CLINICAL STUDIES

Clinical Profile of 128 Subjects Operated for Primary Hyperparathyroidism

LILLIAN HADDOCK, MD, MACP; FRANCISCO AGUILÓ JR., MD, FACP, FACE; ENRIQUE VÁZQUEZ QUINTANA, MD, FACS; MARIA DEL C. VÁZQUEZ BS, MT; VILMA RABELL, MD; MYRIAM ALLENDE, MD, FACP

ABSTRACT. From 1960 to 1990, one hundred twenty eight (128) subjects with primary hyperparathyroidism were operated in the University Hospital. The medical records were reviewed. Serum and urine chemistries were done by conventional methods, serum PTH was done by RIA's (N-, C-, and midregion) and intact by IRMA and 1,25 dihydroxycholecalciferol by a non equilibrium receptor assay from calf thymus and preceded by double Sep-Pak chromatography. The distal third of the radius (nondominant arm) was used to evaluate radial bone density (RBD), using single photon absorptiometry (Norland) and the lumbar bone density (LBD) was measured by dual energy X Ray absorptiometry (DEXA). The RBD was done in 41 females and 15 males and the LBD in 12 females and 4 males. The series comprised 95 females, age range from 15 to 79 years, and 33 males, age range from 14 to 69 years. Prominent clinical features included nephrolithiasis in 72 subjects (56%),osteitis fibrosa cystica in 2, isolated familial hyperparathyroidism in 4 subjects in one family, 7 subjects with MEN-1 in 3 families, and 4 subjects with MEN-2 in one family. Only 7 subjects were asymptomatic. Serum calcium was elevated in all, serum alkaline phosphatase was elevated in 24% and urinary hydroxiproline was increased in 48%. Serum phosphorus was low in 92%. PTH assay was either elevated or inappropiately normal for the serum calcium in all patients tested. Serum 1,25 D was elevated in 57%. The PTH level was positively correlated with the serum calcium (r = 0.70), but had no significant correlation with the serum phosphorus and the 1,25 D. The RBD expressed as the standard deviation from that of the mean for age and sex matched controls was ≥ 2 SD below the mean in 39% of females and in 40% of males. In contrast to the RBD none of the subjects tested had a LBD ≥ 2 SD below the age and sex adjusted mean. 103 subjects had adenomas, 20 primary hyperplasia, 2 carcinomas and in 3 surgical exploration was unsuccesful. As to the outcome of Surgery, 117 (93%) were cured. Thus, in this series, succesful surgery for primary hyperparathyroidism is the rule. Primary hyperparathroidism is rarely asymptomatic and appendicular bone disease and nephrolithiasis are commonly seen. *Keywords: Primary hyperparathyroidism, Bone mineral density, MEN 1, MEN 2, Protean clinical manifestations*

Primary hyperparathyroidism is the most common cause of hypercalcemia in the outpatient population (1,2,3). Since the advent of multichannel screening the diagnosis of this disease is being made early in the course of the disease while the patient may be asymptomatic (4,5,6,7). The course of this illness is that of a chronic condition and may be present for decades without producing any progression in the clinical manifestations of the disease (6,7,8). Although the asymptomatic presentation of the disease has been emphasized in the United States literature (1-8), still the protean manifestations of the disease have been reported in recent literature (9,10) .The aim of this publication is to analyze our experience in the diagnosis and management of 128 cases with primary hyperparathyroidism (PHPTH) seen from 1960 to 1990.

From the Division of Endocrinology and Metabolism of the Department of Medicine of the University of Puerto Rico School of Medicine in San Juan, Puerto Rico.

Address for correspondence: Lillian Haddock, MD, MACP, Professor Emeritus, Division of Endocrinology and Metabolism, University of Puerto Rico School of Medicine, PO Box 365067, San Juan, PR 00936-5067

Subjects and Methods

The subjects were studied in the Clinical Research Center, the Endocrine special clinic and the University

Hospital. Laboratory studies included serum calcium, phosphorus, alkaline phosphatase, creatinine, urine calcium, phosphorus and creatinine by multichannel analyzer. Urinary hydroxyproline was done by the method of Prockopp (11). PTH levels were done by various radioinmunoassays (N terminal, C terminal, midregion and intact by IRMA (12). Calcitriol levels were determined by a competitive receptor protein binding assay (13). Most of the subjects had either a skeletal survey or selected radiographs of the hand, clavicle, pelvis and skull. Radial bone density (RBD) of the distal third of the non dominant arm was performed using a Norland single photon absorptiometer in a group of 56 subjects. Lumbar bone density (LBD) was performed using a dual energy X Ray absorptiometer (Hologic QDR model 1000) in 14 subjects and a dual photon absorptiometer in 2 subjects. Results are expressed as the mean ± standard error of the mean. Linear regression analysis was used to compare the relationship between two variables. $p< 0.05$ was considered significant.

Results

Table 1 depicts the composition of the series. The total number of subjects was 128, 95 females and 33 males. The age ranged from 15 to 75 years in females and 14 to 69 years in males. The mean age for females was 51.5 ± 1.4 years and for males 44.3 ± 3.2 years.

Table 1. Primary Hyperparathyroidism.
University Hospital, Puerto Rico (1960-1990)

Group	Number	Age range (yrs)	Mean + SEM (yrs)
Female	95	15-79	51.5±1.4
Males	33	14-69	44.3±3.2

Table 2 summarizes their mode of presentation. The series was divided in two fifteen years period to see whether there was any difference in the clinical presentation. In both periods the majority of the patients, 58 % and 55 % respectively, presented with renal lithiasis. Three had brown tumors and osteitis fibrosa cystica and 15 had either familial hyperparathyroidism or multiple endocrine neoplasia type 1 and 2. In 31 (24%) the disease was found by multichannel screening and only 9 (7%) were asymptomatic. Of the asymptomatic group three were females ages 20,50, and 53 operated in the years 1978 and 1982 when facilities to measure bone densities were not available. Two patients, a 56 year old colored female and a 35 year old white male had a RBMD of-2 SD from the mean; the other 4 were screenees for MEN 2.

The most common coexistent illnesses were: hypertension (34%), diabetes mellitus (12.5%), cholelithiasis (10.2 %), nodular thyroid (9.5 %) and peptic ulcer disease (7.8%). Microscopic papillary adenocarcinoma of the thyroid was found in 3 subjects (Table 3).

Table 2. Primary Hyperparathyroidism. Mode of Presentation

Period	1960-1975	1976-1990	Total
Number	41	87	128
Renal lithiasis	24 (58%)	48 (55%)	72 (56%)
Nephrocalcinosis, OFC, fracture	1	-	1
Giant cell tumor of ethmoid, OFC	-	1	1
Renal insufficiency	1	-	1
Hypercalcemic crisis	-	1	1
Familial	-	4	4
MEN 1	1	6	7
MEN 2	-	4	4
Peptic ulcer disease	4	-	4
Serendipity (SMA)	8 (18%)	23 (25%)	31
Thyroid mass	4	-	4
Asymptomatic	-	9 (7%)	9
DI-like picture	1	-	1
Mental confusion	-	1	1
MI, Pancreatitis	1	-	1
Severe hypertension	-	1	1

Table 3. Primary Hyperparathyroidism. Prominent Coexisting Illnesses

Disease	Number and Sex	Percentage
Hypertension	43 (F-33, M-2)	34%
Diabetes mellitus (type 2)	16 (F-14, M-2)	12.5%
Choletithiasis	13 (F-11, M-2)	10.2%
Nodular thyroid	12 (F-9, M-3)	9.3%
Peptic ulcer disease	10 (F-7, M-3)	7.8%
Papillary adenorcarcinoma of thyroid	3 (F)	2.3%

Table 4 summarizes the data on familial hyperparathyroidism. Four subjects in one family had primary hyperparathyroidism as the only manifestation, the mother age 59, one daughter age 37 and two sons ages 31 and 32 respectively. Seven in 3 families had MEN 1 and 4 in one family had MEN 2.

Table 4. Familial Hyperparathyroidism

Clinical presentation	No. of families	No. and sex of subjects
PHPTH only	1	4 (F-2, M-2)
MEN 1	3	7 (F-5, M-2)
MEN 2	1	4 (F-1, M-3)

Table 5 details the endocrine manifestations in the

Table 5. Primary Hyperparathyroidism. Multiple Endocrine Adenomas, (Type 1)

Family	Endocrine manifestations	No. and Sex
1	PHPTH (in 3 generations)*	1M
	PHPTH & acromegaly	1M
	PHPTH & carcinoid	1M
2	PHPTH only	1 F
	PHPTH & prolactinoma	2 F
3	PHPTH only	2 M
	PHPTH, prolactima and carcinoid	1 F

*Only one patient belongs to our series: PHPTH in all due to hyperplasia

families with MEN 1 . In the first family 5 patients had PHPTH, one had PHPTH and acromegaly and one had PHPTH and a carcinoid tumor. Only one patient in this family belongs to our series, a 32 year old female with PHPTH only. In the second family one female age 16 had PHPTH and 2 females ages 23 and 26 had PHPTH and a prolactinoma. Their father was operated for a parathyroid tumor in another hospital. In the third family the mother age 62 had PHPTH, prolactinoma and a malignant carcinoid tumor which caused her death; her two sons ages 23 and 26 had PHPTH. The lesion causing hyperparathyroidism in all was hyperplasia.

Table 6 details the endocrine manifestations in the patients with MEN 2 in two generations of the same family. The female, age 42 at the time of diagnosis had medullary thyroid carcinoma (MTC), PHPTH and bilateral pheochromocytoma. Two of her sons ages 22 and 23 at the time of diagnosis had MTC and PHPTH and one nephew age 23 had MTC, PHPTH and bilateral pheochromocytoma. The female died and the remaining still have calcitonemia; PHPTH was due to adenoma in all.

Table 6. Multiple Endocrine Adenomata (Type 2).

Endocrine manifestations	Number and Sex
MTC, PHPTH, Pheo	2 (F-1, M-1)
MTC and PHPTH	2 M
PHPTH due to adenoma in all	

Table 7 gives the most pertinent biochemical findings. All the patients had hypercalcemia which was either sustained or intermittent; 92 % had hypophosphatemia which was usually intermittent; 10 (8%) had normal serum phosphorus at all times.

The percentage tubular reabsorption of phosphate was done in 70 patients and was low in 69 %. The daily urinary excretion of calcium was elevated in 94 % of the subjects and normal in 8 (6%); 4 of these 8 subjects had mild to moderate renal insufficiency.

The PTH level was either elevated or inappropiately normal in 69 subjects in which the test was done. Figure 1 compares the PTH intact levels done in 34 subjects by IRMA with 26 done by the C-terminal assay. PTH intact values ranged from 60 % to 14 times the normal value with an average of 2.65 the normal value; the C-terminal values ranged from 1.1 to 54 times the normal value with an average of 5.7 times the normal value. In 5 patients in which intact PTH was found inappropiately normal, the C-terminal value was above normal. There was a strong correlation between the intact PTH and the serum calcium ($r = 0.70$; $p < 0.0005$ (Figure2). No other correlation was found between PTH and the other biochemical parameters. Figure 3 shows the serum calcitriol level done in 30 subjects. Fifty seven percent had elevated levels; no correlation was found between PTH and calcitriol levels.

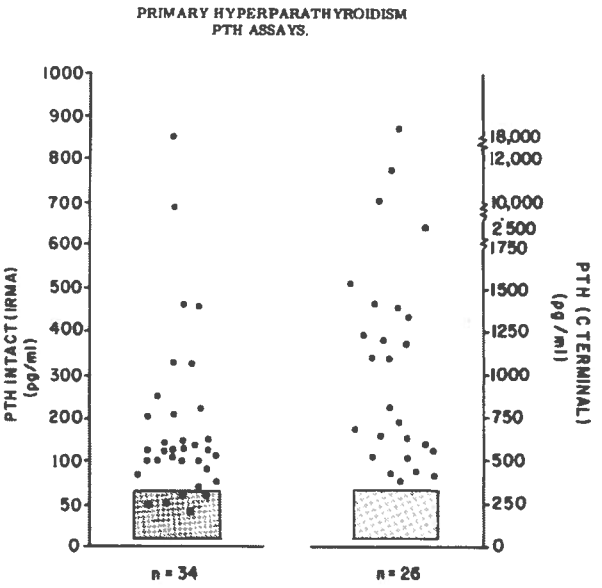

Figure 1. PTH assays in primary hyperparathyroidism series

The radial bone density was performed in 41 females and 15 males. Figure 4 shows the RBD depicted as the

Table 7. Primary Hyperparathyroidism. Biochemical Findings

Laboratory test	Number and Percentage
Serum calcium elevated, sustained or intermittent	128 (100%)
Serum phosphorus low; usually intermittent normal, sustained	 118 (92%) 10 (8%)
TRP (%)	
number done low normal	70 48 (69%) 22 (31%)
Urine calcium/24 hr	
elevated normal	120 (94%) 8 (6%)

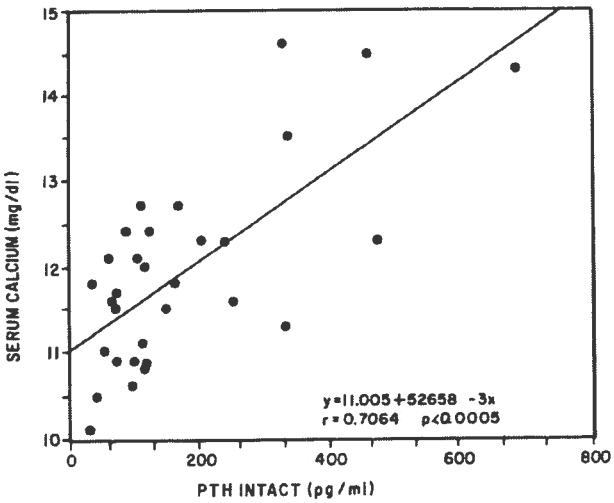

Figure 2. Correlation of the PTH intact serum level with the serum calcium

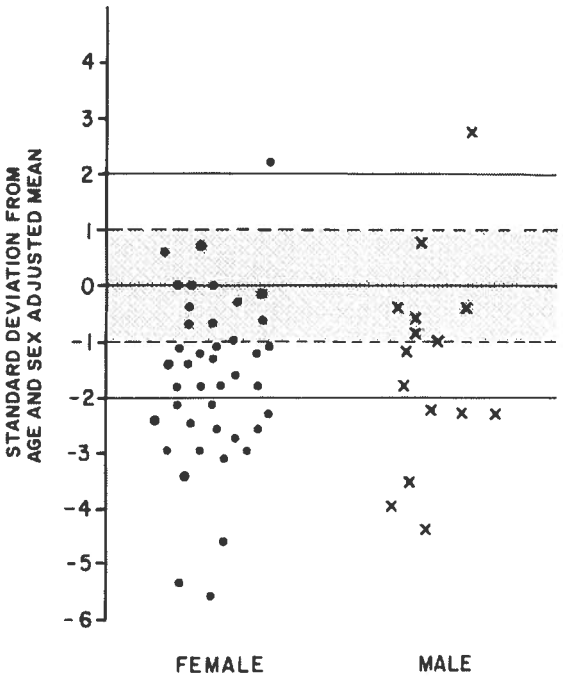

Figure 4. Radial bone density in primary hyperparathyroidism

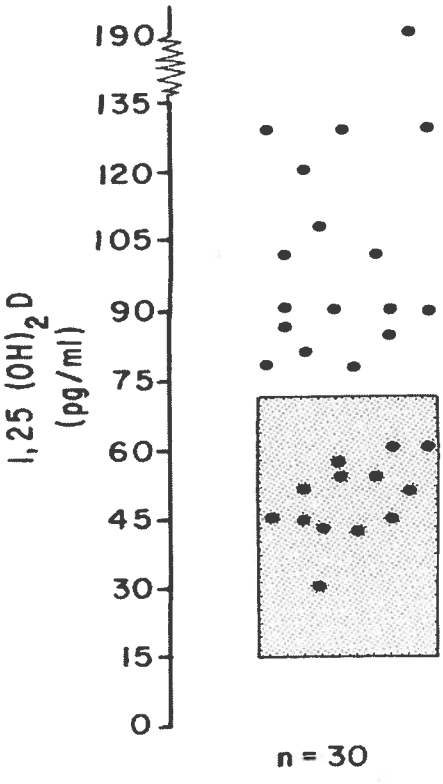

Figure 3. Serum 1,25 dihydroxycholecalciferol levels in primary hyperparathyroidism

standard deviation from age and sex adjusted mean (Z score) for each case. Sixteen females (39%) and 6 males (40%) had the RBD less than 2 SD from the mean. Of these group 40 % had negative radiological findings. Figure 5 depicts the same data taking the age into consideration. The mean age of the females was 52 ± 2.14 years and that of the males 48 ± 4.71 years. Thirty two

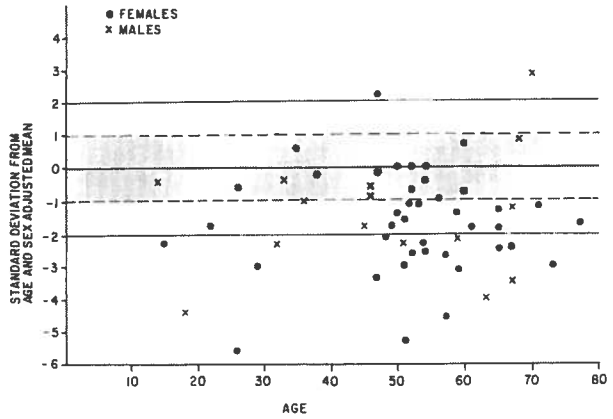

Figure 5. Z score for radial bone density vs age in females and males with primary hyperparathyroidism

(82 %) of the females were peri or postmenopausal while 7 (18 %) were younger than 40. There was no correlation between the age and the RBD. Of the 22 patients that had a RBD less than -2 SD from the mean 10 (7 females and 3 males) or 45 % had renal lithiasis. A 60 year old female who had renal insufficiency (creatinine clearance of 30 ml/min.) had a RBD of -1.8 SD from the mean.

The serum alkaline phosphatase and the daily urinary excretion of hydroxyproline were positively correlated only in subjects with the RBD less than 2 SD from the mean (r=0.598, p=0.03) (table 8).

Table 8. Correlation of Serum Alkaline Phosphatase withh Urinary Hydroxiproline.

AP normal, Urine hypro normal:	48
AP elevated, Urine hypro elevated:	26
AP elevated, Urine hypro normal:	15
AP normal, Urine hypro elevated:	5

Note: positively correlated only in subjects with RBD 2 SD or lower from mean for age and sex. r=0.598, p<0.03; no good correlation with radiological findings; in above group 40% had negative skeletal findings.

The lumbar bone density was performed in 16 subjects, 12 females and 4 males. In all the LBD was within 2 SD of the mean (Figure 6). Figure 7 compares the radial bone density with the LBD in these 16 subjects, using the standard deviation from that of the mean for age and sex matched controls for each (Z). The first 3 females depicted had equal Z scores for the RBD and the LBD. Patient # 6, a 52 year old female, menopausal for 2 years, had the Z score of the LBD less than that of the RBD. Patient # 12 , the 26 year old female with osteitis fibrosa cystica, had a Z score of -0.8 for the LBD and a Z score of -5.6 for the RBD. The remaining females and the 4 males had a Z for the LBD higher than that of the RBD.

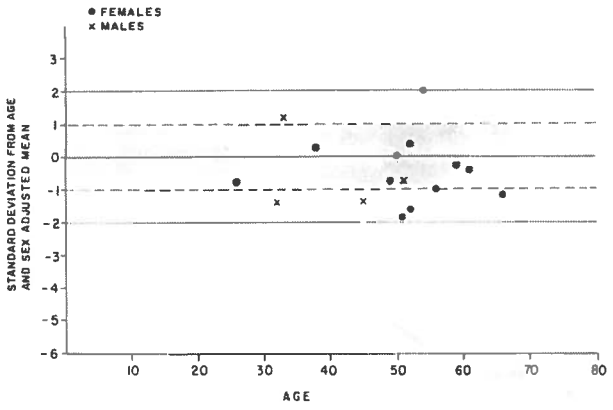

Figure 6. Z score for lumbar bone density vs age in 16 subjects with primary hyperparathyroidism

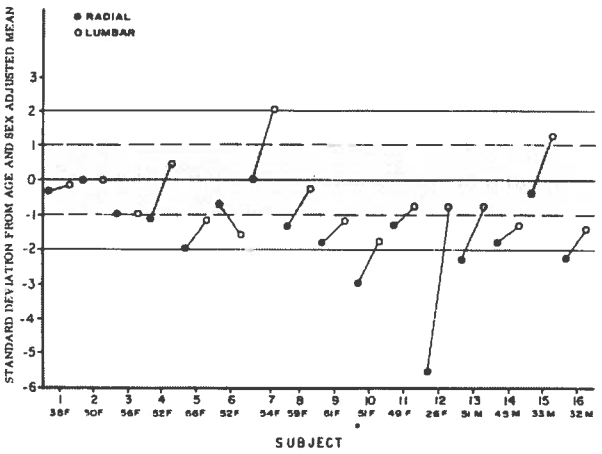

Figure 7. Z scores for the radial and hh bone density in 16 subjects with primary hyperparathyroidism.

Regarding the surgical and pathological findings 93, or 73.8% had a single adenoma, 14.2% had primary hyperplasia, 4 were intrathyroidal lesions (2 adenomas and 2 hyperplasia), one had a huge mediastinal adenoma weighing 113 g and one had a large cystic adenoma (table 9). Two patients had carcinoma and the course of the disease was benign. Only one tumor was found in the mediastinum and the rest were located in the neck. The surgical outcome is summarized in Table 11. In three patients the tumor was not found. Two died in the postoperative period, one had bilateral pneumothorax after exploration of the mediastinum and the other developed acute respiratory failure after extubation on his own. The

Table 9. Primary Hyperparthyroidism. Surgical and Pathological Findings

Lesion	Number	Percentage
Single adenoma	93	73.8
Huge mediastinal adenoma	1	0.8
Large cystic adenoma	1	0.8
Intrathyroidal adenoma	2	1.6
Two adenomas	4	3.2
Hyperplasia	18	14.2
intrathryroidal hyperplastic glands	2	1.6
Carcinoma	2	1.6
Not found	3	2.2

Table 10. Primary Hyperparathyroidism. Location of Parathyroid Adenomas

Location	Number	Percentage
Right or left inferior	56	55
Right or left superior	21	20
Left superior & inferior	1	1
Mediastinal	1	1
Intrathyroidal	2	2
Not specified	19	19
Not found	2	2
Total	102	100

Table 11. Primary Hyperparathyroidism. Surgical Outcome

Outcome	Number
Cured	117
Hypoparathyroidism	4
Hypocalcemia for 6 mos.	1
Vocal cord paralysis	0
Not cured	5
Death	2
Tumor not found	1

other patient was lost to follow up. One hundred seventeen (91%) were cured, 4 had permanent hypoparathyroidism and in all 3.5 glands were removed; one had hypoparathyroidism for 6 months and recovered. Five patients were not cured, three had primary hyperplasia and in the other two an adenoma had been removed.

Discussion

Our series differs from those recently reported in that primary hyperparathyroidism as seen in our tertiary setting is rarely asymptomatic. When this term was first coined it referred to patients that did not present any symptoms suggestive of the disease.

Russell (14) in his analysis of 419 patients with primary hyperparathyroidism classifies one group (64%) as asymptomatic even though 28% of these patients although asymptomatic had undiagnosed renal or skeletal complications of their disease.

The most sensitive test to detect bone disease is the radial bone density. Although SPA has been available for over 35 years it has not been used routinely in the evaluation of bone disease in primary hyperparathyroidism, thus many of the patients labelled as asymptomatic could have had bone disease (14,15,16). Rao and his group (8) in their criteria for withholding surgical intervention in PHPTH included beside an absence of symptoms a forearm density not more than 2.5 SD below the mean expected for age, sex and race (Z score).Silverberg (17) uses a cutoff point of $Z < -2.0$.

The higher incidence of PHPTH in females, 82% of them in the peri or postmenopausal age suggests that estrogen deprivation plays a role in the pathogenesis of this disease.

Estrogen administration in high doses supresses biochemical markers of bone turnover and reduce serum calcium in PHPTH (18,19,20). Estrogen progestin therapy increases bone mineral density (21,22,23,24) and reduces the incidence of osteoporotic fractures (23,24,25). Grey and his group (26) in a double blind randomized, placebo controlled trial gave hormone replacement (conjugated estrogens 0.625 mg and medroxyprogesterone 5 mg daily) to 42 postmenopausal women with mild primary hyperparathyroidism for two years. He showed a decrease in the markers of bone turnover, and an increase in the bone mineral densities in the forearm and all the femoral sites when compared with the placebo group and no change in the serum levels of serum ionized calcium or intact PTH. Since secondary hyperparathyroidism may be seen in the elderly female over 65 years and secondary hyperparathyroidism may lead to autonomous tertiary hyperparathyroidism it can be theorized that estrogen deficiency does play a role in the pathogenesis of hyperparathyroidism in the elderly female. The widespread use of hormone replacement therapy for the prevention of osteoporosis may explain the progressive decrease in the incidence of primary hyperparathyroidism reported by Wermers (27).

Hypertension has been found to be the most common coexistent illness seen in PHPTH (28). A relationship between primary hypertension and PHPTH was first proposed by Hellstrom et al in 1958 (29) when they reported that 53 % of their 95 cases had blood pressures of 150/100 mm Hg or greater. Other series have confirmed this finding plus the fact that there is no reduction in the blood pressure upon parathyroidectomy (30,31,32, 33,34,35) suggesting that PHPTH is associated with, rather than being its cause.

Rosenthal found 7 cases of PHPTH among 900 hypertensives, one case per 130 subjects, a prevalence higher than that found in a general population, one case per every 834 adults. The recent publication of cardiac abnormalities in PHPTH (36) to include left ventricular hypertrophy, myocardial calcific deposits and calcifications of the aortic and mitral valve has focused again on the effect of elevated calcium and PTH on the cardiovascular system.

An elevated serum calcium with an elevated or

inappropiately normal PTH done with the newer sensitive assays is the most accurate, cost effective method of diagnosing PHPTH (37). Familial benign hypercalcemia must be ruled out if the patient is asymptomatic has no evidence of renal nor bone disease and has a normal urinary calcium excretion which can be seen in early PHPTH (38). A family history of hypercalcemia must be taken to rule out the familial forms of PHPTH, diagnosed in 5 families in our series.

Significant appendicular bone loss expressed as a Z score of more than 2SD below the mean for age and sex was present in 40 % of the patients tested while axial bone density was preserved in 15 of 16 subjects studied. Preferential involvement of cortical bone with apparent preservation of cancellous bone has been found by densitometry and histomorphometric analysis (39,40,41,42). PTH has been shown to increase the density of trabecular bone in rats (43) and in osteoporotic subjects (44). Parfitt has suggested that in PHPTH osteoclast resorptive activity is increased in the endocortical surface but not in the trabecular surfaces of bone (45). In a larger group of patients with PHPTH in which dual energy X ray densitometry was performed, not described in this publication, the groups could be divided in two. One group had RBD Z score less than the LBD Z score and the other group had higher RBD Z score than LBD Z score.

The difference between both groups was the age, the latter being a much older group. We concluded that the latter developed PHPTH when already menopausal and they showed the trabecular bone loss as seen in hypoestrogenism (46). Silverberg has shown considerable increase in the l umbar, radial and femoral bone densities in premenopausal and postmenopausal females post parathyroidectomy (17). Thus an elevated PTH also contributes to the loss of axial bone mass in the menopausal female with PHPTH and menopausal females with significant osteopenia should be parathyroidectomized.

The radial bone density is the most sensitive measurement of bone loss in PHPTH and to contain costs skeletal surveys are not needed unless the patient has bone pains and a Z score equal or below 2 SD. In peri and post menopausal females lumbar and femoral bone densities by dual energy X Ray absorptiometry should be done. Imaging of the parathyroids is not needed before an initial neck exploration but can be very helpful in subsequent explorations if the initial try was unsuccesful (47).

Operative exploration of the neck by experienced surgeons has a proven success of 95%. Surgery for PHPTH is remarkably succesful in the University Hospital, for we have a surgical team greatly experienced in parathyroid surgery.

Acknowledgement

The authors wish to thank all the Fellows, Residents and Interns who were involved in the management and care of these patients. We also thank the technologists, nurses and ancillary personnel of the Endocrine Section.

References

1. Boonstra CE, Jackson CE. Hyperparathyroidism detected by routineserum calcium analysis , prevalence in a clinic population. Ann Intern Med 1965;63:468-474.
2. Purnell DC Smith LC, Scholz DA. , Elveback LP, Arnaud C. Primary hyperparathyroidism: a prospective clinical study. Am J Med 1971;50:670-678.
3. Williamson E, Van Peener HJ. Patient benefit in discovering occult hyperparathyroidism. Arch Intern Med 1974;133:430-431.
4. Silverberg SJ, Fitzpatrick LA, Bilezikian JP. Primary hyperparathyroidism. In: Becker KL, Bilezikian JP, Bremner WJ, editors. Principles and practice of endocrinology and metabolism. 2nd ed. Philadelphia: JB Lippincott; 1995.p.512-519.
5. Kleerekoper M. Clinical course of primary hyperparathyroidism In: Bilezikian JP, Marcus R, Levine MA eds. The parathyroids: basic and clinical concepts. New York: Raven Press. 1994. p471-484.
6. Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 1996;81:2036-407.
7. National Institutes of Health. Consensus development conference statement onprimary hyperparathyroidism. Ann Intern Med 1991;114:593-598.
8. Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM. Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. J Clin Endocrinol Metab 1988;67:1294-1298.
9. Mithal A, Agarwal G, Singh AK, Mishra SK,Rao DS. Severe bonedisease in primary hyperparathyroidism in Indians: a reflection of calcium and vitamin D nutritional status. J Bone Miner Res 1997 Program and Abstracts 1997:12 Suppl 1,S522.
10. Guelman R, Fromm G, Galich A, Díaz H, Marchitelli H, Plantalech L. Primary hyperparathyroidism: Clinical, biochemical-histologic correlation in 69 patients parathyroidectomized. J Bone Miner Res 1997 Program and Abstracts 1997:12 Suppl S524.
11. Prockop D J, Udenfriend S. A specific method for the analysis of hydroxyproline in tissues and urine. Analyt Biochem 1960:1;228-239.
12. Levine MA. Diseases of calcium metablism In Moore WT, Eastman RC eds Diagnostic Endocrinology 1st ed. Toronto, Philadelphia:B C Decker; 1990.301-320.
13 . Reinhardt TA, Horst RL, Orf JW, and Hollis BW. A microassay for 1,25 dihydroxycholecalciferol not requiring high performance liquid chromatography. Application to clinical studies. J Clin Endocrinol Met 1984;58:91-98.
14. Russell CF, Edis AJ. Surgery for primary hyperparathyroidism: experience with 500 consecutive cases and the evaluation of surgery in the asymptomatic patient Brit J Surg 1982;69:244-247.
15. Attie, JN, Khafif RA. Surgical exloration in asymptomatic hypercalcemia: early treatment of hyperparathyroidism. Am J Surg 1976;132:449-452.
16. Gisham J J, Harding PE. Hoare LL. Asymptomatic hyperparathyroidism: an assesment of operative intervention. Br J

Surg 1980;67:115-118.
17. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, McMahon DJ, Bilezikian, JP. Increased bone mineral density after parathyroidectomy in primary hyperparathyroidism J Clin Endocrinol Metab 1995;80:729-734.
18. Gallagher JC, Nordin BE. Treatment with estrogens of primary hyperparathyroidism in post menopausal females. Lancet 1972;1:503-507.
19. Marcus R, Madvig P, Crim M, Pont A, Kosek J. Conjugated estrogens in the treatment of postmenopausal females with hyperparathyroidism. Ann Intern Med 1984;100:633-40.
20. Selby PL, Peacock M. Ethynil estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. N Engl J Med 1986:314;1481-1485.
21. Christiansen C, Riss BJ. 17 Beta estradiol and continuous norethisterone: a unique treatment for established osteoporosis in elderly women. J Clin Endocrinol Metab 1990;71:836-841.
22. Lindsay R, Tohme JF. Estrogen treatment of patients with established postmenopausal osteoporosis. Obstet Gynecol 1990;76:290-295.
23. Grey AB, Cundy TF, Reid IR. Continuous combined estrogen/ progestin therapy is well tolerated and icreases bone density at the hip and spine in postmenopausal osteoporosis. Clin Endocrinol (Oxf.)1994;40:671-677.
24. The Writing Group for the PEPI Trial. Effects of Hormone Therapy on Bone Mineral Density. Results from the Postmenopausal Estrogen/Progestin Trial. JAMA 1996;276:1389-1396.
25. Cauley JA, Seely DG, Ensrud K, Ettinger B, Black D, Cummings SR. Estrogen replacement therapy and fractures in older women. Study of Osteoporotic Fractures Study Group. Ann Intern Med 1996;122:9-16.
26. Grey AB, Stapleton JP, Evans MC, Tatnell MA, Reid IR. Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism. Ann Intern Med 1996;125:360-368.
27. Wermers RA, Khosla S, Atkinson EJ, Hodgson SF, O'Fallon WM, Melton III, JM. The Rise and fall in primary hyperparathyroidism: A population based study in Rochester, Minnesota, 1965-1992. Ann Intern Med 1997;126:433-440.
28. Lafferty FW. Primary hyperparathyroidism. Changing clinical spectrum, prevalence of hypertension and discriminant analysis of laboratory tests. Arch Intern Med 1981;141:1761-1766.
29. Hellstrom J, Birke G, Edvall CA. Hypertension in hyperparathyroidism. Br J Urol 1958;30:13-24.
30. Mallete LE, Bilezikian JP, Heath DA. Primary hyperparathyroidism: clinical and biochemical features.Medicine 1974;53:127-146.
31. Gordan GS, Eisenberg E, Laken HF. Clinical endocrinology of parathyroid excess. Recent Prog Horm Res 1962;18:297-326.
32. Pyrah LN, Hodgkinson A, Anderson CK. Primary hyperparathyroidism. Br J Surg 1966;53:245-316.
33. Britton DC, Thompson MH, Johnston IDA. Renal function following parathyroid surgery. Lancet 1971;274-275.
34. Rosenthal FD, Roy S. Hypertension and hyperparathyroidism. Br Med J 1972;4:396-397.
35. Heath H III, Hodgson SF., Kennedy MA. Primary hyperparathyroidism. N Engl J Med 1980;303:189-193.
36. Steffenelli T, Abella C, Frank H, Koller-Strametz J, Globits S, Berger-Klein J, Niederle B. Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow up. J Clin Endocrinol Metab 1997;82:106-112.
37. Silvenberg SJ, Bilezikian JP. Extensive Personal experience: evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab1996;81:2036-2040.
38. Marx SJ, Stock JL, Attie MF et al. Familial hypocalciuric hypercalcemia: recognition among patients referred after unsuccesful parathyroid exploration. Ann Intern Med 1980;92:351-356.
39. Silverberg SJ, Shane E, de la Cruz L et al. Skeletal disease primary hyperparathyroidism. J Bone Miner Res 1989;4:283-291.
40. Parisien M, Silverberg SJ, Shane E et al. The histomorphometry of bone in primary hyperparathyroidism: preservation of cancellous bone . J Clin Endocrinol Metab 1990;70:930-938.
41. Christiansen P, Steiniche T, Vestreby A, Mosekilde L, Hessov I, Melsen F. Primary hyperparathyroidism:iliac crest trabecular bone volume, structure remodeling, and balance evaluated by histomorphometric methods. Bone 1992;13:41-49.
42. Parisien M, Mellish RW, Silverberg SJ et al. Maintenance of cancellous bone connectivity in primary hyperparathyroidism: trabecular and strut analysis. J Bone Miner Res 1992;7:913-920.
43. Shen V, Dempster DW, Birchman R et al. Loss of cancellous bone mass and connectivity in ovariectomized rats can be restored by combined treatment with parathyroid hormone and estradiol. J Clin Invest 1993;91:2479.
44. Lindsay R, Nieves J, Formica C et al. Randomized controlled study of effect of parathyroid hormone on vertebral bone mass and fracture incidence among postmenopausal women on estrogen with osteoporosis Lancet 1997;350:550.
45. Parfitt AM Accelerated cortical bone loss: primary and secondary hyperparathyroidism. In Uhthoff H, JaworskiZFG editors. Current concepi of bone fragility. Berlin, Heidelberg: Springer-Verlag; 1986.p.279-285.
46. Haddock L, Aguiló F, Ortiz V, González C, Vázquez MC, Rabell V, Allende M. Appendicular compared with axial bone loss in Primary Hyperparathyroidism. 75th Annual meeting, Program and Abstracts, The Endocrine Society 1993:305,1018.
47. Shen W, Sabanci U, Monita ET et al. Sestamibi scanning is inadequate for directing unilateral neck exploration for first time parathyroidectomy. Arch Surg 1997;132:969.