These considerations, of course, raise the issue of fracture incidence in primary hyperparathyroidism—do people with primary hyperparathyroidism have a higher than normal risk of vertebral, hip, or other fracture? Studies on sufficiently large populations are just beginning to accru.

While these rather astonishing accomplishments have occurred, other things have not changed. Hyperparathyroidism is still common, although a recent study suggests that the incidence of primary hyperparathyroidism may be declining. In terms of soft surgical indications, while most investigators and clinicians agree on the negative “stone” and “bone” complications of primary hyperparathyroidism, we still argue over whether the “groan” features of

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hyperparathyroidism can truly be attributed to the disease. Silverberg et al. say “maybe no”, while Bone would appear to argue “maybe yes”.

The pace of investigation and access to research funding has increased markedly. During the past decade, funding by the National Institutes of Health for skeletal research has increased by a factor of approximately ten. Congress, women’s groups, densitometry companies, pharmaceutical companies, the lay press, and our patients are forcing scientists and clinical investigators to ask the difficult, large-scale outcome questions, and vitamin suppliers and health food product makers have jumped on the “bone health” bandwagon. Perhaps to the surprise of younger scientists and clinical investigators, it was not always like this—widespread interest in bone health is a relatively new phenomenon.

So, at the conclusion of the decade that has passed since the last NIH Consensus Conference, where do we now stand with respect to optimal evaluation and management of primary hyperparathyroidism? We think it is time for two major events to occur, perhaps separately, perhaps together. First, we now have guidelines, endorsed by the National Osteoporosis Foundation (NOF) and by the American Society for Bone and Mineral Research Society (ASBMR), for the evaluation and management of post-menopausal osteoporosis. It is time to do the same for primary hyperparathyroidism.

Second, it is time for a new millennial NIH Consensus Conference with four goals in mind:

1. **Develop Diagnosis and Treatment Guidelines.** The Consensus Confernees should make another attempt at developing useful evaluation and management guidelines, as suggested above.

2. **Provide Definition and Focus.** The Conference should focus on the compelling questions that need to be answered in the current era. In our minds, some of these questions should be definitional, some operational, and some investigational: What exactly will the criteria be for asymptomatic vs. symptomatic primary hyperparathyroidism in the new millennium? Can we finally put to rest the arguments relating to peptic ulcer disease, hypertension, pancreatitis, marrow suppression, diabetes, and subtle mental changes as indications for surgery? If not, which of these should be studied and how? Which assays for PTH are best? Who should have bone mineral density measurements, and how often should they be performed if surgery is or is not performed? Is the under-50-yr-old cutoff still applicable? And what really are the risks of surgery—minimal (as Bone would have us believe), or more substantial (as our patients who would gladly trade their vocal cord paralysis for a 0.5% decrement in bone mineral density might advocate)? Are we ready for genetic testing in any forms of primary hyperparathyroidism such as the MEN syndromes or familial hypocalciuric hypercalcaemic syndromes? And how does PTH increase or decrease bone mass and strength at the cellular level? Are there pharmacologic or gene therapeutic strategies that might be used to advantage in primary hyperparathyroidism, to take advantage of the osteoblastic, anabolic effects of PTH, while minimizing the osteoclastic, catabolic effects? Most importantly, perhaps, is it time for a multicenter large-scale trial to assess the risk of fracture and overall mortality in subjects with mild, subtle, or asymptomatic primary hyperparathyroidism?

3. **Managed Care and Resource Allocation.** The Consensus Conference could evaluate the data and guide the physician and patient through the confusing roadmap of managed care. Not surprisingly, a recent study reports that surgeons who have the most experience with parathyroid surgery generate the best outcomes. Yet, at the same time, managed care providers are modifying and controlling our referral channels. Should patients with hyperparathyroidism be steered by a primary physician to the surgeon recommended by the local health plan, or should the patient have access to a smaller number of highly skilled and experienced parathyroid surgeons? Or should certain patients be referred to an experienced parathyroid surgeon and others not? What will be the criteria for defining “the experienced parathyroid surgeon”? And, if only a cadre of approved parathyroid surgeons are permitted to do the surgery, how will others be trained and gain the obligate surgical training and experience?

The Consensus Conference should also provide guidance as to whether patients with suspected or documented primary hyperparathyroidism should be routinely referred to an endocrinologist. Should every patient see a specialist who is conversant with the issues raised above, and what are the economic consequences?

Cost issues and technology deployment need to be addressed as they relate to measurements of bone mineral density in primary hyperparathyroidism, both pre- and post-op. What techniques and sites are optimal? How low is low enough to be a clear indication for surgery? And how often should it be measured post-op? Or if patients are not referred to surgery, what is the optimal management in terms of bone mineral density follow-up, serum creatinine, calcium and PTH determinations, and urinary calcium measurements?

Similar issues pertain to PTH immunoassays. As economic decisions impact more and more heavily on assay and laboratory choice, how much information should be provided by clinical laboratories to clinicians who depend on these assay outcomes? Who should select the assays and the laboratories to which they are sent?

4. **Define Opportunities for Future Research.** Finally, the millenium NIH Consensus Conference should develop clear priorities for pressing unanswered questions, clinical and basic, that should be the focus of future Requests for Proposals. A number of questions have been raised above which require further study. For example, what really is the incidence of vertebral,
hip, and forearm fracture in patients with primary hyperparathyroidism? What would be the impact on fracture of therapy with any of the new bisphosphonates such as alendronate, risedronate, or tiludronate in primary hyperparathyroidism? Or with estrogens? Or with the several new selective estrogen receptor modulators? Or with the calcimimetics? These would be ideal questions for large multicenter NIH- and industry-sponsored observational and interventional trials. The design of such trials, and planning the eventual funding thereof, would be excellent subjects for a Consensus Conference.

In the contributions by Silverberg and Bilezikian and by Bone and Talpos, many of the critical “gray areas” are fleshed out. We applaud the authors of the two viewpoints for having raised these important issues. Let’s see what guidance the new millennium brings for the evaluation and management of the complex, common, and confounding clinical conundrum of asymptomatic primary hyperparathyroidism.