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Research Article

The importance of calcitonin in the homeostatic response to the chronic hypercalcemia of primary hyperparathyroidism is uncertain. To clarify this issue, we have used a new, sensitive radioimmunoassay for human calcitonin to measure basal plasma calcitonin concentrations in 50 patients with primary hyperparathyroidism (32 female, 18 male). We assayed calcium-stimulated calcitonin concentrations preoperatively in 22 of the patients (16 female, 6 male) and postoperatively in 6. Finally, we assayed pentagastrin-stimulated calcitonin concentrations preoperatively in eight of the patients (three female, five male). Plasma calcitonin values after an overnight fast were indistinguishable from those in normal subjects (mean±SE, males, 48±3 normal and 46±5 pg/ml hyperparathyroid, females, 31±2 normal and 37±3 pg/ml hyperparathyroid.) Among hyperparathyroid patients of both sexes, increases of calcitonin during Ca infusion (15 mg Ca/kg in 4 h) were within normal limits. However, the mean maximal increase of calcitonin was significantly lower in hyperparathyroid than in normal subjects ($P < 0.05$). In six patients normocalcemic 5-15 mo after parathyroid surgery, fasting plasma calcitonin values were not significantly different, but responses to Ca infusion were greater than preoperatively (Δ calcitonin ±SE: 13±4 preoperatively and 53±35 pg/ml postoperatively). The mean maximal increase of calcitonin after pentagastrin (0.5 μg/kg i.v.) was slightly lower than normal in the patients (mean±SE, males, 45±8 normal and 38±10 pg/ml hyperparathyroid, females, 6±2 normal and 0 pg/ml […]

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ABSTRACT The importance of calcitonin in the homeostatic response to the chronic hypercalcemia of primary hyperparathyroidism is uncertain. To clarify this issue, we have used a new, sensitive radioimmunoassay for human calcitonin to measure basal plasma calcitonin concentrations in 50 patients with primary hyperparathyroidism (32 female, 18 male). We assayed calcium-stimulated calcitonin concentrations preoperatively in 22 of the patients (16 female, 6 male) and postoperatively in 6. Finally, we assayed pentagastrin-stimulated calcitonin concentrations preoperatively in eight of the patients (three female, five male). Plasma calcitonin values after an overnight fast were indistinguishable from those in normal subjects (mean±SE, males, 48±3 normal and 46±5 pg/ml hyperparathyroid, females, 31±2 normal and 37±3 pg/ml hyperparathyroid.) Among hyperparathyroid patients of both sexes, increases of calcitonin during Ca infusion (15 mg Ca/kg in 4 h) were within normal limits. However, the mean maximal increase of calcitonin was significantly lower in hyperparathyroid than in normal subjects ($P < 0.05$). In six patients normocalcemic 5–15 mo after parathyroid surgery, fasting plasma calcitonin values were not significantly different, but responses to Ca infusion were greater than preoperatively (Δ calcitonin ±SE: 13±4 preoperatively and 53±35 pg/ml postoperatively). The mean maximal increase of calcitonin after pentagastrin (0.5 μg/kg i.v.) was slightly lower than normal in the patients (mean±SE, males, 45±8 normal and 38±10 pg/ml hyperparathyroid, females, 6±2 normal and 0 pg/ml hyperparathyroid). Thus, primary hyperparathyroidism is accompanied by normal steady-state concentrations of circulating calcitonin, and normal-to-blunted C-cell responses to pentagastrin or induced hypercalcemia, the response to calcium generally increasing after successful parathyroid surgery. These results clearly show that primary hyperparathyroidism is not characterized by hypercalcitoninemia. The seemingly paradoxical absence of elevated steady-state calcitonin concentrations may be accounted for partly by decreased secretory reserve. However, primary hyperparathyroidism may also be accompanied by an increase in the threshold of sensitivity for calcium stimulation of calcitonin secretion.

INTRODUCTION

Calcium infusion is known to stimulate calcitonin secretion in normal man (1–4), an observation that is in accord with the belief that one function of calcitonin is to combat hypercalcemia. Furthermore, some patients with hypercalcemia not caused by hyperparathyroidism have high basal serum or plasma immunoreactive calcitonin (iCT)[1] concentrations (5, 6). LiVolsi et al. (7) have reported that 36% of 14 patients with primary hyperparathyroidism (1°HPT) had C-cell hyperplasia and the thyroid content of calcitonin (bioassay) is decreased in patients with 1°HPT (8). For these reasons, one might predict that patients with hypercalcemia caused by 1°HPT would have high basal iCT values. However, the basal concentrations of iCT reported by other laboratories in patients with 1°HPT have been variable. Four groups have reported normal basal iCT values in almost all patients with 1°HPT (9–12), whereas three laboratories have found high mean iCT concentrations (1,

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[1] *Abbreviations used in this paper*: ΔCa, Increase of serum calcium during calcium infusion; CT, calcitonin; 1°HPT, primary hyperparathyroidism; iCT, plasma immunoreactive calcitonin; ΔiCT, Increase of iCT after stimulation; iPTH, serum immunoreactive parathyroid hormone.

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5, 13). In addition, two groups have found no increased thyroid venous:peripheral iCT gradient in 1°HPT (9, 14) and one has reported an increased gradient (15).

To characterize C-cell function in 1°HPT, we have compared iCT concentrations measured during steady-state, calcium-, and pentagastrin-stimulated conditions in normal and 1°HPT subjects. The results show that patients with the chronic hypercalcemia of 1°HPT have normal basal iCT concentrations and that during calcium or pentagastrin stimulation the patients have normal or diminished C-cell responsiveness.

METHODS

The procedures employed in this study were approved by the Mayo Foundation Human Studies Committee. After informed consent, we examined 60 normal subjects (35 men and 25 women) and 50 patients with clinically mild to severe 1°HPT (18 men and 32 women). All subjects had normal renal function, as defined by creatinine clearance. 1°HPT was confirmed in all 50 patients by operative findings, histopathology, and response to surgery. Details of calcitonin-stimulation tests in normal men and women have been presented separately (4). The pertinent biochemical characteristics and the parathyroid pathology of the 22 patients who underwent calcium infusion before surgery are summarized in Table I. These 22 subjects were selected for the relative mildness of their hypercalcemia, because we believed Ca infusion would be unsafe in patients with more severe disease. Six patients had the Ca infusion repeated between 5 and 15 mo after operation. The intravenous infusion consisted of 15 mg calcium/kg body wt as the gluconate (calcium gluceptate, Abbott Diagnostics, North Chicago, Ill.) in 500 ml 0.9% NaCl, by Harvard infusion pump over a 4-h period. Blood samples were drawn before and at 1-h intervals during the infusion, from the arm opposite the infusion site. All infusion studies were begun between 0700 and 0900 after an overnight fast. Finally, eight hyperparathyroid patients received pentagastrin (Ayerst Laboratories, New York), 0.5 μg/kg, by rapid intravenous injection, with plasma sampling at 0, 1.5, 5, 10, and 15 min.

iCT was measured by the method of Heath and Sizemore (4), which has recently been described in detail. This assay uses a goat antiserum to human calcitonin (CT) (G1701), which has major recognition for the 11–28 amino acid sequence region of the human CT monomer. It allows measurement of iCT in 60% of normal individuals, with the detection limits being ≤5 pg/assay tube or ≤25 pg/ml of plasma. Intra- and interassay variability for the assay are <20%. The highest basal iCT concentrations found in over 50 normal men and women have been 87 and 66 pg/ml, respectively, 205 and 135 pg/ml after Ca infusion, and 182 and 73 pg/ml after pentagastrin injection. All samples from each hyperparathyroid subject were measured in the same assay. Each normal and patient sample was assayed on 2–3 separate occasions. Preoperative iCT values after storage of plasma samples at −20°C were not lower than the respective values before storage, indicating there was no degradation of CT over the period of this study. For purposes of data analysis, samples that contained no detectable CT were arbitrarily assigned the value of the usual assay detection limit, 25 pg/ml.

Serum immunoreactive parathyroid hormone (iPTH) was measured by the method of Arnaud et al. (16) with a predominantly carboxy-terminal-directed antiserum (GP1M). This antiserum recognizes both the intact parathyroid hormone molecule and carboxyl fragments of parathyroid hormone and is capable of detecting the hormone in the serum of >95% of normal subjects. The iPTH concentration in normal individuals is ≤40 μl eq/ml and it has a negative correlation with serum calcium concentration.

Serum calcium was determined by atomic absorption spectroscopy (17) with normal adult range of 8.9–10.1 mg/dl, and serum phosphorus by a colorimetric method with adult range 2.5–4.5 mg/dl (18). Statistical methods (19) included Student's t test on normally distributed data, and because of undetectable values among iCT data, these data were also analyzed by nonparametric techniques, including rank sum, median, and Chi-square tests. Linear regression analyses were performed by the method of least squares.

RESULTS

Fasting state. Fig. 1 illustrates the basal iCT concentration as a function of serum Ca in the entire group of 50 1°HPT subjects. The individual basal Ca, iPTH, and iCT values characterizing the 22 1°HPT patients who underwent Ca infusion, and the mean±SE values for the normal subjects who had Ca infusion are shown in Table I. In the 1°HPT cases there was neither a correlation between iCT and calcium concentrations, nor between iCT and iPTH concentrations. For patients with 1°HPT there was the expected positive correlation between iPTH and serum Ca ($r = 0.4$, $P < 0.025$). All 18 hyperparathyroid men had normal iCT concentrations, not exceeding 75 pg/ml (mean±SE, 46±5 pg/ml). Among the 32 women with hyperparathyroidism, 2 had values slightly above the normal female range (Fig. 1), but the remainder were entirely normal (mean±SE, 37±3 pg/ml). There was no significant difference of mean basal iCT concentration between normal and 1°HPT groups of either sex.

Calcium stimulation. The iCT response to Ca infusion in the 1°HPT subjects is shown in Fig. 2. Nor-

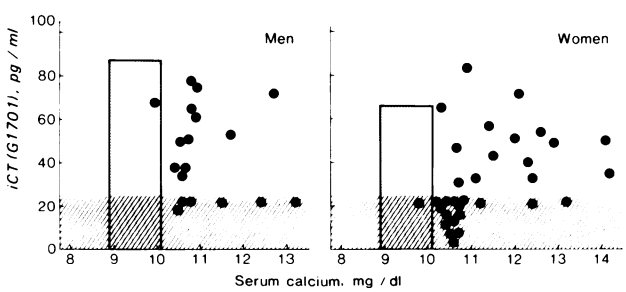

FIGURE 1 Basal iCT concentration is plotted (●) as a function of serum calcium concentration in 50 patients of both sexes who had primary hyperparathyroidism. iCT values falling within the hatched horizontal areas were below assay detection limits. The vertical shaded bars represent normal ranges for iCT and Ca in over 50 normal subjects. Note the lack of correlation between iCT and Ca in the hypercalcemic patients.

TABLE I

Blood Chemical Determinations and Histological Findings in Normal and Hyperparathyroid Subjects Who Received Calcium Infusion

Group	Age	Basal concentration				Calcium infusion			Parathyroid gland pathology
		Ca	P*	iPTH*	iCT	Maximum ΔCa	Maximum ΔiCT	Maximum ΔCT/ΔCA	
		mg/dl	*mg/dl*	*μleq/ml*	*pg/ml*	*mg/dl*	*pg/ml*		
Normal									
Male									
Mean±SE	30±2	9.4±0.1			48±3	4.0±0.2	58.5±9.0	16.3±3.0	
Female									Not applicable
Mean±SE	30±2	9.1±0.1			31±2	4.0±0.2	25.2±5.7	6.8±1.6	
Hyperparathyroid									
Male									
Mean±SE	41.8±5.3	10.7±0.2	2.7±0.2	40±12	51±7	3.9±0.2	26.7±9.4	7.4±2.6	
Patient									
1	54	9.8‡	3.5	31	68	4.0	43	12	RS 245 mg adenoma. LS, RI, and LI biopsied, all NL.
2	25	10.5	3.2	26	50	3.3	8	2.4	LI 440 mg adenoma. RS and RI biopsied, both NL; LS, NF.
3	34	10.6	2.1	32	38	4.2	55	13.1	RS 300 mg adenoma. LI biopsy NL. RI and LS grossly NL.
4	42	10.7	3.0	19	51	3.7	44	14	LS and LI hyperplastic with decreased fat. RS and RI biopsied, hyperplastic.
5	36	10.9	2.2	33	75	3.9	6	1.5	Mediastinal 120 mg adenoma. LS biopsy NL.
6	60	11.5	2.1	101	≤25	4.4	4	0.9	RI 510 mg adenoma. RS biopsy NL.
Female									
Mean±SE	56.8±3.1	10.7±0.1	2.5±0.1	97±43	38±5	3.4±0.2	9.9±3.6	4.5±1.6	
Patient									
7	46	9.8‡	2.5	29	≤25	3.9	0	0	LS 220 mg adenoma. RI biopsy NL.
8	48	10.2	2.8	31	≤25	3.1	0	0.8	RI 60 mg, RS 50 mg and LI 50 mg. LS biopsied. All hyperplastic.
9	56	10.3	2.5	31	≤25	3.6	0	0	LI 230 mg adenoma. RS, RI, and LS grossly NL.
10	65	10.3	2.7	730	66	3.2	3	2.1	RS 7800 mg adenoma. RI grossly NL. LS and LI, NF.
11	65	10.4	2.0	37	≤25	2.4	15	6.3	RI 420 mg adenoma. LI grossly NL. RS and LS, NF.
12	67	10.4	2.0	80	26	2.9	14	11.7	LI 1450 mg adenoma. RS, RI, and LI biopsied, all NL.
13	60	10.6	2.8	26	≤25	4.5	2	0	LI 240 mg, RS 170 mg and RI 10.5 mg. LS biopsied. All hyperplastic.
14	60	10.7	2.1	90	≤25	3.7	0	0	RS 2415 mg adenoma. LI biopsy NL.
15	68	10.7	2.6	31	≤25	2.1	2	1.0	LI 310 mg adenoma. RI grossly NL.
16	63	10.7	3.0	36	47	2.3	50	21.7	RS 970 mg adenoma. RI biopsy NL. LS and LI grossly NL.
17	67	10.7	2.3	90	31	3.2	10	5.3	RS-RI combined 270 mg, LI 50 mg. LS biopsied. All hyperplastic.
18	17	10.8	2.2	34	≤25	3.9	0	0	RI 100 mg, RS 80 mg and LI 55 mg. LS biopsied. All hyperplastic.
19	56	10.9	3.1	35	84	3.2	6	3.8	RS 240 mg, RI 230 mg and LS 170 mg. LI biopsied. All hyperplastic.
20	60	11.1	2.5	105	33	2.6	1	0.6	RI 700 mg adenoma. RS and LI biopsied, both NL.
21	55	11.4	2.3	51	57	5.9	24	4.1	RS 1100 mg adenoma. LI biopsy NL.
22	55	12.1	2.0	123	72	3.1	31	14.1	RS 2000 mg adenoma. RI, LS, and LI, NF.

LI, left inferior; LS, left superior; NL, normal; NF, not found; RI, right inferior; RS, right superior.

* Not determined in all normals; normal range for P, 2.5–4.5 mg/dl and for iPTH, ≤40 μleq/ml.

‡ These serum calcium values were normal, but the mean serum calcium was elevated in these subjects.

mal men had a maximum concentration of 205 pg/ml with a mean value of 106±10 pg/ml at the 4th h. The 1°HPT men generally had small increases of iCT during the infusion; the highest value was 116 pg/ml, only 57% of the normal maximum. The mean iCT concentration at the 4th h was 78±12 pg/ml in the 1°HPT men, not significantly different from that in normal men. The mean maximal increase of iCT after stimulation (ΔiCT) in 1°HPT men (27±9 pg/ml) was significantly lower than that in normal men (58±9 pg/ml) ($P < 0.05$).

As noted previously (4), the iCT response to calcium is low in normal women, and the response in the 1°HPT women appears even lower. Normal women

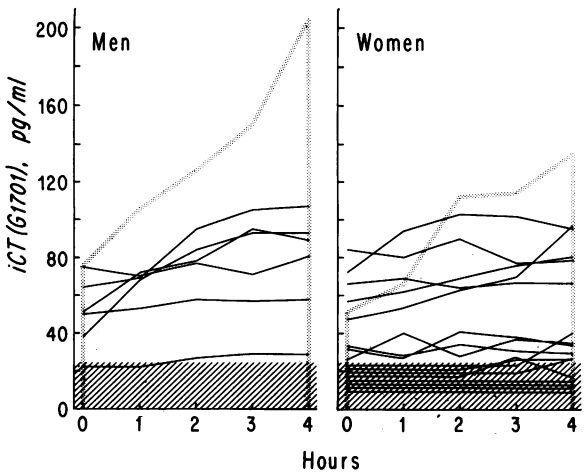

FIGURE 2 Effect of 4-h Ca infusion on iCT concentration in 45 normal subjects (highest values shown by dotted bars) and 22 1°HPT patients (solid lines) of both sexes. Note that the highest normal basal iCT values shown are slightly lower than the absolute upper limits of normal obtained in a larger group (Fig. 1).

had a maximum value of 135 pg/ml with a mean of 55±7 pg/ml at the 4th h. For 1°HPT cases the maximal iCT at the 4th h of infusion was 97 pg/ml or 72% of the maximum in normal women. The mean iCT at the 4th h in the 1°HPT women was 46±7 pg/ml compared to 55 pg/ml in normal women, not a statistically significant difference. However, the mean maximum ΔiCT was significantly lower in 1°HPT women (10±4 pg/ml) than in normal women (25±6 pg/ml), $P < 0.05$ (rank sum).

The maximun increase of serum calcium during calcium infusion (ΔCa) in the 1°HPT patients (mean ±SE, 3.5±0.2) was slightly but not significantly less than in the controls (4±0.2). This phenomenon has been observed before in 1°HPT subjects, and it has been attributed to an increase in the miscible calcium pool and an increase of calcium accretion into bone (20). To see whether the differences in iCT between normal and hyperparathyroid groups were influenced by the differences in Ca increment, the changes in iCT were also examined as a function of changes in Ca. Mean maximal ΔiCT/ΔCa values were lower in 1°HPT than in normal subjects, but these differences just escaped statistical significance. We conclude that a relatively lower ΔCa in 1°HPT cases cannot explain the lower ΔiCT.

Postoperative calcitonin concentrations. To further assess the effect of hyperparathyroidism on C-cell function, repeat calcium infusions were performed in six 1°HPT patients (Nos. 2, 5, 8, 9, 13, 22) between 5 and 15 mo after their recovery from parathyroid surgery. The patients then had normal basal Ca and iPTH values and received no vitamin D or calcium supplements for several weeks before the repeat studies. In these six patients, mean±SE preoperative basal iCT levels were 56±8 pg/ml, and postoperatively, 47±5 pg/ml, not a significant difference, $P \geqslant 0.05$. However, mean iCT responses to Ca infusion were significantly greater ($P < 0.001$) after successful treatment of the hyperparathyroidism than preoperatively (Fig. 3, preoperative ΔiCT 13±4 and postoperative ΔiCT 53±35). This was true whether we examined simply maximal ΔiCT, or maximal ΔiCT/ΔCa. Either way, five of the six had greater postoperative ΔiCT, and one had equal responses. Another patient's (No. 1) postoperative results were eliminated from the study because of concomitant treatment with propranolol at the time of the repeat calcium infusion. In light of the recent report that β-adrenergic blockade decreases CT secretion (21), it is of interest that in this one patient, postoperative iCT response while on β-blocking treatment was lower than preoperatively.

Pentagastrin stimulation. As an independent test of calcitonin secretion, preoperative responses to pentagastrin of 5 male and 3 female hyperparathyroid subjects were compared to those of 25 normal men and 14 normal women (Fig. 4). All iCT values were within normal limits for the patients. The mean maximal iCT concentrations were somewhat higher in normal than in hyperparathyroid subjects (mean ±SE, males: normal, 95±8, and hyperparathyroid, 78±16 pg/ml; female: normal, 35±4, and hyperparathyroid, <25 pg/ml), but not significantly. Similarly, mean maximal ΔiCT values were slightly but not

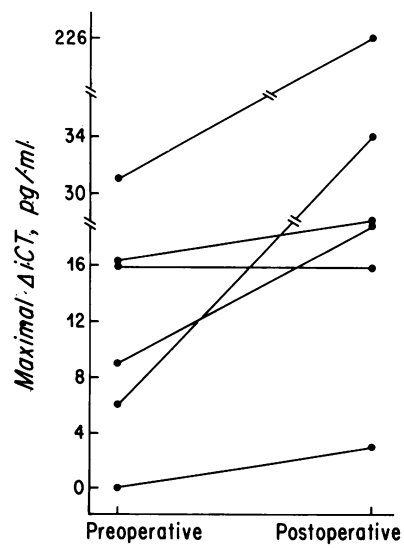

FIGURE 3 Preoperative and postoperative maximal ΔiCT during Ca infusion in six 1°HPT patients. The mean maximal ΔiCT was significantly greater postoperatively ($P < 0.001$).

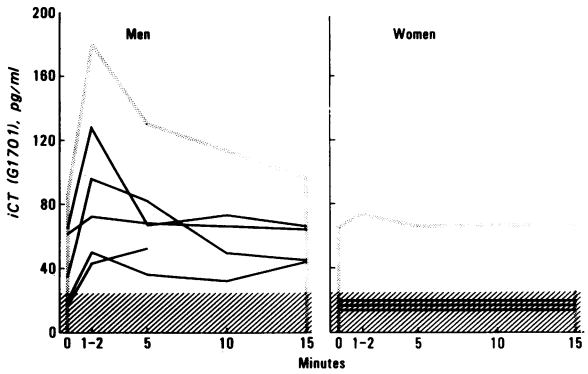

FIGURE 4 Effect of pentagastrin injection on iCT in 39 normal subjects (highest values shown by dotted bars) and 8 1°HPT patients (solid lines) of both sexes. iCT values falling within the hatched areas were below assay detection limits.

significantly lower in 1°HPT patients (males, 45±8 normal and 38±10 pg/ml hyperparathyroid; female, 6±2 normal and 0 pg/ml hyperparathyroid).

DISCUSSION

Since the discovery of calcitonin, speculation has centered about its physiologic and pathophysiologic significance. This has been especially true about a possible compensatory role of CT in the chronic hypercalcemic state of 1°HPT (1, 5, 9, 13, 22). Conflicting results regarding basal iCT values in 1°HPT have appeared, with both normal and high levels reported (1, 5, 9–13). The studies described here further characterize C-cell function in 1°HPT, and suggest that hypercalcitoninemia is not the usual homeostasic response in this disorder.

With regard to the basal iCT values, our results show no significant difference between the 60 control and 50 surgically-proven 1°HPT patients and are in accord with those of several other laboratories (9–12). These findings suggest that CT does not circulate in supranormal concentrations in patients with 1°HPT, whether mild or severe (Fig. 1). The lack of correlation between serum Ca or iPTH values and plasma iCT levels does not support a concept of compensatory hypercalcitoninemia in 1°HPT (13). The basis for the difference between our results and the higher basal values reported by some other investigators (1, 5, 13) is not clear. One possible explanation is that relating to immunoheterogeneity of circulating iCT with the generation of fragments and(or) aggregates not recognized by our antiserum. These forms of CT could either arise from the C-cell or from peripheral metabolism (23–26). In addition, possible differences in patient populations with regard to sex (4), degree of hypercalcemia, or renal function (1) might explain the conflicting results. However, our patients include ample numbers of both sexes, had normal renal function, span the entire range of severity of 1°HPT, and are compared against appropriately sex-matched controls with a well-validated CT assay (4). Therefore, we believe our data are representative and unbiased.

The relatively low levels of iCT in hyperparathyroidism might reflect a decrease in CT synthesis, storage and(or) secretion in the chronic hypercalcemic state, or a change in "set point" for CT secretion. We are unaware of studies that demonstrate an effect of chronic hyper- or hypocalcemia on human CT synthesis. Increased degradation of calcitonin by tissue in hyperparathyroid patients could explain our results, but the studies of Baylin et al. (27) have excluded increased degradation by plasma enzymes. In normal individuals CT secretion is known to be responsive to acute perturbations of serum calcium concentrations (2, 4, 5, 28). Therefore, calcium infusion would appear to be an ideal means for testing hypercalcemic patients with 1°HPT. Our studies suggest a normal or blunted iCT response to calcium infusion in the 1°HPT patients. These findings are in accord with the reports of other investigators who have found decreased thyroidal CT content in 1°HPT (8) and vitamin D-induced hypercalcemia (29). Conversely, chronic hypocalcemia produces increased stores of CT (30, 31) and(or) predisposes to increased secretory responses (32).

If the limited C-cell responsiveness to Ca in 1°HPT were a result of chronic hypercalcemia, then removal of the chronic stimulus might produce an increased C-cell response to calcium infusion. Postoperative calcium infusion studies demonstrated a greater iCT response after successful treatment of the 1°HPT in five of the six patients, and no change from the preoperative results in the remaining patient. These findings show that surgical correction of the hypercalcemia results in an improved secretory response, but the mechanism remains uncertain. The apparently decreased C-cell responsiveness to Ca could be caused by reduced CT stores, or to saturation of a membrane Ca-receptor. Mean ΔCa was not significantly different after surgery, so a greater stimulus is not the explanation. Therefore, the finding of possibly diminished CT responses to a different secretagogue, pentagastrin, is of interest. However, the iCT increases after pentagastrin were normal in most patients with 1°HPT, suggesting that decreased secretory reserve cannot be the sole explanation for blunted iCT secretion during Ca infusion.

Whether 1°HPT is regularly accompanied by changes in C-cell morphology cannot be answered by our data. We have no data that would support speculation that the C-cell hyperplasia observed in 6 of

14 hyperparathyroid patients by LiVolsi et al. (7) was a compensatory phenomenon. Kracht et al. (33) also state that C-cell hyperplasia accompanies hyperparathyroidism, but no details of the studies are presented, and the most specific and relevant technique (immunocytochemical) (7) was not available to them. One additional description of C-cell hyperplasia in a single hyperparathyroid patient has been offered (34), but nonspecific histologic techniques were employed. The finding of decreased thyroidal CT content in 1°HPT (8) is difficult to relate to the histologic picture. It must be concluded that the prevalence of C-cell hyperplasia in 1°HPT, and its relation to CT secretory reserve, is unknown.

We conclude from our findings and previous results (7, 8, 15, 29–31) that steady-state concentrations and presumably secretion of CT are normal in 1°HPT. The C-cell response to Ca infusion is normal to blunted, and increases after successful parathyroid surgery. C-cell responses of hyperparathyroid patients to pentagastrin are grossly normal, with a trend to subnormal responses. In 1°HPT, secretory reserve for CT is normal or only moderately diminished, so decreased synthesis and storage of CT is unlikely to account fully for the seemingly paradoxical absence of hypercalcitoninemia in the disease. It seems likely that chronic hypercalcemia results in blunting of the C-cell reactivity to further acute increments of plasma Ca. In essence, 1°HPT is accompanied by reset upward of the Ca level needed to provoke CT secretion. These results raise questions about the homeostatic importance of CT in 1°HPT, but one cannot be certain whether the patients would have higher serum Ca values if CT were absent.

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