

## Summary Statement from a Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century

JOHN P. BILEZIKIAN, JOHN T. POTTS, JR., GHADA EL-HAJJ FULEIHAN, MICHAEL KLEEREKOPER, ROBERT NEER, MUNRO PEACOCK, JONAS RASTAD, SHONNI J. SILVERBERG, ROBERT UDELSMAN, AND SAMUEL A. WELLS

*Department of Medicine, Columbia University College of Physicians and Surgeons (J.P.B., S.J.S.), New York, New York 10032; Department of Medicine, Massachusetts General Hospital, Harvard Medical School (J.T.P., R.N.), Boston, Massachusetts 02114; American University of Beirut Medical Center (G.E.-H.F.), Beirut, Lebanon; Department of Medicine, Wayne State University School of Medicine (M.K.), Detroit, Michigan 48201; Department of Medicine, Indiana University School of Medicine (M.P.), Indianapolis, Indiana 46202; Department of Surgery, University Hospital (J.R.), Uppsala, Sweden; Department of Surgery, Yale-New Haven Hospital, Yale University School of Medicine (R.U.), New Haven, Connecticut 06520; and Department of Surgery, Duke University Medical Center (S.A.W.), Durham, North Carolina 27710*

Primary hyperparathyroidism is a common endocrine disease in those countries where multichannel screening is in common use, and hypercalcemia is readily detected. As a result of the introduction of the automated serum screening chemistry panel in the United States in the early 1970s, the prevalence and incidence of the disease were found to be much higher than previous estimates. In addition, the clinical profile had shifted from a symptomatic disorder, with hypercalcemic symptoms, kidney stones, overt bone disease, or a specific neuromuscular dysfunction, toward a more asymptomatic state. The modern clinical profile of asymptomatic primary hyperparathyroidism is best characterized as a disorder in which there are neither signs nor symptoms typically associated with hypercalcemia or parathyroid hormone excess.

In light of the shift in the clinical profile of primary hyperparathyroidism, it was no longer clear whether parathyroid surgery was a necessary recommendation for all patients with this disease. Other issues related to medical management, surveillance, and defining criteria for diagnosis as well as the recommendation for surgery all led to the convening of a Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism. This Conference, held at the NIH on October 29–31, 1990, was sponsored by the Office of Medical Applications of Research and the NIDDK.

The recommendations of the panel of experts constituted then to review the evidence presented by authorities in the field led to a set of principles and guidelines for diagnosis as well as for surgical *vs.* nonoperative medical management of patients with asymptomatic primary hyperparathyroidism. Surgery was recognized as the only definitive therapy for primary hyperparathyroidism and was acknowledged to be virtually always an appropriate course of action. In partic-

ular, it was clear that any individual with overt complications of primary hyperparathyroidism, and therefore symptomatic (*i.e.* renal stones, fractures, or neuromuscular syndrome), should have parathyroid surgery. It was also emphasized that in many patients with primary hyperparathyroidism, there were no signs or symptoms commonly associated with the disease. Even though these individuals were asymptomatic, a number of features were identified as possible risk factors for the development of complications of primary hyperparathyroidism. It was recommended that surgery be performed if any of the following indications were present: 1) serum calcium concentration of 1–1.6 mg/dl (0.25–0.4 mM) above the accepted normal reference range; 2) confirmed 24-h total urinary calcium excretion of more than 400 mg (10 mmol); 3) creatinine clearance reduced by 30% compared with age-matched normal subjects; 4) bone mineral density reduced by more than 2 SD below the bone density of age-, gender-, and race-matched control subjects; 5) patients under 50 yr of age; and 6) patients for whom medical surveillance was either not desirable (*e.g.* coexistent illness) or not possible.

The Consensus Development Panel noted that there was a large subgroup of patients who could be followed safely without surgery if they did not meet any of the aforementioned criteria. The Panel commented on patients who may have one or more vague symptoms, especially related to the neurobehavioral axis. The nonspecific nature of these symptoms (weakness and easy fatigability in the absence of overt muscle weakness) led to the recommendation that these symptoms were not sufficient in and of themselves to lead to a recommendation for surgery unless it was perceived that these complaints were indeed related to hyperparathyroidism.

The Panel recommended that patients who were not to have parathyroid surgery be monitored on a regular basis. It was considered important that the patient understand the importance of regular, conscientious, long-term monitoring, the goals of which included early recognition of worsening

Abbreviations: Ca/Cr ratio, Calcium/creatinine ratio; CaSR, calcium-sensing receptor; FBHH, familial benign hypocalciuric hypercalcemia; FHH, familial hypocalciuric hypercalcemia; IRMA, immunoradiometric assay; MIP, minimally invasive parathyroidectomy.

hypercalcemia, loss of bone mass, renal impairment, renal stones, or fractures. To this end, biannual visits were recommended at which blood pressure, serum calcium concentration, serum creatinine, and creatinine clearance would be measured. In addition, on an annual basis, abdominal radiographs (and/or ultrasound), a 24-h urine collection for calcium, and bone mass measurements were advised. The intervals between these measurements could be lengthened after it was established that the patient was showing no changes in any of the indexes being monitored.

Focused medical therapy for the management of primary hyperparathyroidism was not recommended based on lack of evidence for efficacy, but the importance of hydration, adequate mobility, and a diet that was neither restricted nor excessive in calcium was acknowledged. Prompt medical attention for the possibility of worsening hypercalcemia was urged in the event of any serious intercurrent illness accompanied by a risk of dehydration.

Since 1990, many studies have shed new light on the issues considered by the Consensus Development Panel. Considerable data have accumulated on the natural history of asymptomatic primary hyperparathyroidism with or without surgery. We have greater knowledge of bone involvement in primary hyperparathyroidism by use of cross-sectional and prospective studies with dual energy x-ray absorptiometry. Significant advances in surgery, particularly minimally invasive approaches, and in preoperative localization of parathyroid adenomas have occurred. Promising medical therapies for primary hyperparathyroidism have been introduced. In addition, there have been concerns about cardiovascular risk and other atypical manifestations of primary hyperparathyroidism. For these reasons, it was deemed appropriate to convene another conference on this subject with a view to reevaluating the conclusions of the 1990 Consensus Development Panel. Accordingly, a Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century was held at the NIH on April 8–9, 2002. It was sponsored by the NIDDK. The Workshop was cosponsored by the NIAMS, The Endocrine Society, The Paget Foundation for Paget's Disease of Bone and Related Disorders, American Society of Bone and Mineral Research, Office of Research on Women's Health (NIH), Office of Rare Diseases (NIH), International Society of Clinical Densitometry, American Association of Clinical Endocrinology, International Society for Bone and Mineral Research, Eli Lilly & Co., and Amgen, Inc. During the 2-d conference, presentations were made by world experts who covered a wide spectrum of issues related to primary hyperparathyroidism. The topics included the epidemiology of primary hyperparathyroidism in the United States, Europe, and other parts of the world; its pathophysiology and molecular pathogenesis; clinical presentations in the United States, Europe, and other parts of the world; differential diagnosis; bone mass measurements; fracture incidence; histomorphometric analysis; nonclassical presentations; natural history; new surgical and localization procedures; and new approaches to specific medical management of primary hyperparathyroidism.

When the Workshop was formally brought to an end, a group of participants with expertise and interest in primary

hyperparathyroidism convened to discuss how our newer understanding of key issues identified by the 1990 Consensus Development Conference have changed perceptions of this disease. Additionally, the group of experts considered what changes, if any, should be recommended for physicians who care for patients with primary hyperparathyroidism. This document represents a summary statement of the deliberations of this Panel, the members of which were John Bilezikian, John Potts, Ghada El-Hajj Fuleihan, Michael Kleerekoper, Robert Neer, Munro Peacock, Jonas Rastad, Shonni Silverberg, Robert Udelsman, and Samuel Wells. Further, this document was distributed to all Workshop participants before submission, and further changes were incorporated. This Panel was not officially constituted or approved by the primary sponsors of the Workshop, the NIH and the NIDDK.

The emphasis of the Panel was not on symptomatic primary hyperparathyroidism, in which patients suffer with known target organ complications of the disease, such as severe bone disease, fractures, renal stones, or overt neuromuscular dysfunction. Although unusual now, such patients should always be strongly advised to undergo parathyroidectomy. Rather, the Panel considered seven questions specifically directed to asymptomatic primary hyperparathyroidism in the United States, but the input of colleagues abroad was sought and considered. However, applicability of the following commentary regarding asymptomatic primary hyperparathyroidism to patients in other countries is not known.

*Should there be any changes in diagnostic criteria for primary hyperparathyroidism?*

Primary hyperparathyroidism is diagnosed by persistent hypercalcemia in the presence of inappropriately normal elevated levels of PTH. Drugs that could be associated with hypercalcemia, such as thiazide diuretics and lithium, should be withdrawn, if possible, and the patient retested. The first generation immunoradiometric assay for PTH (IRMA PTH-Intact) has proved useful because the majority of patients with primary hyperparathyroidism have elevated levels. In some patients with primary hyperparathyroidism, the IRMA PTH-intact assay will be registered in the upper range of normal, which is consistent with the diagnosis of primary hyperparathyroidism when hypercalcemia is present. The normal range for the IRMA PTH-intact assay (generally 10–65 pg/ml) does not take into account the facts that PTH levels rise with age and differ between Caucasians and African-Americans. In African-Americans, normal PTH levels are typically higher than those in Caucasians. On the other hand, PTH levels are typically lower in younger adults. It was recommended that better defined normative values for age, gender, menopausal status, and race for both PTH and calcium would be helpful.

A second generation IRMA assay for PTH has been developed that appears to measure only the full-length molecule, PTH(1–84). The first generation IRMA PTH-intact assay also detects appreciable quantities of a large fragment(s) of PTH that is apparently missing a portion of the amino terminus of the full-length molecule. It is not known whether

the newer IRMA assay, in which large hormone fragments are not detected, will provide increased diagnostic sensitivity in this disorder. Further investigation is warranted, especially in view of some evidence that favors its superiority.

Familial benign hypocalciuric hypercalcemia (FBHH), also referred to extensively in the literature as familial hypocalciuric hypercalcemia (FHH), is a rare disorder that can also present with hypercalcemia and mildly elevated or inappropriately normal PTH levels. Although some classify FBHH/FHH as a form of atypical primary hyperparathyroidism, it is a generally benign condition that cannot be corrected by parathyroid surgery. Hence, FBHH/FHH must be carefully distinguished from primary hyperparathyroidism. FBHH/FHH, transmitted in an autosomal dominant fashion, is due in most, but not all, cases to a heterozygous mutation in the calcium-sensing receptor (CaSR) gene that is the main regulator of parathyroid cell responsiveness to calcium. The evaluation for FBHH/FHH includes a careful assessment of urine calcium concentrations and measurement of the calcium/creatinine (Ca/Cr) clearance ratio in the patient and family members with hypercalcemia. In FBHH/FHH, the Ca/Cr clearance ratio is typically less than 0.01. In primary hyperparathyroidism, the Ca/Cr clearance ratio is typically greater than 0.02. It is important to distinguish between primary hyperparathyroidism and FBHH, because in the latter condition parathyroid surgery is not indicated. When the genetic disorder is homozygous, however, with two abnormal CaSR genes, neonatal severe hyperparathyroidism results, a true surgical emergency in which total parathyroidectomy is required. If genetic testing for CaSR mutations becomes routinely available, determination of a heterozygous mutation would readily distinguish between FBHH/FHH and primary hyperparathyroidism in most situations.

Primary hyperparathyroidism can also present as part of familial multiple endocrine neoplasia syndromes, but these patients constitute a small minority of patients with primary hyperparathyroidism. This possibility should be suspected in settings of a family history of hypercalcemia or other endocrine neoplasias and when primary hyperparathyroidism occurs in young subjects. The diagnosis should be made according to prevailing clinical principles. Direct DNA testing for specific genetic mutations may become feasible as standardized testing for the genes involved becomes routinely available.

Not all patients with primary hyperparathyroidism have hypercalcemia each time serum calcium is measured. It is common for patients with mild primary hyperparathyroidism and hypercalcemic values (within 0.5 mg/dl above the upper limits of normal) to have normal serum calcium concentrations on some measurements. In such patients, serum calcium is usually in the upper part of the normal range. In a small number of them, only ionized calcium is elevated. In still other unusual patients, neither total nor ionized calcium is elevated. These patients with normal serum calcium concentrations are being discovered when PTH is measured in the course of evaluations for skeletal health or in the context of testing for osteoporosis. They are described as patients with normocalcemic primary hyperparathyroidism. This diagnostic consideration requires that all potential causes of secondary elevations of PTH be ruled out, particularly low

calcium intake due to a gastrointestinal disorder, renal insufficiency, vitamin D deficiency (as defined by serum levels of 25-hydroxyvitamin D <20 ng/ml), or hypercalciuria of renal origin.

#### *Other key elements of the diagnostic evaluation for primary hyperparathyroidism*

The evaluation for primary hyperparathyroidism should typically include a full evaluation of the target organs that are most likely to be affected by primary hyperparathyroidism: the skeleton and the kidneys. As will be discussed, the skeleton is best evaluated by bone densitometry using dual energy x-ray absorptiometry. Routine skeletal x-rays are no longer recommended, because patients in the United States are very unlikely to show typical radiological findings of primary hyperparathyroidism. As kidney stones are still the most common complication of primary hyperparathyroidism, a baseline assessment with renal ultrasound and/or abdominal x-rays is reasonable. Additionally, the 24-h urinary calcium measurement can be useful not only in helping to distinguish between primary hyperparathyroidism and FBHH/FHH (see above), but also in giving a general measure of the renal burden for handling calcium. Although urinary calcium excretion is not well correlated with the risk of kidney stones, it can nevertheless be useful as a baseline assessment. Additionally, urinary creatinine excretion along with the serum creatinine concentration permit an estimate of creatinine clearance.

#### *Should the guidelines for surgery in primary hyperparathyroidism be changed in light of new data over the past decade? What should those guidelines be?*

Over the past decade, progress has been made in understanding how each of the guidelines proposed at the Consensus Development Conference of 1990 may or may not be relevant to decisions at this time regarding the advisability of surgery or no surgery in primary hyperparathyroidism. Each of those guidelines is reviewed here with comments about the Panel's recommendations for change.

1. *Former recommendation: serum calcium concentration of 1–1.6 mg/dl above the accepted normal reference range.* As reviewed at the last Consensus Development Conference, there are many nonanalytical sources of error in the determination of a total serum calcium concentration. There is also a need to carefully maintain reference standards and to establish normative values. Sources of artifact in the measurement should be avoided. All serum calcium concentrations should be corrected to the prevailing serum albumin concentration. For every gram per deciliter reduction in the serum albumin concentration from the midnormal range (4.0 g/dl), the measured serum calcium concentration should be adjusted upward by 0.8 mg/dl. The Panel considered the utility of an ionized serum calcium concentration measurement, as it represents the active moiety and is the regulator of physiological processes mediated by calcium. Measurement of the ionized calcium concentration was not recommended by the panel because most clinicians do not have ready access to a facility that can reproducibly measure it accurately. As there is

greater uniformity among reference laboratories for the total serum calcium concentration, it is usually reasonable to rely on the corrected total serum calcium concentration. The value for the total serum calcium concentration to be regarded as a criterion for surgery was set at 1 mg/dl (0.25 mM) above the upper limits of normal for that laboratory. Patients may still be asymptomatic of hypercalcemia when serum calcium is greater than 1 mg/dl above normal, but the panel of experts believed it prudent to lower the range from 1–1.6 to 1.0 mg/dl above normal limits because patients above this new (decreased) limit may be at greater risk for symptomatic hyperparathyroidism and for complications of the disease. *The current recommendation is serum calcium greater than 1 mg/dl above the upper limits of normal.*

2. *Former recommendation: confirmed 24-h total urinary calcium excretion of more than 400 mg.* The recommendation that the urinary calcium measurement be used as an index for consideration of surgery derives from the idea that urinary calcium excretion above 400 mg/d is a risk factor for the development of kidney stones or may indicate a higher degree of bone resorption. The Panel emphasized the importance of other measurable urinary factors, such as urinary oxalate excretion, as a contributor to stone formation. Moreover, with more recent data, urinary calcium excretion has been shown to be a poor predictor of stone risk among those who have never had a kidney stone. The 24-h urinary calcium excretion reflects the combined effect of dietary calcium intake, calcium absorption, skeletal calcium loss, and the serum calcium level. There is variation due to sex, age, and race and issues related to adequacy of the collection itself. The fasting urinary Ca/Cr ratio is more likely to reflect skeletal calcium losses, but it is not as reliable an index of bone turnover in primary hyperparathyroidism as are the specific bone formation and resorption markers. Nevertheless, a baseline assessment of urinary calcium excretion does give a general measure of the calcium burden on the kidney due to a variety of these factors. If 24-h urinary calcium is markedly elevated (>400 mg) at the time of the initial assessment, most participants of the Workshop agreed that it should still be considered a factor in advising parathyroid surgery. The guideline figure, >400 mg in 24 h, is well above the upper limits of normal and helps to mitigate variations in urinary calcium due to sex and race. Nevertheless, it may be important to consider this number in relation to the facts that men typically excrete 25–30% more calcium than women, whereas African-Americans typically excrete 25–20% less calcium than Caucasians. The Panel members believed that if urinary calcium excretion was not excessive at the time of the initial workup, then monitoring with an annual 24-h urinary calcium was not necessary. *The current recommendation is unchanged: 24-h urinary calcium greater than 400 mg.*

3. *Former recommendation: creatinine clearance reduced by 30% compared with age-matched normal persons.* The Panel acknowledged that renal function could be affected in primary hyperparathyroidism. It concurred with the need to ascertain renal function and recognized that the determination of creatinine clearance is variable and difficult to obtain reliably in the out-patient setting. Nevertheless, along with the 24-h

urinary calcium, the creatinine measurement is helpful with regard to determining both the Ca/Cr clearance ratio and creatinine clearance. Creatinine clearance is therefore recommended in the initial assessment of the patient with primary hyperparathyroidism. If it is more than 30% reduced from age- and sex-matched control values, the Panel recommends that surgery should be advised. Serum creatinine can give a general measure of creatinine clearance when the Cockcroft-Gault equation is used: glomerular filtration rate = [(140 – age) × body weight (kilograms) × 0.85 (if female)]/[72 × creatinine (mg/dl)]. The serum creatinine determination is recommended in those patients who do not have reduced renal function at baseline assessment and are going to be monitored without surgery (see section on monitoring). *The current recommendation is unchanged: creatinine clearance reduced by more than 30% compared with age-matched subjects.*

4. *Former recommendation: bone density reduced more than 2 SD below the bone density of age-, gender-, and race-matched control subjects.* Much more is now known about bone mineral density in primary hyperparathyroidism, because dual energy x-ray absorptiometry has become a key instrument in the measurement of bone mass among these patients. In patients with asymptomatic primary hyperparathyroidism, the typical pattern of bone loss reflects the actions of PTH being more catabolic at skeletal sites enriched in cortical bone (*i.e.* the distal one third radius site) than in cancellous bone (*i.e.* the lumbar spine). It has been assumed, but not established, that a reduction in bone mineral density in primary hyperparathyroidism predicts fracture risk to a similar extent as reductions in bone mineral density predict fractures in populations without primary hyperparathyroidism. Cross-sectional data would seem to confirm this expectation at cortical sites, although there are no longitudinal prospective data yet available to confirm this impression. On the basis of this information, albeit still incomplete, the Panel recommended a change from using the z-score to the t-score as a criterion for surgical intervention. The former recommendation, that the z-score be used as a criterion, was based on the idea that it reveals the effect of the disease itself on bone mass, as the z-score represents the extent of departure in bone mineral density from age- and sex-matched cohorts. However, if bone mass measurements reflect fracture risk to the same extent in primary hyperparathyroidism as they do in other populations, it seems more reasonable in adults to use the t-score, which reflects frank departures from peak bone mass.

The Panel also recommended that in addition to measurement of the distal radius, one third site, lumbar spine density and hip density be routinely measured in primary hyperparathyroidism. Although forearm bone density reflects more precisely the catabolic effects of PTH, a small subset of patients with primary hyperparathyroidism will have more marked reductions in the spine than at other sites. Moreover, some studies suggest that vertebral fracture risk is increased in primary hyperparathyroidism, but these studies are uncertain because of their cross-sectional nature and issues of possible ascertainment bias. Finally, the remarkable increases in bone mass at sites of cancellous bone after suc-

successful parathyroidectomy argues more persuasively for a proactive approach in detecting significant reductions in bone mass at any site in this disease.

Based upon these recent data, the Panel recommends that patients be referred to surgery if the *t*-score at the lumbar spine, hip, or distal radius is below  $-2.5$ . This threshold *t*-score is consistent with definitions of osteoporosis established by the WHO and other authoritative agencies. Measurements of other sites, such as heel, tibia, or distal phalanges, are not recommended, because there are insufficient data on these sites of measurement in primary hyperparathyroidism.

Although there are questions about what database to reference in ascertaining the *t*-score, the Panel believes that sex- and race-matched databases should be used wherever possible. For example, men with primary hyperparathyroidism would be compared with the database established for men. When such referent databases are not available, as in certain non-Caucasian women, however, the determination of *t*-score should use the database for Caucasian women. As alternatives to surgery continue to be explored, it is possible that this recommendation for surgery, based upon the *t*-score, could be modified when specific medical approaches are shown to be associated with substantial increases in bone mass. *The current recommendation is bone density at the lumbar spine, hip, or distal radius that is more than 2.5 SD below peak bone mass (t-score,  $< -2.5$ ).*

*5. Former recommendation: patients under 50 yr of age.* The panel reviewed new evidence substantiating the impression that patients who are under the age of 50 yr are at greater risk for developing complications in primary hyperparathyroidism. Now, solid evidence implicates age less than 50 yr alone as a risk factor for developing complications of primary hyperparathyroidism, such as reduced bone mineral density. This evidence extends to individuals under the age of 50 yr who meet or do not meet other previously noted guidelines for surgery. The current recommendation is unchanged. All individuals with primary hyperparathyroidism under the age of 50 yr should be referred for surgery.

*6. Former recommendation: patients for whom medical surveillance was either not desirable or not possible.* The Panel recognized that some patients with primary hyperparathyroidism who do not meet any guidelines for surgery would progress over time to develop one or more criteria. 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, the Panel recommends that this point alone is sufficient to recommend parathyroid surgery at the time the diagnosis of primary hyperparathyroidism is made. *The current recommendation is unchanged.*

#### *Other considerations*

The Panel considered other possible factors, such as neuropsychological dysfunction, menopause, cardiovascular abnormalities, gastrointestinal symptoms, and serum or urinary indexes of bone metabolism, that could enter into the decision-making process in asymptomatic primary hyperparathyroidism. Because of continued uncertainty over the

specificity of the factors listed below for the disease under discussion, the Panel believes that they should not be regarded as sole criteria for surgery. Depending upon the clinical circumstances, however, the clinician might want to weigh them in the overall consideration of the patients' presenting clinical profile.

*Neuropsychological abnormalities.* There are data associating primary hyperparathyroidism with neuropsychological disturbances. Complaints include weakness and easy fatigability (in the absence of overt muscular weakness), depression, intellectual weariness, and increased sleep requirement. In addition, some centers have reported on patient-related outcome variables in primary hyperparathyroidism that can negatively influence estimates of quality of life. The panel acknowledged that improvement in some of these indexes has been reported after successful parathyroidectomy, but also noted that it is not possible at this time to predict which patients will benefit.

*Onset of menopause.* The onset of estrogen deficiency in menopause among patients with primary hyperparathyroidism leads to the same accelerated bone loss that occurs in early postmenopausal women without primary hyperparathyroidism. Therefore, in this setting excess PTH does not seem to protect women from bone loss due to estrogen deficiency. This point should be considered in early postmenopausal women who do not meet other criteria for surgery.

*Cardiovascular abnormalities.* To the extent that there are data available, asymptomatic primary hyperparathyroidism in the United States is not associated with overt cardiovascular abnormalities. However, in multivariate adjusted analyses, patients with the highest serum calcium levels were at increased risk for all causes of mortality. This may be consistent with reports of increased cardiovascular mortality from European centers where the disease is biochemically more severe. Hypertension, when present, is not improved after successful parathyroid surgery and therefore should not be considered an indication for parathyroidectomy.

*Gastrointestinal symptoms.* Asymptomatic primary hyperparathyroidism in the United States is not associated with peptic ulcer disease (unless it is associated with multiple endocrine neoplasia type 1 syndrome) or pancreatitis. These gastrointestinal disturbances therefore should not be regarded as independent criteria for surgery in primary hyperparathyroidism.

*Serum or urinary indexes of bone metabolism (bone markers).* Although the panel recognized the potential value of bone markers in assessing the level of skeletal metabolic activity in primary hyperparathyroidism, it is not clear that elevated levels of bone markers are predictive of the likelihood of bone loss or fractures as they are in individuals without primary hyperparathyroidism. Asymptomatic primary hyperparathyroidism is associated with levels of bone formation and resorption markers that may be at the upper limits of normal or even frankly elevated. A comparison of the indications for surgery recommended by the 1990 Consensus Development Panel and the current recommendations by the Primary Hyperparathyroidism Working group is listed in Table 1.

**TABLE 1.** A comparison of new and old guidelines for parathyroid surgery in asymptomatic primary hyperparathyroidism

Measurement	Guidelines (1990)	Guidelines (2002)
Serum calcium (above upper limit of normal)	1–1.6 mg/dl	1.0 mg/dl
24-h urinary calcium	>400 mg	>400 mg
Creatinine clearance	Reduced by 30%	Reduced by 30%
Bone mineral density	<i>z</i> -score <–2.0 (forearm)	<i>t</i> -score <–2.5 at any site
Age	<50	<50

Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.

*At present, is there sufficient evidence of clinical benefit with specific medical therapies to recommend their use? In which patients?*

The Panel concurred with the previous recommendations that for asymptomatic primary hyperparathyroidism, there are no medical therapies for which data are convincing regarding either efficacy or safety. Estrogens may be useful in early postmenopausal women for the same reasons they are recommended by some physicians for postmenopausal women who do not have primary hyperparathyroidism. As specific therapy for the hypercalcemia of primary hyperparathyroidism, however, the Panel continues to believe that estrogen may reduce the serum calcium somewhat, but is not generally effective until levels of estrogen are reached that are higher than most women or their physicians would consider acceptable.

The Panel was interested in new data becoming available regarding three classes of agents that might have particular promise with regard to the medical management of asymptomatic primary hyperparathyroidism. The early data were reviewed regarding the potential usefulness of raloxifene, bisphosphonates, and calcimimetics in primary hyperparathyroidism. The information presented for all three classes of drugs was limited to showing preliminary efficacy on surrogate makers such as serum calcium and bone density, but not on verifiable clinical outcomes. If further data are confirmatory, however, these agents may become useful in patients meeting guidelines for surgery who, for one reason or another, seek a medical alternative. They may also become useful in patients for whom surgery is not a primary recommendation.

The importance of sufficient calcium intake was emphasized. There is no rationale for diets restricted in calcium in this disease. In fact, there may be reason to be concerned that restricted calcium diets might fuel the pathophysiological processes associated with excess secretion of PTH. Similarly, there is concern for diets enriched in calcium. The most prudent advice is to adhere to the current standards for optimal calcium intake for adults in the United States, 1000–1200 mg/d.

The importance of vitamin D sufficiency was also emphasized. In primary hyperparathyroidism, levels of 25-hydroxyvitamin D below 20 ng/ml could stimulate the mechanisms associated with excess PTH secretion. In individuals whose 25-hydroxyvitamin D levels are below this range, it is prudent to provide replacement cautiously. Amounts approximating physiological replacement doses (400–600 IU/d), would seem to be safe, but the serum calcium concentration must be monitored frequently on the chance that in some patients serum calcium levels could rise further.

*Can some patients be followed without surgery? If so, how should they be monitored?*

The Panel recognized that some patients with asymptomatic primary hyperparathyroidism will not meet any of the newly recommended criteria for surgery, although it emphasized once again that surgery is the only definitive treatment for this disease. The Panel also appreciated that there are patients for whom surgery will not be accepted as a choice as well as the fact that there are other patients for whom comorbid medical issues might limit enthusiasm for a surgical procedure. Moreover, some patients with asymptomatic primary hyperparathyroidism will show signs of progression over the years. The group of subjects destined to demonstrate worsening disease cannot be identified at the time of presentation.

Therefore, monitoring is essential if patients are not to undergo parathyroid surgery. The serum calcium concentration should be measured twice yearly. Bone mass measurements at all three sites (lumbar spine, hip, and forearm) are recommended on a yearly basis. The Panel has carefully distinguished between the initial assessment of the patient and the recommendations for monitoring with specific reference to renal studies. For baseline evaluation, the Panel agrees to continue to recommend baseline abdominal radiographs or ultrasound to detect silent stones and an assessment of urinary calcium and creatinine clearance. However, the Panel saw no need to obtain measurements of the urinary calcium, creatinine clearance, or radiological studies for follow-up monitoring in those patients who did not meet initial renal criteria for surgery. Rather, it was considered useful to monitor serum creatinine on a yearly basis, with an estimate of creatinine clearance provided by the serum creatinine concentration and application of the Cockcroft-Gault equation. A comparison of indexes recommended by the 1990 Consensus Development Panel for monitoring patients who are not going to have surgery and the current recommendations by the Panel is listed in Table 2.

*When surgery is the preferred option, what are the relative merits of minimally invasive procedures compared with more conventional surgery?*

The Panel emphasized the need for parathyroidectomy to be performed by surgeons who are highly experienced and skilled in the operation. The standard operation for parathyroidectomy is full exploration of the neck with identification of all four 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 will be discovered. Recent advances in

**TABLE 2.** A comparison of new and old management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroid surgery

Measurement	Older guidelines	Newer guidelines
Serum calcium	Biannually	Biannually
24-h urinary calcium	Annually	Not recommended <sup>a</sup>
Creatinine clearance	Annually	Not recommended <sup>a</sup>
Serum creatinine	Annually	Annually <sup>b</sup>
Bone density	Annually (forearm)	Annually (three sites: lumbar spine, hip, forearm)
Abdominal x-ray (±ultrasound)	Annually	Not recommended <sup>a</sup>

<sup>a</sup> Except at the time of the initial evaluation.

<sup>b</sup> If the serum creatinine concentration suggests a change in the creatinine clearance, when the Cockcroft-Gault equation is applied (see text), further, more direct, assessments of the creatinine clearance are recommended.

the use of local anesthesia have led many parathyroid surgeons to perform standard parathyroidectomy with local, rather than general, anesthesia.

A variety of minimally invasive procedures have been introduced. One of the most promising techniques, minimally invasive parathyroidectomy (MIP), is performed with preoperative localization using <sup>99</sup>Tc-labeled Sestamibi-SPECT (single photon emission computed tomography) imaging. MIP is intended for sporadic primary hyperparathyroidism and only if a single adenoma is visualized preoperatively. The operation consists of identification and removal, under local anesthesia, of the abnormal tissue without visualization of other glands by the surgeon. Before and after the adenoma is removed, an intraoperative PTH level is determined to ascertain that the gland removed is the only source of excess PTH. Such intraoperative PTH assays can be performed within minutes and thereby do not significantly extend the duration of the operation. If, after removal of the adenoma, the intraoperative PTH level falls by greater than 50%, the operation is terminated. If the intraoperative PTH level does not fall by greater than 50%, the operation is extended, and if necessary, a full neck exploration is performed to seek other overactive glands.

Compared with the conventional neck exploration for primary hyperparathyroidism, MIP appears to offer some advantages. This surgical method could become the procedure of choice if long-term patient evaluation confirms early results and practicing surgeons can learn to master the operation. As is true for the conventional parathyroidectomy, MIP requires a highly skilled and experienced parathyroid surgeon.

*What is the role of localization techniques in identifying abnormal parathyroid tissue preoperatively and intraoperatively? Are they sufficiently helpful and cost-effective to warrant their use in all patients who undergo parathyroid surgery? If not, in what patients should they be recommended?*

The Panel agreed with the spirit of the statement made by the late Dr. John Doppman at the last Consensus Development Conference in 1990 that the greatest challenge in preoperative

localization of the parathyroid adenoma is locating an experienced parathyroid surgeon. There was strong concurrence that parathyroidectomy should be performed only by experienced, expert parathyroid surgeons (who, in turn, should be carefully training the next generation of expert parathyroid surgeons). Nevertheless, advances in imaging of abnormal parathyroid tissue have led many surgeons to use preoperative localization tests. Such preoperative localization testing is mandatory when the MIP procedure is used. Preoperative localization tests should not be used to make, confirm, or exclude the diagnosis of primary hyperparathyroidism.

The most widely used localization procedure is <sup>99</sup>Tc-labeled Sestamibi with SPECT imaging. In the most experienced centers, this imaging approach can successfully visualize up to 85% of parathyroid adenomas. In centers that are not as experienced, this figure drops to 50–60%. Other noninvasive imaging modalities, such as ultrasound, magnetic resonance imaging, and computed tomographic scanning, can be helpful at times. Even in highly specialized centers, however, no single procedure or combination of noninvasive imaging studies has a better localization rate than the expert parathyroid surgeon who typically reports success rates of 90–95%.

In the patient who has had previous failed neck surgery, the Panel emphasized the need to reaffirm the diagnosis of primary hyperparathyroidism and confirmed the opinion offered at the last Consensus Development Conference that noninvasive preoperative studies be obtained. The <sup>99</sup>Tc-labeled Sestamibi scan should be the first procedure with SPECT imaging whenever possible. Other procedures, such as ultrasound, computed tomography, and magnetic resonance imaging can be useful. It is advisable to refer such patients with previous unsuccessful neck surgery to centers with the requisite expertise to perform and interpret these tests. Invasive localization studies, arteriography, and selective venous sampling with measurements of PTH from draining veins of the thyro-parathyroid bed are best reserved for those patients in whom all noninvasive localization procedures have failed. In reports from the centers most experienced with these procedures, successful localization in patients who have had previous neck surgery approach the same percentage as those who have not had previous neck surgery.

In addition to surgical adjuncts, such as the use of rapid intraoperative PTH assays, intraoperative <sup>99</sup>Tc-labeled Sestamibi with  $\gamma$ -detection probes and intraoperative ultrasound have been found to be helpful in some centers, but their utility remains to be confirmed.

*What items should be placed on the research agenda for primary hyperparathyroidism over the next decade?*

Progress made in understanding primary hyperparathyroidism over the past decade has led to a series of important research questions that the Panel highlighted for future investigation over the next decade.

There is need for more information about the epidemiology of primary hyperparathyroidism in the United States, especially with regard to developing databases with which populations can be studied cross-sectionally and longitudinally.

nally. Incidence and prevalence figures lag behind the careful reporting systems available in some European countries. A national registry of patients with primary hyperparathyroidism might be helpful in this regard.

Studies of the natural history of primary hyperparathyroidism should continue to explore key aspects of this disease not only with patients who are monitored without intervention or after parathyroidectomy, but also with patients in whom specific medical therapies are used.

The genetics and molecular pathogenesis of primary hyperparathyroidism need to be pursued with regard to plausible mechanisms that have been identified as well as newer concepts by which the development of the hyperparathyroid state can be understood. Genetic models being developed should prove useful. Additionally, the emergence of clonal tumors in some patients with poorly controlled secondary hyperparathyroidism may yield other insights. Underlying differences between single clonal expansion, typical of a parathyroid adenoma, and other mechanisms that lead to multiple gland hyperplasia will be of particular importance to pursue.

The utility of immunoradiometric assays for PTH in establishing the diagnosis of primary hyperparathyroidism can now be studied with regard to the newly recognized larger amino-terminal truncated fragments of PTH. The relative merits of first generation immunometric assays *vs.* newer assays that detect only PTH(1–84) should be evaluated in the diagnosis of primary hyperparathyroidism, the pathophysiology of secondary hyperparathyroidism, and the intraoperative monitoring of PTH during parathyroid surgery. The relative usefulness of first and second generation assays of PTH should become clear after further research. Moreover, detailed study of the precise nature of the circulating species of PTH under normal conditions and those associated with primary hyperparathyroidism may reveal previously unappreciated features of underlying glandular and peripheral cleavage of PTH and their physiological and pathophysiological significance.

The dual functions of PTH, harboring both catabolic and anabolic potential in bone, should be investigated by further study of bone involvement in asymptomatic primary hyperparathyroidism. Not only will studies of bone geometry in primary hyperparathyroidism be of importance, but newer histomorphometric techniques by which cancellous and cortical elements in bone can be specifically defined in the context of this disease should lead to new knowledge.

Clearer distinction clinically between primary hyperparathyroidism and FBHH/FHH may be helped by more extensive family testing, newer immunoradiometric assays, as well as more accurate studies of urinary calcium excretion in FBHH/FHH and primary hyperparathyroidism. If genotyping becomes more readily available, patients in whom the diagnosis is not clear can be subjected to diagnostic molecular genetic approaches. Clearer distinction between patients with normocalcemic primary hyperparathyroidism and those with secondary hyperparathyroidism is needed, particularly in newly estrogen-deficient women, and can be provided by long-term follow-up studies of normocalcemic patients with elevated PTH levels.

Now that bone densitometry is used widely and is indi-

cated in the evaluation of patients with primary hyperparathyroidism, information on fracture incidence and its relationship to bone mass in this disease is needed. More normative data on bone mass specific for age, gender, and race are needed not only for primary hyperparathyroidism, but also for other disorders. It is assumed, but not known, that the relationship between bone density and fracture incidence is the same as that established in postmenopausal Caucasian women. Similarly, it is assumed that the marked increase in bone mass after successful parathyroid surgery is associated with a reduction in fracture incidence. It would be helpful to measure geometric parameters of bone in view of the fact that these indexes can influence fracture risk and are likely to be altered in primary hyperparathyroidism.

Along with additional studies of bone mass and bone density in this disease, further work is needed at the histomorphometric level of bone. Of particular value would be studies before and after successful parathyroid surgery using micro-computed tomography and other state of the art analyses of bone biopsy specimens. Dynamic issues related to the bone remodeling unit in primary hyperparathyroidism before and after surgery can now be studied with even more sophisticated tools and should help to clarify structural and microarchitectural details of this disease that up to now have been elusive.

Ongoing discussions of nontraditional aspects of asymptomatic primary hyperparathyroidism lead to a need for more controlled studies. The nontraditional elements of primary hyperparathyroidism extend in particular to cardiovascular and neurobehavioral functioning and reports of increased mortality especially in more severe disease. Reports from European centers, in particular, where the disease can often more advanced biochemically at the time of diagnosis call attention to these problems. The relationship of these possible systemic manifestations of primary hyperparathyroidism to indexes of disease activity before and after parathyroid surgery would be of particular interest. Are these atypical features, especially cardiovascular manifestations, seen only in more severely affected patients? Further controlled studies of patients with differing severity of primary hyperparathyroidism would be helpful in addressing this question.

Newer pharmacological approaches to the management of primary hyperparathyroidism are being developed and are recommended for further study. The likelihood that some of these therapies will favorably influence bone turnover, bone density, serum calcium, and even the secretion of PTH in primary hyperparathyroidism lends promise to the concept that specific medical therapy for primary hyperparathyroidism might become available in the near future. As these agents are developed for primary hyperparathyroidism, questions regarding the reversibility of the manifestations of primary hyperparathyroidism could conceivably be studied with these new pharmacological tools.

Health care policy and nutritional issues in the United States may well influence the presentation and clinical profile of primary hyperparathyroidism in the years to come. With greater emphasis placed on skeletal health in many centers for women's health in the United States, surveillance programs could include measurements of PTH even in patients

whose serum calcium is normal. Early information regarding a population of women with elevated PTH levels without any evidence for hypercalcemia or secondary causes of elevated PTH may lead to recognition of primary hyperparathyroidism during its putative first phase when the only manifestation is an elevated level of PTH. Patients who present with this normocalcemic picture should be studied to determine whether this is indeed a forerunner of what we still recognize to be well established primary hyperparathyroidism, namely, hypercalcemia with elevated PTH levels. Incidence rates, diagnostic criteria, bone densitometry, bone histomorphometry, and management issues will be of paramount importance to study as this form of primary hyperparathyroidism emerges over the next decade.

In contrast to the idea that some health surveillance programs have become highly proactive, other programs are abandoning the multichannel screening test in favor of specific requests for analytes, such as the serum calcium concentration. It is not known to what extent this shift in ready availability of serum calcium measurements by multichannel screening will have an impact on the recognition of primary hyperparathyroidism.

Nutritional issues are also important to pursue from an investigative viewpoint. The apparent relationship between low vitamin D stores and disease activity of primary hyperparathyroidism raises questions of how vitamin D deficiency may be related to the pathophysiology of primary hyperparathyroidism. Moreover, if vitamin D deficiency becomes more pervasive in the population, patients with primary hyperparathyroidism may present with evidence for more active disease. How this consideration interfaces with issues of greater or lesser surveillance of the population *vis-à-vis*

serum calcium and PTH levels are challenging issues to investigate over the next decade.

With the advent of newer surgical approaches to parathyroidectomy, research is needed to determine which procedures are to be recommended and in which patients. Controlled trials will be required to determine optimal surgical techniques, their relative costs, success, and complications. The cost-effectiveness of preoperative and intraoperative localization procedures in patients who have or have not had previous neck surgery also needs further evaluation, as do efforts to improve the sensitivity and specificity of the techniques.

### Acknowledgments

The Panel acknowledges the following organizations: The Endocrine Society, The Paget Foundation for Paget's Disease of Bone and Related Disorders, American Society of Bone and Mineral Research, International Society of Clinical Densitometry, American Association of Clinical Endocrinology, International Society for Bone and Mineral Research, Eli Lilly & Co., and Amgen, Inc. The participants of the workshop contributed not only their manuscripts for this supplement, but also were active discussants and presenters at the workshop itself: Sylvano Adami, Richard Alexander, Andrew Arnold, Francisco Bandeira, Roger Bouillon, Maria-Luisa Brandi, Ed Brown, Orlo Clark, Erik Erickson, Lorraine Fitzpatrick, Robert Heaney, Karl Insogna, Harald Jueppner, Aliya Kahn, Sundeep Khosla, Michael Levine, Robert Marcus, Stephen Marx, Joe Melton, Paul Miller, Ed Nemeth, D. Sudhaker Rao, Gideon Rodan, Elizabeth Shane, Dolores Shoback, and Norman Thompson.

Received August 23, 2002. Accepted August 26, 2002.

Address all correspondence and requests for reprints to: John P. Bilezikian, M.D., Department of Medicine, College of Physicians and Surgeons, 630 West 168th Street, New York, New York 10032. E-mail: jpb2@columbia.edu.

This summary statement appeared in *J Bone Miner Res* (Suppl 2), 2002. It is reprinted here with permission from the American Society of Bone and Mineral Research.