Endocrine

Southwestern Medical School

Grand Rounds

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PROBLEMS IN THE DIAGNOSIS OF HYPERPARATHYROIDISM

Neil A. Breslau, M.D.

"If the thyroid is not the most interesting gland in the world, it's next to it."

Sidney Ingbar

TABLE OF CONTENTS

Table 2. Clinical Characteristics of Patients with Primary Hyperparathyroidism in Rochester, Minnesota.

CHARACTERISTIC*	NO. OF CASES†	
	1/1/65 to 6/30/74	*7/1/74 to 12/31/76*
Total	39 (100)	51 (100)
Urolithiasis	20 (51)	2 (4)‡
Hypercalciuria (>250 mg/d)§	14 (36)	11 (22)
Emotional disorder¶	10 (26)	10 (20)
Osteoporosis	8 (21)	6 (12)
Diminished renal function	7 (18)	7 (14)
Hyperparathyroid bone disease	4 (10)	4 (8)
Peptic-ulcer disease	2 (5)	4 (8)
Pancreatitis	2 (5)	0 (0)
No problems related to primary hyperparathyroidism‖	7 (18)	26 (51)**

In both the Mayo study and a series reported from our unit [4], the incidence of hypertension in patients with hyperparathyroidism is about 48 percent which is actually less than 1 1/2 times the relative risk in age and sex matched controls. If hypertension is considered to be largely unrelated to hyperparathyroidism, then both series would agree that over half the cases of hyperparathyroidism currently diagnosed are totally asymptomatic. (Perhaps because of the type of patient referred to us, our group still finds a higher incidence of nephrolithiasis -- 28 percent [4]).

Although the majority of cases will no longer present with the traditional triad of renal stones, bone disease or peptic ulcer, routine multichannel chemical screening has facilitated the diagnosis of hyperparathyroidism. Certainly, problems in the diagnosis of hyperparathyroidism still occur and will constitute today's discussion, but the issue of what to do with the increasing number of patients presenting with mild asymptomatic disease is worthy of a Grand Rounds in its own right [5]. On-going studies at this institution [6] and elsewhere [7] are attempting to grapple with the question of which is more dangerous, parathyroidectomy or the untreated disease.

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Diagnosis of Hyperparathyroidism

An elevated mean serum calcium level in the absence of malignancy, sarcoidosis, hypervitaminosis D,hyperthyroidism, thiazides, hypocalciuria, milk alkali syndrome or immobilization is still the best test for primary hyperparathyroidism. If the hypercalcemia can be demonstrated to have been present for a long time, or if it is associated with elements of the triad previously mentioned (stones, bone fractures or ulcers) then the diagnosis is virtually assured. Following a careful history and physical exam, a CBC, SPEP, chest x-ray and IVP may be the only tests required to rule out the other potential causes of hypercalcemia. Of course serum phosphate would tend to be low or at least low normal due to the enhancement of renal phosphate excretion by PTH. Since PTH also increases renal bicarbonate excretion and tends to produce a mild hyperchloremic acidosis, some authors have utilized the chloride to phosphate ratio as a diagnostic parameter [8]. A ratio of greater than 33 favors the diagnosis of hyperparathyroidism, although there may be some overlap with normal controls and patients with malignancy [9,10]. Subperiosteal bone resorption on hand and clavicle x-ray films is not often seen anymore, but would be a helpful additional clue if present.

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The above data are sufficient in most cases for the diagnosis of primary hyperparathyroidism, but we are now able to achieve even greater certainty through the measurement of serum immunoreactive PTH and urinary cyclic adenosine monophosphate (cAMP).

The PTH Assay

The determination of the serum immunoreactive PTH (iPTH) level potentially provides the most direct measure of parathyroid function. However, several problems have limited the reliability of this measurement. Radioimmunoassays for human iPTH are heterologous, using radiolabeled tracers and antisera produced against PTH obtained from animal (bovine and provine) sources. Dependence of these assays on relatively low cross-reactivity with human iPTH so restricts their sensitivity that most radioimmunoassays for human hormone in plasma operate near the limits of their sensitivity. The precision of determinations made in

this portion of the displacement curve is poor. In addition, immunoreactive PTH in the circulation is heterogeneous and each antiserum may react differently with different portions of the molecule. The heterogeneity of plasma iPTH derives from the secretion of fragments and metabolism of intact hormone by kidney and liver after secretion [11]. Anti-sera to the longer-lived C-terminal fragments may give information of a relatively time-integrated character (improved discrimination at picking up hyperparathyroid states), while N-terminal systems are more sensitive to fluctuations in secretory rates [12]. It is apparent why different laboratories obtain different results on the same serum samples, and why differential diagnosis of hypercalcemia on the basis of iPTH levels can be confusing [13].

For these reasons, normal values must be established in each laboratory. Interpretation of iPTH levels also requires consideration of the serum calcium level; it is important to recognize that iPTH levels that might be considered normal in a normocalcemic patient may be inappropriately high in a patient with hypercalcemia [12]. With most assay techniques, detectable levels of iPTH, in the presence of hypercalcemia, suggest hyperparathyroidism. For this reason it is important that the assay system used by sensitive enough to measure iPTH in the serum of a fair proportion of normal subjects. Otherwise, iPTH may be unmeasureable in a significant number of patients with hyperparathyroidism. The final test of any assay used is its clinical correlation.

With these criteria in mind, we are quite pleased with our current PTH radioimmunoassay. (Fig. 1). We utilize the Iso-tex Diagnostics PTH Radioimmunoassay system, which contains a C-terminal antiserum. This is a guinea pig antiserum directed against bovine PTH and utilizes a bovine PTH-^{125}I tracer. We have modified the kit by using a human PTH standard (kindly supplied by Dr. Bernie Roos) which assures that the antibody will have an equal affinity for the standard and the iPTH in the patients serum. After an adequate incubation period, bound and free fractions are separated by a double antibody technique, employing goat anti-guinea pig gamma globulin. As can be seen in Fig. 1 , iPTH is detectable in virtually all normals with a range of 10 to 35 μℓ-eq/mℓ. iPTH levels are inversely correlated to serum calcium levels in normals, and as the dotted circles indicate, when serum calcium is raised above normal by calcium infusion, iPTH becomes undetectable. Thus detectable iPTH levels in the hypercalcemic range suggest hyperparathyroidism. We have not yet evaluated iPTH levels in the hypercalcemia of malignancy. This will be of practical importance because using some assays, iPTH levels are always normal or suppressed in the hypercalcemia of malignancy, such that an elevated level indicates the coexistence of primary hyperparathyroidism [11]. Another unique feature of the Isotex assay kit is that the entire procedure requires less than 24 hours to accomplish.
Case: The wife of a medical student who recently had a kidney stone removed elsewhere was transferred to PMH because of a frightening rise in her blood calcium to 14.9 mg/dℓ. Full scale work-up had not yet been performed, but within one day serum iPTH was available (109 μℓ-eq/mℓ); neck exploration revealed a 2.2 Gm parathyroid adenoma. Post-op calcium was 9.7 mg/dℓ.

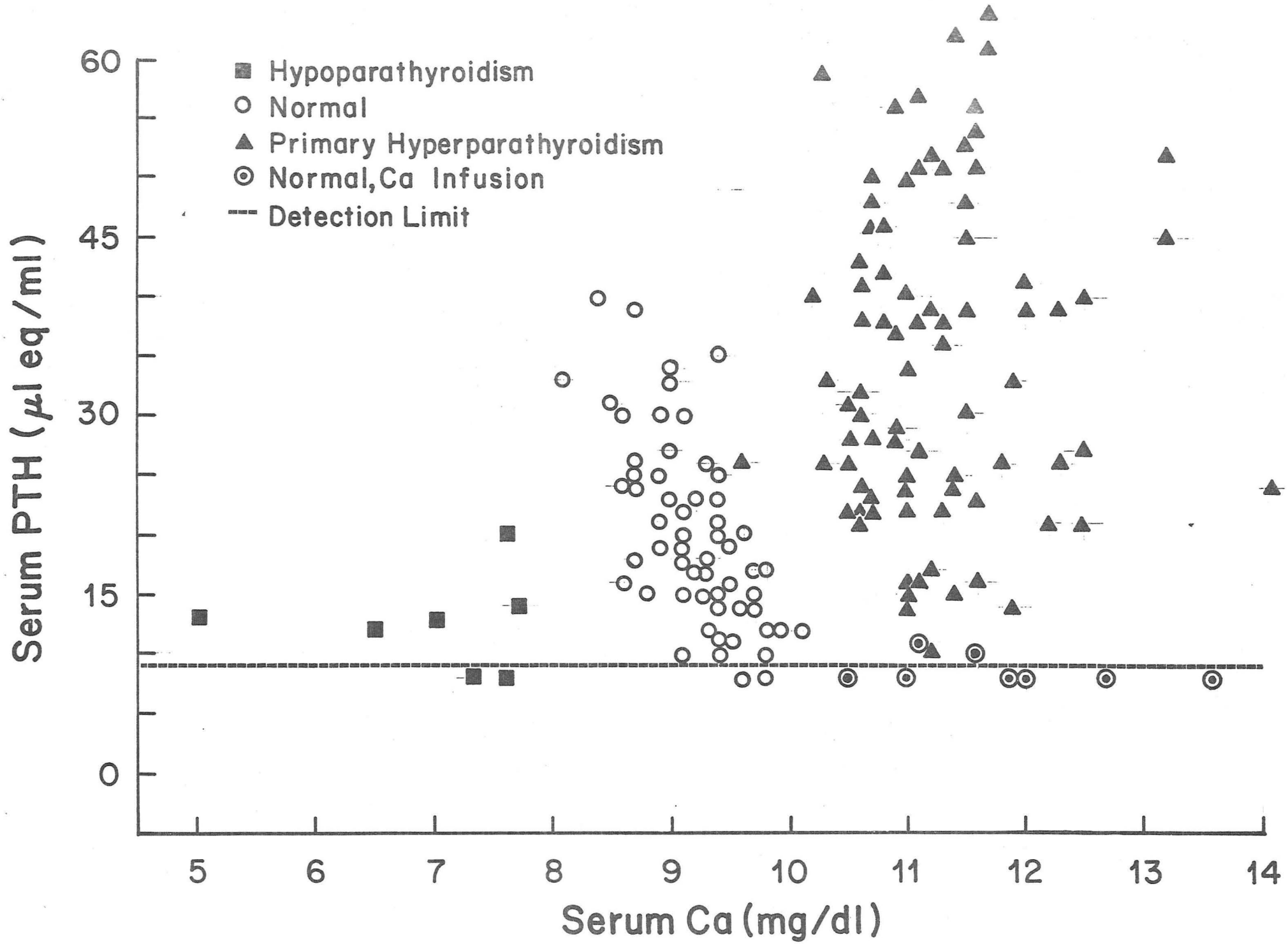
Hypoparathyroidism
Normal
Primary Hyperparathyroidism
Normal, Ca Infusion
Detection Limit
Serum PTH (μl eq/ml)
60
45
30
15
0
5
6
7
8
9
10
11
12
13
14
Serum Ca (mg/dl)

Figure 1

References

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Urinary Cyclic AMP

Because of the heterogeneity of circulating PTH and the variable effectiveness of different antisera in detecting it, and because as much as 95% of circulating iPTH may represent the inactive carboxy-terminal fragment[11], measurement of urinary cyclic AMP has proven useful as an in vivo bioassay of PTH activity. PTH, of course, provides a potent stimulus to renal adenylate cyclase and augments the renal excretion of cyclic AMP[14]. Figure 2 attempts to show that normally, 60 percent of the total urinary cyclic AMP is represented by the filtered fraction, and the remaining 40 percent by the nephrogenous fraction. The action of PTH

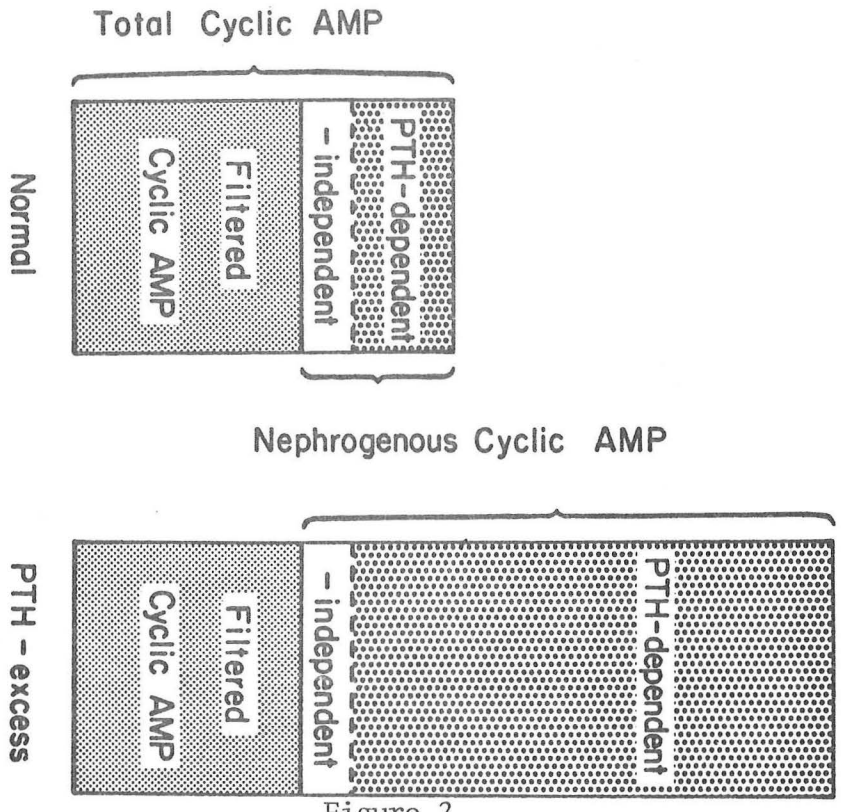

Figure 2

accounts for 65 percent of nephrogenous cyclic AMP, but none of the filtered fraction. During PTH-excess, total urinary cyclic AMP is increased 2-fold. This increase is accomplished by a dramatic rise in nephrogenous cyclic AMP. The amounts of filtered cyclic AMP remain relatively constant. A proportionately greater rise in nephrogenous cyclic AMP (3-fold) from that of total cyclic AMP (2-fold) serves to provide an improved discrimination of the hyperparathyroid state with the former mode of presentation. Moreover, there are few non-PTH mediated influences on nephrogenous cyclic AMP, whereas glucagon and β-adrenergic agents (potentially important in pheochromocytoma or hyperthyroidism) may augment the total cyclic AMP excretion by increasing the filtered fraction [15]. The nephrogenous cyclic AMP is calculated by subtracting the filtered cyclic AMP from the total urinary cyclic AMP. It therefore requires determination of plasma cyclic AMP, which is technically somewhat difficult and varies from moment to moment with exercise or excitement.

Whether determined as total or nephrogenous fraction, urinary cyclic AMP excretion may be expressed relative to the period of measurement, corresponding urinary creatinine or to glomerular filtration rate. As Broadus has shown, the latter is the most physiologically meaningful mode of expression because it take into account both variation in body size and renal functional mass [16]. The expression of total or nephrogenous cyclic AMP as a function of glomerular filtration rate may be calculated simply as the product of urinary cyclic AMP in nmoles/mg creatinine by serum creatinine in mg/dℓ, to yield the value in nmoles/100 mlGF. It is worth pointing out that since generally the filtered component contributes a relatively constant background over the variable nephrogenous fraction (Fig. 2), the variations in total urinary cyclic AMP reflect principally changes in the nephrogenous fraction. Thus, Broadus found that total urinary cyclic AMP, expressed as nmoles/100 mlGF, was equally reliable as the nephrogenous cyclic AMP in the detection of disturbed parathyroid function [16]. Both methods were able to distinguish patients with hyperparathyroidism from normal subjects in about 95 percent of the cases. At this institution, measurement of total urinary cyclic AMP has thus far proven more simple and reliable.

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Despite this rather sophisticated armamentarium for the diagnosis of parathyroid disease, problems occasionally arise. The remainder of this discussion deals with some of these difficult situations. We shall first discuss problems in distinguishing hyperparathyroidism from other causes of hypercalcemia, following the scheme outlined in Table 3 . We shall then discuss the problem of "normocalcemic" hyperparathyroidism.

Table 3
Distinguishing Hyperparathyroidism From Other Hypercalcemias

A. Increased Calcium Input Into Circulation
   1. Neoplasm
      a. Ectopic PTH production
      b. Prostoglandin Production
      c. Production of Ostoeclast Activating Factor
      d. Direct Osteolysis
   2. Vitamin D Excess
      a. Vitamin D Toxicity
      b. Sarcoidosis
   3. Thyrotoxicosis

B. Reduced Calcium Removal From Circulation
   1. Thiazide Therapy
   2. Familial Hypocalciuric Hypercalcemia
   3. Milk-Alkali Syndrome
   4. Immobilization (reduced bone formation).

Features which distinguish the hypercalcemia of hyperparathyroidism from that of malignancy are shown in Table 4 .

Table 4

Differential Diagnosis of Hypercalcemias

	Primary Hyperparathyroidism	Neoplastic PTH Production	Neoplastic PGE Production	Neoplastic OAF Production
Renal stone				
Skeletal fracture	Frequent	Rare	Rare	Rare
Peptic ulcer				
Weight loss	Rare	Frequent	Frequent	Frequent
Onset	Slow	Rapid	Rapid	Rapid
Localizing symptoms of malignancy	Absent	Frequent	Frequent	Frequent
Neoplasm	Uncommon	Solid>Soft	Solid	Lymphoid
Treatment	Parathyroidectomy		Indomethacin aspirin	Corticosteroids
Serum calcium	↑	↑↑	↑↑	↑↑
Serum phosphorus	↓,N	↓	↓	↓
Urinary calcium	↑,N	↑↑	↑↑	↑↑
Serum PTH	↑	↑	↓	↓
Urinary cyclic AMP	↑	↑	↓	↓

Generally the distinction is not too difficult. A sudden onset of hypercalcemia, especially if it is greater than 14mg/dℓ, absence of the diagnostic triad, history of recent weight loss, anemia or localizing symptoms of malignancy would be important clues. The suspicion of malignancy, particularly if bone pain is present, should prompt a skeletal survey or bone scan. The majority of patients with hypercalcemia of malignancy (83%) have malignant lesions within the skeleton [17] . Breast carcinoma is clearly the most common malignancy associated with hypercalcemia in women and carcinoma of the lung is the most common in men. Multiple myeloma, head and neck tumors, esophageal tumors and hypernephromas were other malignant lesions most often found to cause hypercalcemia in a prospective ongoing study at Los Angeles County/University of Southern California Medical Center ([17] Table 5).

Table 5 Types of malignancy in hypercalcemic inpatients at Los Angeles County/University of Southern California Medical Center, March, 1976 to May, 1978

Malignancy	Number of patients
Lung carcinoma	33
Breast carcinoma	23
Multiple myeloma	22
Head and neck carcinoma	14
Esophageal carcinoma	8
Renal carcinoma	6
Ovarian carcinoma	5
Cervical carcinoma	3
Hepatic carcinoma	3
Lymphocytic lymphoma	3
Colon carcinoma	2
Gastric carcinoma	2
Pancreatic carcinoma	1
Thyroid carcinoma	1
Uterine carcinoma	1
Bladder carcinoma	1
Gallbladder carcinoma	1
Skin carcinoma	1
Carcinoma, ? primary site	6
	136

Not all patients with the hypercalcemia of malignancy show evidence of skeletal lesions. The term pseudohyperparathyroidism was introduced to describe the biochemical changes seen in some cancer patients consisting of high serum calcium and low serum phosphate in the absence of parathyroid gland enlargement or bony metastases [18]. The hypercalcemia would return to normal following resection or radiotherapy of the tumor, and it was surmised that certain tumors may produce hypercalcemic humoral factors. To date, there is convincing evidence for the three humoral factors listed in Table 4[17]. Osteoclast Activating Factor (OAF) has been generally associated with multiple myeloma and various lymphomas, and is generally steroid responsive [19]. Increased prostaglandin E production has been most often found in squamous cell carcinoma of the lung, and when not associated with bony metastases, the hypercalcemia responds well to the protaglandin synthesis inhibitors aspirin and indomethacin [20]. These two types of humoral hypercalcemia of malignancy should be easy to differentiate from primary hyperparathyroidism. Both OAF and PGE stimulate osteoclastic bone resorption directly, and the increased calcium entering the circulation suppresses PTH and urine cyclic AMP.

The third humoral factor which is a PTH-like substance creates greater problems in diagnosis. This is particularly true since an association between malignancies and functioning parathyroid adenomas is now well recognized [21]. Thirty percent or more of patients with primary hyperparathyroidism usually due to a single adenoma, may develop cancer either before, during or after the discovery of parathyroid disease. Serum PTH and urine cyclic AMP will be increased in both primary hyperparathyroidism and in ectopic PTH production (lung carcinoma and hypernephroma head the list). Even with multivalent and carboxy-terminal PTH anti-serum, some investigators do not find increased PTH levels in patients with humoral hypercalcemia of malignancy [22]. Those who find PTH to be inappropriately elevated for the hypercalcemia, detect lower levels of PTH in cancer patients than in patients with comparable serum calcium who have primary hyperparathyroidism [23]. Apparently the PTH fragments produced by tumors are different from those of the parathyroid gland and each PTH antiserum must be evaluated as to how well it detects these fragments (as we are currently doing with our own assay). One point that emerges however, is that a high urinary cyclic AMP level in a hypercalcemic patient that is not associated with a very high PTH level should raise the suspicion of malignancy [24]. If a patient with a malignancy has hypercalcemia associated with both high serum PTH and high urinary cyclic AMP levels, and if treatment of the malignancy could provide the patient with reasonable life expectancy, it may be worthwhile to determine whether primary hyperparathyroidism is also present. To accomplish this, the principal veins draining the parathyroid gland may be catheterized, and serum PTH assayed at various levels. A gradient of PTH levels in the presence of hypercalcemia, establishes the existence of hyperfunctioning parathyroids.

Case Report: W.T.B. is a 67 year old white male who presented with serum calcium 14.0 mg/dℓ, phosphate 3.5 mg/dℓ, serum PTH 18-30 μℓ-eq/mℓ and urine cyclic AMP 6.33 nmol/mg creatinine. The presence of anemia led to a hematologic evaluation which resulted in a diagnosis of non-Hodgkin's Lymphoma-mixed lymphocytic and histiocytic confined to the bone marrow. The patient did well on chemotherapy but hypercalcemia persisted. There was a previous history of neck surgery in which one enlarged parathyroid gland was removed. The following venous drainage study was performed:

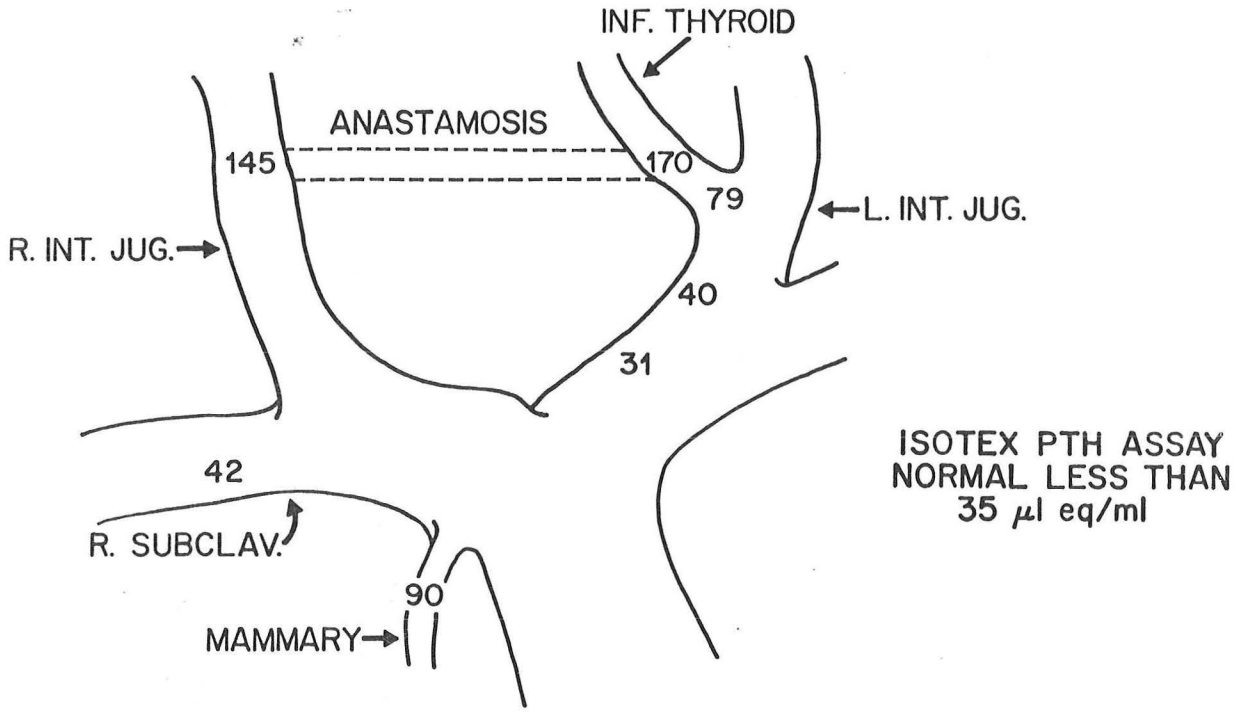
W.T. BOWEN–PARATHYROID VENOUS DRAINAGE STUDY
INF. THYROID
ANASTAMOSIS
145
170
79
L. INT. JUG.
R. INT. JUG.
40
31
ISOTEX PTH ASSAY
NORMAL LESS THAN
35 μl eq/ml
42
R. SUBCLAV.
90
MAMMARY

Figure 3

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SARCOIDOSIS

As Norman Bell has shown, the increased sensitivity to vitamin D in sarcoidosis is due to enhanced production of 1,25(OH)$_2$-cholecalciferol [25]. It has not been established whether the granulomatous tissue itself possess a 1-hydroxylase or directs the 1-hydroxylation of 25-OH-cholecalciferol by the kidneys. The increased circulating level of this potent vitamin D metabolite causes enhanced intestinal calcium absorption and increased bone resorption. Therefore, hypercalcemia may occur in sarcoidosis. Various series report an incidence of from 1.3 to 63 percent, the two largest series comprising 509 and 345 patients with the disease, show close agreement with 17 percent and 16.5 percent evidencing hypercalcemia [27]. There is also a highly significant correlation between plasma 1,25-(OH)$_2$D and urinary calcium excretion in these patients [25]. The hypercalciuria which is even more common than the hypercalcemia may be associated with renal stones, nephrocalcinosis, and impaired renal function.

Increased serum 1,25(OH)$_2$D, increased intestinal calcium absorption and increased bone resorption also contribute to the hypercalcemia and hypercalciuria of primary hyperparathyroidism [26]. There are several features which may help distinguish these two conditions however. A history of cough or shortness of breath, chest x-ray revealing bilateral hilar adenopathy or diffuse fibro-nodular infiltrate, and SPEP revealing high total protein with increased globulin, would, of course, suggest the diagnosis of sarcoidosis. Serum phosphate may be normal or increased in sarcoidosis, but is generally on the low side in primary hyperparathyroidism. Of extreme importance in the differential diagnosis of the two conditions is measurement of serum PTH and/or urine cyclic AMP. As shown in Figure 4, most patients with sarcoidosis have functional hypoparathyroidism [28].

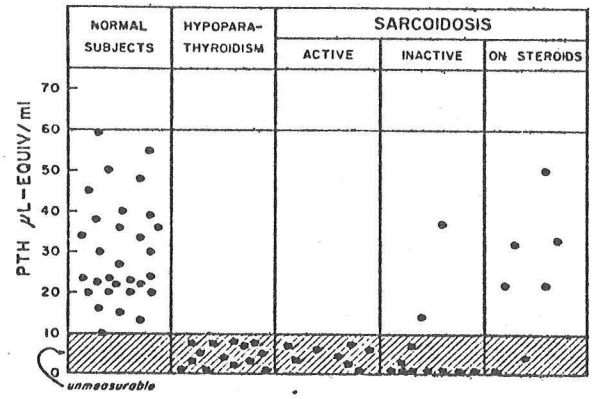

Figure 4 Serum PTH in Normal Subjects and in Patients with Hypoparathyroidism and with Sarcoidosis.
The horizontal lines limit the normal range. The shaded area indicates the unmeasurably low range. The steroid dosage varied from 5 to 20 mg of prednisone daily. Each dot represents a different patient.

This fits well with the recognized abnormalities of calcium metabolism in sarcoidosis, since excessive absorption of calcium from the gastrointestinal tract should reduce PTH secretion. It will be noted in the figure that of the few patients with sarcoidosis who had normal PTH levels, most were being treated with steroids which are known to reverse the "vitamin D sensitivity" and return serum calcium to normal. The urinary cyclic AMP would also be decreased in uncomplicated sarcoidosis reflecting the reduced serum PTH levels. When dependable assays for serum PTH and urinary cyclic AMP are readily available, the separation of these two causes of hypercalcemia should not be too difficult. However, as these assays are not always trustworthy, another means of distinguishing these two conditions i.e. the prednisone suppression test, still occasionally proves useful.

The Prednisone Suppression Test

Dent was the first to suggest in 1953, that cortisone may be of value in the differential diagnosis of hypercalcemia due to hyperparathyroidism and that due to sarcoidosis. This assessment was based on the observation that a daily dose of 150 mg cortisone given for 10 days would lower the serum calcium in patients with sarcoidosis, but not in a patient with primary hyperparathyroidism[29,30]. Subsequently, many other investigators and clinicians have obtained the same results using various glucocorticoids. Bell has recently obtained evidence that prednisone may act to correct the abnormal calcium metabolism in sarcoidosis by reducing circulating $1,25(OH)_2D$ [25]. In three patients with sarcoidosis, hypercalcemia and low or undetectable PTH, treatment with prednisone significantly lowered serum calcium from 13.3 to 9.7 as it significantly reduced serum $1,25(OH)_2D$ from 62 pg/mℓ to 26 pg/mℓ (normal range 20-50 pg/mℓ). Our own group has confirmed this observation in 8 patients with sarcoidosis, finding a significant reduction in serum $1,25(OH)_2D$ (48 pg/mℓ to 33 pg/mℓ) in response to 8 days of prednisolone (50 mg/day) [31]. Corresponding to this reduction in the active vitamin D metabolite, we have also found a significant reduction in fractional intestinal calcium absorption (.58 to .46; normal .40 to .60). More recently, in order to learn more about the mechanism of the short-term prednisone suppression test, we have evaluated the responsiveness of 8 patients with primary hyperparathyroidism [32]. Some of the key parameters of response are compared with those of patients with sarcoidosis and normal subjects in Table 6.

As already noted, our patients with sarcoidosis had a significant decrease in serum $1,25(OH)_2D$ and intestinal calcium absorption in response to prednisolone. They were not hypercalcemic at the time of this study, and therefore we could not demonstrate the usual decrease to a normal serum calcium level. Serum PTH was low normal to undetectable as expected. Urine calcium excretion on a low calcium diet was high normal, but did not change with treatment. In the normal subjects, prednisolone did not alter serum $1,25(OH)_2D$ or intestinal calcium absorption, but a significant calciuric response was noted. The patients with primary hyperparathyroidism who started out with increased serum calcium, $1,25(OH)_2D$ and intestinal calcium absorption, essentially had a "normal" response to prednisolone. None of the aforementioned parameters decreased, and they too had a marked calciuric response. This calciuric response to steroid therapy may be the result of a direct effect of the steroid in inhibiting renal tubular reabsorption of calcium[33] or may result from enhanced mobilization of calcium and phosphate out of bone. Favoring the "renal hypercalciuria" theory would be the observed tendency for PTH, urine cyclic AMP and serum $1,25(OH)_2D$ to increase (albeit not significantly) in some of the normal subjects and patients with primary hyperparathyroidism. Moreover, Hahn and associates recently found significant increases in urinary calcium and in serum $1,25(OH)_2D$ during subacute prednisone administration in normal subjects [34].

TABLE 6

EFFECT OF PREDNISOLONE ON LABORATORY PRESENTATIONS

	SARCOIDOSIS (n=8)		NORMALS (n=7)		PRIMARY HYPERPARATHYROIDISM (n=	
	CONTROL	PREDNISOLONE	CONTROL	PREDNISOLONE	CONTROL	PREDNISOLONE
Serum calcium (mg/dℓ)	9.7±0.5	9.6±0.6	9.5±0.3	9.6±0.4	11.5±1.2	11.9±1.5 *
Serum phosphate (mg/dℓ)	3.4±0.4	3.2±0.5	3.3±0.5	3.7±0.4 *	2.6±0.3	3.1±0.4 *
Serum PTH (μℓ-eq/mℓ)	16 ±10	24±20	35±38	40±27	51±32	59±42
Urine cyclic AMP (nmol/100mℓGF)	4.09±2.10	4.40±2.60	4.23±0.97	4.42±0.98	5.22±1	6.63±2.26
Serum 1,25$(OH)_2$D (pg/mℓ)	48 ±19	33±10 *	41±9	47±10	75±27	77±36
Intestinal Ca Abs (fraction)	0.58±0.14	0.46±0.13 *	0.44±0.11	0.43±0.12	0.79±0.11	0.76±0.09
Urine calcium (mg/day)	181±107	174±121	130±43	228±47 *	390±174	531±172 *

The lack of a calciuric effect in sarcoidosis could be explained by a concurrent decrease in intestinal calcium absorption. Whatever the mechanism for this calciuric response, its presence or absence is another feature which serves to distinguish the patient with primary hyperparathyroidism from the patient with sarcoidosis respectively. High levels of $1,25(OH)_2D$ with associated hypercalcemia may characterize both conditions, but the 1-hydroxylation mediated by the granulomatous tissue in sarcoidosis (and possibly in other granulomatous conditions such as tuberculosis and coccidioidomycosis) is much more sensitive to short-term steroid suppression. It should be noted that long-term steroid administration may decrease serum $1,25(OH)_2D$[35] and intestinal calcium absorption[36] even in patients without granulomatous diseases, and may contribute to the severe bone loss observed with prolonged glucocorticoid therapy.

The utility of the prednisone suppression test may be appreciated from the following case report:

J.D., a 51 year old white female beautician passed her first kidney stone in 1976. In April, 1978 an IVP revealed two left ureteral stones and a stone in the lower pole of the right kidney. Left ureterolithotomy was performed because of obstruction, revealing a stone composed of calcium oxalate and phosphate. At that time, serum calcium was noted to be elevated at 11.1 mg/dℓ, with a corresponding PTH level of 204 pg/mℓ by the UpJohn Laboratory (normal range: 163-347). This was interpreted to indicate 79% probability of hypercalcemia not due to PTH, and 21% probability that the hypercalcemia was due to increased PTH. A chest x-ray revealed extensive bilateral fibronodular disease consistent with sarcoidosis. The patient was referred to our Mineral Metabolism Section for further evaluation.

The biochemical profile revealed serum calcium ranging from 11.4 to 12.4, phosphate 2.5 to 3.0, and PTH-20 μℓ-eq/mℓ, which was inappropriately elevated for that degree of hypercalcemia. Tubular reabsorption of phosphate was low at 50 percent. Thyroid hormone was normal. 24-hour urine calciums were extremely elevated at 915 mg, 638 mg and 700 mg, even on a low calcium diet. Fasting urine calcium was increased at .40 mg calcium/mg creatinine (normal less than .11) and urine cyclic AMP was 4.23 nmol/100 mℓGF (normal 1.5-5.4). Following a 1 gram calcium load, urine calcium was .70 mg/mg creatinine (normal less than .20) with urine cyclic AMP 2.97 nmol/mg creatinine. These findings would suggest increased bone resorption as well as enhanced intestinal calcium absorption. Again, chest x-ray confirmed fibronodular changes consistent with sarcoidosis, and the patient admitted to symptoms of dyspnea and cough which had previously been attributed to hair spray. Total protein was 8.6 Gm/dℓ with 4.4 Gm/dℓ globulin.

It was recognized that features of both primary hyperparathyroidism (inappropriate PTH level, low serum phosphate, low TRP) and of sarcoidosis (CxR, high serum globulin) were present. A prednisone suppression test was performed on an out-patient basis and serum calcium which was 11.3 baseline, barely decreased to 10.7 mg/dℓ. This was interpreted as an inadequate decrease in calcium, consistent with hyperparathyroidism. In September of 1978, the patient underwent neck exploration where two enlarged parathyroid glands, which were hyperplastic, were found at the upper poles. The lower parathyroids could never

be found because they were lost in a cluster of lymph nodes which extended from the lower neck into the mediastinum and contained non-caseating granulomas.

After removal of the two hyperplastic parathyroid glands, the patient did well initially with serum calcium dropping to 9.5 mg/dℓ in October. By December of 1978 however, the patient complained of polyuria, polydipsia, anorexia and constipation and a serum calcium was 13.5 mg/dℓ. In February of 1979, she passed another stone. The question was did she have persistent hyperparathyroidism requiring re-exploration of the neck, or were the abnormalities in calcium metabolism related to sarcoidosis. The patient was admitted to the General Clinical Research Center. After an initial calcium of 11.0 mg/dℓ was obtained, the patient was permitted to equilibrate on a 400mg calcium, 100meq sodium diet and a complete prednisone suppression test was performed. The results are shown in Table [7].

Table 7

EFFECT OF PREDNISOLONE ON LABORATORY PRESENTATION OF PATIENT J. D.

	CONTROL	PREDNISOLONE
Serum calcium (mg/dℓ)	10± 0.6	9.4 ±0.3
Serum phosphate (mg/dℓ)	2.8± 0.1	2.7 ±0.2
Serum PTH (μℓ-eq/mℓ)	2	5
Urine cyclic AMP (nmol/100mℓ GF)	4.97± .05	3.96 ±.61
Serum 1,25(OH)$_2$D (pg/mℓ)	65	45
Intestinal Calcium Abs (fraction)	.73	.45
Urine calcium	173± 10	98 ±13

The increased serum 1,25(OH)$_2$D level with associated intestinal hyperabsorption of calcium in the presence of a suppressed PTH level strongly suggest sarcoidosis as the cause of the persistent calcium abnormalities. This is supported by the clear-cut reduction in 1,25-(OH)$_2$D, intestinal calcium absorption, and in urinary calcium excretion following the course of prednisolone. The patients hypercalcemia, hypercalciuria and stone diathesis could therefore be managed by dietary calcium restriction, and if necessary, the addition of steroids.

It is worth noting that there have been at least twelve recorded cases of coexistent sarcoidosis and primary hyperparathyroidism[27,28]. It is a puzzling association since the metabolic alterations of sarcoidosis would tend to suppress PTH secretion. Whenever a patient with histologically proven sarcoidosis presents with hypercalcemia that is prednisone-resistant and an inappropriately elevated serum PTH level, the co-occurrence of primary hyperparathyroidism should be suspected [28].

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THYROTOXICOSIS

Abnormalities in calcium metabolism seen in thyrotoxicosis have recently been well reviewed by Mundy and Raisz [37]. Serum calcium may be increased in 10-20% of patients with thyrotoxicosis although the increases are usually not severe enough to cause symptoms. In studies in which serum ionized calcium has been measured directly, the frequency of hypercalcemia has approached 50 percent. Direct stimulation of bone resorption by both thyroxine (T4) and tri-iodothyronine (T3), but not by reverse T3, has been demonstrated by Mundy et al. in their fetal rat long bone culture system [38]. The pathogenesis of the disordered calcium metabolism consists of increased calcium and phosphate entering the circulation from bone, suppression of PTH, hypercalciuria and occasionally hypercalcemia. Because PTH is suppressed and serum phosphate may be increased, levels of $1,25(OH)_2D$ and intestinal calcium absorption are reduced. There are thus many differential features to distinguish the hypercalcemia of hyperthyroidism from that of primary hyperparathyroidism, and diagnosis should not be difficult if the possibility of thyrotoxicosis is kept in mind. The generally mild asymptomatic hypercalcemia will respond to treatment of the hyperthyroidism, and also to steroids [39] and propanalol [40]. When severe hypercalcemia does occur in a patient with thyrotoxicosis, the possibility of coexistent but unrelated primary hyperparathyroidism must be considered.

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THIAZIDE THERAPY

Thiazide decreases urinary calcium excretion in two ways. First, by reducing sodium reabsorption in the distal convoluted tubule without proportionate calcium loss [41], the drug causes reduced extracellular volume. This reduction in extracellular volume leads to increased proximal calcium reabsorption [42]. The critical role of volume contraction in the hypocalciuric action of thiazide is supported by an accentuation of this action after prior volume contraction with furosemide [43] and by its attenuation with sodium load. The second mechanism for the hypocalciuric action of thiazide is a direct stimulation of distal tubule calcium reabsorption, as demonstrated in micropuncture studies [44], PTH also stimulates renal tubule calcium reabsorption, but unlike PTH, thiazide does not alter urinary cyclic AMP [45]. In fact, the retained calcium caused by thiazide normally suppresses parathyroid function. Low levels of urinary cyclic AMP have been observed in thiazide-induced hypercalcemia [46], as well as an inverse relationship between serum ionized calcium and PTH in normal subjects receiving the drug [47]. Thiazides may also accentuate osteocytic bone resorption in situations where it is already stimulated (e.g. primary hyperparathyroidism, immobilization, Pagets, vitamin D treatment and renal failure). Thus the induction of hypercalcemia by thiazide has been reported in patients on maintenance hemodialysis, despite negligible change in urinary calcium [48].

In patients with normal calcium metabolism, thiazide generally does not increase serum calcium to greater than 10.5 [49], but occasionally to greater than 11 mg/dℓ [50]. However, the ionized calcium remains normal and unchanged [50]. The increased total calcium is due to thiazide-induced hemoconcentration and increased protein binding of calcium. Retained calcium (from reduced calcium excretion) probably does not contribute to serum calcium because of compensatory mechanisms in intestine and bone:

Reduced Ca Excretion →	Parathyroid Suppression →	Reduced $1,25(OH)_2D$ Synthesis →	Decreased Ca Absorption and Decreased Bone Resorption

Increased total calcium is typically self-limited, may occur at various times of therapy [50] and subsides within 2 weeks of thiazide withdrawal.

In primary hyperparathyroidism, both total and ionized calcium rise in response to thiazide [51]. In fact, a thiazide provocation test may be used to unmask suspected cases of primary hyperparathyroidism (rise in ionized calcium above the normal range after hydrochlorothiazide 50mg q 8h for 4 days) [51]. Not all patients with primary hyperparathyroidism show a positive response to the thiazide provocation test. Thiazide may cause an increase in serum ionized

calcium in patients with primary hyperparathyroidism by potentiation of osteocytic resorption, or by lack of compensatory responses to reduced calcium excretion:

Reduced Ca Excretion	→	Relative non-suppressibility of PTH and $1,25(OH)_2D$ synthesis	→	Incomplete reduction in Ca absorption and Bone Resorption

In conclusion therefore, the patient who develops hypercalcemia while on thiazides should be suspected of having primary hyperparathyroidism:

(a) if there is true hypercalcemia (reflected by increased ionized calcium)
(b) if there is an inappropriately elevated serum PTH level or urinary cyclic AMP
(c) if the hypercalcemia persists 2 weeks after the thiazide is discontinued.

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FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

The peculiar syndrome of familial hypocalciuric hypercalcemia (FHH) was described by Marx and his associates at the NIH [52] . They had decided to screen the families of 25 index patients with primary parathyroid hyperplasia for hypercalcemia. About half of these patients had one or more first degree relatives with hypercalcemia. It soon became clear however that there were two distinct familial syndromes, each with autosomal dominant transmission. One group presented with all the usual features of primary hyperparathyroidism plus features of MEN type I (pituitary or pancreatic adenomas). The other group, consisting of 2 kindreds, did not have any evidence of MEN type I, but had the following peculiarities:

TABLE 8 FEATURES OF FHH

A. Features shared with typical primary hyperparathyroidism
   1. Hypercalcemia (10.9 - 13.0 mg/dℓ)
   2. Hypophosphatemia (2.8 mg/dℓ)
   3. Mild hyperchloremic acidosis (Chloride - 104 meq/L)
   4. Serum PTH-variable, but increased in 4/20 FHH patients
   5. Urinary cyclic AMP-usually normal, but occasionally increased
   6. Parathyroid hyperplasia usually found at surgery

B. Features that differ from primary hyperparathyroidism
   1. 50 percent of offspring develop hypercalcemia before age 10.
   2. Relative hypocalciuria (mean 24hr urine Ca 107 mg, compared to greater than 300 mg in hyperparathyroidism).
   3. Hypermagnesemia (FHH: 2.05 meq/L, 1ºHP: 1.71, N1: 1.5-2.0) with hypomagnesuria.
   4. Nephrolithiasis and peptic ulcer very rare
   5. Subtotal parathyroidectomy does not abolish hypercalcemia, although total parathyroidectomy may cause hypoparathyroidism.

Further studies on the pathophysiology of this unusual syndrome disclose that the ultrafilterable calcium and magnesium as well as the ionized calcium are truly increased in the same proportion as in other hyperparathyroid patients. Therefore, there must be enhanced renal reabsorption of these divalent cations in FHH [53] . Unlike in the usual forms of hyperparathyroidism where serum calcium and magnesium are inversely related, in patients with FHH there is a direct correlation of serum calcium and magnesium levels (Fig.5 [53]). Although PTH is capable of stimulating renal calcium and magnesium absorption, the evidence suggests that higher serum concentrations of PTH do not account for the lower renal clearance of calcium and magnesium in FHH. When compared to patients with primary hyperparathyroidism at any elevation of serum calcium concentration, the group with FHH had lower serum PTH, urinary cyclic AMP excretion

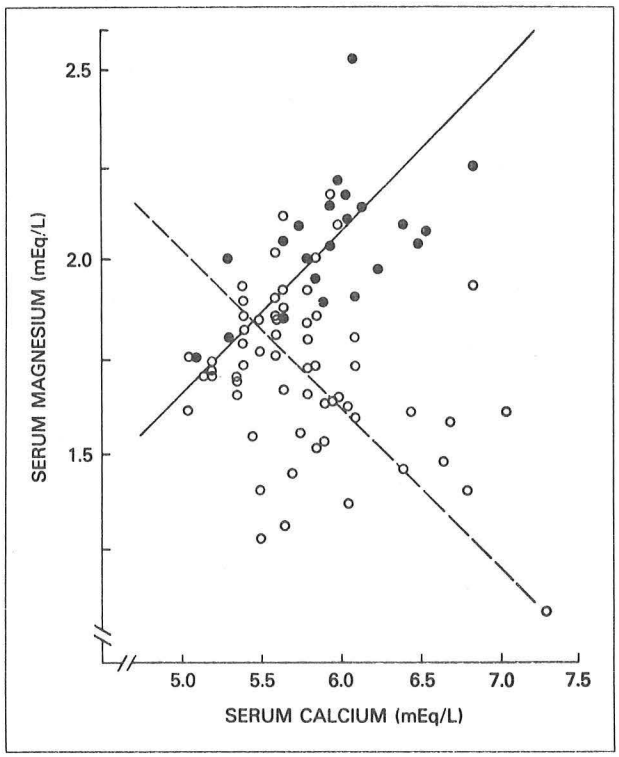

Figure 5 *Relationship of calcium and magnesium concentrations in serum. (●) Familial hypocalciuric hypercalcemia; (○) Primary hyperparathyroidism. Each point represents data from one patient. The linear regression equations are as follows: familial hypocalciuric hypercalcemia: magnesium = −0.414 + 0.413 ∗ calcium. Primary hyperparathyroidism: magnesium = 4.233 − 0.437 ∗ calcium. ∗ = multiplication.*

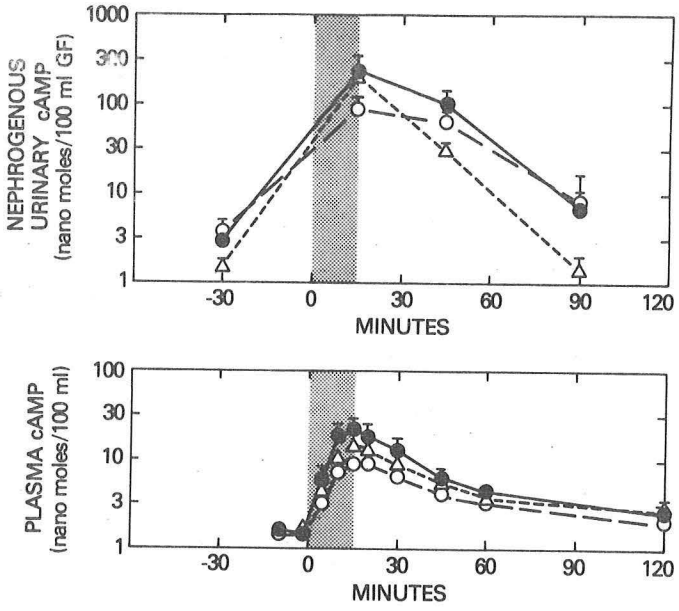

FIG. 6 Time course of changes in neph. cAMP (*upper panel*) and in plasma cAMP concentration (*lower panel*) in response to infusion of PTH. ▨, Duration of the PTH infusion. ●—●, FHH. ○—○, 1HPT. △- -△, Normal. Vertical bars indicate 1 SE. The SE bar is omitted when it would overlap the plotted symbol of its respective mean. GF, Glomerular filtrate.

and TmP/GFR [54]. Following 15 minute PTH infusion, patients with FHH have a higher urinary and plasma cyclic AMP response than do patients with primary hyperparathyroidism (Fig. 6 [55]). Heath and Purnell have also shown in a recent abstract that when challenged by acute hypocalcemia, patients with "familial benign hypercalcemia" (a disorder similar or identical to FHH) show a greater urinary cyclic AMP response to endogenous PTH than do normals or patients with primary hyperparathyroidism [56]. Renal clearance of calcium is decreased by PTH probably via a cyclic AMP-mediated process [57]. However, an underlying increase of renal responsiveness to PTH cannot account for all features of FHH. In particular,

the presence of varying degrees of parathyroid hyperplasia in hypercalcemic subjects with FHH would not be explained.

Recently, the NIH group searched for FHH among patients referred to that institution after unsuccessful parathyroid exploration [58]. Of 67 patients referred, 6 were shown to be members of kindreds with FHH. Thus, at least 9 percent of patients referred after unsuccessful parathyroidectomy had FHH. A diagnosis of FHH was made when at least one first degree relative manifested hypercalcemia and when all hypercalcemic members of the kindred excreted less than 250 mg calcium per 24 hour urine specimen. Urine calcium excretion expressed as the calcium:creatinine clearance ratio provided an easily measureable and effective index to separate the groups with FHH, typical primary hyperparathyroidism and suppressed parathyroids (e.g. surreptitious vitamin D ingestion) (Fig.7), [58].

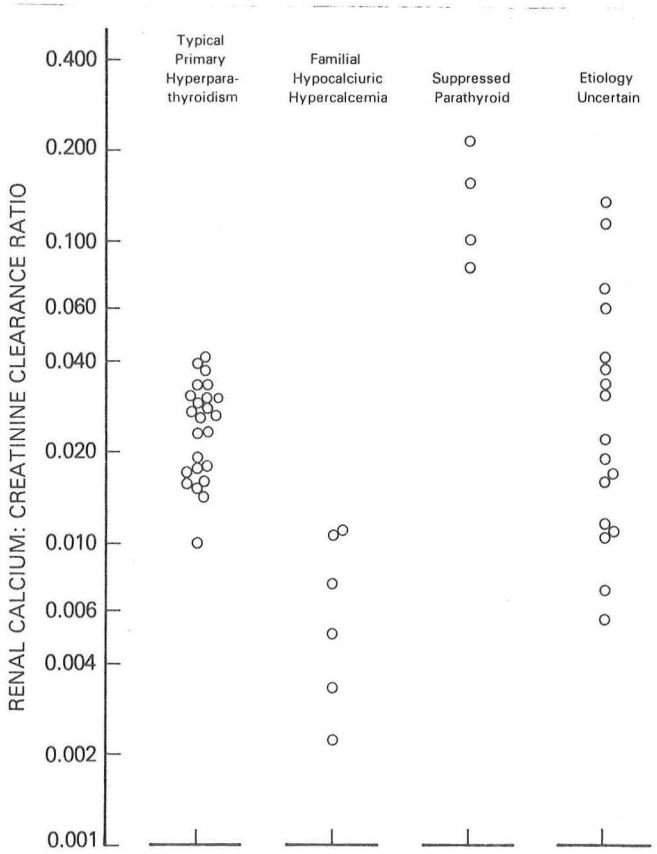

Figure 7 Renal calcium:creatinine clearance ratio in hypercalcemic patients. Each datum point represents a different patient. Data are shown for the same patients as included in Table 2; patients receiving drugs known to have major effects on divalent cation metabolism were excluded (*see* Materials and Methods section).

The NIH group is now following 9 kindreds with FHH and the earlier observations of an extremely low incidence of nephrolithiasis or other complications have been supported. Although these patients usually present with asymptomatic

hypercalcemia, rarely, non-specific hypercalcemic symptoms (myalgias, fatigue) may be present. Since these patients are largely asymptomatic and are almost never cured by subtotal parathyroidectomy, they should be distinguished from patients with typical primary hyperparathyroidism. A low 24 hour urine calcium (less than 250mg) in the presence of hypercalcemia should raise suspicion and be followed by a determination of the calcium:creatinine clearance ratio. The diagnosis also depends on familial occurrence of hypercalcemia at an early age. Hypermagnesemia would be supportive but not required. Optimal management of patients with FHH remains unclear, but if asymptomatic, follow-up appears superior to parathyroidectomy.

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MILK-ALKALI SYNDROME

The milk-alkali syndrome which is caused by the ingestion of large quantities of calcium and absorbable alkali (e.g. sodium bicarbonate, calcium carbonate) is still a rare cause of hypercalcemia today. The hallmark is the co-occurrence of renal insufficiency with alkalosis instead of acidosis. The alkali are thought to both facilitate intestinal calcium absorption and to enhance renal tubular calcium reabsorption. The resultant hypercalcemia lends to a progressive diuresis, azotemia, and eventually to renal tubular calcium deposits. In addition to the history of excessive milk and absorbable antacid ingestion, and the azotemia with alkalosis, this disorder may be distinguished from primary hyperparathyroidism by the suppressed parathyroid function, increased serum phosphate and low urinary calcium excretion. As in the case of the other conditions discussed thus far, there have been instances of combined primary hyperparathyroidism with milk-alkali syndrome.

IMMOBILIZATION

The hypercalcemia of immobilization is uncommon and usually mild, but in young patients with rapid bone turnover, it may become severe and even life-threatening. One would think that there would be no difficulty in distinguishing this form of hypercalcemia from primary hyperparathyroidism. In the absence of pressures generated in bone by movement, there is reduced osteoblastic activity and less calcium enters bone from the circulation. Calcium is also mobilized from the skeleton by still-undefined factors. In this context, one would anticipate a tendency toward hypercalcemia with suppression of PTH secretion. Surprisingly, in the following two young patients, both with normal renal function, immobilization was associated with increased serum calcium and increased PTH. (Figs. 8 and 9 , [59]).

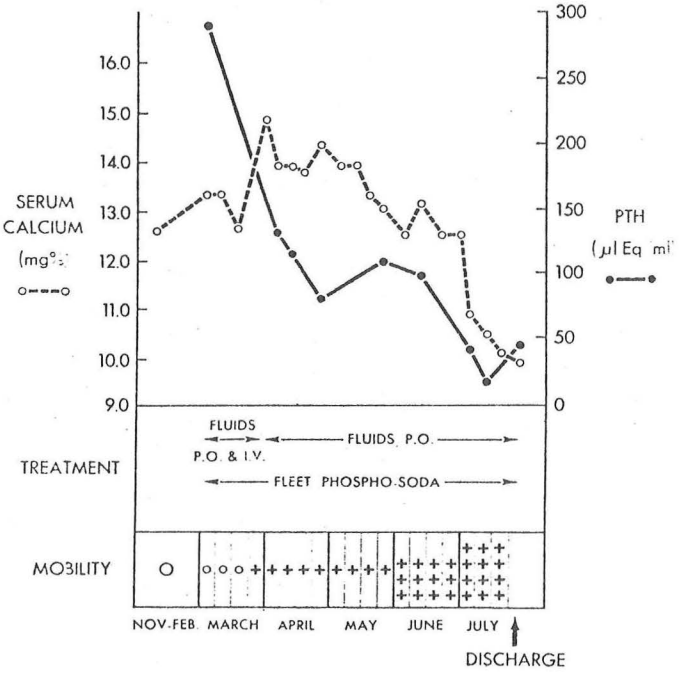

FIG. 8 Patient No. 1. Serum calcium was measured by SMA-12 Colorimetric method. The average value for November to February followed by weekly values are plotted. Normal range, 8.5–10.5 mg%. PTH represents individual assays. Normal range for PTH, 10–60 μlEq/ml. Mobility: 0, immobile; +, up in chair or tilt table once daily; ++, tilt table and use of parallel bars; +++, walking with assistance but infrequently; ++++ walking without assistance at least three times daily.

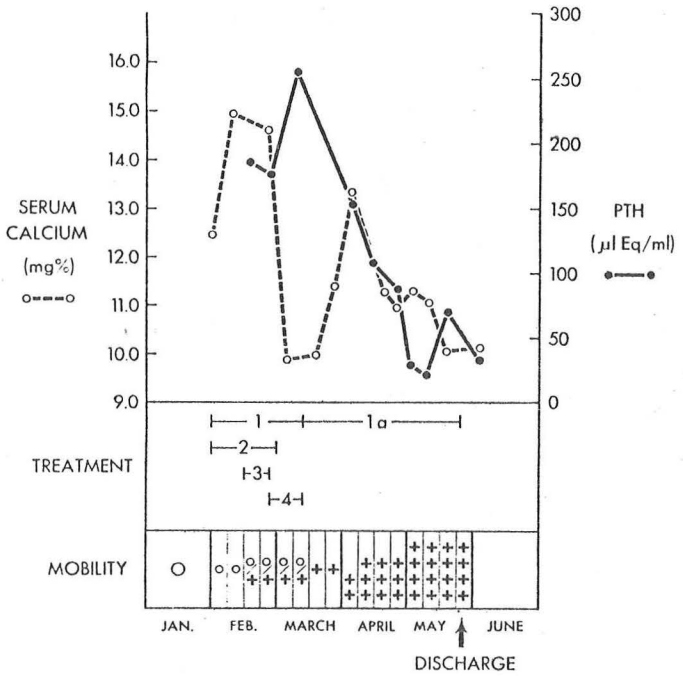

FIG. 9 Patient No. 2. Serum calcium was measured by atomic absorption spectrophotometry. The weekly average values are plotted. Normal range, 9.1–10.6 mg%. For mobility, see legend of Fig. 1. Treatment: 1—Intravenous and oral fluids; 1a—Oral fluids only; 2—Furosemide; 3—Steroids; 4—Fleet Phospho-Soda.

Both calcium and PTH returned to normal as mobilization could be accomplished, and remained so at 6 month follow-up. The cause of the increased PTH seen in immobilized patients is uncertain, but stress induced catecholamine (PTH-secretagogue) release has been postulated. In any event, the hypercalcemia of immobilization associated with increased circulating levels of PTH is a medical rather than a surgical problem. The hyperparathyroidism is reversible by mobilization.

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Normocalcemic Hyperparathyroidism

Table 9 . Categories of Normocalcemic Hyperparathyroidism

1. "Normal" range for serum calcium too wide.

2. Complicating metabolic factors:
   a. renal failure
   b. hypoalbuminemia
   c. vitamin D deficiency
   d. hypomagnesemia

3. Masking of hyperparathyroidism by drugs:
   a. drugs that block the action of PTH on bone
      e.g. estrogens, dilantin
   b. drugs that may reduce secretion of PTH
      e.g. propranolol, cimetadine

4. Renal hypercalciuria with or without varying degrees of parathyroid autonomy.

5. Normocalcemic phase of PTH-resistant (pseudo)-hypoparathyroidism.

The problem of normocalcemic hyperparathyroidism has been nicely discussed by Professor Lynwood Smith in a New England Journal case record [60]. As expanded in Table 9, there are several instances in which hyperparathyroidism may be associated with a normal serum calcium, thus creating difficulty in diagnosis. In the first instance, laboratories tend to use too wide a normal range for serum calcium [61]. A range of 9.0 to 11.0 mg/dℓ is still commonly used by laboratories across the country, although the method of measurement is the same as that used in other laboratories with an upper limit of normal of 10.1 to 10.4 mg/dℓ. At the Mayo Clinic, where the normal range is 8.9 to 10.1 mg/dℓ, 53 of 171 patients with surgically documented hyperparathyroidism had a mean preoperative serum calcium of less than 11 mg/dℓ [62]. Yendt has pointed out that the upper normal serum calcium level in women may be 0.2 mg/dℓ lower than in men, with a mean upper normal of 10.05 mg/dℓ in his laboratory [61]. If the serum calcium is borderline in a patient suspected of having hyperparathyroidism, measurement of ionized or ultrafilterable calcium will occasionally establish the diagnosis [61].

Unlike in the first category where the "normocalcemia" may be only apparent, in the remaining categories it can be real. Complicating metabolic factors can clearly lower the level of serum calcium in the presence of hyperparathyroidism [60]. The diagnosis in this situation is based on the recognition of the underlying metabolic factor that has altered the serum calcium level in the presence of increased parathyroid hormone. Drugs may also mask the presence of hyperparathyroidism, and it may not become apparent until the drug is discontinued [63].

Patients with renal hypercalciuria and nephrolithiasis tend to have increased serum PTH and urinary cyclic AMP levels in the presence of normocalcemia [64]. Some of these patients may have a reduction in bone density because of this compensatory hyperparathyroidism [65]. If there is suppression of urinary cyclic AMP back into the normal range following an oral calcium load [66] or calcium infusion [67] and if thiazide treatment suppresses serum PTH and does not cause hypercalcemia [68], then the treatment of this condition is medical (i.e. thiazide). However, if these patients fail to suppress their urinary cyclic AMP after a calcium load, or if they become hypercalcemic and fail to suppress their PTH level on course of thiazide therapy, they may be classified as having nonsuppressible normocalcemic hyperparathyroidism [68]. In this instance they should have parathyroidectomy, but persistent post-operative hypercalciuria should be treated with thiazide to prevent re-development of the syndrome.

The final instance of normocalcemic hyperparathyroidism is that which may be seen in patients with PTH-resistant (pseudo) hypoparathyroidism when they undergo transition to a normocalcemic phase [69].

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