ASYMPTOMATIC
PRIMARY HYPERPARATHYROIDISM

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Initially in the mid-1920's, primary hyperparathyroidism (PHPT) was regarded as a rare and severe disease of bone, "osteitis fibrosa cystica"(1). Subsequently, in the 1940's and 1950's, Albright's group recognized a different clinical presentation of PHPT in patients with renal stones but without evidence of overt bone disease(2,3). It soon became clear that renal stones were a far more frequent complication of PHPT than overt osteitis, being the presenting complaint in as many as 50 percent of patients in some series(4). In recent years, routine screening of serum Ca by automated clinical chemistry techniques has contributed to an increased rate of detection of PHPT in the population. For example, introduction of multichannel screening at the Mayo Clinic resulted in a fourfold increase in the diagnosis of PHPT among local residents(4). It is currently estimated that the prevalence of PHPT is approximately one case per thousand population or about 0.1 percent of the American population(5). For the middle-aged, the annual incidence rate is 100-200 cases per 100,000 (higher in women) representing 60,000 new cases of PHPT occurring each year in the United States(6).

In association with widespread chemical screening, the typical presentation of PHPT in the 1970's and 1980's has become more subtle. Bone disease is now rare(<10%), and even the incidence of kidney stones has diminished. For example, at the Mayo Clinic, the frequency of urolithiasis in patients with PHPT declined from 51 percent to 4 percent after Ca screening began(4). The proportion of patients with no symptoms or objective adverse effects of PHPT rose from 18 percent to 51 percent. Other series, as well, confirm that over half the cases of PHPT currently diagnosed are totally asymptomatic(7). What to do with the increasing number of patients presenting with mild asymptomatic PHPT is a pressing, but as yet, unresolved problem. A review of studies attempting to grapple with the question of which is more dangerous: parathyroidectomy or the untreated disease, will constitute this Grand Rounds.

THE CASE FOR MEDICAL MANAGEMENT

Perhaps the earliest, serious study of asymptomatic PHPT was that performed at the Mayo Clinic by Scholz and Purnell(8). This was a 10 year prospective study, started in 1968, that involved 142 patients with asymptomatic PHPT. Patients were enrolled in this study if they did not meet any of the criteria for surgical treatment as shown in Table 1.

Table 1.—**Criteria for Surgical Treatment in Provisional Hyperparathyroidism**

1. Mean serum calcium >11.0 mg/dl
2. Roentgenographic evidence of bone disease
   a. Subperiosteal resorption of phalanges, distal clavicles, or other bones
   b. Fraying, distal phalangeal tufts
   c. Bone cyst (brown tumor)
   d. Granular demineralization of skull
   e. Osteoporosis with vertebral compression or other bone disease
3. Decreased renal function
4. Metabolically active or infected renal lithiasis*
5. Prolonged observation impractical
   a. Patient cooperation unsatisfactory
   b. Geographic remoteness
   c. Psychiatric complications
6. Gastrointestinal complications
   a. Peptic ulcer not controlled by medical management
   b. Recurrent or chronic pancreatitis

*Metabolic activity of renal lithiasis refers to roentgenographic evidence of new stone formation, enlargement of existing stones, or passage of documented gravel from the urinary tract within past year. Metabolic activity of renal lithiasis is classified as "indeterminate" if inadequate data are available to assess activity and the patient is observed until activity can be established.

During the course of follow-up, approximately 20 percent of the patients developed surgical indications within the first 5 years, and a total of nearly 25 percent of the patients required surgery by the end of 10 years. The indications for surgery that occurred are shown in Table 2.

Table 2.—**Indications for Surgery**

Indication	No. of patients
Increased serum calcium	8
Decreased renal function	6
Active stone disease	5
Psychologic	4
Bone disease (x-ray)	4
Unknown	4
Prophylactic	1
Renal colic	1
Total	33

Thus, 75 percent of patients with PHPT who presented asymptomatically did not develop a surgical indication over a 10 year period. Unfortunately, it was not possible to predict from the initial presentation which patients would ultimately require surgery and which would not. Also, a sizeable portion of the initial patient group (15-20 percent) stopped coming for follow-up. For these reasons and because of concern about insidious spinal bone mineral loss(6,9) or progressive renal impairment (which was believed to occur in up to 5 percent of patients)(10), some investigators had suggested that perhaps all patients in whom the diagnosis of PHPT is made should be operted upon.

Another early contribution to the assessment of patients with asymptomatic PHPT came from our own group(11). In comparing 6

patients with asymptomatic PHPT to 7 hyperparathyroid patients with bone disease or nephrolithiasis, we found that both groups of patients demonstrated evidence of the sequelae of PTH excess including: low radial bone density by ^{125}I-photon absorption, hypercalciuria (urinary Ca >200 mg/day on an intake of 400 mg/day), negative Ca balance (absorbed Ca less than urinary Ca), elevated fasting urinary Ca (greater than .11 mg/mg creatinine) and decreased renal function (creatinine clearance of less than 65 ml/min). Following parathyroidectomy, most of these deleterious effects were reversed commensurate with the return of serum PTH, serum Ca and urinary cyclic AMP toward normal. Parathyroidectomy was felt to be indicated in this subgroup of patients with asymptomatic PHPT who had underlying physiologic derangements because these abnormalities could herald the eventual development of overt symptoms (stones and bones) and were corrected by parathyroid surgery. However, another group of patients with asymptomatic PHPT were detected who did not have any underlying physiologic derangements (Table 3).

Table 3. Features of Asymptomatic PHPT Without Physiologic Derangement (N=10)

		Normal
Serum Ca, mg/dl	11.1	<10.5
Serum P, mg/dl	2.8	>2.5
Serum Mg, mg/dl	2.0	1.7-2.4
Serum PTH, µl-eq/ml	65	<40
Urine Cyclic AMP, nmol/100ml GF	7.26	< 5.40
24-hr Urine Ca, mg/day	142	<200
Fasting Urine Ca, mg/mg cr	.07	<0.11
Bone Density, fractional change	+0.01	0.0
Intes ^{47}Ca Absorption, fraction	.55	<.61

The need for parathyroid exploration in the asymptomatic patients without physiologic derangements is not established. Preliminary data in six of these patients show a lack of progression of the disease over 4-6 years of follow-up. Assessment of bone histomorphometry revealed that only about 10 percent of these patients had abnormalities of bone (increased rsorption surface, increased bone turnover) compared to 75 percent of those with physiologic derangements. Further characterization and long term follow-up will be required before it is known whether the asymptomatic hyperparathyroid patients without physiologic derangements represent an early stage of the disease or a pathogenetically unique subset characterized by skeletal resistance to PTH and an exaggerated renal tubular reabsorption of Ca. This group, which comprises up to 10 percent of patients with PHPT, probably does not have familial hypocalciuria hypercalcemic (see later), since there was no hypermagnesemia or family history of hypercalcemia.

Based on our past work, we have classified patients with PHPT as shown in Fig. 1.

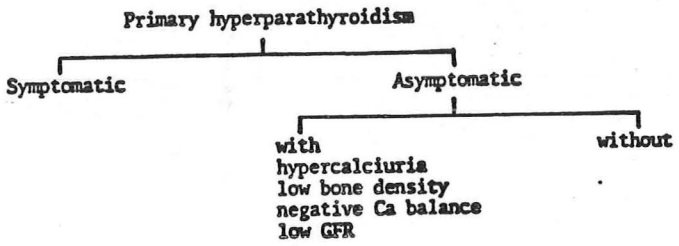


Figure 1.

For those patients with overt symptoms (stones, bones, ulcers, symptomatic hypercalcemia) we have recommended surgery. For those patients that have been asymptomatic, but who manifest underlying physiologic abnormalities, we have also recommended parathyroidectomy, or in some cases, medical therapy (see later). However, for the group with asymptomatic PHPT in the absence of physiologic derangements, our management has been conservative (serial observation). Although this approach to asymptomatic PHPT appears reasonable, it can be validated only by comparing the outcome for each subset over time with and without intervention. Much of this data has been accumulated and awaits analysis.

Meanwhile, several other longitudinal studies were reported from Australia(12) and England(13,14) which provided more support for a conservative approach to asymptomatic PHPT. For example, Rohl et al. reported the follow-up over 3 years of 15 patients with negative cervical exploration or no fall in serum Ca postoperatively(12). There was no deterioration in serum Ca or creatinine levels or progression in parathyroid hormone levels. Seven patients with repeat abdominal radiography showed either no stones or no increase in the size of stones already present. They also followed 30 patients with PHPT who avoided operation because of age, lack of symptoms or other pathology. These were followed for 89 patient years and showed no hypercalcemic crisis, no significant new symptoms and no deterioration in renal function, even in the presence of stones. Twenty-one patients had abdominal radiography at presentation and on follow-up, 17 were normal, 3 showed no increase in the size of the stones already present, and in 1 patient the stones were said to have increased slightly. Vant Hoff et al. studied 32 patients with mild PHPT for a mean of 4.2 years(13). One patient required an operation because of a rise in plasma calcium concentration. There was no significant change in the mean plasma Ca and creatinine concentrations or in blood pressure during the period of follow-up. The progress of these patients who were managed medically was compared with that of a group of 60 patients who had had successful operations for PHPT. There was no significant change in mean plasma creatinine concentration or in blood pressure in the group who had operations during a mean follow-up period of 5.9 years. This would suggest that hypertension which occurs in 20-50 percent of patients with PHPT (compared to 20% of United States adults in general) generally does not respond to parathyroidectomy, and should not be considered

an indication for surgery in patients with asymptomatic PHPT(15). In another British study, Adams followed up 31 patients with mild PHPT for a mean of 4 years(14). There was no significant change in the mean serum creatinine concentration during the period of observation, and only 1 patient required an operation because of a rise in serum Ca concentration.

Although the aforementioned studies may be faulted for rather imprecise descriptions of the "mild" PHPT groups and did not distinguish patients with and without physiologic derangements, in the aggregate they make a strong case for conservative management of mild asymptomatic PHPT(12-14). Collectively, these studies involved 118 non-operated patients studied over a mean period of 3-6 years, and except for a rare patient, there was no change in serum Ca or creatinine (Fig. 2), or other parathyroid-related problems.

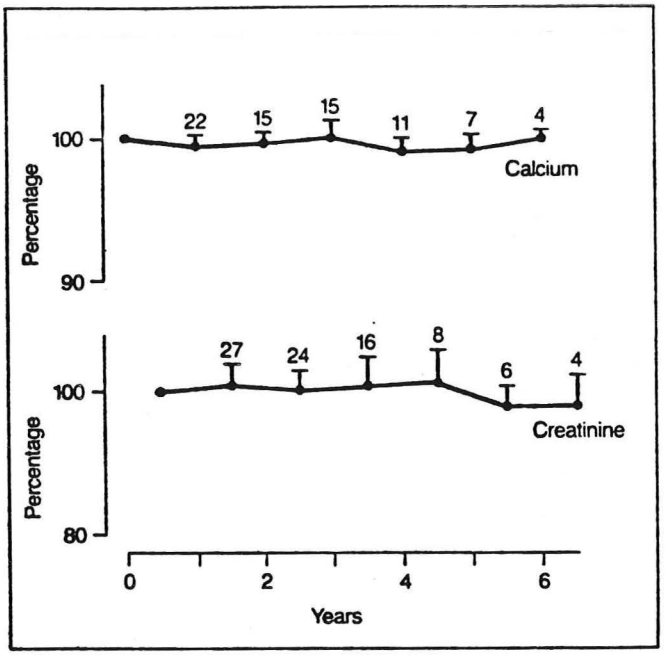


Fig. 2. *Sequential changes in the serum calcium and creatinine concentrations in asymptomatic hyperparathyroidism. Serum calcium is expressed as a percentage of initial value, serum creatinine is the average value for each year expressed as a percentage of the mean value of the first year. Numbers represent numbers in each group. Mean and SE shown.*

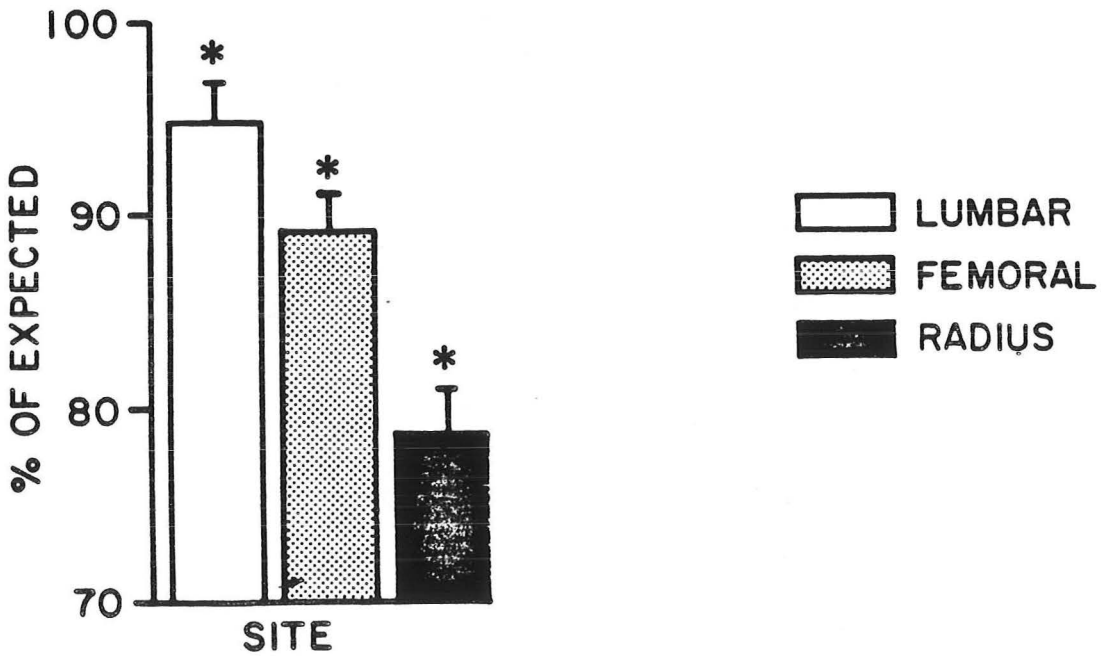
It appeared that the natural history of mild asymptomatic PHPT is probably different from and better than that of the type of PHPT that was usually seen before the advent of routine chemical screening. The type of PHPT that we are seeing now may be at one end of the range of PHPT that was rarely manifest before the advent of routine chemical screening and that may not require operation.

Although most patients with asymptomatic PHPT seem to be at little risk of severe hypercalcemia or progressive renal impairment, there has been nagging concern about the long-term effect of

sustained hyperparathyroidism on the skeleton, particularly in postmenopausal women(6,9). Based on bone mineral density measurements of the radius, a more sensitive index than skeletal x-ray, it has been known for some time that many patients with PHPT have less bone than normal for their age(16,17), a deficiency that becomes more apparent after the postmenopause(18). In contrast to cortical bone, there has been controversy as to whether PTH causes increased loss of trabecular bone (spine). Seeman et al. reported that trabecular bone is reduced preferentially in PHPT(9), and the Mayo Clinic group has also described vertebral crush fractures occurring as an unemphasized mode of presentation for PHPT(6,19). Convincing recent work from Bilizikian at Columbia(20) and Parfitt's group in Detroit(21), which will now be described, has lessened concern about the development of spinal osteoporosis in patients with asymptomatic PHPT.

Bilezikan's group investigated 52 patients with PHPT(20). They had mild hypercalcemia (Ca 11.1 ± 0.1 mg/dl), and no symptoms or specific radiologic signs of skeletal involvement. Although they were asymptomatic with respect to bone disease, 20 percent of the patients did give a history of nephrolithiasis. The purpose of the study was to determine whether skeletal involvement could be appreciated when more sensitive techniques such as bone densitometry and bone biopsy were utilized. A major subset of this population, 31 patients, had complete densitometric studies of three skeletal sites that correspond principally to cortical bone (diaphyseal radius), cancellous bone (lumbar spine) or a combination of both (femoral neck). The bone density at each site in comparison to expected values for age, sex and ethnic-matched normal subjects is shown in Fig. 3.

FIGURE 3



At the lumbar spine, the average bone mineral density was 1.07 ± 0.03 g/cm^2 which is within 5 percent of the expected mean for matched normal subjects. At the femoral neck, the hyperparathyroid population began to diverge from normal with a mean value of 0.78 ± 0.14 g/cm^2, 89 ± 2% of the expected value. The radius showed the greatest difference from normal. Mean bone density at this site was 0.54 ± .10 g/cm^2, only 79 ± 2% of the expected mean. The three sites were significantly different from each other in terms of the extent of their divergence from their expected value ($P<.0001$). Another way of showing that sites comprised primarily of cortical bone are most frequently affected by the hyperparathyroid state is depicted in Table 4.

Table 4. Bone Densitometry in PHPT

	Lumbar	Femoral Neck	Radius
<80% of age/sex matched control	13%	23%	58%

The extent to which bone mineral density was reduced did not correlate significantly with the level of the serum or urinary Ca, the serum PTH concentration, or any other biochemical index of PHPT(20).

Twenty of Bilezikian's patients had histomorphometric analysis of bone obtained by percutaneous trans-iliac biopsy(20). Mean cortical width and cancellous bone volume are shown in Figs. 3 and 4, respectively. Values for hyperparathyroid men are shown in solid circles and those for women in open circles. The solid lines depict mean ±SD values for control men and the dashed lines for control women.

FIGURE 3

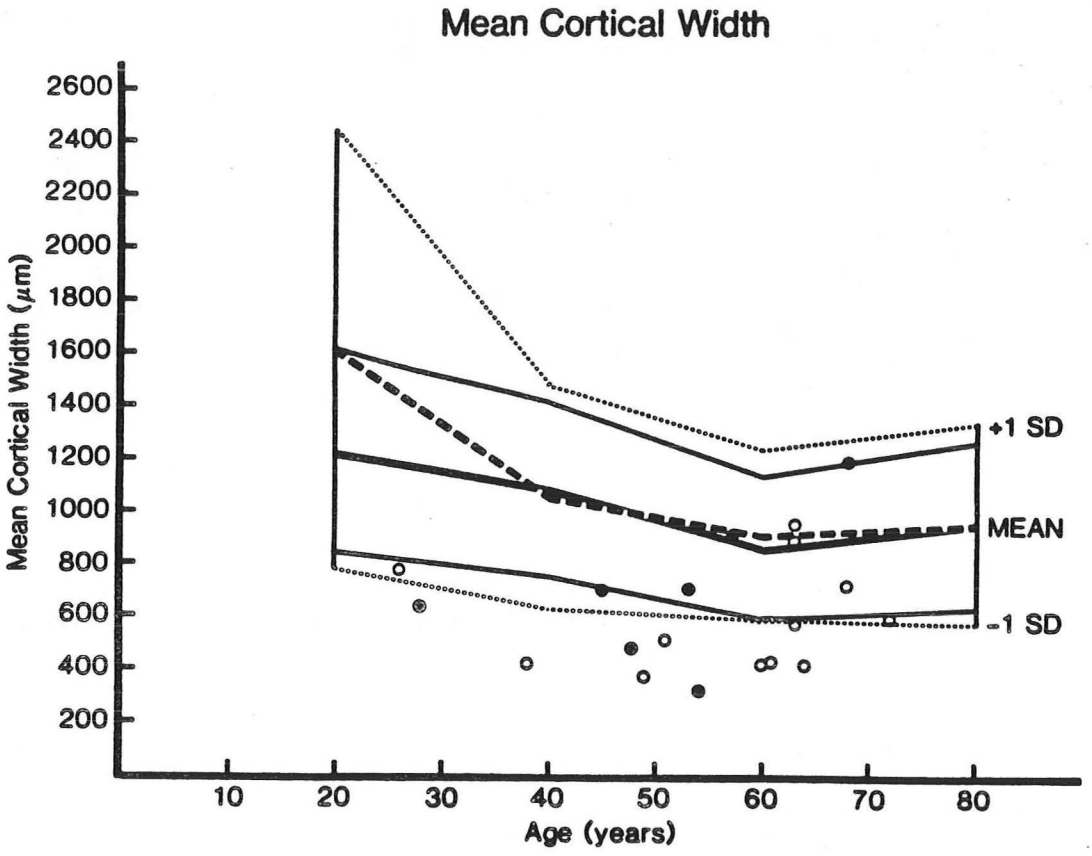
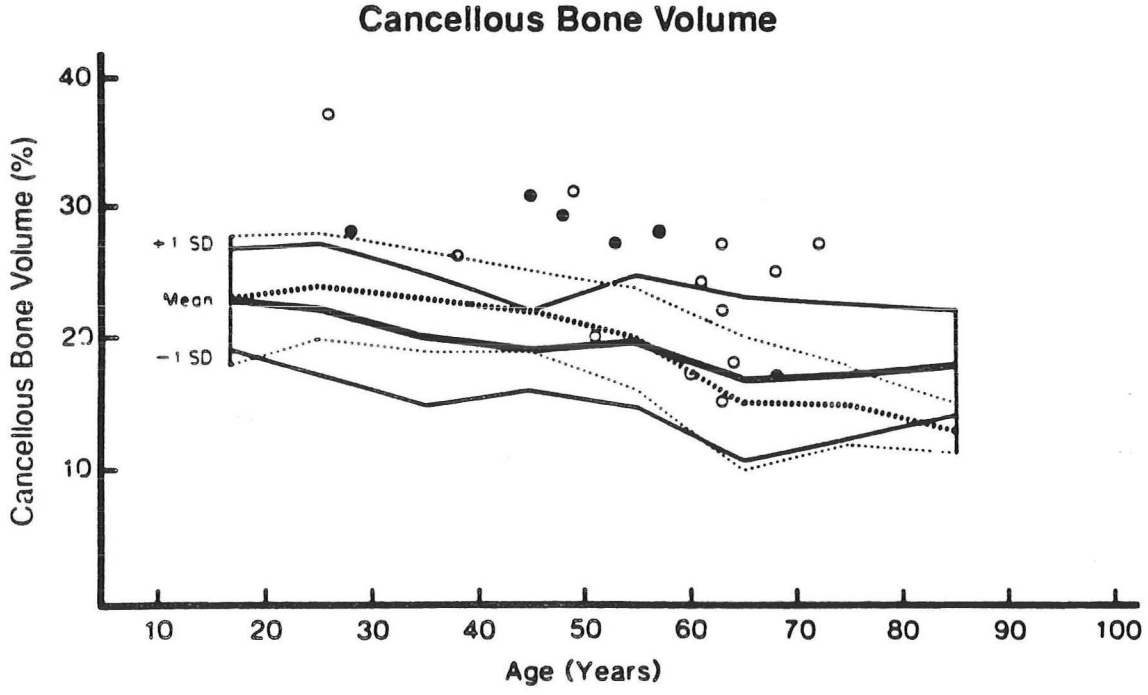


Figure 4



Most patients (84%) with PHPT had cortical width below the control mean, consistent with the data obtained by single photon absorptiometry showing decreased radial bone mineral density. In contrast to the relative decrease in mean cortical width, cancellous bone volume was preserved. Representative scanning electron micrographs of bone biopsy specimens from normal (Fig. 5A) and hyperparathyroid (Fig. 5B) subjects show loss of cortical bone and preservation of cancellous bone in PHPT. Loss of cortical thickness (C) with preservation of trabecular plates (P) can be seen in the hyperparathyroid subject (Fig. 5B).

FIGURE 5A

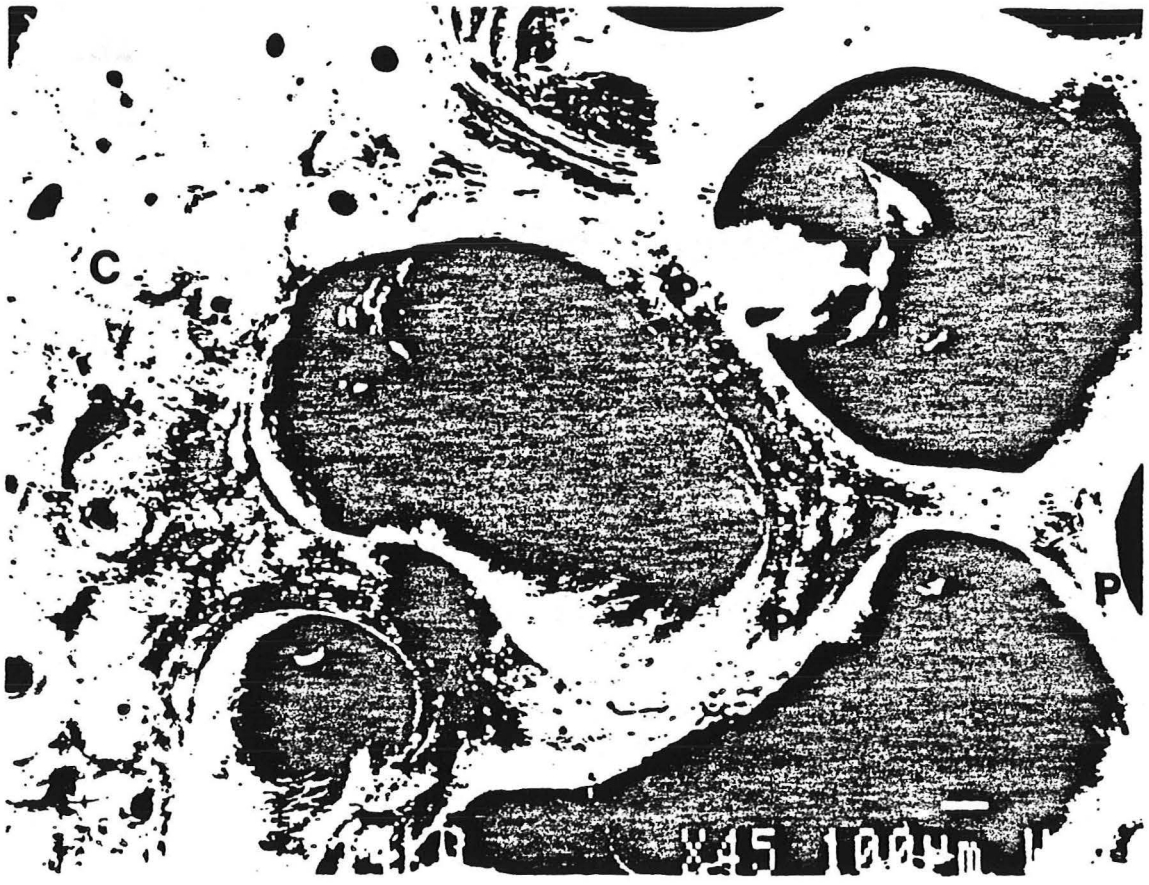
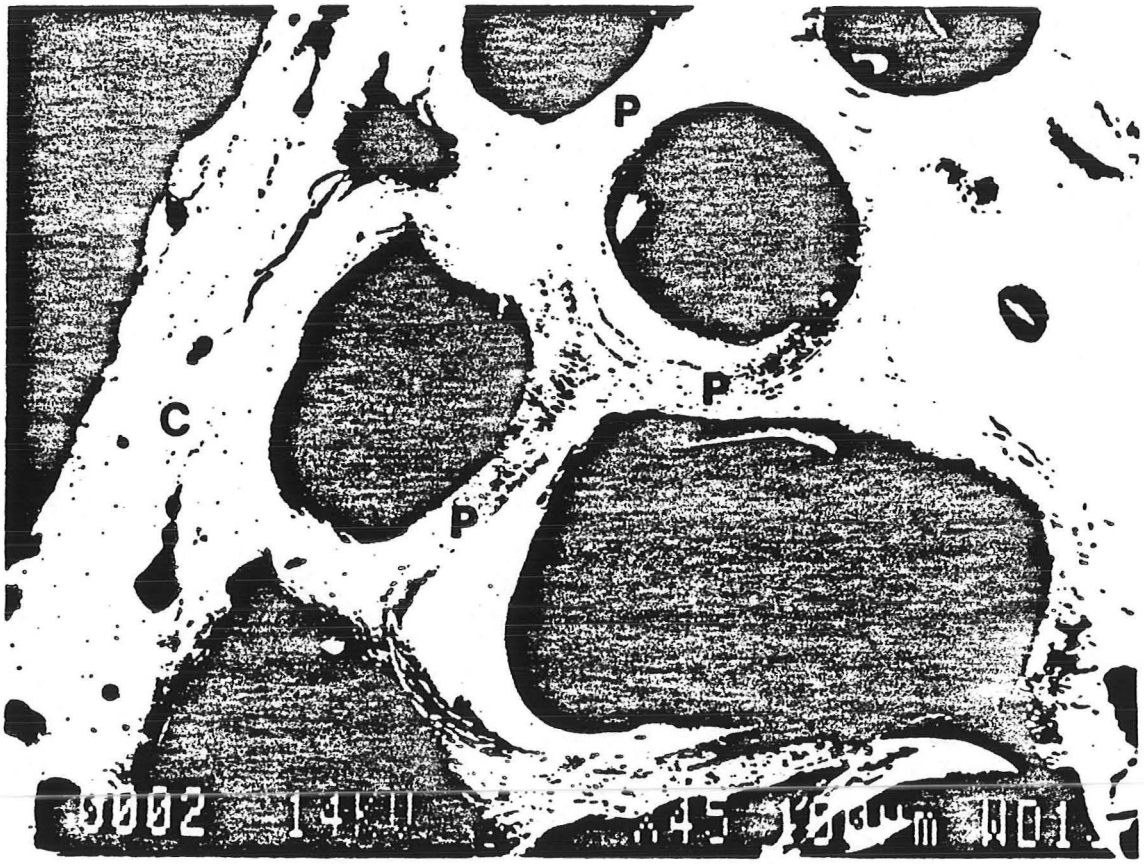


FIGURE 5B



Compared to control subjects, 85 percent of PHPT patients had greater than average values for cancellous bone volume (Fig. 4). Preservation of cancellous bone, as determined by histomorphometric analysis, was consistent with normal bone mineral density of trabecular sites (lumbar spine) as determined by dual photon absorptiometry. There were no significant correlations between cortical width or cancellous bone volume and serum or urinary Ca, PTH level or bone density at any site.

One may conclude from Dr. Bilezikian's studies that the majority of patients with asymptomatic PHPT have evidence by bone densitometry and bone biopsy for cortical bone disease. The significance of this pervasive but subtle cortical bone loss in patients with "asymptomatic" PHPT with respect to potential increase in fracture incidence at the radius or at the femoral neck (a site of mixed cortical and cancellous bone) must await the results of on-going longitudinal follow-up of these individuals. The good news in Bilezikian's report is that the mild hyperparathyroid state may be protective of cancellous bone. Most reports that have measured cancellous bone volume confirm its

preservation in PHPT(22,23). Preliminary data from Parfitt, Kleerekoper et al. have suggested that in PHPT, osteoclast resorptive activity is increased on the endocortical, but not on the trabecular surfaces of bone(24). It has been speculated that the endocortical surface of bone gradually becomes "trabecularized" with maintenance of total bone volume at the expense of the cortical elements. The important clinical implication of this data is that postmenopausal women with asymptomatic PHPT have preservation of cancellous bone and may actually be protected against spinal osteoporosis. It is conceivable that the increased level of PTH in these patients is actually helping to preserve cancellous bone. In this regard, treatment of osteoporosis with low dose PTH has led to an increase in cancellous bone mass(25,26).

Parfitt's group has provided additional evidence for protection of the trabecular skeleton in the postmenopausal woman with asymptomatic PHPT (Table 5)(21). The prevalence of vertebral

Table 5. Prevalence of Vertebral Fractures in White Women (Age: 55-74 Years)

Asymptomatic PHPT(N=72)	Healthy Controls(N=63)
2.8%	5.2%

Derived from Wilson et al., Ann Int Med 109:959-962, 1988.

fractures in 174 patients (mean age 62 years) with mild asymptomatic PHPT was 1.7 percent; in a subset of white women, the prevalence was 2.8 percent. These rates were not higher than those found in a retrospective control group on in a historical control group of similar age, and may even be lower. Parfitt's group concluded that the risk for vertebral fractures is not increased in patients with mild asymptomatic PHPT and is not a reason to recommend surgical intervention in these patients. The increased rates of vertebral fractures reported in previous series(6,9,19) were attributed to inappropriate control groups, the influence of referral or selection bias (e.g. patients referred to Mayo Clinic with co-existent osteoporosis), the inclusion of patients with severe disease, and the effect of geographic differences in vitamin D nutrition on the expression of disease.

The Detroit group has also recently summarized a set of very complete data on the natural history of asymptomatic PHPT(27). They selected patients in whom the disease was discovered fortuitously by multi-channel biochemical screening and whom they elected to follow conservatively because they met the following criteria: asymptomatic, no renal stone disease, no radiographic osteitis fibrosa, serum Ca below 12 mg/dl, serum creatinine below 133 µmol/L, and forearm bone density not more than 2.5 SD below the

mean expected for age, sex and race. Thus, they had a well-defined group of patients with asymptomatic PHPT, although the patients were not divided into those with and without physiologic derangements. One hundred and seventy-four patients met their criteria during a 10 yr period from 1976 to 1985, of whom 80 (mean age, 61 yr) had adequate follow-up. These 80 patients were followed for 1-11 yr (mean, 46 months; median, 38 months), during which there was no change, mean or individual, in any index of PTH secretion or any of its biochemical effects (Table 6) and no decline in forearm bone density apart from that expected from increased age (Table 7).

TABLE 6. Biochemical measurements in patients with PHrPT

	n	Initial	Final
Serum calcium (mmol/L)	80	2.77 ± 0.09	2.77 ± 0.11
Serum phosphate (mmol/L)	80	0.87 ± 0.14	0.87 ± 0.13
Serum creatinine (μmol/L)	80	87.5 ± 17.7	87.5 ± 20.3
Serum alkaline phosphatase (μkat/L)	76	1.7 ± 0.7	1.9 ± 0.9[a]
Serum PTH (ng/L; C-terminal assay)	49	1110 ± 640[b]	1040 ± 570
Serum PTH (ng/L; midregion assay)	13	2360 ± 1090[c]	2160 ± 1770
NcAMP/GFR (nmol/L)	42	3.98 ± 1.48	4.19 ± 1.63
TmP/GFR (mmol/L)	42	0.76 ± 0.17	0.77 ± 0.19
Urinary calcium (mmol/day)	42	6.5 ± 3.3	6.1 ± 3.3
Creatinine clearance (mL/min)	42	82 ± 26	85 ± 27

Values are the mean ± SD. None of the differences is significant. Some of the values differ from those in Table 1 because of restriction to patients with repeat measurements.

[a] $P < 0.01$ for a single comparison between initial and final values, but not significant as 1 of 14 comparisons (4 other comparisons not shown).

[b] Actual measured values.

[c] Initial values × 1060/470 (see text).

TABLE 7. Changes in forearm bone densitometry measured by single photon absorptiometry in patients with PHrPT

	Proximal		Distal	
	Initial	Final	Initial	Final
Bone mineral (g/cm)	0.843 ± 0.108	0.815 ± 0.198[a]	0.839 ± 0.199	0.831 ± 0.192
Bone width (cm)	1.288 ± 0.166	1.287 ± 0.156	1.814 ± 0.242	1.781 ± 0.191
BM/BW (g/cm^2)	0.657 ± 0.107	0.631 ± 0.112[a]	0.466 ± 0.079	0.464 ± 0.083
z Score	−0.929 ± 0.891	−0.987 ± 0.944	−1.305 ± 1.223	−1.059 ± 1.263[b]

Values are the mean ± SD. Comparisons are between initial and final values.

[a] $P < 0.001$.

[b] $P < 0.05$.

The report from Parfitt's group is particularly relevant because of concern over the potential risk with conservative management of

persistent cortical bone loss. As already noted, patients with asymptomatic PHPT have a disproportionate loss of appendicular cortical bone by the time of diagnosis. Increased cortical bone loss would be expected to increase the risk of long bone fractures in general and hip fractures in particular, and it would be unwise to withhold surgery in patients losing cortical bone more rapidly than normal. But Parfitt's data suggests that mild asymptomatic PHPT follows a biphasic course, with a short period of disease progression (accounting for the initial biochemical and bone density presentation) followed by a long period of disease stability. In Table 7, note that for proximal BM/BW there was no change in z score (number of SD's below normal mean) indicating that bone density fell at the rate expected for age. Distal BM/BW actually showed an increase in z score, indicating slower than expected loss at this site, consistent with a beneficial effect of mild asymptomatic PHPT on cancellous bone. During the course of the 4 year study, one 80 year old woman sustained a traumatic hip fracture, which healed uneventfully, but no non-tramatic fractures occurred. There were no episodes of temporary worsening of hypercalcemia or hypercalcemic crisis, no changes in renal function, and no symptoms attributable to renal stone disease. In no patient were the initial criteria for surgery satisfied. Therefore, the data appeared to support the decision to withhold surgical intervention in patients with mild asymptomatic PHPT, but the Detroit group recognized that a larger, controlled clinical trial would be necessary, before definitive recommendations could be made.

THE CASE FOR SURGICAL INTERVENTION

1. Insidious nature of "asymptomatic" PHPT

Some patients who are truly symptomatic may be unaware of their disease until surgery relieves their symptoms(28). These symptoms are often very vague and include weakness, fatigue, arthralgia and personality changes. In one series of 289 patients operated on for PHPT, 35 percent were picked up by routine chemical screening and were considered asymptomatic(29). On specific, careful questioning, most admitted to various symptoms which disappeared following surgery: malaise, fatigue and muscular weakness disappeared in 79%, upper abdominal pains in 66%, constipation in 63%, pains in the extremities in 51% and depression in 65%. In another series involving 17 patients with so-called asymptomatic PHPT, 75% of symptoms elicited by more careful probing improved following surgery (Table 8)(30). In contrast, a similar group of "asymptomatic" patients undergoing operations for thyroid nodules only had a 9% improvement in elicited symptoms. It was gratifying to the surgeons that most patients with asymptomatic PHPT showed subjective improvement in symptoms which had not seemed remarkable to them before their operation.

TABLE 8 *Symptoms elicited by questioning 17 'asymptomatic' patients undergoing parathyroidectomy whose hypercalcaemia was an unexpected finding on routine blood testing and 17 patients undergoing operation for otherwise symptomless thyroid swellings. Symptoms improved or cured following operation are shown for each group*

	Symptoms	*Gastro-intestinal*	*Urological*	*Psychi-atric*	*Lethargy*	*Bone pain*	*Neuro-logical*	*Total*
'Asymptomatic' hyperparathyroid patients	Elicited	12	11	3*	9*	4	5	44
	Improved/cured	9	6	2	8	3	5	33 (= 75%)
Symptomless thyroid patients	Elicited	4	6	2	4	3	13	32
	Improved/cured	0	1	0	0	0	2	3 (= 9%)

* Persistent symptoms of depression, confusion and lethargy suffered by a patient with pre-existing stroke and lethargy in a patient with chronic renal failure (attributable to the respective underlying disease) are omitted from this table.

2. Underlying physiologic derangements

As noted earlier, if carefully evaluated, many patients with asymptomatic PHPT will be found to have important, though subtle physiologic derangements (hypercalciuria, reduced bone density, negative Ca balance, decreased creatinine clearance)(11). Although not yet proven, these abnormalities may herald potential target organ damage (kidney, bone). There is persistent concern about progressive bone loss and increased fracture incidence, especially in those predisposed to osteopenia (patients with diabetes, those taking steroids, the immobilized, postmenopausal women). It is noteworthy that following parathyroidectomy there is a partial improvement in radial bone density(16,17).

3. Relatively high complication rate in some longitudinal studies

In some longitudinal studies, an unacceptably high number of patients with asymptomatic PHPT eventually developed overt symptoms requiring surgical intervention or even more serious complications(8,31). It will be recalled that in Purnell's study at the Mayo Clinic, 25 percent of patients with asymptomatic PHPT developed surgical indications (hypercalcemia, decreased renal function, stones, bone disease) during the 10 year follow-up (Table 2)(8). In another study, Corlew et al. followed 47 patients with PHPT for at least 5 years and for an average of 8-1/2 years(31). Although there was no progressive increase in serum Ca or PTH, 16 of the 47 patients (34%) experienced a complication usually associated with PHPT: peptic ulcer disease (8 patients), decreased renal function (5 patients), renal stone (1 patient), hypercalcemic crisis (1 patient) and ventricular conduction defect (1 patient). Four deaths were attributed to these complications. None of the parameters studied offered an accurate prediction of the liklihood of progression or severity of complications in a given patient. This study, however, did not involve typical patients with mild, asymptomatic PHPT, but rather any patients who were unwilling or unable to have parathyroidectomy. Many of these patients had serum Ca greater than 11.5 mg/dl and up to 12.9 mg/dl. Moreover, some of the deaths as shown in Table 9 could easily have been explained by causes unrelated to PHPT e.g. renal failure in an 85 year-old woman with hypertension and gout or ventricular arrhythmia in a 78 year-old woman with hypertension and IHSS. Nevertheless, the risks associated with long-term non-operative

management of asymptomatic PHPT are condiderable in some series and exceed the morbidity and mortality rates resulting from neck exploration.

Table 9. Deaths attributable to a complication of untreated primary hyperparathyroidism in forty-seven patients during long-term follow-up

Type	*Group*	*Age (yr)*	*Sex*	*Associated condition*
Hypercalcemic crisis	A	70	M	Hypertension, diabetes
Progressive renal failure	C	85	F	Hypertension, gout
Ventricular arrhythmia	C	78	F	Hypertension, IHSS
Gastrointestinal hemorrhage	C	74	F	Duodenal ulcer

Legend: IHSS, idiopathic hypertrophic subaortic stenosis.

4. High success rate, low complication rate of parathyroidectomy

When performed by skilled, experienced neck surgeons, the cure rate for PHPT (asymptomatic or overt) consistently exceeds 90%, and the morbidity and mortality rate is very low (Table 10) (32,33).

Table 10. Safety and Efficacy of Parathyroidectomy at Major Centers

Center	N	Successful	Morbidity			Mortality
			Recurrent Laryngeal Nerve	Hypopara	Other*	
Gaz and Wang (MGH)	242	238 (98%)	0	1 (0.4%)	6 (2.5%)	0
Russell & Edis (Mayo Clinic)	500	461 (92%)	1 (0.2%)	10 (2%)	17 (3.4%)	1 (0.2%)

*Other category includes miscellaneous transient complications such as wound hematoma, stitch abscess, gouty attack, thrombophlebitis, wound infection and atrial fibrillation.

Derived from Gaz and Wang, Am. J. Surg. 147:498, 1984 and Russell and Edis, Br. J. Surg. 69:244, 1982.

Of interest, in Gaz and Wang's series of 242 patients with asymptomatic PHPT, over 90% had confirmation of parathyroid disease(32). The pathologic breakdown was similar to that seen in patients with overt parathyroid disease (Table 11).

11. Pathologic Diagnosis in 242 Patients with Asymptomatic Hyperparathyroidism

Diagnosis	Percent of Total
Adenoma	83%
Hyperplasia	16%
Normal Glands	1%
Carcinoma	0%

From: Gaz and Wang, Am. J. Surg. 147:498, 1984.

The criteria used by the MGH surgeons for surgical intervention in asymptomatic PHPT have been similar to the approach taken in Dallas. They operate on those patients with physiologic derangements and follow the others "expectantly." But they also utilize a serum Ca rising above 11 mg/dl as an indication to operate.

In contrast, the surgeons at the Mayo Clinic favor operating on all patients with a bona fide diagnosis of PHPT(33). Their results in patients with asymptomatic or "biochemical" PHPT compared to overt or "non-biochemical" PHPT are shown in Table 12.

Table 12: *COMPARISON OF SURGICAL OUTCOMES FOR PATIENTS WITH 'BIOCHEMICAL' HYPERPARATHYROIDISM AND 'NON-BIOCHEMICAL' HYPERPARATHYROIDISM*

Outcome	*'Biochemcial' HPT (n = 84)* *No.*	*%*	*'Non-biochemical' HPT (n = 311)* *No.*	*%*
Cured	77	91·7	291	93·6
Four normal glands, no disease found	7	8·3*	9	2·9*
Vocal cord paralysis	0	0	0	0
Protracted hypoparathyroidism	2	2·4	7	2·2

* Significant difference between groups ($P < 0·025$).

In both groups, they achieved greater than a 90% success rate, although there was a higher incidence of negative neck exploration in the asymptomatic group (perhaps some were normal subjects at the high range of serum Ca or patients with familial hypocalciuric hypercalcemia--see below). In any event, they argue that cervical exploration in patients with asymptomatic PHPT is safe (no deaths, no permanent cord paralysis, only 2 patients with hypoparathyroidism among 84 patients) and effective (92% cure rate). In contrast to some series of prolonged clinical observation, morbidity and mortality are negligible.

5. Non-invasive parathyroid localization tests may facilitate the decision for surgical intervention

Pre-operative confirmation and localization of enlarged parathyroid glands may facilitate the decision for surgical intervention in asymptomatic PHPT(34,35). Current techniques have an 80% sensitivity and 65-70% true positivity (specificity) in localizing abnormal parathyroid glands (Table 13)(35).

13.
Comparison of Parathyroid Localization Tests in 26 Consecutive Patients with Confirmed Parathyroid Adenomas

	Sensitivity	True-Positive Ratio
NM	65%	82%
CT	76%	64%
US	77%	71%
MRI	81%	77%

From: Erdman, Breslau, Weinreb et al., Magnetic Resonance Imaging, in press 1989.

A combination of two techniques may be just as sensitive in localizing parathyroid adenomas, but more specific (Table 14)(35).

Table 14. Sensitivity and Specificity of Any Combination of Parathyroid Localization Tests

	Sensitivity	True-Positive Ratio
Two Techniques	79%	86%
Three Techniques	63%	92%
Four Techniques	40%	100%

From: Erdman, Breslau, Weinreb et al., Magnetic Resonance Imaging, In Press 1989.

In one minor study, the duration of operation and post-operative complications were significantly reduced compared to a retrospective control group, when sonographic localization was

applied(34). There was a higher cure rate of hypercalcemia, and a lower incidence of hypoparathyroidism and recurrent laryngeal nerve damage. If the utility of non-invasive localization tests were confirmed, it could have bearing on the approach to asymptomatic PHPT because of the further reduction in surgical risk.

6. Prolonged observation impractical - high dropout rate

Many non-operated PHPT patients are lost to medical follow-up for a variety of reasons: lack of symptoms, expense, inconvenience, mobile society, etc. Over the 10 year period of Purnell's Mayo Clinic series, the dropout rate was 15-20%(8).

7. Prolonged medical observation is expensive

It has been calculated that repeated visits and tests obtained during long-term conservative management of asymptomatic PHPT exceeds the cost of surgery after 5 years(4,6).

8. Changes in health status during prolonged observation may preclude needed surgery

If surgery is deferred, the patient may acquire independent systemic or vascular disease, jeopardizing or contra-indicating neck exploration when complications of PHPT eventually occur(28). Moreover, if other conditions develop, they may be complicated by co-existant PHPT. For example, there may be a risk of severe life-threatening hypercalcemia during periods of dehydration or immobilization.

9. Medical therapy of PHPT leaves much to be desired(36)

10. Young patients with long life-expectancy

Young individuals with PHPT are not only excellent surgical risks, but if un-operated have a long time to develop complications.

MEDICAL THERAPY OF PHPT

It is not clear that the increasingly large number of patients with only mild hypercalcemia and no other manifestations of disease should undergo surgery(36). It may be difficult for physicians to recommend surgery for these patients, whose mild PHPT could have been discovered as an incidental finding on a routine health screening test. It may be difficult to convince patients, even with underlying physiologic derangements, to undergo surgery--yet one might wish to do something about the postmenopausal woman with hypercalciuria and low bone density, or the young male with intestinal Ca hyperabsorption and hypercalciuria. For those patients, non-surgical approaches to the disease might be beneficial (Table 15).

Table 15. Medical Therapy for PHPT

1. Estrogen (37-42)
2. Phosphate (43-45)
3. Diphosphonates (46)

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

It is necessary to comment briefly on this syndrome since it may be confused with asymptomatic PHPT. This is a familial form of hypercalcemia with an autosomal dominant mode of inheritance, which has been extensively investigated by Marx and co-workers(47,48). Fifty percent of offspring in affected families will develop hypercalcemia before the age of 10 years. Despite mean serum Ca values in the range of 12 mg/dl, patients with FHH typically lack the characteristic manifestations of PHPT, such as kidney stones, bone disease, or peptic ulcers. A key feature of FHH is a clear-cut reduction in the fractional excretion of both calcium and magnesium, so that these patients display a proportional degree of hypercalcemia and hypermagnesemia. Mean 24-hr urine Ca excretion is in the range of 100 mg (compared with the daily output characteristic of PHPT of greater than 300 mg) and the calcium to creatinine clearance ratio is less than 0.01. Despite the enhanced renal reabsorption of divalent cations, values for serum PTH and urinary cyclic AMP are usually in the mid- to high-normal range and occasionally are frankly elevated. Parathyroid hyperplasia has been reported in a few patients who have undergone parathyroid exploration. These observations suggest abnormal Ca transport occurs at a minimum of two sites: kidney and parathyroid glands. Subtotal parathyroidectomy generally does not abolish the hypercalcemia, although total parathyroidectomy may cause hypoparathyroidism. Since patients with FHH usually remain asymptomatic, the condition should be recognized, and they should not be operated upon.

CONCLUSIONS

With the wide-spread application of multichannel biochemical screening, the expression of PHPT has changed from a rare disease with serious complications to a common disorder usually discovered incidentally in an asymptomatic patient. Some authorities continue to recommend surgery for such patients, but many patients are being followed conservatively for as long as they remain free of harmful effects. In the absence of a large scale, controlled clinical trial, the long term balance of risks and benefits of these alternative treatment policies remains unknown(10,27,49).

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