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## A 10-YEAR PROSPECTIVE STUDY OF PRIMARY HYPERPARATHYROIDISM WITH OR WITHOUT PARATHYROID SURGERY

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### ABSTRACT

**Background** In the United States, most patients with primary hyperparathyroidism have few or no symptoms. The need for parathyroidectomy to treat all patients with this disorder has therefore been questioned.

**Methods** We studied the clinical course and development of complications for periods of up to 10 years in 121 patients with primary hyperparathyroidism, 101 (83 percent) of whom were asymptomatic. There were 30 men and 91 women (age range, 20 to 79 years). During the study, 61 patients (50 percent) underwent parathyroidectomy, and 60 patients were followed without surgery.

**Results** Parathyroidectomy in patients with or without symptoms led to normalization of serum calcium concentrations and a mean ( $\pm$ SE) increase in lumbar-spine bone mineral density of  $8\pm 2$  percent after 1 year ( $P=0.005$ ) and  $12\pm 3$  percent after 10 years ( $P=0.03$ ). Bone mineral density of the femoral neck increased  $6\pm 1$  percent after 1 year ( $P=0.002$ ) and  $14\pm 4$  percent after 10 years ( $P=0.002$ ). Bone mineral density of the radius did not change significantly. The 52 asymptomatic patients who did not undergo surgery had no change in serum calcium concentration, urinary calcium excretion, or bone mineral density. However, 14 of these 52 patients (27 percent) had progression of disease, defined as the development of at least one new indication for parathyroidectomy. All 20 patients with symptoms had kidney stones. None of the 12 who underwent parathyroidectomy had recurrent kidney stones, whereas 6 of the 8 patients who did not undergo surgery did have a recurrence.

**Conclusions** In patients with primary hyperparathyroidism, parathyroidectomy results in the normalization of biochemical values and increased bone mineral density. Most asymptomatic patients who did not undergo surgery did not have progression of disease, but approximately one quarter of them did have some progression. (N Engl J Med 1999;341:1249-55.)

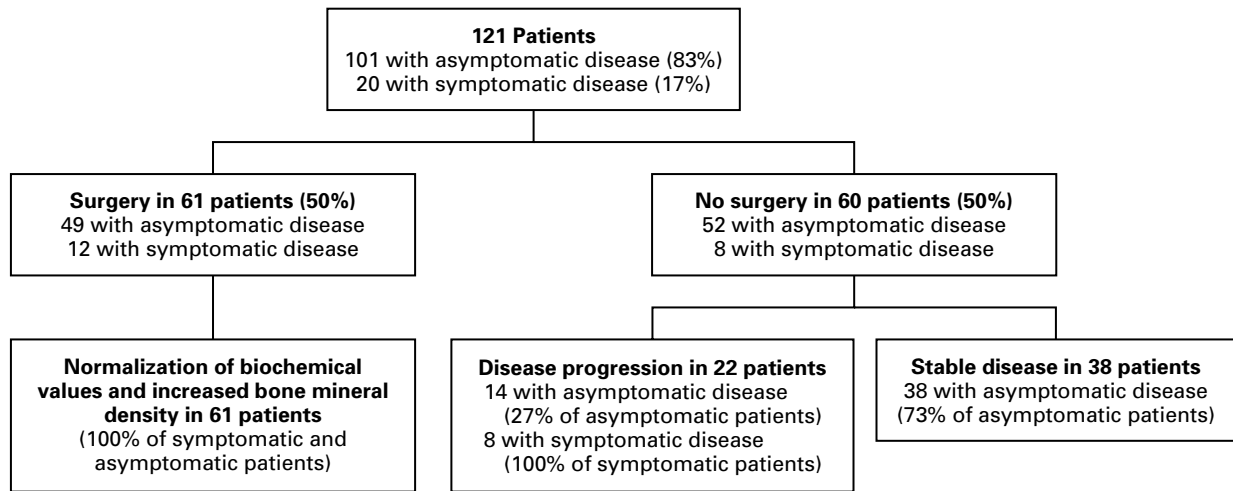
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PRIMARY hyperparathyroidism in the Western world has evolved from a disease of “bones, stones, and groans” to a disorder that is asymptomatic in most patients.<sup>1-5</sup> As a result, common questions include the following: When is surgery — the definitive therapy for this disorder — indicated in patients with primary hyperparathyroidism who have no symptoms,<sup>6-8</sup> and what is the natural history of the disease in such patients?

Early studies of patients with primary hyperparathyroidism do not help to answer these questions, because many of the patients had symptomatic disease. In a 1981 study of 197 patients, for example, 51 percent had nephrolithiasis and 24 percent had radiographic evidence of bone involvement.<sup>9</sup> Today, only about 20 percent of patients have nephrolithiasis, and radiographically detectable bone disease is rare.<sup>5</sup> To address some of these issues, in 1990 the National Institutes of Health Consensus Development Conference on the Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism recommended criteria for surgery, while recognizing that prospective data were needed to “define this disease’s multisystem effects” and to “assess the long-term incidence and progression of complications” in asymptomatic patients.<sup>10</sup>

Fifteen years ago, we initiated a prospective study of primary hyperparathyroidism to define the biochemical, bone densitometric, and histomorphometric features of the disorder; to determine its natural history; and to assess the results of surgery. In this report, we describe our findings during 10 years of follow-up in two cohorts of patients: one treated by successful parathyroidectomy and the other observed without intervention.

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**Figure 1.** Base-Line Characteristics and Outcome in 121 Patients with Primary Hyperparathyroidism.

All patients with symptomatic disease had kidney stones. In patients with disease progression, either an indication for surgery (according to NIH Consensus Conference guidelines<sup>10</sup>) developed or an overt complication of hyperparathyroidism (such as kidney stones, fracture, or osteitis fibrosa cystica) occurred during follow-up.

## METHODS

### Patients

Over a seven-year period we enrolled 137 patients in a prospective study of primary hyperparathyroidism. Of these patients, 121 (88 percent) participated for at least one year and are included in this report (Fig. 1). The study was approved by the institutional review board of Columbia–Presbyterian Medical Center, and all patients gave written informed consent. These patients were also included in earlier cross-sectional<sup>11,12</sup> and longitudinal<sup>13,14</sup> studies conducted by our group. Primary hyperparathyroidism was diagnosed when the patient had hypercalcemia and high serum parathyroid hormone concentrations. Patients who were receiving thiazide or lithium therapy were excluded.

The decision to recommend parathyroidectomy was based on guidelines adopted by the NIH Consensus Conference.<sup>10</sup> Thus, all patients with signs of hyperparathyroidism — osteitis fibrosa cystica, nephrolithiasis, classic neuromuscular symptoms (proximal muscle weakness, atrophy, hyperreflexia, and gait disturbances),<sup>12,15</sup> and hyperparathyroid crisis (a discrete episode of life-threatening hypercalcemia) — were referred for surgery. Nephrolithiasis was documented by a review of the medical records. Screening radiography for nephrolithiasis or nephrocalcinosis was not routinely performed. A complete neurologic evaluation was performed for the first 42 patients enrolled<sup>12</sup> and as needed for subsequent patients. Some patients described vague constitutional symptoms that are often associated with primary hyperparathyroidism, including fatigue, weakness with no objective signs, and constipation. However, since such symptoms are common and are not clearly caused by either mild hypercalcemia or high serum parathyroid hormone concentrations, these patients were not considered to have symptoms.

We recommended surgery for patients without symptoms if they met at least one of the following criteria<sup>10</sup>: a serum calcium concentration of greater than 12 mg per deciliter (3 mmol per liter), marked hypercalciuria (urinary calcium excretion, greater than 400 mg per day [10 mmol per day]), markedly reduced cortical bone density (z score for the distal third of the radius, less than  $-2$ ; the z score reflects the standard deviation from the mean for a sex-matched and age-matched reference population), an unexplained reduction in creatinine clearance, and an age of less than 50 years. Moderate calcium intake without vitamin D supplementa-

tion was recommended for patients who did not undergo surgery. No particular recommendations were made with regard to exercise. Five postmenopausal women took estrogen–progestin therapy for at least one year during follow-up.

Although 75 patients (62 percent) met the criteria for parathyroidectomy at enrollment, 29 did not undergo surgery, for the following reasons: previous parathyroid surgery that was not curative (5 patients), an intercurrent medical condition or advanced age (4 patients), and the patient's choice (20 patients). Fifteen of the 46 patients (33 percent) who did not meet the criteria for parathyroidectomy elected to undergo the procedure. Eleven patients, six of whom met guidelines for surgery at enrollment, underwent parathyroidectomy after follow-up for 2 to 11 years (mean, 5 years). This group of 11 patients included 6 of the 14 patients in whom an indication for surgery, which was not present at base line, developed during follow-up.

### Study Protocol

All patients underwent biochemical studies at base line and every four months thereafter if they were followed with no intervention, or every six months thereafter if they underwent parathyroidectomy. Serum calcium, phosphorus, and alkaline phosphatase were measured by automated techniques (Technicon Instruments, Tarrytown, N.Y.). Serum parathyroid hormone was measured by immunoradiometric assay (interassay coefficient of variation, 5.6 percent),<sup>16</sup> and serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured as previously described (interassay coefficients of variation, 9.6 percent and 9.8 percent, respectively).<sup>11</sup> Serum osteocalcin was measured by radioimmunoassay (interassay coefficient of variation, 4.8 percent).<sup>17</sup> Urinary pyridinoline and deoxypyridinoline were measured by high-performance liquid chromatography,<sup>18</sup> and urinary calcium by atomic absorption spectrophotometry.

The bone mineral density of the lumbar spine (L2, L3, and L4), femoral neck, and distal third of the nondominant radius was measured at enrollment and yearly thereafter. Before 1991, we used single-photon and dual-photon absorptiometry (SP2 and DP3 scanners, respectively; Lunar Radiation, Madison, Wis.), and thereafter we used dual-energy x-ray absorptiometry (model QDR-1000 bone densitometer, Hologic, Waltham, Mass.). The coefficient of variation of these measurements on a phantom spine

was 0.4 percent. The data on bone density are reported both as absolute measurements and as z scores.<sup>19</sup> The results obtained with the two densitometric techniques were compared by means of a series of equations we developed,<sup>13</sup> and all measurements are presented in terms of dual-energy x-ray absorptiometry values (in grams per centimeter squared). The contrast between the increase in bone mineral density in the patients who underwent parathyroidectomy and the lack of change in patients who did not argues against systematic errors resulting from the conversion to the use of dual-energy x-ray absorptiometry.

**Statistical Analysis**

For each patient, we determined the change in bone mineral density from base line at each site during each year of follow-up and then averaged the changes for all the patients for each year of follow-up. Student's paired t-tests were used to evaluate changes in biochemical values and bone mineral density over time, and Student's unpaired t-tests were used to compare biochemical values and changes in bone mineral density between the group that underwent surgery and the group that received no intervention. Logistic-regression analysis was used to identify factors associated with loss of bone mineral density.

**RESULTS**

**Characteristics of the Patients**

The cohort of 121 patients was made up of 29 premenopausal women (24 percent), 62 postmenopausal women (51 percent), and 30 men (25 percent) with mild primary hyperparathyroidism. Only 20 patients (17 percent) had symptoms of hyperparathyroidism — specifically, a history of kidney stones. None of the 121 patients had clinical bone disease or fractures, neuromuscular symptoms, or hyperparathyroid crisis. Because there is little debate about the importance of surgery in symptomatic patients with primary hyperparathyroidism, a central goal of this study was to characterize the course of the disease and its complications in the 101 patients who were asymptomatic. Therefore, patients were studied according to treatment and according to the presence or absence of symptoms referable to their hyperparathyroidism (Fig. 1 and Table 1).

The 61 patients who underwent parathyroidectomy were younger and had higher serum calcium concentrations and urinary calcium excretion than the 60 who did not undergo surgery (Table 1). The patients who underwent surgery also had significantly lower z scores for bone mineral density at the lumbar spine and femoral neck, but not at the radius. The serum parathyroid hormone, alkaline phosphatase, and vitamin D concentrations were similar in these two groups.

**Course of Disease among Patients Who Underwent Parathyroidectomy**

Of the 61 patients who underwent parathyroidectomy, 49 (80 percent) had an adenoma, 7 (11 percent) had hyperplasia, and 5 (8 percent) had a mixture of adenomatous and hyperplastic disease. All had normal biochemical values after surgery (Table 2).

Increases in bone mineral density at the lumbar spine and femoral neck in these patients have previ-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH PRIMARY HYPERPARATHYROIDISM.\***

CHARACTERISTIC	SURGERY (N=61)	No SURGERY (N=60)	NORMAL RANGE
Age (yr)	51±1	58±2†	
Sex (M/F)	16/45	14/46	
Kidney stones (no. of patients)‡	12	8	
Serum calcium (mg/dl)	10.8±0.1	10.4±0.1§	8.4–10.2
Serum parathyroid hormone (pg/ml)	126±10	117±9	10–65
Urinary calcium (mg/g of creatinine)	271±17	225±15¶	<300
Serum alkaline phosphatase (U/liter)	93±4	98±6	<100
Serum osteocalcin (ng/ml)	9.7±6.5	9.3±3.1	3.4–11.7
Urinary pyridinoline (nmol/mmol of creatinine)	63±15	57±19	22–89
Urinary deoxypyridinoline (nmol/mmol of creatinine)	17±6	18±7	4–21
Serum 25-hydroxyvitamin D (ng/ml)	22±2	22±1	9–52
Serum 1,25-dihydroxyvitamin D (pg/ml)	62±3	56±2	15–60
Bone mineral density (z score)			
Lumbar spine	-0.84±0.19	0.00±0.23†	
Femoral neck	-1.31±0.11	-0.67±0.14§	
Radius	-1.20±0.20	-1.00±0.21	

\*Plus-minus values are means ±SD. To convert values for serum calcium to millimoles per liter, multiply by 0.25; to convert values for urinary calcium to millimoles per liter, multiply by 0.025.

†P=0.006 for the comparison with the value in patients who had surgery.

‡The patients had no other symptoms or signs of primary hyperparathyroidism (e.g., bone disease or fractures, neuromuscular symptoms, or hyperparathyroid crisis).

§P<0.001 for the comparison with the value in patients who had surgery.

¶P=0.05 for the comparison with the value in patients who had surgery.

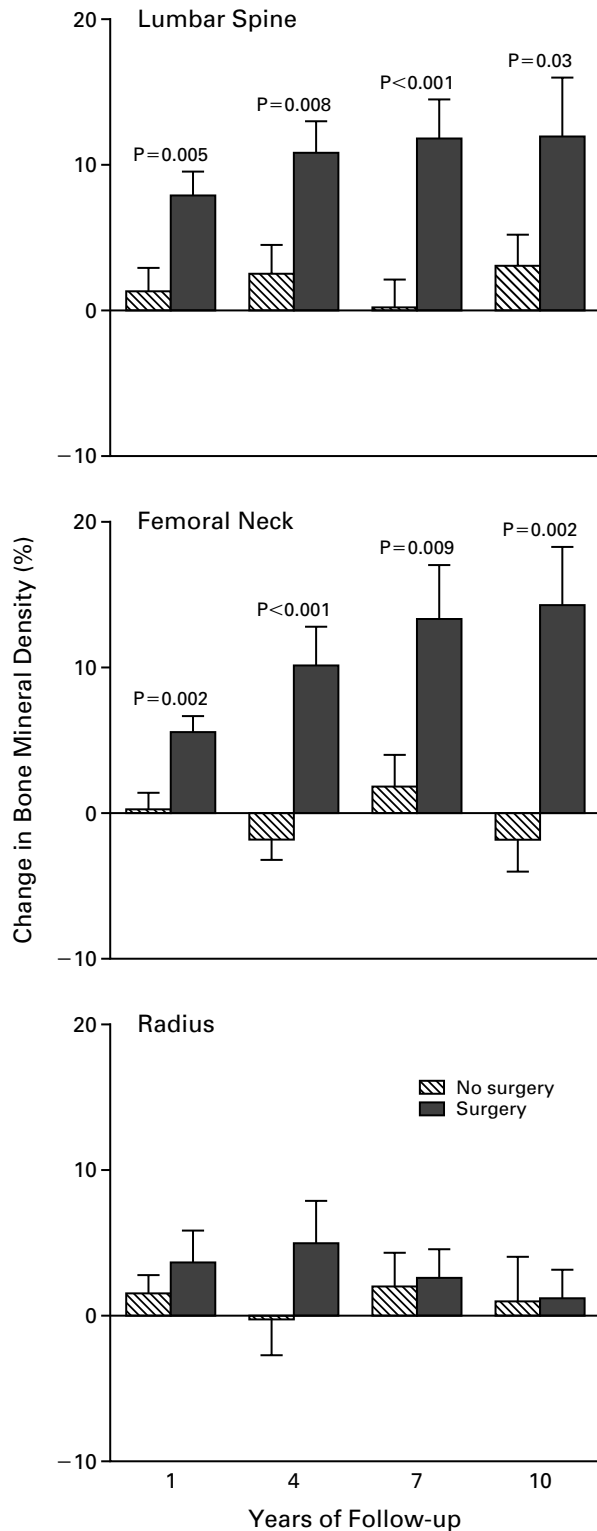
||The z score reflects the standard deviation from the mean for a sex-matched and age-matched reference population.

**TABLE 2. EFFECT OF PARATHYROIDECTOMY IN 61 PATIENTS WITH PRIMARY HYPERPARATHYROIDISM.\***

VARIABLE	BASE LINE (N=61)	YEAR 1 AFTER SURGERY (N=58)	YEAR 10 AFTER SURGERY (N=17)
Kidney stones (no. of patients)	12	0	0
Serum calcium (mg/dl)	10.8±0.1	9.1±0.1†	9.4±0.3†
Serum parathyroid hormone (pg/ml)	126±10	49±3†	49±6†
Urinary calcium (mg/day)	271±17	151±15†	131±56†
Serum alkaline phosphatase (U/liter)	93±4	77±5†	93±11

\*Plus-minus values are means ±SD. The base-line values are the means of three measurements in each patient. To convert values for serum calcium to millimoles per liter, multiply by 0.25; to convert values for urinary calcium to millimoles per liter, multiply by 0.025.

†P<0.001 for the comparison with the base-line value.



NO. OF PATIENTS		1	4	7	10
No surgery	44	28	21	14	
Surgery	39	24	17	17	

ously been reported for a four-year period after parathyroidectomy.<sup>14</sup> During the 10-year follow-up, the increases in bone density at these sites, as compared with base-line (preoperative) values, in this group were prompt and sustained (Fig. 2), although the trend toward a further increase after year 1 was significant only for the femoral-neck values ( $P=0.02$  after 4 years and  $P=0.03$  after 7 and after 10 years, by paired t-tests). Bone mineral density of the lumbar spine and femoral neck increased to the same extent in the 28 postmenopausal women who underwent surgery as in premenopausal women and men who underwent surgery (data not shown). There was no significant change in the bone mineral density of the radius.

Among the 61 patients who underwent parathyroidectomy, 49 were asymptomatic and 12 were symptomatic (all had kidney stones) (Fig. 1). After surgery, the increases in bone mineral density at the lumbar spine and femoral neck in the patients without symptoms were similar to those in the patients with symptoms (data not shown). None of the 12 patients with symptoms who underwent parathyroidectomy had recurrence of kidney stones postoperatively (Table 2).

#### Course of Disease among Patients Who Did Not Undergo Parathyroidectomy

Of the 60 patients who did not undergo parathyroidectomy, 52 were asymptomatic (Fig. 1). The eight symptomatic patients, all of whom had kidney stones, either refused surgery or had previously undergone unsuccessful surgery.

There were no significant changes from base-line values in serum calcium, parathyroid hormone, or alkaline phosphatase concentrations; urinary calcium excretion (Table 3); or bone mineral density at any site during the 10-year period in these 52 asymptomatic patients. There also were no significant changes in biochemical values or bone mineral density from base line in the subgroup of 29 postmenopausal women who had asymptomatic disease and did not undergo surgery (data not shown).

However, 11 of these 52 patients (21 percent) had a decrease of more than 10 percent in bone density at one or more sites over the 10-year period. All but 1 of these 11 patients were women, and 5 became menopausal during follow-up. These 11 patients had higher mean ( $\pm$ SD) serum calcium concentrations at base line than those in whom bone density did not

**Figure 2.** Mean ( $\pm$ SE) Change in Bone Mineral Density at Three Sites in Patients with Primary Hyperparathyroidism, According to Treatment.

Data shown are the cumulative percent changes from base line at each site after 1, 4, 7, and 10 years of follow-up in patients who did not undergo parathyroidectomy and in those who underwent parathyroidectomy. There were no significant changes from base line in radial bone mineral density.

**TABLE 3.** BIOCHEMICAL VALUES IN 52 ASYMPTOMATIC PATIENTS WITH PRIMARY HYPERPARATHYROIDISM WHO DID NOT UNDERGO PARATHYROIDECTOMY.\*

VARIABLE	BASE LINE (N=52)	YEAR 5 OF FOLLOW-UP (N=35)	YEAR 10 OF FOLLOW-UP (N=14)
Serum calcium (mg/dl)	10.5±0.1	10.6±0.1	10.3±0.2
Serum parathyroid hormone (pg/ml)	118±9	113±67	106±26
Urinary calcium (mg/day)	232±18	193±20	152±34
Alkaline phosphatase (U/liter)	98±6	101±9	110±13
Serum 1,25-dihydroxyvitamin D (pg/ml)	56±2	55±3	53±6

\*Values are means ±SD. The base-line values are the means of three measurements in each patient. There were no significant differences from base line in any of the variables shown during follow-up. To convert values for serum calcium to millimoles per liter, multiply by 0.25; to convert values for urinary calcium to millimoles per liter, multiply by 0.025.

change ( $10.7 \pm 0.5$  vs.  $10.3 \pm 0.4$  mg per deciliter [ $2.68 \pm 0.12$  vs.  $2.58 \pm 0.10$  mmol per liter],  $P=0.03$ ); 4 met criteria for surgery at base line and thus had more severe disease than those in whom bone density did not change. Other than the base-line serum calcium concentration, onset of menopause during follow-up was the only factor identified in the logistic-regression analysis as having an association with a risk of loss of bone mineral density ( $P=0.006$ ).

Fourteen of the 52 asymptomatic patients (27 percent) who did not undergo surgery had evidence of disease progression (Fig. 1), defined as the development of one or more new indications for parathyroidectomy during follow-up. Marked hypercalcemia (serum calcium concentration of more than 12 mg per deciliter) developed in two patients, marked hypercalciuria (urinary calcium excretion of more than 400 mg per day) in eight, and low cortical bone density ( $z$  score for the distal third of the radius, less than  $-2$ ) in six. These patients were younger at base line than those with no disease progression ( $52 \pm 12$  vs.  $60 \pm 10$  years old,  $P=0.02$ ), and six became menopausal during follow-up. Their serum calcium and parathyroid hormone concentrations, urinary calcium excretion, and bone mineral density at base line were similar to those of the asymptomatic patients in whom there was no progression of disease. None of these 14 patients had nephrolithiasis, an unexplained decrease in creatinine clearance, a fracture, or hyperparathyroid crisis. Six of the 14 underwent parathyroidectomy after the development of an indication for surgery. In addition, four asymptomatic patients who did not meet criteria for surgery chose to have surgery after several years of follow-up.

Among the eight patients who had kidney stones at base line but who did not undergo parathyroidectomy, all eight had at least one sign of progression: six had a recurrence of kidney stones and three had

new indications for surgery during follow-up (Fig. 1). Only one of these eight patients eventually underwent parathyroidectomy. In contrast, none of the 12 patients with kidney stones who underwent surgery initially had a recurrence (Table 2).

## DISCUSSION

The questions underlying this study were clearly delineated at the NIH Consensus Conference in 1990: What are the benefits of curing primary hyperparathyroidism? What are the consequences of nonintervention? On the basis of our results we can now comment on the long-term course of treated and untreated asymptomatic primary hyperparathyroidism.

In the 61 patients who underwent surgery, biochemical values normalized and bone density increased. These results, which extend those of previous studies,<sup>14,20</sup> reveal that successful surgery leads to sustained increases in bone mineral density at sites rich in cancellous bone (such as the lumbar spine and femoral neck) in patients with primary hyperparathyroidism, including postmenopausal women. A satisfactory explanation for this sustained increase in bone mineral density remains elusive. One hypothesis attributes the increase to mineralization of the expanded remodeling space that is characteristic of primary hyperparathyroidism.<sup>21</sup> This hypothesis, however, does not explain why the increase in bone mineral density is sustained. A second hypothesis is that surgery restores normal pulsatility to the secretion of parathyroid hormone, which is thought to stimulate the formation of cancellous bone.<sup>22,23</sup> Paradoxically, although cortical bone is more vulnerable than cancellous bone to the catabolic effects of parathyroid hormone,<sup>24</sup> parathyroidectomy is not followed by an increase in radial bone mineral density. Our results substantiate earlier observations that cortical bone loss in patients with primary hyperparathyroidism is not readily reversible.<sup>25-28</sup>

Our data are in agreement with those of previous, shorter-term studies that found that asymptomatic patients who did not undergo parathyroidectomy had stable bone mineral density.<sup>13,26,29-31</sup> In one study, however, bone density at the radius did decrease during follow-up.<sup>26</sup> Although age-related decreases in bone mineral density are expected during middle age, bone mineral density in most of our patients who did not undergo surgery remained stable during a decade of observation. Our inability to detect decreases in bone mineral density could be due to limitations related to sample size or the presence of vertebral degenerative joint disease, which can alter bone mineral density values at the lumbar spine, but the finding that femoral-neck bone mineral density was stable makes the latter explanation less likely. Alternatively, the stable bone mineral density could reflect our finding that patients with primary hyper-

parathyroidism do not have the expected age-related changes on bone histomorphometry, perhaps because of the continued anabolic effect of parathyroid hormone on cancellous bone.<sup>32-34</sup>

Bone density was not stable in all our patients. Those who entered menopause during follow-up were at risk for bone loss, as are normal women at the onset of menopause. The absence of reliable predictors of bone loss in most patients makes regular measurement of bone density mandatory in patients who do not undergo parathyroidectomy.

Although no symptomatic complications such as fractures or kidney stones developed during follow-up in any of the patients with asymptomatic primary hyperparathyroidism who did not undergo surgery, hypercalcemia and hypercalciuria did worsen and bone mineral density decreased in approximately one quarter of this subgroup. On the other hand, the majority of patients who initially had symptoms of primary hyperparathyroidism (kidney stones) but did not undergo surgery had recurrent kidney stones during follow-up.

Our results suggest that patients with symptomatic primary hyperparathyroidism should undergo surgery. In both patients with and those without symptoms, parathyroidectomy can be expected to result in biochemical cure and increases in bone mineral density at the lumbar spine and femoral neck. Thus, surgery can be a particularly suitable treatment option for patients who have low bone mineral density at these sites at the time of diagnosis.

This study has several limitations. First, our results are observational. Second, we did not include the nonspecific manifestations of hyperparathyroidism in our criteria for symptomatic disease, because validated, quantitative measures of these manifestations are not yet available.

In conclusion, biochemical test results and bone mineral density did not change significantly during follow-up in most patients with asymptomatic primary hyperparathyroidism who do not undergo surgery. Since women with hyperparathyroidism seem to be at risk for the progression of disease at the time of menopause, they should consider parathyroidectomy. Because some asymptomatic patients have progression of disease over time, biannual measurements of serum calcium concentrations and annual measurements of urinary calcium excretion and bone mineral density should be performed in all patients who do not undergo surgery. These tests will permit the timely recognition of any indications for surgery as they develop and should allow most patients with asymptomatic primary hyperparathyroidism to be monitored safely without surgery.

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**CORRECTION**

**A 10-Year Prospective Study of Primary Hyperparathyroidism with or without Parathyroid Surgery**

A 10-Year Prospective Study of Primary Hyperparathyroidism with or without Parathyroid Surgery . On page 1251, in Table 1, the units for urinary calcium should have been mg/day, not mg/g of creatinine, as printed. The first footnote to Tables 1 and 2, on page 1251, and Table 3, on page 1253, should have stated that the "Values are means  $\pm$ SE," not "means  $\pm$ SD," as printed; and "to convert values for urinary calcium to millimoles per day," not "per liter," as printed. Also, in Table 3, the values for serum parathyroid hormone after 5 and 10 years of follow-up should have been  $113\pm 14$  and  $106\pm 8$ , respectively, not  $113\pm 67$  and  $106\pm 26$ , as printed.