Double-Phase Parathyroid Technetium-99m-MIBI Scintigraphy to Identify Functional Autonomy in Secondary Hyperparathyroidism

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Double-phase ^{99m}Tc-methoxyisobutylisonitrile (MIBI) parathyroid scintigraphy has been proposed to detect hyperplastic parathyroid tissue, but the clinical usefulness of this technique in secondary hyperparathyroidism is still debated. **Methods:** Technetium-99m-MIBI parathyroid scintigraphy associated with parathyroid echography and [^{99m}Tc]pertechnetate thyroid scans were performed on 38 patients with chronic renal failure (CRF) and secondary hyperparathyroidism. In all patients, serum calcium, phosphorus, FT3, FT4, TSH, calcitonin and intact PTH (iPTH) were determined. Nine patients eventually underwent neck exploration and 28 parathyroid glands were removed. **Results:** Thyroid diseases were excluded in all patients. Echography revealed parathyroid enlargement in 22/38 (58%) patients, while MIBI scintigraphy was positive in 28/38 (74%), including 5-ectopic glands. Mean serum iPTH concentration was significantly higher in MIBI-positive patients compared to MIBI-negative patients. Mean echographic and surgical parathyroid size were significantly higher in MIBI-positive glands compared to MIBI-negative glands, but several discrepancies were observed in single patients. A significant positive correlation between serum iPTH and gland size was observed when MIBI-positive, but not MIBI-negative, parathyroids were considered. A paradoxical positive correlation between serum calcium and iPTH concentrations was found in MIBI-positive patients. **Conclusion:** Double-phase ^{99m}Tc-MIBI scintigraphy is positive in the majority of patients with uremic hyperparathyroidism. Comparison of scintigraphic data with morphological and functional data strongly suggests that ^{99m}Tc-MIBI scans do not reveal simple parathyroid enlargement but rather, identify the presence of hyperfunctioning (autonomous) parathyroid tissue suggestive of tertiary hyperparathyroidism.

Key Words: uremic secondary hyperparathyroidism; technetium-99m-MIBI; parathyroid hyperfunction; parathyroid hyperplasia

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Technetium-99m-methoxyisobutylisonitrile (MIBI) scintigraphy has been recently proposed (*1,2*) and used (*3*) as an alternative method to ^{201}Tl/[^{99m}Tc]pertechnetate subtraction scintigraphy (*4,5*) to visualization of parathyroid glands. Much like thallium, MIBI is concentrated within the cells through active transport and passive diffusion (*6*), a process facilitated by negative transmembrane potential such as that found in metabolically hyperactive cells. The lipophilic nature of MIBI allows easier transmembrane passage than is possible with thallium given its hydrated structure. Intramitochondrial sequestration is an additional mechanism of MIBI tissue binding (*7*). Accordingly, many mitochondria have been found in hyperactive parathyroid cells (*8*). This accounts for slower MIBI washout from the hyperactive compared to the normal thyroid and parathyroid tissues (*2,9*). More recently, Taillefer et al. (*9*) proposed a simplified approach to parathyroid scintigraphy using a double-phase procedure after intravenous injection of MIBI. During the first phase after the injection (thyroid phase), MIBI concentrates in thyroid and parathyroid tissues. In the second phase (parathyroid phase), radiotracer activity decreases in the normal thyroid, while residual uptake persists in the presence of parathyroid adenomas throughout the long residence time of MIBI in hyperactive tissue. This technique appears to be highly sensitive in detecting parathyroid adenomas (*9*), but the data accumulated so far in other hyperparathyroid conditions are limited. Thus, further studies are needed to determine the degree of accuracy of double-phase MIBI scans in the diagnostic evaluation of hyperparathyroid states (*10*).

Therefore, the aim of the present study was to assess the role of double-phase MIBI scintigraphy in the morphological and functional assessment of parathyroid glands in uremic hyperparathyroidism.

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MATERIALS AND METHODS

Patients

The study group included 38 patients (17 women, 21 men; aged 25–79 yr) with chronic renal failure (CRF) and secondary hyperparathyroidism. The patients were seen consecutively. Thirty-three patients were on chronic hemodialysis, one on chronic peritoneal dialysis and four had severe predialytic CRF. All patients received oral supplementation therapy with calcium and/or calcitriol, which was not interrupted during the course of the present study. In all cases, serum calcium and phosphorus concentrations were assayed by standard clinical chemistry techniques. Circulating intact PTH (iPTH), calcitonin, FT3, FT4 and TSH were assayed by specific radioimmunoassays using commercially available kits.

Echography

Thyroid and parathyroid echography were performed on all patients. Echographic parathyroid size was estimated by measuring the maximum diameter of each gland.

Surgical Pathology

Nine patients eventually underwent surgical neck exploration. Criteria for surgery were independent of MIBI results and included: high serum iPTH levels which were unresponsive to oral calcitriol therapy and/or severe osteodystrophy, acceptable surgical risk and patient consent. One patient underwent the procedure again after unsuccessful past subtotal parathyroidectomy. All parathyroid glands found during surgical exploration (28 glands) were removed. The volume of each gland was calculated by measuring the three maximum diameters according to the following formula of the ellipsoid model: width × length × thickness × 0.52 (*11,12*). Histological examination of enlarged parathyroids was performed in all patients.

TABLE 1
Clinical, Biochemical, Scintigraphic and Echographic Data (Patients with MIBI-Positive Scans)

Patient no.	Age (yr)	Dialytic age* (yr)	Ca (mmole/liter)	P (mmole/liter)	iPTH (pg/ml)	MIBI uptake†			Echo size‡(cm)	
1	59	7	2,7	1,2	1019	RL			RU = 0.8	
2	32	3	2,6	1,7	575		Jugular		No enlargement	
3	25	2	2,3	2,5	1616	RL		LL	RU = 1.6, RL = 2.0	LU = 2.5, LL = 2.0
4	65	15	2,5	1,9	618	RL		LL	RL = 1.3	LL = 1.6
5	64	20	2,7	1,2	509	RL			No enlargement	
6	63	7	2,3	2,7	463			LU		LL = 1.5
7	70	18	2,6	2,1	782	RL		LL	RL = 1.9	
8	59	2	1,7	2,5	218	RL			RL = 0.9	
9	71	1	2,0	1,7	671	RL		LL	No enlargement	
10	57	5	2,2	1,3	272	RU		LU	No enlargement	
11	70	11§	2,3	1,2	1000	RL		LL	No enlargement	
12	53	1	2,4	1,2	770	RL			No enlargement	
13	32	8	2,7	2,2	1385	RL		LL	RU = 0.6, RL = 2.0	LU = 0.7, LL = 2.5
14	61	21	2,5	1,4	630		Jugular	LL	No enlargement	
15	30	5§	1,8	1,8	683	RL		LL	No enlargement	
16	39	15	2,2	1,9	479	RL			No enlargement	
17	70	9	2,7	1,6	352	RL			RL = 1.8	
18	27	4	2,6	1,8	699			LL	RU = 1.2, RL = 1.5	LL = 1.5
19	62	6	2,5	2,3	1107	RL		LL	RU = 0.7, RL = 0.9	LU = 0.9, LL = 0.6
20	62	8	2,3	2,0	549	RU			RU = 2.0, RL = 1.5	LU = 2.5, LL = 0.5
21	63	4	2,3	1,5	1154	RL	Mediastinum			LL = 0.5
22	51	5	3,2	1,9	2096	RU			RU = 5.5, RL = 0.5	
23	71	14§	2,3	1,6	2000		Mediastinum		No enlargement	
24	64	10	2,5	2,0	1453	RU, RL		LU, LL	RU = 0.8, RL = 1.3	LL = 0.8
25	50	5	2,7	2,1	706		Jugular	LU, LL		LU = 1.2, LL = 1.0
26	55	7	2,4	1,8	1200			LL		LL = 1.5
27	57	1	2,3	2,0	310			LL		LL = 1.5
28	52	5	2,2	2,2	408			LL		LL = 3.0
Mean ± s.d.	55 ± 14	8 ± 6	2.4 ± 0.3	1.8 ± 0.4	847 ± 498					

*Yr after beginning of dialysis.
†Uptake localization is as follow: RU = right upper, RL = right lower, LU = left upper, LL = left lower.
‡Parathyroid gland diameters >0.5 cm are indicated separately along with their location.
§Predialysis CRF.
No enlargement = parathyroid gland diameter <0.5 cm.

Technetium-99m-MIBI Parathyroid Scintigraphy

Technetium-99m-MIBI (300 MBq) was intravenously injected in all patients. Ten minutes postinjection, planar imaging of the neck and the upper thorax in the anterior view of the supine patients was performed (thyroid phase) using a large field of view gamma camera with a low-energy, ultra-high resolution, parallel-hole collimator. The second phase study (parathyroid phase) was performed between 1 and 2 hr postinjection of MIBI. Hemodialysis was performed the day before the scan. All patients had preliminary [^{99m}Tc]pertechnetate thyroid scintigraphy and serum calcitonin determination 1 wk prior to the start of the study to exclude the presence of thyroid hot nodules or medullary thyroid carcinoma, since both conditions are known to be associated with focal MIBI uptake (*8,13*).

Statistical Analysis

Data are expressed as means ± s.d. Paired and unpaired Student's t-tests were used to analyze the differences between means. Probability values of <0.05 were considered significant. Linear regression analysis was used to calculate the dependence of iPTH values on parathyroid sizes and serum calcium concentrations. Sensitivity, accuracy and the positive results were calculated by standard methods.

RESULTS

Biochemical Data

Clinical and biochemical data of individual patients are summarized in Tables 1 and 2. Serum calcium and phosphorus concentrations were always comprised within the normal range, while a markedly increased circulating iPTH concentration was observed in all cases. Normal serum FT3, FT4, TSH and calcitonin concentrations were observed in all patients (data not shown).

Scintigraphic and Echographic Data

Thyroid scintigraphy and echography were normal in all patients. Parathyroid ultrasonography revealed at least one enlarged gland in 22/38 patients (58%), with the maximum gland diameter ranging from 0.7 to 5.5 cm. First-phase MIBI scintigraphy showed normal thyroid uptake in all cases associated with focal extrathyroid hot spots in the parajugular region (3) and in the mediastinum (2). In the delayed phase, MIBI uptake in the thyroid decreased, while its relative focal concentration increased in the parathyroid tissue of 28/38 patients (74%). At the same time, five extrathyroid hot spots were confirmed. A representative case of MIBI-positive parathyroid scan is depicted in Figure 1. Details on individual patients are summarized in Tables 1 and 2.

MIBI Scans, Parathyroid Echographic Dimensions, Serum iPTH and Serum Calcium Concentrations

Serum iPTH concentrations were significantly higher in patients with MIBI-positive glands than in those with MIBI-negative glands (847 ± 498 versus 363 ± 186 pg/ml, $p < 0.0005$). Patients with MIBI-positive glands also had a longer disease duration (8 ± 6 yr) compared to those with negative

TABLE 2
Clinical, Biochemical, Scintigraphic and Echographic Data (Patients with MIBI-Negative Scans)

Patient no.	Age (yr)	Dialytic age* (yr)	Ca (mmole/liter)	P (mmole/liter)	iPTH (pg/ml)	Echo size (cm)†
1	58	7	2,7	1,7	389	RU = 0.5, RL = 0.7, LU = 1.0, LL = 1.2
2	73	8	2,3	2,4	509	RL = 0.7
3	74	11	2,0	1,3	356	RU = 0.6
4	63	1	2,1	2,3	318	RL = 0.7
5	62	2	2,0	2,7	468	No enlargement
6	29	3	2,0	2,1	633	No enlargement
7	29	4	2,0	2,3	104	No enlargement
8	60	1	2,2	1,3	187	No enlargement
9	63	4‡	2,2	1,3	564	RU = 1.0
10	74	13	2,7	2,3	105	RU = 0.7, RL = 0.4
Mean ± s.d.	58 ± 17	5 ± 4	2,2 ± 0,3	1,9 ± 0,5	363 ± 186	

*Yr after beginning of dialysis.
†Echographic parathyroid size expressed as in Table 1.
‡Predialysis CRF.

MIBI scans (5 ± 4 yr), although this difference was not statistically significant. When age, serum calcium concentration, serum phosphorus concentration and the calcitriol/calcium therapeutic dose were considered, no differences were found between patients with MIBI-positive and MIBI-negative glands. Mean ultrasound parathyroid size of MIBI-positive glands was 3.04 ± 1.81 cm. This value was significantly greater ($p < 0.01$) than that of MIBI-negative glands (1.4 ± 0.5 cm). A significant positive correlation ($r = 0.62$, $p < 0.001$) was found between the serum iPTH concentration and the echographic parathyroid size of MIBI-positive glands (Fig. 2), while no correlation was observed when the size of MIBI-negative glands was considered.

A significant positive correlation was also shown between serum iPTH and calcium concentrations in patients with at least one MIBI-positive parathyroid ($r = 0.40$, $p < 0.05$) (Fig. 3). In contrast, no significant correlation between serum iPTH and calcium concentrations was found in patients with no focal parathyroid uptake. It should be noted, however, that patients with negative MIBI scans had lower serum iPTH concentrations in the presence of higher calcium levels (Fig. 4).

Comparison of MIBI Scans Parathyroid Volume and Histology in Surgical Patients

Nine MIBI-positive patients with markedly increased serum iPTH concentrations underwent surgical neck exploration, and 28 parathyroid glands were removed. After surgery, the serum iPTH concentration dramatically dropped within the normal range in all but two patients in whom responsiveness to medical treatment was eventually restored. Histological examination revealed 27 hyperplastic parathyroid glands and one parathyroid adenoma. The MIBI scan correctly identified the adenoma

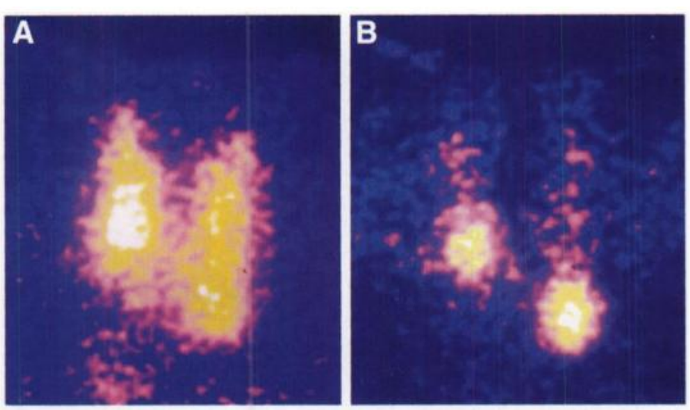

FIGURE 1. Representative case of double-phase ^{99m}Tc-MIBI scan in a patient with uremic hyperparathyroidism 10 min (A; thyroid phase) and 2 hr (B; parathyroid phase) postinjection. (A) Relatively homogeneous thyroid distribution of the radiotracer and (B) focal parathyroid uptake after thyroid MIBI clearance.

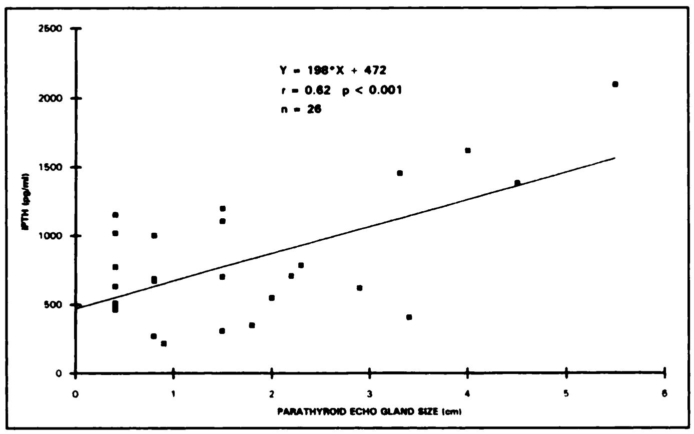

FIGURE 2. Comparison between echographic size of MIBI-positive parathyroid glands and serum iPTH concentration in 26 patients. Two patients (cases 2 and 23) were excluded since MIBI-positive ectopic parathyroid tissue was undetectable by echography (see Table 1).

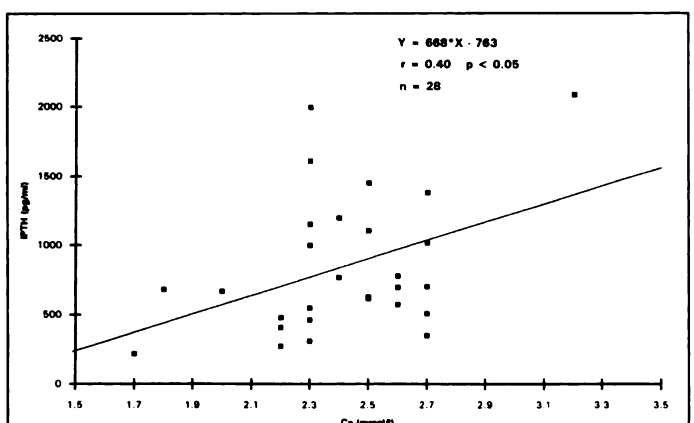

FIGURE 3. Comparison between serum calcium and iPTH concentration in 28 patients with uremic hyperparathyroidism and positive MIBI parathyroid uptake.

subjects, suggesting that the parathyroid tissue of this subgroup was still partially sensitive to calcium inhibition. These results further support the belief that MIBI uptake may be a hallmark of parathyroid functional autonomy. In keeping with this hypothesis, we have also observed a trend to a higher frequency of MIBI positive glands in patients with longer disease duration.

Uremic hyperparathyroidism is also characterized by a marked variation in parathyroid gland size observed in individual patients (*24,30*). On the basis of this observation, Brown et al. (*24*) have argued that variation rather than uniformity in function might be expected among different glands in a given patient with secondary parathyroid hyperplasia. Direct support of this interpretation is provided by the present study, in that we show that MIBI-negative and MIBI-positive glands of different size can co-exist in most patients with uremic hyperparathyroidism. This finding may be the consequence of the varying suppressibility thresholds in different glands, which lead to hyperactive non-suppressible MIBI-positive parathyroids along with relatively suppressed MIBI-negative hyperplastic glands. This phenomenon might be equivalent to the coexistence of hyperfunctioning tumors with fully suppressed extra-adenomatous parathyroid tissue in parathyroid adenomas (*31,32*).

CONCLUSION

It is possible to localize parathyroid tissue in most, but not all patients with uremic secondary hyperparathyroidism with double-phase MIBI scintigraphy. The comparison of scintigraphic, morphological and biochemical data supports the concept that positive MIBI scans may be the hallmark of the parathyroid functional autonomy that is characteristic of "tertiary" hyperparathyroidism.

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REFERENCES

1. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins REC. Technetium-99m-sestamibi—a new agent for parathyroid imaging. *Nucl Med Commun* 1989;10:791-794.
2. O'Doherty MJ, Kettle AG, Wells P, Collins REC, Coakley AJ. Parathyroid imaging with technetium-99m-sestamibi: preoperative localization and tissue uptake studies. *J Nucl Med* 1992;33:313-318.
3. Geatti O, Shapiro B, Orsolon PG, et al. Localization of parathyroid enlargement: experience with technetium-99m methoxyisobutilisonitrile and thallium-201 scintigraphy, ultrasonography and computed tomography. *Eur J Nucl Med* 1994;21:17-22.
4. Ferlin G, Borsato N, Camerani M, Conte N, Zotti D. New perspectives in localizing enlarged parathyroids by thallium-technetium subtraction scan. *J Nucl Med* 1983;24:438-441.
5. Young AE, Gaunt JI, Croft DN, et al. Localization of parathyroid adenomas by thallium-201 and technetium-99m subtraction scanning. *Br Med J* 1983;286:1384-1386.
6. Strauss HW, Pitt B. Thallium-201 as a myocardial imaging agent. *Semin Nucl Med* 1977;7:49-58.
7. Piwnica-Worms D, Holman BL. Noncardiac applications of hexakis (alkylisonitrile)-technetium-99m complexes. *J Nucl Med* 1990;31:1166-1167.
8. Sandrock D, Merino MJ, Norton JA, et al. Thallium-201/^{99m}Tc parathyroid scintigraphy [Abstract]. *Eur J Nucl Med* 1989;15:410.
9. Taillefer R, Boucher Y, Potvin C, Lambert R. Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). *J Nucl Med* 1992;33:1801-1807.
10. Potchen EJ. Parathyroid imaging. Current status and future prospects. *J Nucl Med* 1992;33:1807-1809.
11. Brunn J, Blocjk U, Ruf J, et al. Volumetrie der schildrusenlappen mittels real-time sonographie. *Dtsch Med J* 1983;287:1206-1207.
12. Takalo RM, Makarainen HP, Jaakkola RK. Thyroid gland volume and echo structure in 13-yr-old children in northern Finland. *Acta Endocrinol* 1991;124:238-244.
13. O'Driscoll CM, Baker F, Casey MJ, Duffy GJ. Localization of recurrent medullary thyroid carcinoma with technetium-99m-methoxyisobutylnitrile scintigraphy: a case report. *J Nucl Med* 1991;32:2281-2283.
14. Rademaker P, Meijer S, Pierce DA. Parathyroid localization by ^{201}Tl ^{99m}Tc subtraction scintigraphy: results in secondary hyperparathyroidism. *Acta Endocrinol* 1990;123:402-404.
15. Fabretti F, Calabrese V, Fornasari V, Poletti I. Subtotal parathyroidectomy for secondary hyperparathyroidism in chronic renal failure. *J Laryngol Otol* 1991;105:562-567.
16. Adalet I, Hawkins T, Clarke F, Wilkinson R. Thallium-technetium subtraction scintigraphy in secondary hyperparathyroidism. *Eur J Nucl Med* 1994;21:509-513.
17. Sandrock D, Merino MJ, Norton JA, Neumann RD. Ultrastructural histology correlates with results of thallium-201/technetium-99m parathyroid subtraction scintigraphy. *J Nucl Med* 1993;34:24-29.
18. Pijpers R, Potter van Loon BJ, Roos JC, Hoekstra OS. Technetium-99m-sestamibi/thallium-201 mismatch of thyroid and parathyroid adenoma in chronic renal failure. *J Nucl Med* 1995;36:826-828.
19. Lemmi A, Baroni M, Corneli P, et al. Ultrasonography and combined imaging techniques in hyperparathyroidism. *Radiol Med* 1994;88:606-611.
20. Arnaud CD. Hyperparathyroidism and renal failure. *Kidney Int* 1973;4:89-95.
21. Freitag J, Martin KJ, Hruska KA, et al. Impaired parathyroid hormone metabolism in patients with chronic renal failure. *N Engl J Med* 1978;298:29-32.
22. Slatopolsky E, Weerts C, Thielan J, et al. Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxycholecalcifero-l in uremic patients. *J Clin Invest* 1984;74:2136-2143.
23. Morrin PAF. Phosphate excretion in chronic uremia with observations on the effect of intravenous infusion of calcium. *Metabolism* 1965;14:674-683.
24. Brown EM, Wilson RE, Eastman RC, Pallotta J, Marynick SP. Abnormal regulation of parathyroid hormone release by calcium in secondary hyperparathyroidism due to chronic renal failure. *J Clin Endocrinol Metab* 1982;54:172-179.
25. Delmez JA, Slatopolsky E. Recent advances in the pathogenesis and therapy of uremic secondary hyperparathyroidism. *J Clin Endocrinol Metab* 1991;72:735-739.
26. Slatopolsky E, Delmez JA. Pathogenesis of secondary hyperparathyroidism. *Am J Kidney Dis* 1994;23:229-236.
27. Korkor AB. Reduced binding of [^{3}H]1,25-dihidroxyvitamin D3 in the parathyroid glands of patients with renal failure. *N Engl J Med* 1987;316:1573-1577.
28. McPhaul JJ, McIntosh DA, Hammond WS, Park OK. Autonomous secondary (renal) parathyroid hyperplasia. *N Engl J Med* 1964;271:1342-1345.
29. Bordier PJ, Marie PJ, Arnaud CD. Evolution of renal osteodystrophy: correlation of bone histomorphometry and serum mineral and immunoreactive parathyroid hormone values before and after treatment with calcium carbonate or 25-hydroxycholecalciferol. *Kidney Int* 1975;2:(suppl):102-112.
30. McCarron DA, Lenfesty B, Velt M. Post-renal transplant parathyroid hyperplasia: the anatomical distribution. *Cli Res* 1980;29:471A.
31. Pirah LN, Hodgkinson A, Anderson CV. Primary hyperparathyroidism. *Br J Surg* 1966;53:245-316.
32. Brown EM, Wilson RE, Thatcher JG. Abnormal calcium-regulated PTH release in normal parathyroid tissue from patients with adenoma. *Am J Med* 1981;71:565-570.