Dr. Charles Y. C. Pak

Primary Hyperparathyroidism and Hypercalciuria: Etiology and Management

[Charles Y. C. Pak]

Medical Grand Rounds

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Excessive renal excretion of calcium is frequently encountered in primary hyperparathyroidism and is the hallmark of idiopathic hypercalciuria (1,2). It probably constitutes the major cause for renal stone formation (3-6). Despite its obvious clinical importance, a definitive criterion for the diagnosis and treatment for the various forms of hypercalciuria has been lacking. This situation has sometimes resulted in the dilemma illustrated by the following case.

> J. B. is 57 years old. He makes his living as a plumber, in which work he is very good at and rightly proud of. He is also very proud of organizing his town's only Barber Shop Quartet, in which he had served as a tenor. His medical problem dates back to 22 years of age when he first passed a renal stone. He was well until age 30 years, when he began to pass numerous renal stones of calcium oxalate and calcium phosphate at a frequency of nearly two per month. While most of the stones were passed spontaneously, some had to be removed by nephrolithotomy for obstruction. Six nephrolithomies were required, three on each kidney. He found his situation very disdainful. As a stoic, he could tolerate renal colic, but he found himself at a psychological disadvantage. "H___ of a fix for a plumber to be in not being able to p__," he would complain. At age 50 years, an evaluation elsewhere disclosed a serum concentration of calcium of 10.3 mg/100 ml, phosphorus of 3.0 mg/100 ml, and alkaline phosphatase of 10 King-Armstrong units. Urinary calcium was 350 mg/day. He was considered to have an abnormal parathyroid function, on the basis of high phosphorus clearance, and reduced tubular reabsorption of phosphorus. When parathyroid exploration was advised, he readily consented even though he was told of the uncertainty of the results of the tests. During parathyroid exploration, three "normal" parathyroid glands were found in the neck. Despite 8 hours of heroic search, the fourth gland was not found. After surgery, J. B. was not particularly disturbed that his "chest had been split", but he was somewhat ruffled when he was told he may not be able to sing again because of injury to the recurrent laryngeal nerve. The parathyroid operation did not abate recurrent renal stone formation. At age 53 years, a more extensive evaluation disclosed that his hypercalciuria was probably secondary to an intestinal hyperabsorption of calcium. On a medical regimen, his enhanced intestinal absorption and renal excretion of calcium have been corrected, and he has ceased to form renal stones for the past four years. He is again a happy and proud plumber, even though he had to forsake his membership in the Barber Shop Quartet.

This case illustrates inappropriate treatment rendered for an incorrect diagnosis. Recently, considerable progress has been made in the understanding of the pathogenesis of hypercalciuria. My objectives today are threefold: (a) consider the mechanism for the hypercalciuria, (b) examine the clinical

and diagnostic features of the various forms of hypercalciuria, (c) evaluate indications and rationale for treatment. During last year's medical grand rounds, I have covered the theoretical basis for stone formation and treatment. My discussion today is a much more clinical one, which I trust will be useful in the management of patients with primary hyperparathyroidism and nephrolithiasis.

Mechanism for Hypercalciuria

Hypercalciuria may result from an excessive resorption of bone, an enhanced intestinal absorption of calcium, or an impaired renal tubular reabsorption of calcium. Nordin et al, have termed the first two forms of hypercalciuria as resorptive and absorptive hypercalciurias (7). The hypercalciuria of "renal leak" may be called renal hypercalciuria (8).

In resorptive hypercalciuria, the primary defect is the excessive skeletal mobilization of calcium, as in primary hyperparathyroidism, malignant invasion of bone, and in "active" stage of degenerative diseases of bone. This situation is illustrated by the prototype: primary hyperparathyroidism (Fig. 1).

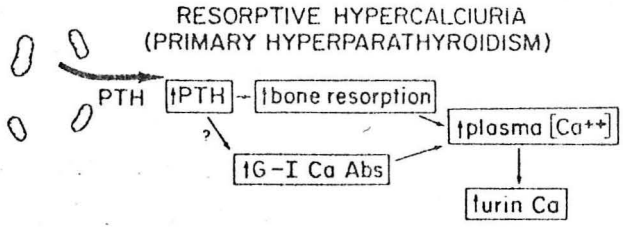

Fig. 1

The enhanced secretion of parathyroid hormone (PTH) by adenomatous or hyperplastic parathyroid gland(s) causes excessive skeletal resorption. The state of hyperparathyroidism is frequently associated with an intestinal hyperabsorption of calcium; the exact etiologic relationship has yet to be discerned. Hypercalcemia ensues from the combined effects of enhanced skeletal resorption and intestinal calcium absorption. The consequent increase in the renal filtered load of calcium accounts for the hypercalciuria. Even though PTH acts primarily to increase renal tubular reabsorption of calcium and to reduce urinary calcium (9), its effect is usually overcome by the increase in the filtered load.

In absorptive hypercalciuria, the primary abnormality is the excessive intestinal absorption of calcium, as in sarcoidosis

and hypervitaminosis D (Fig. 2). The commonest cause is probably the condition previously called "idiopathic hypercalciuria" (2). The increase is the plasma concentration of calcium, resulting from the intestinal hyperabsorption of calcium, increases the renal filtered load of calcium and suppresses parathyroid function. Although the hypercalciuria is probably the result principally of the increase in the delivery of calcium to the renal tubule, it is probably accentuated by the impaired renal tubular reabsorption of calcium resulting from parathyroid suppression.

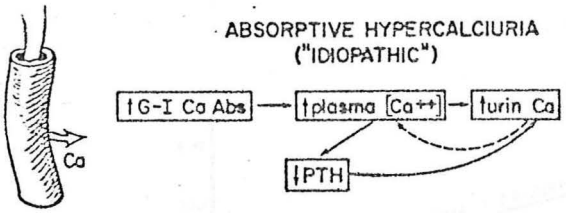

Fig. 2

In renal hypercalciuria, the hypercalciuria is the result of primary reduction in the renal tubular reabsorption of calcium (Fig. 3). Such a situation may be encountered in renal tubular acidosis (untreated) and in hypoparathyroidism (treated). These forms of renal hypercalciuria will be discussed later. The commonest cause for the renal hypercalciuria is probably the subgroup of "idiopathic hypercalciuria" (10). Thus, the term idiopathic hypercalciuria probably describes at least two separate entities,- absorptive hypercalciuria and renal hypercalciuria. The reduction in the plasma concentration of calcium, resulting from the primary renal loss of calcium, stimulates parathyroid function (10). Unlike in primary hyperparathyroidism, the plasma concentration of calcium is not elevated, and the state of hyperparathyroidism is still under the control of plasma calcium concentration (i.e. "secondary").

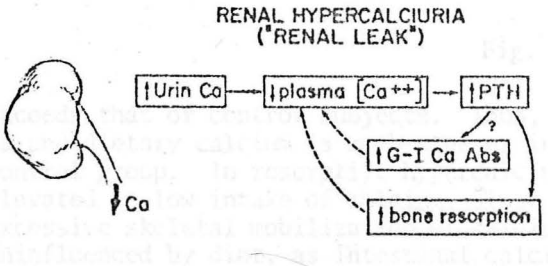

Fig. 3

In absorptive hypercalciuria, urinary calcium may be normal at low dietary intake of calcium (7) (Fig. 4). At high intake of calcium, urinary calcium

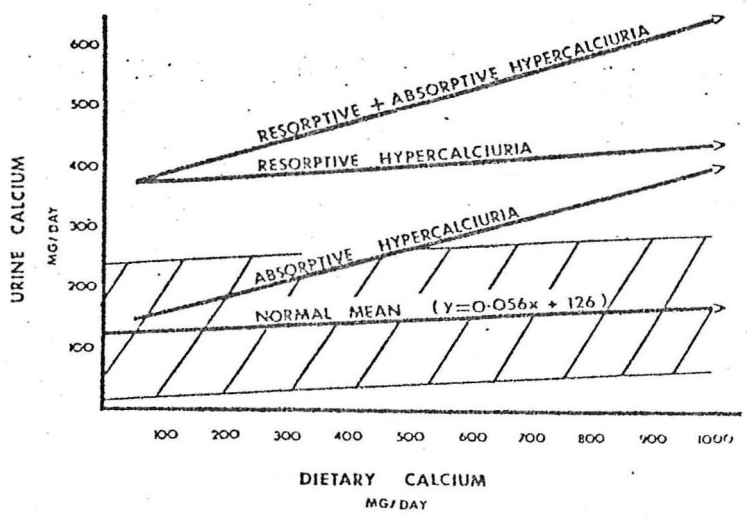

Fig. 4

exceeds that of control subjects. Thus, the slope of the line relating urinary Ca and dietary calcium is much steeper in absorptive hypercalciuria than in the control group. In resorptive hypercalciuria, the urinary calcium is significantly elevated at low intake of calcium, since the urinary calcium reflects chiefly the excessive skeletal mobilization of calcium. However, the urinary Ca is relatively uninfluenced by diet, as intestinal calcium absorption is not elevated. In certain situations, hypercalciuria may be both resorptive and absorptive. In this combined form, both the intercept and the slope are increased. Thus, the urinary Ca is elevated at low dietary intake of calcium, and is increased further as dietary calcium is raised. The majority of cases of primary hyperparathyroidism probably demonstrate the combined form of hypercalciuria.

We shall now consider the clinical presentation, diagnostic criteria and treatment for the various forms of hypercalciuria. We shall examine the prototypes, that is, primary hyperparathyroidism for resorptive hypercalciuria, and the two

variants of "idiopathic hypercalciuria" for absorptive hypercalciuria and renal hypercalciuria.

Clinical Presentation and Pathogenetic Mechanism

There has been a dramatic change in the clinical presentation of primary hyperparathyroidism since the introduction of the systematic analysis of serum calcium (SMA). The study of Cope in 1966 (11) probably reflects the situation during the "pre-SMA" era (Fig. 5). Nephrolithiasis was the most frequent complication, occurring in 57 per cent. Bone disease was present in 23 per cent and peptic ulceration in 8 per cent. A lump in the neck, later identified as parathyroid adenoma, was the presenting symptom in one of 343 cases. It is indeed an infrequent finding. If a mass is palpated in the neck, it must be presumed to be thyroid unless proven otherwise. In this series, only 2 of 343 cases (1 per cent) were considered to be asymptomatic.

Clues to the Diagnosis of Hyperparathyroidism in the First 343 Cases at the Massachusetts General Hospital.

Clue	No. of Cases
Bone disease	80
Renal stones	195
Peptic ulcer	27
Pancreatitis	9
Fatigue	10
Hypertension	6
Mental disturbance	3
Central-nervous-system signs	7
No symptoms	2
Multiple endocrine abnormalities	3
Lump in neck	1

Fig. 5

The study of Posen et al in 1973 (12) reflects the presentation during the "SMA" era (Fig. 6). Nephrolithiasis was again the most common presentation (50 per cent), followed by bone disease (35 per cent) and peptic ulceration (20 per cent). However, unlike the earlier series of Cope, 10 per cent of cases were asymptomatic. Our own experience at Parkland

Clinical Presentation of Primary Hyperparathyroidism

	Cope (1966) %	Posen (1973) %	Parkland (1973) %
Renal Stones	57	50	38
Bone Disease	23	35	15
Peptic Ulceration	8	20	15
Hypertension	2	-	31
Asymptomatic	1	10	27

Fig. 6

Memorial Hospital and related hospitals support the finding of Posen et al. Seven of 26 patients (27 per cent) were asymptomatic. In the series of Purnell et al, at Mayo Clinics, 100 of 318 cases (31 per cent) had no significant symptoms attributable to hyperparathyroidism (13). This increase in the frequency of asymptomatic primary hyperparathyroidism probably reflects improved methods for the assessment of parathyroid function and earlier disclosure from the routine analysis of serum calcium.

The formation of renal stones in primary hyperparathyroidism is probably related to the development of hypercalciuria, the cause for which has already been discussed, and to the increase in urinary pH. The PTH increases urinary pH probably by stimulating the renal secretion of bicarbonate (14). This action of PTH probably accounts for the reported increase in the incidence of renal tubular acidosis and of nephrocalcinosis in primary hyperparathyroidism. My general impression is that hyperchloremic metabolic acidosis is much less frequent in the United States than in Ireland. I have always thought that Irish whiskey has something to do with it. The actual stone formation may be caused by the marked increase in the state of saturation of urine with respect to calcium phosphates as the result of the increase in urinary pH (and hence dissociation of phosphate) and in the renal excretion of calcium. The majority of urine specimens from patients with primary hyperparathyroidism were supersaturated with respect to brushite ($CaHPO_4 \cdot 2H_2O$), the probable nidus for many renal stones (Fig. 7).

The bone disease in primary hyperparathyroidism may take several forms. There may be bone cysts (brown tumors) or subperiosteal resorption. The most frequent site of subperiosteal resorption is the phalanges and distal clavicles. Usually, the subperiosteal involvement appears as fraying of margins. In severe forms, the granular demineralization of skull may occur. Finally, the bone disease may appear as osteoporosis with vertebral compression. The etiology for the bone disease is probably related to the accentuation of PTH-medicated skeletal resorption.

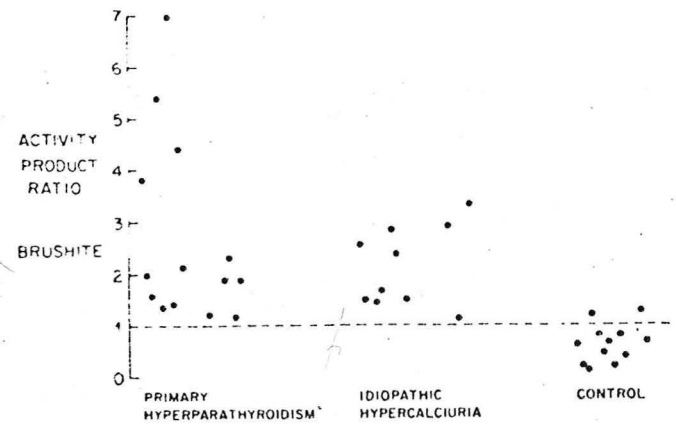

Fig. 7

The exact mechanism for the peptic ulceration in primary hyperparathyriodism is not known. However, there is some evidence that it may result from hypercalcemia rather than from PTH-excess (15). First, there is usually a significant hypercalcemia among patients with primary hyperparathyroidism suffering from peptic ulceration. It is very uncommon

among patients, whose serum calcium is only slightly elevated or within the normal range. Secondly, hypercalcemia itself, rather than PTH excess, is associated with hypersecretion of gastrin and hydrochloric acid (15,16) (Fig. 8). This patient, for example, had hypersecretion of acid prior to parathyroidectomy. Following parathyroid operation, gastric acid secretion decreased, commensurate with a fall in serum calcium. Hypersecretion of acid could again be produced by an induced hypercalcemia.

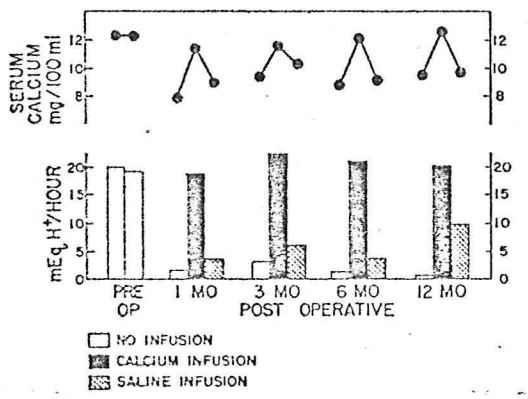

Fig. 8

In contrast to the situation in primary hyperparathyroidism, the only significant symptomatology in absorptive hypercalciuria is the recurrent passage of calcium-containing renal stones. Bone disease, peptic ulceration and pancreatitis are not encountered. Renal function is intact except those who have undergone nephrolithotomy or nephrectomy, or those in whom nephrolithiasis was complicated by recurrent urinary tract infections. The patients with renal hypercalciuria also present with nephrolithiasis. One of our two patients had osteoporosis with vertebral fractures as well. However, Coe et al did not mention any other complication except for nephrolithiasis in their patients with renal hypercalciuria (10).

Diagnostic Criteria for Resorptive, Absorptive and Renal Hypercalciurias

The differentiation of the three forms of hypercalciuria has been greatly hampered by the lack of a clear-cut definition of hypercalciuria. It is well known that the renal excretion of calcium is influenced by the variation in the intakes of calcium (7), phosphorus (6,17), sodium (18), and proteins (19). The urinary calcium is usually much higher at a higher intake of calcium (Fig. 9). The calcium clearance increases in direct proportion to the sodium clearance. Thus, the wide variation in the limits of hypercalciuria may reflect a lack of dietary control.

In Great Britain, for example, the upper range of normal for urinary calcium has been set at as high as 400 mg/day (7). Several years ago, my good friend

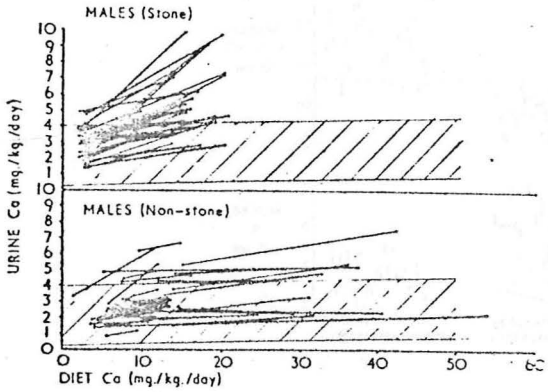

Fig. 9

and colleague from London was visiting the United States on a sabbatical. He was surprised to learn that his urinary calcium, which had been ranging from 300-400 mg/day in England, was consistently less than 200 mg/day in the United States. He refused to accept my explanation that this difference was the result of differences in the dietary calcium intake, and was adamant that we should search for a mythical "hypocalciuric" principle. During my visit to London last year, he told me that his urinary Ca had again increased to above 300 mg/day. It did not take long for me to appreciate why it had occurred. His coffee was drunk as a generous mixture with milk, and he was drinking water which had a distinct metallic taste. I learned later that the calcium content of water in London is approximately 150 mg/liter whereas in Dallas, it is less than 15 mg/liter.

We have therefore devised a constant liquid synthetic diet, which is normal in distribution between fat, carbohydrate and protein, and normal in ionic constituents except for calcium. The calcium content of 400 mg/day was lower than that for the average intake of calcium in the United States (20), but probably closely approximated the calcium intake in our patients with nephrolithiasis or hypercalciuria who were withheld from ingestion of dairy products. On this standard diet, the urinary Ca was 108 ± 42 SD mg/day in the control group. We therefore define hypercalciuria as renal excretion of calcium of more than 200 mg/day, in support of the conclusion of Albright and Reifenstein (21).

Based on this protocol, we have formulated a 3-5 day study protocol which is capable of assessing the role of intestinal calcium absorption and of PTH-mediated skeletal resorption in the development of hypercalciuria. The results of our studies are as follows:

The serum concentration was elevated in the majority of patients with primary hyperparathyroidism, whereas it was normal in absorptive hypercalciuria (Fig.10). Serum phosphorus was below the normal range in 10 of 26 cases with primary hyperparathyroidism. It was within the normal range in absorptive hypercalciuria.

In primary hyperparathyroidism, urinary Ca was greater than 200 mg/day in 21 cases, and less than 200 mg/day in the remaining five (Fig.11). Thus, most but not all cases of primary hyperparathyroidism presented with resorptive hyper-

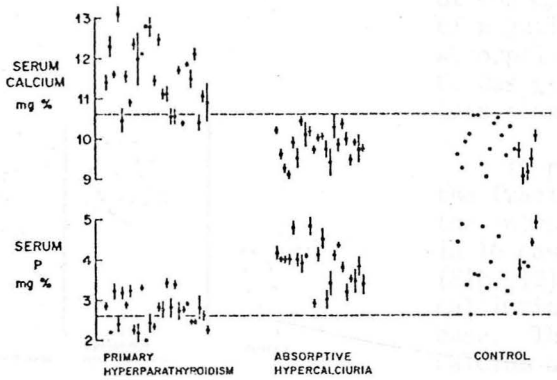
SERUM
CALCIUM
mg %
13
12
11
10
9
SERUM
P
mg %
5
4
3
2
PRIMARY
HYPERPARATHYROIDISM
ABSORPTIVE
HYPERCALCIURIA
CONTROL

Fig. 10

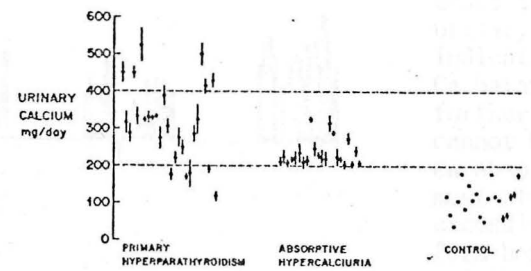
URINARY
CALCIUM
mg/day
600
500
400
300
200
100
0
PRIMARY
HYPERPARATHYROIDISM
ABSORPTIVE
HYPERCALCIURIA
CONTROL

Fig. 11

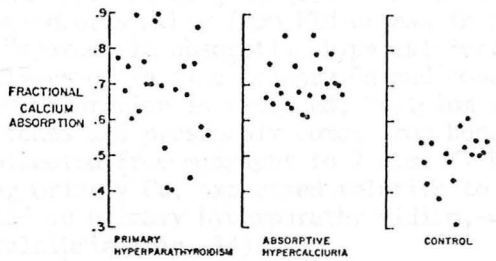

Fig. 12

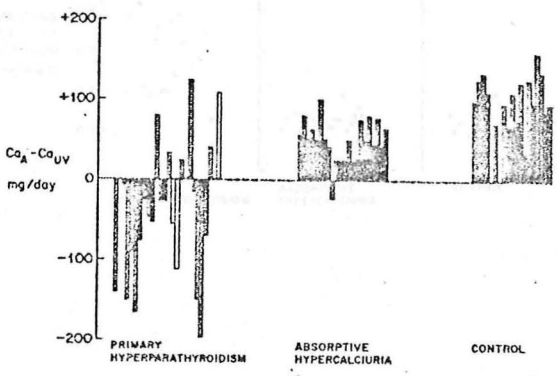

Fig. 13

calciuria. In 6 cases, urinary Ca exceeded the dietary intake of 400 mg/day, indicating a state of negative Ca balance. In absorptive hypercalciuria, urinary Ca was greater than 200 mg/day and less than 400 mg/day in every case.

In primary hyperparathyroidism, the fractional Ca absorption from the intestinal tract was elevated in 16 cases, and normal in 6 (Fig. 12). In absorptive hypercalciuria, it was elevated in every case. The product of fractional calcium absorption and dietary Ca gave a measure of true Ca absorption (Ca_A). Rose et al (22) has shown that Ca_A was highly correlated with net Ca absorption obtained from Ca balance.

The state of calcium balance was estimated from the difference between calcium absorbed from the intestinal tract (Ca_A) and urinary Ca (Ca_{UV}). In the majority of cases of primary hyperparathyroidism, urinary Ca exceeded absorbed Ca indicating a state of negative Ca balance (Fig. 13). The results further suggest that hypercalciuria cannot be accounted by intestinal Ca absorption alone, and that it must at least in part result from excessive mobilization of calcium form bone. In absorptive hypercalciuria, the absorbed Ca exceeded urinary Ca in every case except one. Thus hypercalciuria may be accounted by intestinal Ca absorption alone. The positive values of $Ca_A - Ca_{UV}$ do not indicate positive Ca balance, as it probably represents the net secreted Ca (23). For example, the mean value of 102 mg/day closely approximates the value for endogenous

fecal calcium for normal subjects maintained on a calcium intake of 400 mg/day. The value for Ca_A-Ca_{UV} in absorptive hypercalciuria was less positive than in the control group. This may simply reflect a greater degree of absorption of secreted calcium (24). The control subjects and those with absorptive hypercalciuria were probably in Ca balance (23).

The above finding suggests that bone is subjected to an excessive resorption presumably from PTH-excess in primary hyperparathyroidism, whereas it is "spared" in absorptive hypercalciuria. This conclusion was supported by analyses of fasting urinary Ca and bone density. During fast when intestinal calcium absorption is excluded, "calcium appearing in urine must be taken from body stones and presumably comes from bone" (7). After a 6-hour fast, urine was collected from midnight to 7 a.m. (7 hours) while fast was continued. The fasting urinary Ca, expressed relative to urinary creatinine, was significantly elevated in primary hyperparathyroidism, whereas it was normal in absorptive hypercalciuria (Fig. 14).

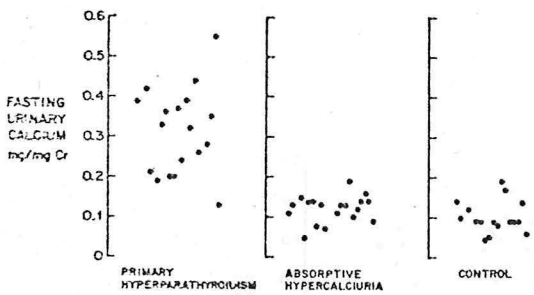

Fig. 14

Quantitative assessment of bone density was measured in vivo from the absorption of ^{125}I-photon (25). This technique gives a precision of measurement of 3 per cent, as is therefore much more sensitive than skeletal roentgenogram in assessing bone mineral content. Using this technique, Forland et al (26) found that density of the middle finger was significantly reduced in the majority of patients with primary hyperparathyroidism (Fig. 15). In our experience, the density (BM/BW) of the distal third of the radius of the non-dominant forearm was below 96 percentile of age-and-sex-matched control values in 16 of 24 cases of primary hyperparathyroidism (Fig. 16). The radiological evidence of bone disease was demonstrated in only 4 of 16 cases with low bone density, and in none of the cases with normal bone density. In contrast, all but one case with absorptive hypercalciuria had normal bone density. The slightly reduced value in one case may have resulted from a long-term therapy with orthophosphates.

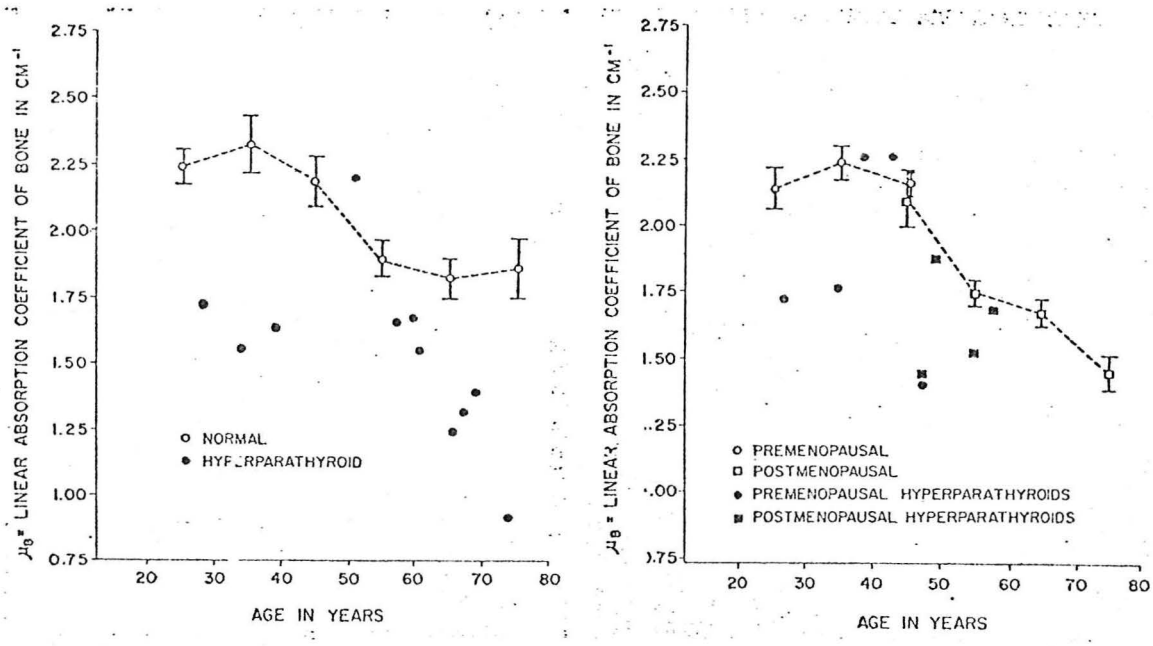
μ_B = LINEAR ABSORPTION COEFFICIENT OF BONE IN CM^{-1}
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
20
30
40
50
60
70
80
AGE IN YEARS
NORMAL
HYPERPARATHYROID
PREMENOPAUSAL
POSTMENOPAUSAL
PREMENOPAUSAL HYPERPARATHYROIDS
POSTMENOPAUSAL HYPERPARATHYROIDS

Fig. 15

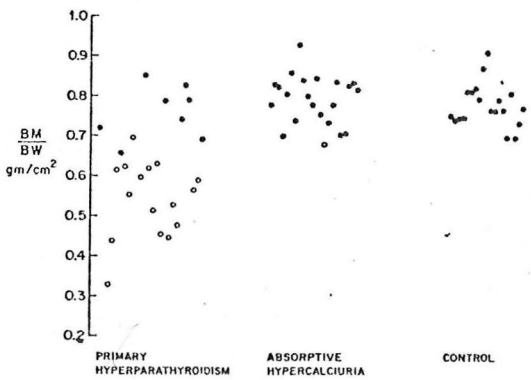
$\frac{BM}{BW}$ gm/cm^2
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
PRIMARY HYPERPARATHYROIDISM
ABSORPTIVE HYPERCALCIURIA
CONTROL

Fig. 16

The serial measurements of bone density have provided further evidence for the excessive skeletal resorption in primary hyperparathyroidism, and for the lack of bone involvement in absorptive hypercalciuria (Fig. 17). In patients with hyperparathyroidism with negative values of Ca_A-Ca_{UV}, the bone density progressively declined. In contrast, in patients with positive values of Ca_A-Ca_{UV} (2 control subjects, one with primary hyperparathyroidism, and 8 with absorptive hypercalciuria), no significant change in bone density was observed.

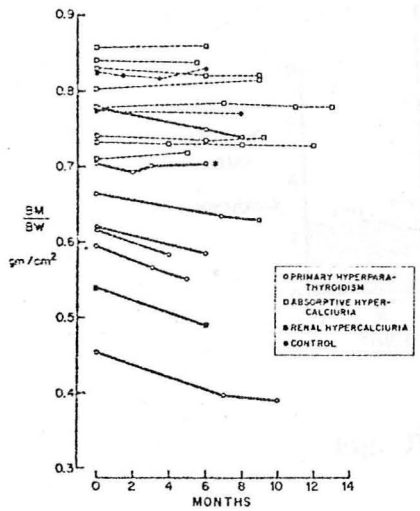

Fig. 17

We shall now discuss the more direct measures of parathyroid function. The serum concentration of PTH, measured using the antibody CH 14M of Arnaud (27), was elevated in two-third of cases with primary hyperparathyroidism (Fig. 18). However, it was normal or undectable in absorptive hypercalciuria. Urinary cyclic AMP may provide an accurate measure of parathyroid function since parathyroid hormone provides the major stimulus to the renal adenyl cyclase activity (28,29). It is significantly increased following the administration of parathyroid extract (Fig. 19). Our recent studies suggest that urinary cAMP is highly correlated with serum concentration of immunoreactive PTH (Fig. 20). The renal excretion of cyclic AMP, measured from 24-hour specimen during synthetic dietary regimen, was elevated in 24 of 26 cases with primary hyperparathyroidism (Fig. 21). It was significantly reduced in absorptive hypercalciuria, as compared to the control group, suggesting that parathyroid function

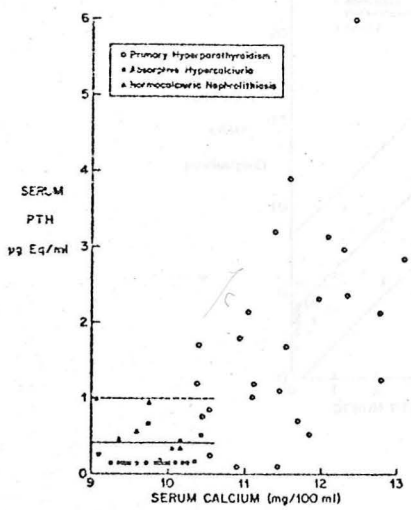

Fig. 18

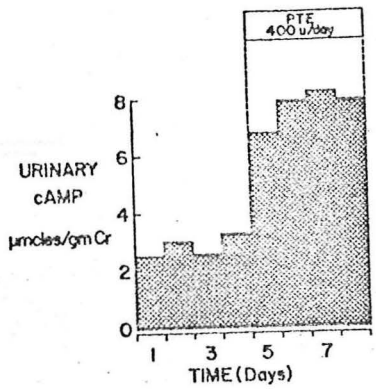
PTE
400 u/day
URINARY
cAMP
μmoles/gm Cr
8
6
4
2
0
1
3
5
7
TIME (Days)

Fig. 19

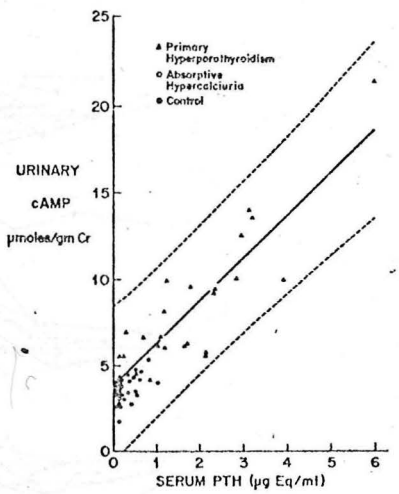
▲ Primary Hyperparathyroidism
○ Absorptive Hypercalciuria
● Control
URINARY
cAMP
μmoles/gm Cr
25
20
15
10
5
0
0
1
2
3
4
5
6
SERUM PTH (μg Eq/ml)

Fig. 20

may be partially suppressed.

Two patients with renal hypercalciuria have been evaluated to date. The characteristic features were: normocalcemia, hypercalciuria, a state of negative calcium balance, high urinary cAMP and serum PTH. A suppressible parathyroid function (by an induced hypercalcemia) and a reduced bone density were disclosed in one case.

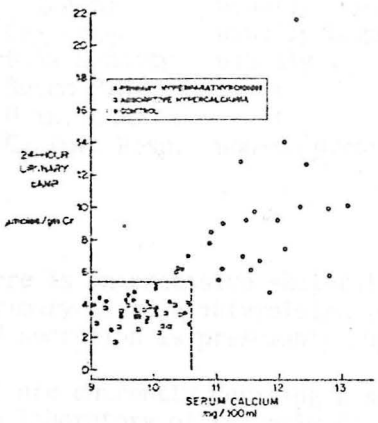

Fig. 21

Thus, we have found two cases of renal hypercalciuria and 22 with absorptive hypercalciuria among 24 patients who were previously diagnosed as idiopathic hypercalciuria. On the other hand, Coe et al (10) reported a much higher incidence of renal hypercalciuria. Their cases were characterized by a marked persistent hypercalciuria, and a high serum concentration of PTH, which declined towards normal following thiazide therapy (Fig. 22). Unfortunately, no assessment of bone metabolism, intestinal calcium absorption, and other measures of parathyroid function were carried out.

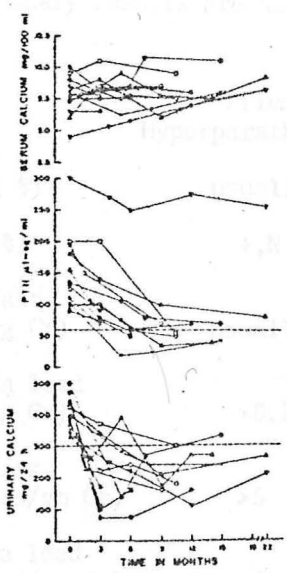

Fig. 22

The diagnostic criteria of the three forms of hypercalciuria are summarized in Fig. 23. The distinguishing features are a normal or partly suppressed parathyroid function in absorptive hypercalciuria and parathyroid stimulation in primary hyperparathyroidism and in renal hypercalciuria. Thus, patients with absorptive hypercalciuria are in calcium balance; bone is therefore "spared". In contrast, in resorptive and renal hypercalciuria, calcium balance is usually negative

	Primary Hyperparathyroidism	Absorptive Hypercalciuria	Renal Hypercalciuria
Serum Ca	usually ↑	N	N
Serum P	usually ↓	N	N
G-I Ca Abs.	usually ↑	↑	N,↑
Urin. Ca (mg/d)	usually >200	>200	>200
Ca_A-Ca_{UV}	usually negative	positive	negative
Bone Density	usually ↓	N	↓,N
Serum PTH	↑	N,↓	↑
Urin. cAMP	↑	N,↓	↑
Ca Inf. Resp.	non-suppressible	suppressible	suppressible

Fig. 23

and there is an excessive skeletal resorption. The renal hypercalciuria differs from primary hyperparahtyroidism in two important regards: serum Ca is normal and PTH secretion is presumably suppressible by an induced hypercalcemia.

We are currently devising a simple technique which may be readily adapted for the laboratory of the private practioner for the diagnosis of the three forms of hypercalciuria. The patients are told to fast except for water from 6 p.m. A glass of water is drunk at 9 p.m., 12 midnight, 7 a.m., and again at 11 a.m. While fast is maintained, 2-hour urine is collected from 7 a.m. to 9 a.m. (morning-fast). Venous blood is obtained without stasis for Ca and P before 9 a.m. At 9 a.m., 500 mg of calcium in a synthetic meal is given orally; urine is collected from 9 a.m. to 1 p.m. (calcium-load). Urine specimens are analyzed for Ca, Cr and cAMP. Preliminary results are as follows (Fig. 24).

	Primary Hyperparathyroidism	Absorptive Hypercalciuria	Renal Hypercalciuria
Ca_S (mg %)	usually ↑	N	N
P_S (mg %)	↓,N	N	N
Ca_{UV}, fast (mg/mg Cr)	usually >0.2	<0.15	>0.15
Ca_{UV}, Ca load (mg/mg Cr)	>0.2	>0.2	>0.2
cAMP, fast (μmoles/gm Cr)	>5	4-6	>5
cAMP, Ca load (μmoles/gm Cr)	>5	<4	?

Fig. 24

In primary hyperparathyroidism, the urinary Ca and cAMP are high during both fast and Ca load. In absorptive hypercalciuria, urinary Ca is normal during fast, but high during oral Ca load. Urinary cyclic AMP decreases during Ca load. ~~fast~~. In renal hypercalciuria, serum Ca is normal and urinary cyclic AMP and fasting Ca are high. As compared with the results of the more complete evaluation previously discussed, this simple test yields correct diagnosis in approximately 90 per cent of cases. The correct diagnosis of absorptive hypercalciuria may be made in nearly every case without urinary cAMP.

Secondary Hypercalciurias

We shall now consider the less common forms of hypercalciuria. For convenience, they will be referred to as secondary hypercalciurias to contrast them from the prototypes we have just examined.

Malignant invasion of bone may manifest as resorptive hypercalciuria. The diagnosis may usually be made from the demonstration of osteolytic involvement. Unlike in primary hyperparathyroidism, the hypophosphatemia is uncommon, serum immunoreactive PTH and urinary cAMP are usually reduced (30), and urinary Ca is frequently very high. Occasionally, hypercalcemia and hypophosphatemia may be encountered in non-parathyroid malignancy without osteolytic metastasis (31). Hyperchloremic renal tubular acidosis, nephrolithiasis and peptic ulceration are less frequently encountered than in primary hyperparathyroidism. Serum concentration of immunoreactive PTH is inappropriately low or undectable (32,33), but urinary cAMP is frequently elevated (Fig. 25). In some cases, the tumor extract has been shown to cause phosphaturia and to stimulate bone resorption. An effective antitumor therapy usually ameliorates hypercalcemia and hypercalciuria. It is believed that these cases represent elaboration by malignant tissue of PTH-like substance (31), or other factors such as prostaglandins (34), or leukocytic bone resorption factor (35).

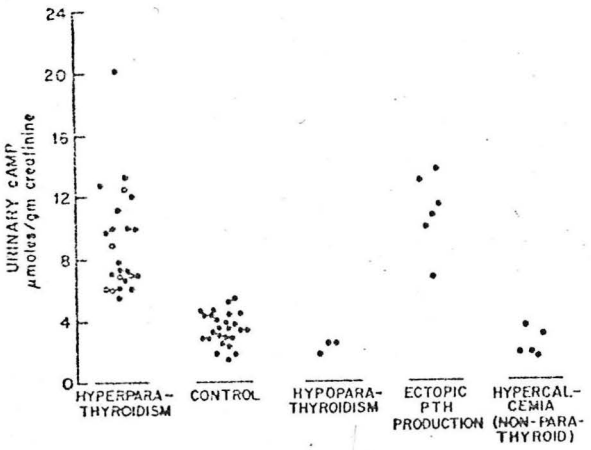

Fig. 25

Absorptive hypercalciuria may be secondary to sarcoidosis or vitamin D excess. Unlike in absorptive hypercalciuria of "idiopathic hypercalciuria", hypercalcemia is usually encountered, and both hypercalcemia and hypercalciuria may be corrected by exogenous adrenocorticosteroid therapy (36).

Renal tubular acidosis (untreated) and hypoparathyroidism (treated) may manifest as renal hypercalciuria. Hypercalciuria results from a decrease in renal tubular reabsorption of calcium from an acidotic state (37), or from PTH-lack (9). An induced acidosis has been shown to stimulate PTH secretion, commensurate with an increase in urinary calcium.

It is generally assumed that in renal hypercalciuria, the state of hyperparathyroidism is "secondary"; the PTH secretion, though excessive, may be suppressible by an induced hypercalcemia. This feature distinguishes this condition from "normocalcemic" primary hyperparathyroidism (1), in which PTH secretion is presumed to be independent of control by plasma calcium concentration. Unfortunately, the commonly used test of calcium infusion, which relies on changes in urinary P (38), does not directly measure the suppressibility of parathyroid function. The calcium infusion test, relying on serum PTH or urinary cAMP, has yielded conflicting or inconclusive results (39,40,28). Thus, without a better test, the diagnosis of normocalcemic primary hyperparathyroidism cannot be clearly excluded in patients with renal hypercalciuria. Alternatively, there is a possibility that some of the previously reported cases of normocalcemic primary hyperparathyroidism may have had a "renal leak" of calcium.

Treatment for the Hypercalciurias

The theoretical basis for therapy was extensively discussed during last year's medical grand rounds (41). We shall therefore consider more practical aspects of therapy.

The treatment of choice for resorptive hypercalciuria of primary hyperparathyroidism is the surgical removal of abnormal parathyroid gland(s). After parathyroidectomy, urinary Ca invariably returns to normal. Recent studies by Dr. Roy Kaplan in my laboratory demonstrate that, following parathyroid exploration, fasting urinary Ca decreases, absorbed calcium exceeds urinary Ca, and bone density increases, commensurate with a return to normal of serum Ca and PTH and urinary cAMP. However, we agree with Purnell et al (13) that not all cases with a biochemical evidence for primary hyperparathyroidism need to undergo parathyroid exploration (Fig. 26). In addition, the measurements of bone density by ^{125}I-photon absorption and of urinary state of saturation with respect to brushite are often very useful in assessing the need for parathyroidectomy. If the bone density is low and continues to decline during serial measurements, the parathyroid exploration should be seriously considered even if the patient is asymptomatic. An examination of urine *in vitro* of the propensity for the spontaneous precipitation of calcium phosphate can often predict whether the patient is likely to form renal stones. Medical therapy should not be attempted, except in unusual circumstances where the patient cannot undergo parathyroid exploration. Thiazides may accentuate hypercalcemia (42), orthophosphates may cause extra-skeletal calcification (43,44), and cellulose phosphate may induce a state of negative Ca balance.

1. Mean serum calcium >11.0 mg/100 ml
2. Roentgenographic evidence of bone disease
   a. Subperiosteal resorption of phalanges, distal clavicles, or other bones
   b. Fraying, distal phalangeal tufts
   c. Bone cyst (brown tumor)
   d. Granular demineralization of skull
   e. Osteoporosis with vertebral compression or other bone disease
3. Decreased renal function
4. Metabolically active or infected renal lithiasis*
5. Prolonged observation is impractical
   a. Patient cooperation unsatisfactory
   b. Geographic remoteness
   c. Psychiatric complications
6. Gastrointestinal complications
   a. Peptic ulcer not controlled by medical management
   b. Recurrent or chronic pancreatitis

Fig. 26

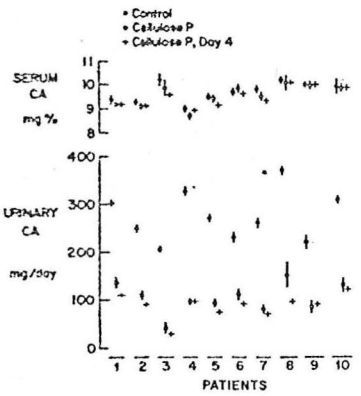

Fig. 27

In absorptive hypercalciuria, the treatment of choice is sodium cellulose phosphate, which specifically inhibits the intestinal Ca absorption (45-47) (Fig. 27). Thus, urinary calcium is reduced to normal by "correcting the state of intestinal hyperabsorption of calcium. This can be achieved in few days. New stone formation virtually ceases (48). If the dose is adjusted to lower intestinal Ca absorption to the normal range, but not below, no signifcant side-effects have been encountered. Serum concentrations of copper, zinc and iron, and urinary zinc are not altered significantly. Bone density by ^{125}I-photon absorption has not changed significantly or remained within the normal range. The only significant side-effect occurred during the first month of my experience with this drug. The drug was sent to me in a form of a large tablet, about the size of a silver dollar. Not thinking very hard about the matter, I instructed the patient to chew on it, since it was too big to swallow. The patient called me the following day to assure me that she did not particularly mind the taste of the drug. However, she politely inquired how she could avoid losing fillings in her teeth. Fortunately, the drug is now available in a powder form, which can easily be suspended in fruit juice. The recommended dose of sodium cellulose phosphate is 5 gm two or three times a day with meals. While it is currently an investigational drug in the United States, it will probably be marketed in approximately 18 months. Until it becomes available, the preferred drugs are the thiazide diuretic,

followed by orthophosphates. Parathyroid exploration is clearly contraindicated, as illustrated by the case presentation in my introduction.

In renal hypercalciuria, the drug of choice is the thiazide diuretic. As shown before in Fig. 22, thiazides may correct hypercalciuria and secondary hyperparathyroidism. The recommended dose is hydrochlorothiazide 50 mg twice a day orally, or comparable amounts of its analogues. Parathyroidectomy is contraindicated, as it may induce a state of hypocalcemia and hypoparathyroidism. Cellulose phosphate either may not be very effective, or it may aggravate the state of negative Ca balance.

While we have emphasized that an optimal treatment depends on the exact etiology for the hypercalciuria, there may be a drug which may be effective in all forms of hypercalciuria. For the past two years, Dr. Ohata of my laboratory has been examining the physicochemical and physiological properties of disodium etidronate, a form of diphosphate. This compound has already gained reputation for its many uses. It prevents tooth decay when it is added to toothpaste. In Paget's disease of bone, it decreases serum alkaline phosphatase activity and urinary hydroxyproline, communsurate with subjective improvement (49). In calcinosis universalis and myositis ossificans, it causes dissolution of metastatic calcification (50, 51). It is believed to stop further progression of osteoporosis.

In experimental hypercalcemia produced by PTH or vitamin D, diphosphonate averts the development of hypercalcemia. We are therefore exploring the possibility of its use in patients with primary hyperparathyroidism, who cannot undergo parathyroid exploration. Diphosphonate may also be useful in prevention of renal stones in other forms of hypercalciuria. When it is added to urine in vitro, it inhibits the nucleation of brushite, the probable nidus for calcium stones (52). Further, it inhibits the crystal growth of brushite. When it is given to patients with renal stones, their urine showed marked inhibition of the crystal growth of brushite (Fig.28).

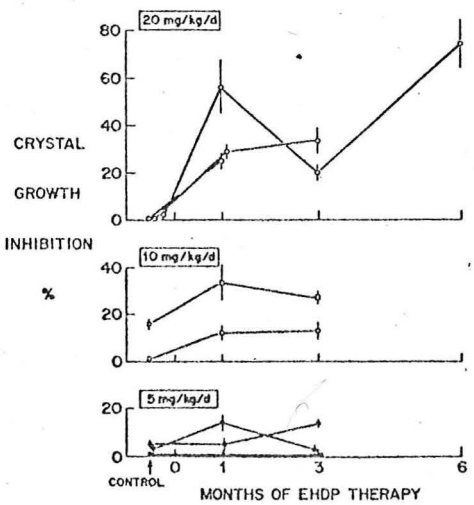

Fig. 28

Despite its wide application, its future usefulness should be guarded until all of its side-effects have been fully appreciated. In large doses, it has already been shown to cause osteomalacia. (53

Concluding Remarks

We have reviewed the clinical features and diagnostic criteria of the various forms of hypercalciuria. We emphasized the importance of arriving at the correct diagnosis, since the optimal treatment depends on the exact etiology for the hypercalciuria. Notwithstanding the ubiquitous properties and potential wide application of diphosphates, it was noted that a particular therapy, which may be effective in one form of hypercalciuria, may be contraindicated in another. It is not sufficient simply to arrive at the diagnosis of idiopathic hypercalciuria; it is essential to establish whether the hypercalciuria is secondary to intestinal hyperabsorption of calcium or to an impaired renal tubular reabsorption of calcium. It is no longer adequate simply to arrive at the diagnosis of primary hyperparathyroidism; indications for parathyroid exploration should be carefully considered. It is my sincere hope that the unfortunate error in diagnosis and treatment, as was rendered to our patient J.B., will be avoided in the future.

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