The Hypercalciurias

CAUSES, PARATHYROID FUNCTIONS, AND DIAGNOSTIC CRITERIA

CHARLES Y. C. PAK, MASAHIRO OHATA, E. CLINT LAWRENCE, and W. SNYDER

From the Department of Internal Medicine, Southwestern Medical School, The University of Texas Health Science Center, Dallas, Texas 75235

ABSTRACT The causes for the hypercalciuria and diagnostic criteria for the various forms of hypercalciuria were sought in 56 patients with hypercalcemia or nephrolithiasis (Ca stones), by a careful assessment of parathyroid function and calcium metabolism. A study protocol for the evaluation of hypercalciuria, based on a constant liquid synthetic diet, was developed. In 26 cases of primary hyperparathyroidism, characteristic features were: hypercalcemia, high urinary cyclic AMP (cAMP, 8.58±3.63 SD μmol/g creatinine; normal, 4.02±0.70 μmol/g creatinine), high immunoreactive serum parathyroid hormone (PTH), hypercalciuria, the urinary Ca exceeding absorbed Ca from intestinal tract (Ca_A), high fasting urinary Ca (0.2 mg/mg creatinine or greater), and low bone density by ^{125}I photon absorption. The results suggest that hypercalciuria is partly secondary to an excessive skeletal resorption (resorptive hypercalciuria). The 22 cases with renal stones had normocalcemia, hypercalciuria, intestinal hyperabsorption of calcium, normal or low serum PTH and urinary cAMP, normal fasting urinary Ca, and normal bone density. Since their Ca_A exceeded urinary Ca, the hypercalciuria probably resulted from an intestinal hyperabsorption of Ca (absorptive hypercalciuria). The primacy of intestinal Ca hyperabsorption was confirmed by responses to Ca load and deprivation under a metabolic dietary regimen. During a Ca load of 1,700 mg/day, there was an exaggerated increase in the renal excretion of Ca and a suppression of cAMP excretion. The urinary Ca of 453±154 SD mg/day was significantly higher than the control group's 211±42 mg/day. The urinary cAMP of 2.26±0.56 μmol/g creatinine was significantly lower than in the control group. In contrast, when the intestinal absorption of calcium was limited by cellulose phosphate, the hypercalciuria was corrected and the suppressed renal excretion of cAMP returned towards normal. Two cases with renal stones had normocalcemia, hypercalciuria, and high urinary cAMP or serum PTH. Since Ca_A was less than urinary Ca, the hypercalciuria may have been secondary to an impaired renal tubular reabsorption of Ca (renal hypercalciuria). Six cases with renal stones had normal values of serum Ca, urinary Ca, urinary cAMP, and serum PTH (normocalciuric nephrolithiasis). Their Ca_A exceeded urinary Ca, and fasting urinary Ca and bone density were normal. The results support the proposed mechanisms for the hypercalciuria and provide reliable diagnostic criteria for the various forms of hypercalciuria.

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INTRODUCTION

Hypercalciuria is frequently encountered in primary hyperparathyroidism and is the hallmark of idiopathic hypercalciuria (1, 2). The term resorptive hypercalciuria has been used to describe the hypercalciuria of primary hyperparathyroidism because of the frequent association of excessive skeletal resorption (3). There are two major proposed causes for the hypercalciuria in idiopathic hypercalciuria. The first is an enhanced intestinal absorption of calcium (absorptive hypercalciuria) (3–5) and the second is a primary defect in the renal tubular reabsorption of calcium ("renal leak" or renal hypercalciuria) (5, 6). However, these pathogenetic mechanisms have not been fully documented or characterized and their relative frequencies and importance are controversial.

Practically, it is imperative that the three forms of hypercalciuria be differentiated, since the optimal treatment depends on the exact etiology for the hypercalciuria. For example, the treatment of choice for the hypercalciuria of primary hyperparathyroidism is the

surgical removal of the abnormal parathyroid gland.[1] In contrast, the therapy for absorptive hypercalciuria should ideally be directed at reducing intestinal absorption of calcium (7). In renal hypercalciuria, the thiazide diuretics have been shown to "correct" both the hypercalciuria and the secondary hyperparathyroidism (6). Unfortunately, it has been often difficult to differentiate the three forms of hypercalciuria, because of the lack of clear-cut diagnostic criteria.

In this report, we provide supporting evidence for the primary intestinal hyperabsorption of calcium in certain patients with idiopathic hypercalciuria. Our patients had an exaggerated renal excretion of calcium and suppressed parathyroid function during an oral calcium load, and normal urinary Ca when intestinal Ca absorption was limited by fasting or by cellulose phosphate. We also present diagnostic criteria and clinical features for primary hyperparathyroidism, absorptive hypercalciuria, and renal hypercalciuria. On a well-defined synthetic diet, accurate measures of parathyroid function and calcium metabolism were made by several independent techniques. It was thus possible to devise a reliable protocol for the evaluation of hypercalciuria.

METHODS

Clinical data

This report considers study in 56 patients referred to us for the evaluation of hypercalcemia or calcium-containing renal stones. They were classified into various groups according to the following provisional criteria. The diagnosis of primary hyperparathyroidism was suspected when hypercalcemia and high serum immunoreactive parathyroid hormone (PTH)[2] or urinary cyclic AMP (cAMP) were encountered. Those with normocalcemia, hypercalciuria (urinary Ca exceeding 200 mg/day on an intake of 400 mg Ca/day), and calcareous renal stones were considered to suffer from renal hypercalciuria when serum PTH or urinary cAMP was elevated (6), and from absorptive hypercalciuria when serum PTH or urinary cAMP was normal or low. The cases with recurrent nephrolithiasis with normocalcemia and normocalciuria constituted normocalciuric nephrolithiasis.

26 patients had primary hyperparathyroidism, 22 absorptive hypercalciuria, 2 probable renal hypercalciuria, and 6 had normocalciuric nephrolithiasis. Among patients with primary hyperparathyroidism, 21 were women and 5 men, with a mean age of 52 yr. All 26 patients were referred to us for persistent or transient hypercalcemia. Subsequent to this study, 22 cases underwent parathyroid exploration. The diagnosis of hyperparathyroidism was confirmed by the demonstration of parathyroid adenoma in 21 and parathyroid hyperplasia in 1. Renal stones (mixed calcium phosphate and calcium oxalate) were found in 10 cases (38%), hypertension in 8 (31%), bone disease (osteitis, fracture, osteoporosis) in 4 (15%), and peptic ulceration in 4 (15%). No symptoms attributable to hyperparathyroidism or hypercalcemia were encountered in 7 cases (27%).

Among patients with absorptive hypercalciuria, 3 were women and 19 were men, with a mean age of 41 yr. They had a history of recurrent passage of calcium-containing renal stones, ranging from 7 mo to 38 yr (mean duration of 9.5 yr). None had pathological skeletal fracture, bone disease, or peptic ulceration. In all cases, the following serum concentrations were within the normal range: alkaline phosphatase activity, magnesium, sodium, potassium, chloride, carbon dioxide, albumin, globulins, triiodothyronine, and thyroxine.

The two patients with probable renal hypercalciuria were both women (47 and 56 yr old). They suffered from recurrent passage of calcium-containing renal stones. One, the 56-yr-old woman, presented with severe osteoporosis, with vertebral skeletal fractures. Neither patient had peptic ulceration, hypertension, renal tubular acidosis, or Cushing's syndrome.

In the group with normocalciuric nephrolithiasis, all were men, with a mean age of 51 yr. They all passed renal stones, which were either calcium oxalate or mixtures of calcium oxalate and calcium phosphate. None had pathological skeletal fractures, peptic ulceration, or evidence for renal tubular acidosis. Three had chronic urinary tract infection with *E. coli* and required continuous treatment with sulfonamides or methenamine mandelate. These treatments were withheld during study.

The control group consisted of 10 women and 10 men, with a mean age of 40 yr. They were all normal volunteers who did not suffer from renal stones or bone disease.

Two objectives of the study were: (*a*) to determine if there is a primary intestinal hyperabsorption of calcium in certain cases of idiopathic hypercalciuria, and (*b*) to develop a study protocol for the evaluation of hypercalciuria. The first goal was pursued under a constant metabolic dietary regimen, the latter under a synthetic dietary regimen.

Studies under metabolic diet: demonstration of primary intestinal hyperabsorption of calcium

10 patients with the provisional diagnosis of absorptive hypercalciuria participated in the study. The following studies were undertaken under a constant metabolic dietary regimen.

Effect of oral calcium load and calcium restriction on urinary calcium and cAMP and on renal clearance of phosphorus. Nine patients with the provisional diagnosis of absorptive hypercalciuria (one woman and eight men, with a mean age of 47 yr) and six normal volunteers (two women and four men with a mean age of 31 yr) were maintained on a constant metabolic diet, containing 400 mg calcium, 800 mg phosphorus, and 100 meq Na/day. Fluid intake was constant and sufficient to provide urine volume of approximately 2 liters daily. After 4 days of "stabilization" on the diet, they underwent a control study period of 4 days. The following regimens were undertaken in successive order: cellulose phosphate, 5 g three times a day orally with meals for 4 days; oral supplemental calcium, 220 mg daily for 5 days; and oral supplemental calcium 1,300 mg daily for 5 days. The supplemental calcium was given as calcium gluconate in four divided doses each day. These study periods corresponded to total daily calcium intake of 400 mg during the control period and cellulose phosphate

[1] R. Kaplan and C. Y. C. Pak. 1974. Quantitative evaluation of indications for and response to parathyroidectomy in primary hyperparathyroidism. In preparation.

[2] *Abbreviations used in this paper:* α, fractional calcium reabsorption; Ca_A, total calcium absorbed; cAMP, cyclic AMP; Ca_{UV}, urinary calcium; Cr, creatinine; EFC, endogenous fecal calcium; PTH, parathyroid hormone.

treatment, and 620 mg and 1,700 mg during calcium loading periods. The majority of patients and control subjects underwent studies with more than one of these regimens. After conclusion of one regimen, they were restabilized on the original metabolic diet for 3–4 days before they began the next regimen. Urine was collected daily in 24-h pools during 4 days of the control period and of cellulose phosphate administration, and during the last 4 days of calcium loading periods for Ca, P, cAMP, and creatinine (Cr). Venous blood was obtained daily without stasis before breakfast for Ca, P, and Cr.

Effect of cellulose phosphate on urinary and serum calcium. This study was carried out in 10 patients with hypercalciuria, 6 of whom were from the previous study, with calcium load and restriction. The study was conducted under the same metabolic balance regimen as before, with 4 days of control period and 4 days of treatment with cellulose phosphate (5 g three times a day). Urine was collected daily in 24-h pools for calcium. Venous blood was obtained daily without stasis before breakfast for calcium.

Studies under synthetic diet: protocol for the evaluation of hypercalciuria

The majority of patients underwent studies according to the following study protocol: They were placed on a constant liquid synthetic diet for 3 days (day 1–day 3). The daily composition of the diet included 400 mg calcium, 800 mg phosphorus, 213 mg magnesium, 100 meq sodium, 60 meq potassium, 51 g fat, 195 g carbohydrate, 63 g protein, and 1,500 cal. The ash content of the diet was neutral to 10 meq acid/day. Each day's diet was mixed in 1 liter of distilled water and given in four equally divided portions at 9 a.m., 1 p.m., 5 p.m., and at 9 p.m. In addition, 900 ml of distilled water was given between 9 a.m. and 9 p.m. and again from 9 p.m. to 9 a.m. The total fluid intake was therefore 2,800 ml/day. Since the diet did not contain bulk, 1 g of methylcellulose was given orally with each meal. Urine specimens were collected under refrigeration in 24-h pools from 9 a.m. to 9 a.m. from day 1 to day 3. These specimens were analyzed for Ca, Cr, and cAMP.

On the day before synthetic diet was started, urine was collected from midnight to 7 a.m. (7-h nighttime fast) for Ca, Cr, and Na (in selected samples). Patients fasted except for distilled water for 6 h preceding and throughout urine collection.

Venous blood was obtained daily without stasis before 9 a.m. for Ca, P, and Cr on day 1 to day 4, and for radioimmunoassayable PTH on day 2. On day 2 or day 3, ^{47}Ca was given orally for the measurement of fractional calcium absorption (α) from the intestinal tract, and "bone density" of the distal third of the radius of the nondominant forearm was measured in vivo.

Most of the patients had been maintained on a low-calcium diet, consisting usually of avoidance of dairy products, for several months to several years by their referring physicians because of hypercalcemia or stones. Calcium intake estimated from dietary history was 300–500 mg/day among patients and 400–800 mg/day among control subjects. All the cases were asked not to ingest dairy products and to avoid excess salt in their foods for at least 1 wk before evaluation under synthetic diet. During the 3 days of synthetic diet, the urinary calcium usually varied by less than 10% and not by more than 20%. Further, urinary sodium generally approximated the intake of 100 meq/day.

Analytic procedures and other methods

Calcium was determined by atomic absorption spectrophotometry, and phosphorus by the method of Fiske and Subba-Row (8). Urinary cAMP was analyzed by the protein-binding assay of Gilman (9). Urinary Na was determined by flame photometry. Renal clearances of phosphorus and creatinine were calculated from the urinary phosphorus and creatinine during the whole collection period and the serum values of phosphorus and creatinine obtained at the end of urine collection.

The radioimmunoassay of parathyroid hormone in serum was performed according to the procedure of Arnaud, Tsao, and Littledike (10), with CH 14M as antiserum. This antiserum recognizes predominantly the NH_2-terminal portion of the PTH molecule, and is suited for determining short-term secretory rates of parathyroid glands. Radioiodination of purified bovine PTH (a gift of Dr. B. Brewer) was accomplished as described. The culture medium of human parathyroid gland was utilized for standard PTH. Therefore, serum concentration of PTH was expressed in terms of equivalent protein contained in the culture medium used for standard PTH. An expression of "x μg eq/ml" indicates that one milliliter of serum sample contains the same amount of PTH as is present in x micrograms protein equivalent of the medium. Samples were assayed in duplicate at three different dilutions, and results were acceptable only if the mean of duplicate values at three dilutions agreed within 10%. In addition, randomly selected samples of serum were sent to Dr. Eric Reiss for analysis of immunoreactive PTH according to the technique of Reiss and Canterbury (11).

In patients who underwent studies with calcium load under metabolic diet, the amount of calcium absorbed from gut during the control period (oral calcium intake of 400 mg/day) and during Ca load (1,700 mg Ca/day) was estimated as follows. The α was obtained from the recovery of fecal radioactivity after an oral administration of ^{47}Ca, according to the technique previously described (4). Control absorption was done with 2–5 μCi of ^{47}Ca as chloride (Amersham/Searle Corp., Arlington Heights, Ill.) which was added to 250 ml of liquid synthetic diet, containing 100 mg calcium, 200 mg phosphorus, 25 meq sodium, and 375 cal. The test was repeated with the same amount of synthetic diet, to which 325 mg calcium as calcium gluconate was added (total calcium, 425 mg). The total Ca_A, was estimated as the product of α and the calcium intake, as was done previously (4, 12). Thus, assuming ingestion of food four times a day, Ca_A during an intake of 400 mg Ca/day was the product of 400 mg and α, obtained with 100 mg Ca carrier. Similarly Ca_A during an intake of 1,700 mg Ca/day was the product of 1,700 mg and α obtained with 425 mg Ca carrier.

In patients who underwent studies under synthetic dietary regimen, α was measured as before by mixing radiocalcium with the 9 a.m. meal (synthetic diet). Since the synthetic diet was given in four equal portions for a total intake of 400 mg Ca/day, the product of α and 400 mg gave Ca_A. In this calculation, it is assumed that α does not differ significantly between the four meals in the same subject. Samachson, Scheck, and Spencer (13) reported that the variation in α between morning and evening is not greater than the reproducibility of the measurement. Rose, Reed, and Smith (12) have shown that Ca_A (true calcium absorption) is highly correlated with net calcium absorption, or the difference between dietary and fecal calcium. The Ca_A is equal to the sum of net Ca absorption and the net

TABLE I

Effect of Calcium Loading and Restriction

	400 mg Ca/day and cellulose PO_4	400 mg Ca/day	620 mg Ca/day	1,700 mg Ca/day
Control group (n = 6)				
α	—	0.50±0.08	—	0.31±0.05
Ca_A, *mg/day*	—	200±32	—	533±85
Urinary Ca, *mg/day*	62±37	117±46	—	211±42
Urinary cAMP, *μmol/g Cr*	4.66±0.92	3.90±0.44	—	3.21±0.33
Serum Ca, *mg/100 ml*	9.73±0.44	9.68±0.48	—	9.94±0.58
Cr clearance, *ml/min*	103±11	99±13	—	98±11
Absorptive hypercalciuria (n = 9)				
α	—	0.73±0.07§	—	0.51±0.06§
Ca_A, *mg/day*	—	292±28§	—	873±102§
Urinary Ca, *mg/day*	106±29*	256±42§	417±91	453±154§
Urinary cAMP, *μmol/g Cr*	3.34±0.65*	2.93±0.68‡	2.54±0.57	2.26±0.56‡
Serum Ca, *mg/100 ml*	9.69±0.24	9.82±0.30	10.01±0.25	9.94±0.30
Serum P, *mg/100 ml*	3.97±0.65	3.89±0.61	4.43±0.40	4.37±0.61
Urinary P, *mg/day*	1,021±178	717±190	750±214	618±140
P clearance, *ml/min*	18.30±4.38	13.08±3.40	12.00±4.38	9.92±2.03
Cr clearance, *ml/min*	101±19	104±18	95±8	96±15

α, Ca_A, Ca_{UV}, urinary cAMP, serum calcium, serum P, urinary P, P clearance, and Cr clearance are shown for four study periods: during cellulose phosphate therapy and during daily calcium intakes of 400 mg, 620 mg, and 1,700 mg. P clearance and Cr clearance were obtained from 24-h values for urinary P and Cr, and serum P and Cr, obtained at the end of the corresponding 24-h urine collection periods. Values are presented as mean±SD for the mean of values during each period for six control subjects and nine patients with absorptive hypercalciuria. The significant difference for the values in absorptive hypercalciuria from the corresponding values in the control group was calculated with the Student t test and is indicated by * for $P < 0.05$, ‡ for $P < 0.01$, and § for $P < 0.001$.

secreted Ca. Thus Ca_A indicates unidirectional uptake of calcium from the intestinal tract, exclusive of intestinal secretion (4). The comparison of Ca_A and urinary calcium (Ca_{UV}) may give an estimate of the state of calcium balance, provided the extent of net secreted calcium can be approximated. The calcium balance is equal to $Ca_A - Ca_{UV}$ − net secreted Ca. If the calcium balance is zero, $Ca_A - Ca_{UV}$ should be equal to the net secreted Ca.

The bone density was determined from the absorption of ^{125}I photon by bone with Norland-Cameron bone mineral analyzer (14). It was expressed as the ratio of bone mineral content and bone width in grams per square centimeter. The reproducibility of measurement in the same patient was within 3%.

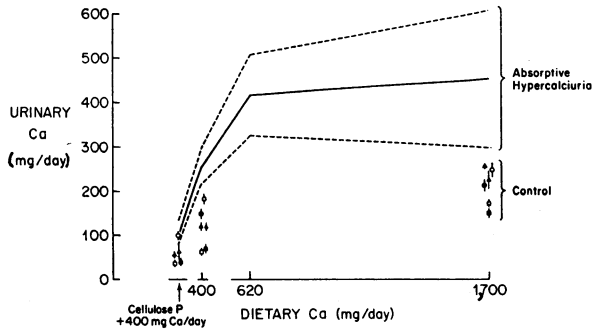

FIGURE 1 The effect of cellulose phosphate and oral calcium load on urinary calcium in the control group. Different symbols represent studies in separate subjects. The bars adjoining the symbols indicate mean±SE for the values in each study period for each subject. For comparison, the response in the group with absorptive hypercalciuria is presented by solid and dashed lines, representing mean±SD for the mean of values from all patients. The urinary Ca in the control group was lower than in the group with hypercalciuria.

RESULTS

Studies under metabolic diet in absorptive hypercalciuria and control group

Effects of oral calcium load and calcium restriction on intestinal calcium absorption and urinary calcium. Among patients with absorptive hypercalciuria, the intestinal absorption of calcium was higher than that of the control group at both intakes of calcium (Table I). It was 292±28 SD mg/day on an intake of 400 mg calcium/day and increased to 873±102 mg/day on an intake of 1,700 mg calcium/day. In contrast, the estimated absorbed calcium in the control group was 200± 32 mg/day on a calcium intake of 400 mg/day, and

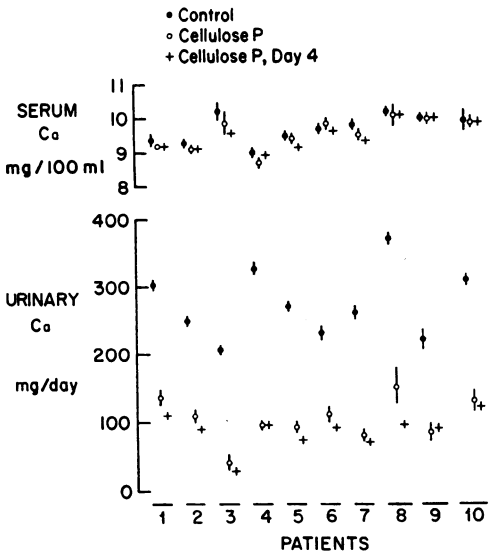

FIGURE 2 The effect of cellulose phosphate on urinary calcium in the group with absorptive hypercalciuria. During the control period (closed circles), urinary calcium exceeded 200 mg/day. Cellulose phosphate (open circles) decreased urinary calcium to less than 200 mg/day. The urinary calcium on the last day of treatment (crosses) was slightly less than the mean value for 4 days of treatment in most cases. Serum calcium, obtained at the conclusion of each 24-h urine collection period, remained within the normal range. Values are presented as mean±SE for the values in each study period.

rose to 533±85 mg/day on a calcium intake of 1,700 mg/day.

These changes in calcium absorption were paralleled by changes in urinary calcium. Among patients with hypercalciuria, renal excretion of calcium exceeded that of the control group at all ranges of calcium intake (Fig. 1, Table I). It was 106±29 SD mg/day during cellulose phosphate administration and calcium intake of 400 mg/day, and rose progressively to 256±42 mg/day, 417±91 mg/day, and 453±154 mg/day during daily calcium intakes of 400 mg, 620 mg, and 1,700 mg, respectively. Among control subjects, urinary calcium was less than 100 mg/day with a mean value 62±37 SD mg/day during administration of cellulose phosphate. It increased to 117±46 mg/day on an intake of 400 mg Ca/day and to 211±42 mg/day on an intake of 1,700 mg Ca/day (Fig. 1). In each group, the urinary calcium was less than the amount of calcium absorbed from the intestinal tract on both calcium intakes of 400 mg/day and 1,700 mg/day (Table I).

There was no significant or consistent change in serum concentration of calcium with calcium load or restriction. Serum calcium remained within the normal range (Table I). The failure of serum calcium to change with calcium load or restriction may be partly accounted for by the fact that venous blood was obtained for Ca in a fasting state, 10–12 h after the last meal.

Effect of cellulose phosphate on urinary calcium. The effect of cellulose phosphate on urinary calcium in patients with absorptive hypercalciuria is more closely examined in Fig. 2. During the control period (an intake of 400 mg Ca/day), all patients had hypercalciuria, as the urinary calcium exceeded 200 mg/day. During 4 days of cellulose phosphate administration, the urinary calcium declined by 120–230 mg/day to the normal range (less than 200 mg/day). The urinary calcium on the last day of treatment was slightly less than the mean value of 4 days of treatment in most cases. Serum calcium concentration decreased slightly or not at all; it remained within the normal range in every case.

Effect of oral calcium restriction and calcium load on urinary cAMP. Renal excretion of cAMP was increased by cellulose phosphate, and reduced by oral calcium load (Table I, Fig. 3). Among patients with absorptive hypercalciuria, the highest value of cAMP was noted during the administration of cellulose phosphate (3.34±0.65 SD μmol/g creatinine). It decreased progressively to a value of 2.26±0.56 μmol/g creatinine on a calcium intake of 1,700 mg/day; this decrease was significant ($P < 0.01$). Among control subjects, urinary cAMP decreased from 4.66±0.92 μmol/g creatinine during the administration of cellulose phosphate to 3.21±0.33 μmol/g creatinine during a calcium load of 1,700 mg/day (Fig. 3); this decrease was significant ($P < 0.02$).

The renal excretion of cAMP was signficantly lower among patients with hypercalciuria than among control subjects during both calcium restriction and load (Fig.

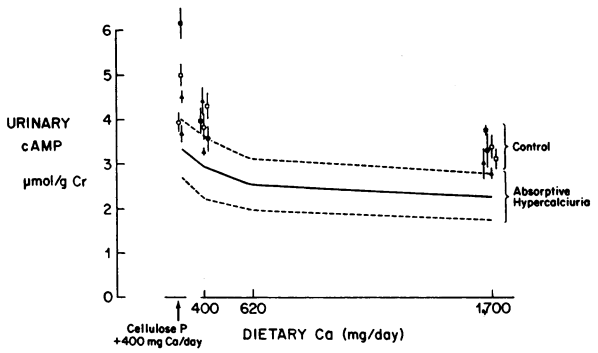

FIGURE 3 The effect of cellulose phosphate and calcium load on urinary cAMP in the control group. Different symbols represent studies in separate subjects. The bars adjoining symbols indicate mean±SE for the values in each period for each subject. For comparison, the response in the group with absorptive hypercalciuria is presented by solid and dashed lines, representing mean±SD for the mean values from all patients. The urinary cAMP in the control group was higher than that of the hypercalciuric group.

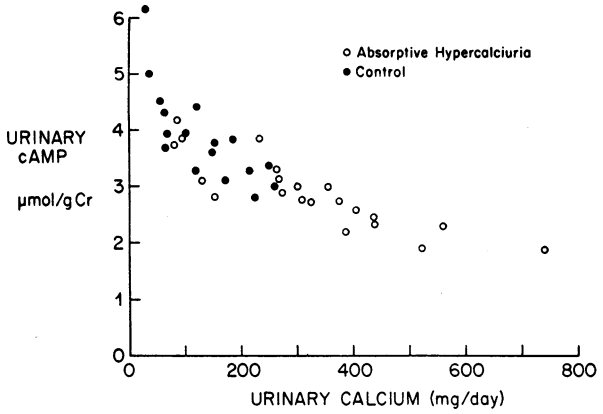

FIGURE 4 The dependence of urinary cAMP on renal excretion of calcium. The open circles represent the mean of values in each study period for each patient with absorptive hypercalciuria. The closed circles represent the mean values in each study period for each control subject.

3, Table I). However, a more clear separation of values between the two groups was demonstrated at the high calcium intake of 1,700 mg/day.

In Fig. 4, the relationship between the mean urinary cAMP and mean urinary calcium during each study period for all cases is shown. Renal excretion of cAMP was inversely related to urinary calcium. Lower values of urinary cAMP were seen among patients with hypercalciuria.

Effect of oral calcium restriction and calcium load on renal clearance of phosphorus in absorptive hypercalciuria. During the calcium load of 1,700 mg/day, urinary P, as compared to that of the control period of 400 mg Ca/day, significantly decreased in two cases. Serum P increased significantly in two cases. The phosphorus clearance was significantly reduced in four cases of hypercalciuria, and unchanged in others.

During the administration of cellulose phosphate, urinary P and P clearance, as compared to those of the control period of 400 mg Ca/day, significantly increased in every case. There was no consistent change in serum P.

The mean values for urinary P and P clearance decreased and serum P increased during Ca load of 1,700 mg/day as compared to those of the control period of 400 mg Ca/day (Table I). However, these changes were not significant. During cellulose phosphate administration, urinary P and P clearance significantly increased from the control period ($P < 0.05$). However, serum P did not change significantly.

Studies under synthetic diet

Serum concentrations of calcium and phosphorus (Table II). Among control subjects, serum concentration of calcium was less than 10.6 mg/100 ml, with a mean value of 9.79±0.50 SD mg/100 ml. In primary hyperparathyroidism, serum Ca was elevated (greater than 10.6 mg/100 ml) in 21 cases, and within the normal range in the remaining 5. The mean value was 11.55±0.79 mg/100 ml. In absorptive hypercalciuria, renal hypercalciuria, and normocalciuria nephrolithiasis, serum Ca was within the normal range in every case.

Among control subjects, serum concentration of P was greater than 2.6 mg/100 ml and less than 5.0 mg/100 ml. In primary hyperparathyroidism, serum P was low (less than 2.6 mg/100 ml) in 10. The mean value of 2.71±0.40 SD mg/100 ml was significantly lower than that for the control group of 3.76±0.71 mg/100 ml ($P < 0.001$). Serum concentration of P was within

TABLE II

Comparison of Presentations in Five Groups

	Primary hyperparathyroidism	Absorptive hypercalciuria	Renal hypercalciuria	Normocalciuric nephrolithiasis	Control group
No. cases	26	22	2	6	20
Ca_s, *mg/100 ml*	11.55±0.79*	9.84±0.36	9.49±0.67	9.62±0.30	9.79±0.50
P_s, *mg/100 ml*	2.71±0.40*	3.87±0.52	3.71±0.04	3.30±0.49	3.76±0.71
Ca_{UV}, *mg/day*	314±105*	234±35*	246±47*	163±10*	108±42
α	0.68±0.15*	0.71±0.07*	0.50±0.17	0.58±0.10	0.50±0.07
Ca_A-Ca_{UV}, *mg/day*	−44±87*	+49±27*	−46±22	+68±42	+102±30
Fasting urinary Ca/Cr, *mg/mg Cr*	0.31±0.10	0.12±0.04	—	0.10±0.07	0.10±0.04
Fasting urinary Na, *meq/h*	—	5.42±1.12	—	—	5.81±1.40
Urinary cAMP, *μmol/g Cr*	8.58±3.63	3.22±0.59*	6.17±0.32	3.64±0.69	4.02±0.70
Cr clearance, *ml/min*	82±18	95±19	91±19	69±9	104±20
Serum PTH, *μg eq/ml*	1.82±0.27*	0.28±0.24	1.25±0.65	0.41±0.33	0.42±0.29

In each group, the results are presented as mean±SD of mean of values from individual patients. The significant difference from control values is indicated by * for $P < 0.001$. Abbreviations: Ca_s, serum calcium; P_s, serum phosphorus.

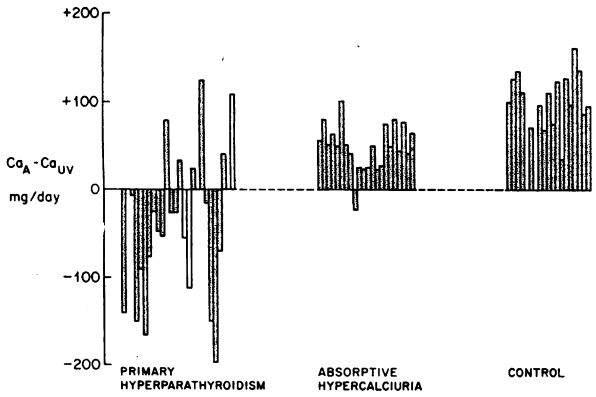

FIGURE 5 The comparison of Ca_A with Ca_{UV} in primary hyperparathyroidism, absorptive hypercalciuria, and in the control group. Each block represents the study in a separate patient. In primary hyperparathyroidism, the shaded blocks represent studies in patients with surgically proved hyperparathyroidism, and open blocks indicate studies from those who have not yet undergone parathyroid exploration.

the normal range in absorptive hypercalciuria, renal hypercalciuria, and normocalciuria nephrolithiasis.

24-h renal excretion of calcium (*Table II*). Among control subjects, the urinary Ca was less than 200 mg/day, with a mean of 108±42 SD mg/day.

In primary hyperparathyroidism, urinary Ca was greater than 200 mg/day in 21 cases, and less than 200 mg/day in the remaining five. In six cases, urinary Ca exceeded the dietary intake of 400 mg/day. In absorptive hypercalciuria, urinary calcium was greater than 200 mg/day and less than 400 mg/day in every case. In renal hypercalciuria, urinary Ca exceeded 200 mg/day (213 and 279 mg/day). In normocalciuric nephrolithiasis, urinary Ca was less than 200 mg/day. However, the mean value of 163±10 mg/day was significantly higher than in the control group ($P < 0.001$).

α (*Table II*). Among control subjects, α, measured in 17 cases, was less than 0.61, with a mean of 0.50± 0.07 SD. In primary hyperparathyroidism, it was elevated (greater than 0.61) in 16 of 23 patients in whom it was measured, and within the normal range in 6.

In absorptive hypercalciuria, the fractional calcium absorption was elevated in every patient. In renal hypercalciuria, it was slightly elevated in one (0.62), and low normal in the other (0.38). In normocalciuric nephrolithiasis, α was elevated in one (0.74), and within the normal range in the remaining cases. The mean value for α of 0.58±0.10 SD was slightly higher than in the control groups of 0.50±0.07 but this difference was not significant. However, α in normocalciuric nephrolithiasis was significantly less than in absorptive hypercalciuria (0.71±0.07) ($P < 0.05$).

Comparison of Ca_{UV} with Ca_A (*Fig. 5, Table II*). Among control subjects, the amount of Ca absorbed from the intestinal tract exceeded urinary calcium in all 17 cases. The mean value for Ca_A-Ca_{UV} was + 102± 30 SD mg/day. In primary hyperparathyroidism, Ca_{UV} exceeded Ca_A in 17 of 23 cases in whom it was measured, indicating a state of negative Ca balance. In the remaining six cases, Ca_{UV} was less than Ca_A.

In absorptive hypercalciuria, Ca_{UV} was less than Ca_A, except in one patient. The mean value for $Ca_A - Ca_{UV}$ of 49±27 SD mg/day was less than in the control group ($P < 0.001$). Both patients with renal hypercalciuria had negative values of $Ca_A - Ca_{UV}$, whereas all patients with normocalciuric nephrolithiasis had positive values. The mean value in normocalciuric nephrolithiasis of 68±42 mg/day was less than in control subjects but greater than in absorptive hypercalciuria. However, these differences were not significant.

Fasting urinary calcium (*Table II*). Among control subjects, the fasting urinary calcium was less than 0.20 mg/mg urinary Cr, with a mean value of 0.10±0.04 SD mg/mg Ca. In primary hyperparathyroidism, it was elevated (0.20 mg/mg Ca or more) in 16 of 18 cases in whom it was measured, and normal in two. The mean value of 0.31±0.10 mg/mg Cr was significantly higher than that of the control group ($P < 0.001$).

The fasting urinary calcium was within the normal range in absorptive hypercalciuria and normocalciuric nephrolithiasis. However, it could not be obtained in renal hypercalciuria. Urinary sodium and endogenous creatinine clearance were not significantly different between the group with absorptive hypercalciuria and the control group.

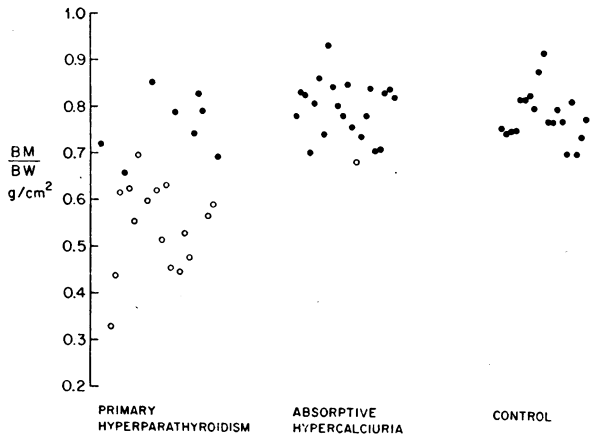

FIGURE 6 The in vivo bone density (BM/BW) in primary hyperparathyroidism, absorptive hypercalciuria, and in the control group. Each point represents the study in separate cases. The closed circles indicate that the values are within the 96th percentile of age- and sex-matched control values, and the open circles show that the values of BM/BW are below the 4th percentile.

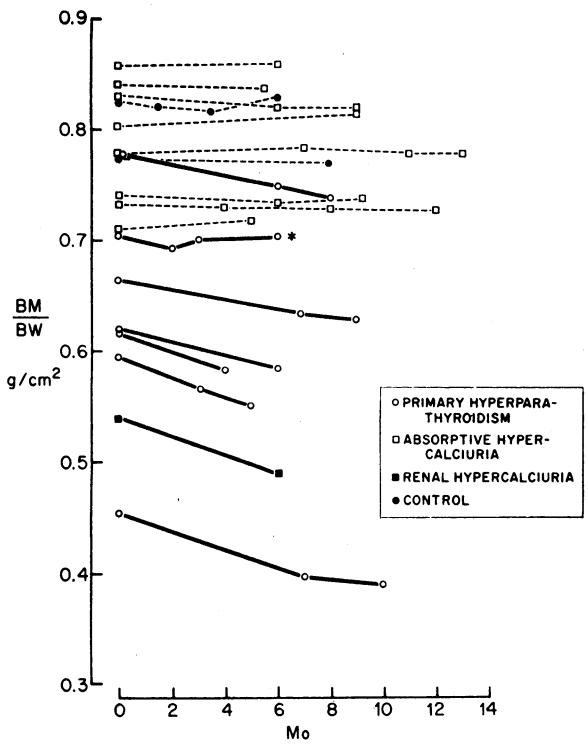

FIGURE 7 Serial measurements of bone density (BM/BW). The bone density did not change significantly in eight cases of absorptive hypercalciuria (open squares) and in two control subjects (closed circles). However, it decreased significantly in one case of renal hypercalciuria (closed square) and six of seven cases with primary hyperparathyroidism (open circles). The case of primary hyperparathyroidism with positive value of $Ca_A - Ca_{UV}$ is shown by an asterisk.

Bone density (*Fig. 6*). In primary hyperparathyroidism, the bone density was below 4th percentile of age- and sex-matched control values in 16 of 24 cases in whom it was measured. The radiological evidence of bone disease (fractures, osteitis, or osteoporosis) was demonstrated in only 4 of 16 cases with low bone density, and in none of the cases with normal bone density. One case in whom bone density could not be measured had radiological evidence of osteoporosis and skeletal fractures.

In absorptive hypercalciuria, the values of bone density were normal except in one patient who had a slightly reduced value. This patient had been taking sodium phosphates (2 g P/day) orally for more than 3 yr for the control of stone formation.

One of the patients with renal hypercalciuria with normal intestinal calcium absorption (α of 0.38) had a reduced bone density of 0.538 g/cm^2. This 56-yr-old woman had the diagnosis of osteoporosis, which was confirmed by histological examination of bone biopsy specimen. The other patient, with a 2-yr history of recurrent stone formation, had a normal bone density, and no evidence of bone disease. All patients with normocalciuric nephrolithiasis had normal values of bone density.

The measurement of bone density was repeated over 4–13 months in seven cases of primary hyperparathyroidism before parathyroid operation, in eight cases of absorptive hypercalciuria, two control subjects, and in one case of renal hypercalciuria (with osteoporosis) (Fig. 7). The bone density did not change in patients with absorptive hypercalciuria, control subjects, or in one patient with primary hyperparathyroidism (shown by asterisk in Fig. 7), all of whom had positive values of $Ca_A - Ca_{UV}$. However, it declined significantly in the six cases of primary hyperparathyroidism and one case of renal hypercalciuria, who had negative values of $Ca_A - Ca_{UV}$.

Urinary cAMP (*Fig. 8, Table II*). Among control subjects, urinary cAMP was less than 5.4 μmol/g Cr, with a mean value of 4.02±0.70 SD μmol/g Cr. In absorptive hypercalciuria, urinary cAMP was

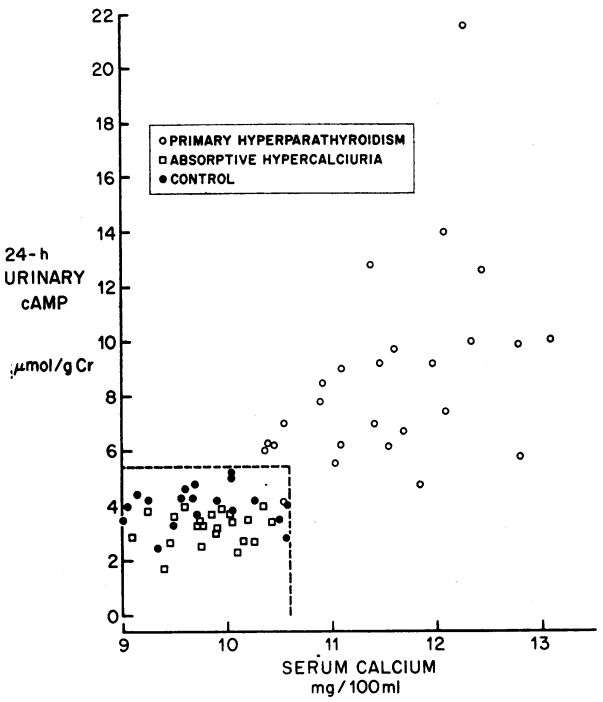

FIGURE 8 The relationship between urinary cyclic AMP and serum Ca. For each case, the mean of urinary cAMP was plotted against the mean serum Ca. In absorptive hypercalciuria (open squares), urinary cAMP was significantly less than in the control subjects (closed circles). All the values in absorptive hypercalciuria were within the area described by upper ranges of normal for urinary cAMP and for serum Ca (shown by dashed horizontal and vertical lines). In contrast, all but one value in primary hyperparathyroidism were outside this area.

less than 4.1 μmol/g Cr. The mean value of 3.22± 0.59 μmol/g Cr was slightly less than in the control group ($P < 0.001$). In these two groups, urinary cAMP was indepedent of serum concentration of calcium.

In primary hyperparathyroidism, the mean value for urinary cAMP, 8.58±3.63 SD μmol/g Cr, was significantly higher than in the control group ($P < 0.001$). The urinary cAMP was elevated (greater than 5.4 μmol/g Cr) in 24 cases, and within the normal range in 2 cases. In one case with normal urinary cAMP, serum Ca was also normal. In the other, serum Ca was 11.85 mg/100 ml. In this case the urinary cAMP of 4.77 μmol/g Cr is probably inappropriately high for the degree of increased serum Ca.

The urinary cAMP was slightly elevated in renal hypercalciuria and within the normal range in normocalciuric nephrolithiasis.

Serum PTH (Fig. 9, Table II). The mean value for serum immunoreactive PTH, assayed with antiserum CH 14M (10), was 0.42±0.29 SD μg eq/ml among control subjects. In this small control group, serum PTH was independent of serum Ca concentration. Among patients with primary hyperparathyroidism, serum PTH was elevated (greater than 1 μg eq/ml) in 18 of 25 cases. Three of seven cases with normal serum PTH were normocalcemic. None of the cases of absorptive hypercalciuria or normocalciuric nephrolithiasis had a high value for serum PTH. In renal hypercalciuria, the patient with osteoporosis had a high value of 1.7 μg eq/ml. The other patient had a normal value.

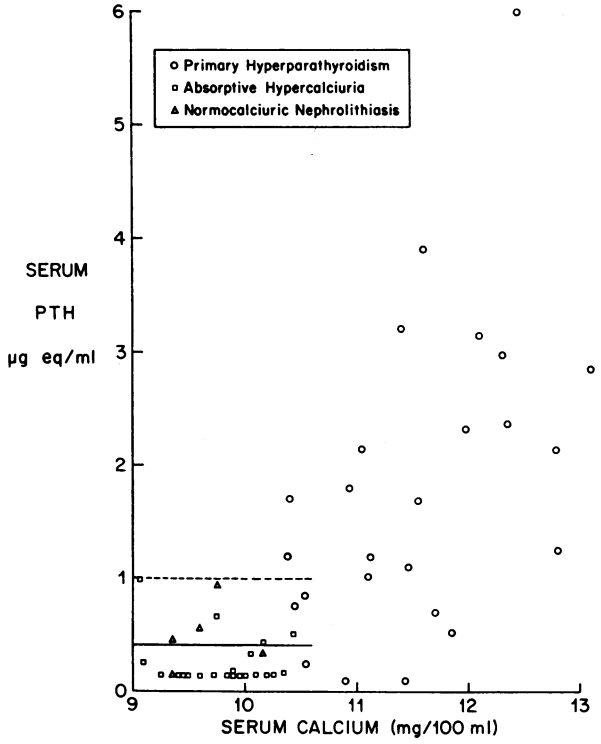

FIGURE 9 Serum immunoreactive PTH in primary hyperparathyroidism, absorptive hypercalciuria, and in normocalciuric nephrolithiasis. Serum PTH was assayed with antiserum CH 14M (10). The undetectable values are presented as 0.15 μg eq/ml, which represents the lower limit of detection. The horizontal solid line and dashed line indicate mean±SD for the control subjects. The serum PTH was elevated in 18 cases of primary hyperparathyroidism (shown by open circles). Serum PTH was within the normal range in absorptive hypercalciuria (open squares) and normocalciuric nephrolithiasis (open triangles).

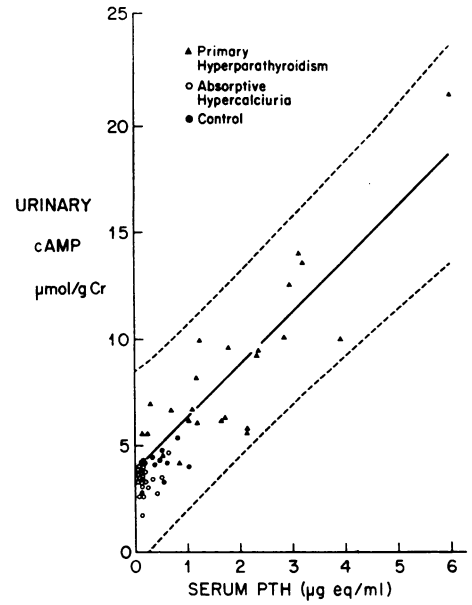

FIGURE 10 Dependence of urinary cAMP on serum PTH. Solid line indicates the regression line and dashed lines represent 95% confidence intervals on the observation for the value from patients with primary hyperparathyroidism (shown by closed triangles). The relationship between 24-h urinary cAMP and serum PTH (assayed with antiserum CH 14M [10]) was highly significant ($r = 0.86$, $P < 0.001$).

Among seven control subjects, the serum immunoreactive PTH, measured by the assay of Reiss and Canterbury (11), ranged from 30 to 79 μl eq/ml, with a mean of 53±21 SD μl eq/ml. Among 12 patients with primary hyperparathyroidism, serum PTH was outside the range of normal (greater than 79 μl eq/ml) in 9 cases. In nine cases of absorptive hypercalciuria, serum PTH was within the normal range in eight and was slightly elevated in one (88 μl eq/ml). The mean value of serum PTH was 47±24 SD μl eq/ml.

Dependent relationships in primary hyperparathyroidism. Urinary cAMP was highly correlated with serum immunoreactive PTH, assayed with antiserum CH 14M (10) ($r = 0.86$; $P < 0.001$) (Fig. 10), and with serum PTH, assayed by the technique of Reiss and Canterbury (11) ($r = 0.82$; $P < 0.001$).

The five patients with primary hyperparathyroidism with normal serum calcium had a significantly lower renal excretion of calcium and cAMP than the 21 cases with hypercalcemia. The urinary Ca and cAMP were 246±67 SD mg/day and 5.90±1.05 SD μmol/g Cr in normocalcemia patients, whereas they were 330±107 mg/day and 9.02±3.84 μmol/g Cr in the hypercalcemic patients ($P < 0.05$ for urinary Ca and $P < 0.01$ for cAMP). Three cases with normocalcemia had negative values of $Ca_A - Ca_{UV}$ and four cases had reduced bone density. Although these five cases were normocalemic during this study, they had documented hypercalcemia before evaluation.

The five patients with normocalciuria had positive values of $Ca_A - Ca_{UV}$ with a mean value of +76±46 SD mg/day, whereas those with hypercalcemia had a mean value for $Ca_A - Ca_{UV}$ of −69±71 mg/day ($P < 0.001$). In the seven patients with normal fractional calcium absorption (less than 0.61), the urinary calcium of 217±74 SD mg/day was significantly less than in the 16 cases with high α who excreted 350±92 mg Ca/day ($P < 0.01$).

All four patients with radiologic evidence of bone disease had hypercalciuria, negative values of $Ca_A - Ca_{UV}$, and reduced bone density. All 10 cases with renal stones had hypercalciuria the mean urinary Ca was 342±91 SD mg/day.

DISCUSSION

Accurate assessments of renal excretion of calcium and of parathyroid function are essential to the understanding of the mechanism of hypercalciuria and for the differentiation of the various forms of hypercalciuria (3, 5). Such assessments require an evaluation under a carefully controlled dietary regimen, since these measurements are markedly sensitive to dietary perturbations. It is well known that the renal excretion of calcium is influenced by variation in the dietary intakes of calcium (3), phosphorus (15), sodium (16), and proteins (17). Further, parathyroid function may be normally dependent on the oral intake of calcium (Fig. 3). An oral load of calcium may suppress, whereas calcium restriction may stimulate parathyroid function.

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 the average intake of calcium in the United States (18), but probably closely approximated the calcium intake in our patients with nephrolithiasis or hypercalcemia who refrained from dairy products. On this standard diet, the urinary calcium ranged from 36 mg to 180 mg/day with a mean of 108±42 SD mg/day in the control group. For the sake of simplicity, we therefore define hypercalciuria as renal excretion of calcium exceeding 200 mg/day, while on this diet. Based on this diet, we have formulated a study protocol in which the parathyroid function and calcium metabolism were assessed by several independent techniques. The results of our study are as follows:

In primary hyperparathyroidism, the diagnosis of hyperparathyroidism was made biochemically by an elevation of urinary cAMP in 24 of 26 cases and of serum immunoreactive PTH in 18 (Fig. 9), and was confirmed surgically in 22. The mean serum concentration of calcium was significantly elevated and that of P was significantly reduced. Although serum Ca was normal in five cases during evaluation under synthetic diet, it is unlikely that they suffered from "normocalcemic" primary hyperparathyroidism, as they were shown to be hypercalcemic before evaluation.

Seven patients had normal urinary Ca or a positive value of $Ca_A - Ca_{UV}$. However, 17 had hypercalciuria and negative values for $Ca_A - Ca_{UV}$, indicating a state of negative Ca balance (4). Thus hypercalciuria could not be accounted for by an intestinal absorption of calcium alone it was partly the result of an excessive skeletal mobilization of calcium, probably from PTH excess. The skeletal involvement was confirmed by the presence of reduced bone density, which progressively declined during serial measurements, and by a high fasting urinary calcium in the majority of patients. Since intestinal Ca absorption does not significantly contribute to urinary Ca during fast, the fasting urinary Ca reflects chiefly the skeletal mobilization of calcium (3). The reduced bone density was previously demonstrated in primary hyperparathyroidism by Forland, Strandjord, Paloyan, and Cox (19) even in some of the patients who did not disclose any evidence for bone disease on routine roentgenologic examination. These 17 cases of primary hyperparathyroidism probably had resorptive hypercalciuria. 13 of them probably had a combined form of resorptive and absorptive hypercalciurias (3), as they had intestinal hyperabsorption of calcium as well.

In absorptive hypercalciuria, the primary abnormality is presumed to be an intestinal hyperabsorption of calcium (3–5). According to this hypothesis, the excessive intestinal absorption of calcium increases the circulating concentration of calcium and suppresses parathyroid function. The ensuing increase in the renal filtered load of calcium and the decrease in the renal tubular reabsorption of calcium from parathyroid suppression result in hypercalciuria. The excessive renal excretion of calcium usually compensates for the high intestinal calcium absorption and maintains serum

calcium concentration in the normal range. This hypothesis was tested by studies of oral calcium load and restriction under constant metabolic dietary regimen. Calcium load should accentuate intestinal calcium absorption and exaggerate hypercalciuria, whereas calcium restriction should limit intestinal calcium absorption and alleviate or correct hypercalciuria. Commensurate with these changes, calcium load should suppress parathyroid function whereas calcium restriction should restore suppressed parathyroid function to normal.

These predictions were largely met. During calcium load, all patients with absorptive hypercalciuria showed an exaggerated increase in the renal excretion of calcium. On an intake of 1,700 mg calcium/day, the mean urinary calcium ranged from 300 to 740 mg/day, whereas in the conrtol subjects it was less than 250 mg/day.

Restrictions of oral calcium was achieved by administration orally of cellulose phosphate. Cellulose phosphate is a nonabsorbable ion-exchange resin, which, when given orally, "binds" calcium and inhibits its absorption from the intestinal tract (20). The mode of action of this compound differs fundamentally from that of soluble orthophosphates (20, 21). At the dose utilized in this study, 5 g three times a day orally, cellulose phosphate has been shown to reduce intestinal calcium absorption by as much as 165 mg/day (20). Among patients with absorptive hypercalciuria, cellulose phosphate decreased urinary calcium by 120–230 mg/day to the normal range (less than 200 mg/day). Thus hypercalciuria was corrected by limiting intestinal calcium absorption with cellulose phosphate.

During cellulose phosphate administration, urinary Ca in hypercalciuric group was less than 200 mg/day, but was still higher than that of the control group (Table I). As emphasized before (4), this may be caused by a greater degree of intestinal calcium absorption by hypercalciuric patients even when the available calcium in the intestinal tract is reduced by cellulose phosphate.

The possible effect of calcium load and deprivation on parathyroid function was assessed from the change in the renal excretion of cAMP (22–25), rather than in serum immunoreactive PTH, for the following reasons. In patients with primary hyperparathyroidism, the 24-h urinary cAMP, obtained during a controlled dietary regimen, was highly correlated with serum immunoreactive PTH, obtained before breakfast on the day of urine collection (Fig. 10). Unfortunately, in our hands, the values for PTH were frequently undetectable in absorptive hypercalciuria. Thus, the concentrations of immunoreactive serum PTH were sufficiently low that the extinction limit of the assay available to us prevented the detection of the small changes in serum PTH that might ensue from oral calcium load and deprivation.

In patients with absorptive hypercalciuria, calcium load reduced renal excretion of cAMP and calcium restriction increased it. These results suggest that parathyroid function was probably suppressed by calcium load and stimulated by calcium restriction. This conclusion was supported by the finding that urinary P and endogenous phosphorus clearance decreased in some cases during calcium load, and increased in every case during calcium restriction by cellulose phosphate. Although the absolute value of phosphorus clearance, obtained from 24-h value for urinary P and a single fasting serum P, may not provide a reliable measure of parathyroid function, its change may indicate alteration of parathyroid activity.

During all study periods, the urinary cAMP was lower in hypercalciuric patients than in the control subjects, although the difference was not as great during calcium restriction with cellulose phosphate. The results suggest that parathyroid function was partly suppressed in hypercalciuric patients, particularly during calcium load, presumably by the enhanced intestinal absorption of calcium.

Although urinary cAMP was inversely related to urinary Ca (Fig. 4), it is unlikely that hypercalciuria has a direct inhibitory influence on cAMP excretion. Our recent studies indicate that in patients with primary hyperparathyroidism or hypoparathyroidism, urinary cAMP does not change significantly despite wide variation in urinary Ca produced by oral calcium loads. After an excessive renal loss of calcium from the administration of furosemide or adrenocorticosteroid hormone in control subjects, the urinary cAMP increases. In patients with primary hyperparathyroidism, there is no evidence that urinary cAMP is inappropriately low relative to serum PTH, among those with marked hypercalciuria.

Studies performed under synthetic dietary regimen provided further evidence for the primacy of intestinal hyperabsorption of calcium in these patients with hypercalciuria. Among 22 patients with absorptive hypercalciuria, serum immunoreactive PTH, assayed with antiserum CH 14M of Arnaud et al. (10), was within the normal range or undetectable. When assayed by the technique of Reiss and Canterbury (11), it was within the normal range except in one patient, in whom it was slightly elevated. Urinary cAMP was significantly less than in the control group. All patients were normocalcemic and normophosphatemic. Thus, they probably had a normal or partly suppressed parathyroid function, as was suggested previously by studies of Ca load and restriction.

All patients with absorptive hypercalciuria had an enhanced intestinal absorption of calcium and hypercalciuria. However, in contrast to primary hyperparathyroidism, the urinary Ca was less than the amount of absorbed Ca, except in one case. Although the value of $Ca_A - Ca_{UV}$ of $+49 \pm 27$ SD mg/day was less than in the control group, it may have still reflected the net secreted calcium. The endogenous fecal calcium (EFC) has been shown to be inversely related to the fractional Ca absorption (26, 27), and directly related to calcium intake (26). Since α is high in absorptive hypercalciuria, one would expect EFC or net secreted Ca to be lower than in the control group. In the study of Liberman et al (27). EFC varied from 31 mg to 178 mg/day with a mean value of 99 mg/day among patients with idiopathic hypercalciuria. In these patients, dietary Ca intake was generally higher and mean value for α was lower than in our hypercalciuric patients. Thus, the value for EFC of 49 mg/day would not be unexpected in our patients. The results suggest that our patients were probably in Ca balance. This conclusion was supported by the demonstration of normal bone density, which did not decline during serial measurements, and by the lack of evidence for bone disease, despite long history of hypercalciuria and renal stone formation.

Further, the fasting urinary calcium was within the normal range, in accordance with the finding of Nordin, Peacock, and Wilkinson (3). While fasting could produce varying degrees of volume depletion, and thereby change tubular calcium reabsorption (28), there was no evidence that patients with absorptive hypercalciuria could conserve sodium less perfectly than control subjects. The renal excretion of sodium was not significantly different between the two groups. In our recent study, urine was collected during a 12-h fast immediately after a meal containing 25 meq of Na and 100 mg of Ca at 9 p.m. For the preceding 2–3 days, patients were maintained on a diet containing 100 meq of Na and 400 mg of Ca daily. The urinary sodium was 45.8 ± 8.8 SD meq/12 h in six patients with absorptive hypercalciuria, which was not significantly different from that of seven control subjects, 52.6 ± 8.5 meq/12 h.

Thus, in our patients with absorptive hypercalciuria, the high renal excretion of calcium could be accounted for by an intestinal hyperabsorption of Ca alone, and need not implicate an excessive skeletal mobilization of calcium.

Two patients problably suffered from renal hypercalciuria, although they were not able to undergo complete evaluation. They had a biochemical evidence for hyperparathyroidism, since urinary cAMP was elevated in both and serum PTH was high in one. However, unlike in primary hyperparathyroidism, both patients were normocalcemic. Both had hypercalciuria. They were probably in a state of negative Ca balance, as urinary Ca exceeded the absorbed Ca. Bone density was reduced in one patient, who suffered from osteoporosis. The calcium infusion test (29) was carried out in one patient (one with osteoporosis). Urinary P decreased by 61% during the latter half of the infusion day, indicating a normal response.

Although the results are not conclusive, these patients probably suffered from secondary hyperparathyroidism, as in the cases of renal hypercalciuria reported by Coe, Canterbury, Firpo, and Reiss (6). However, the features presented by these patients were the same as those found in patients with "normocalcemic" primary hyperparathyroidism (30). Unlike our patient with renal hypercalciuria, the patients with normocalcemic primary hyperparathyroidism were reported to respond abnormally to the calcium infusion test, suggesting a primary hypersecretion of PTH (4). Unfortunately, the calcium infusion test employed there, which relies on changes in urinary P, does not directly measure the suppressibility of parathyroid function (4, 29). Thus, without a better test for the suppressibility of parathyroid function, the diagnosis of normocalcemic primary hyperparathyroidism cannot be clearly excluded in our patients. Alternatively, there is a possibility that some of the previously reported cases of normocalcemic primary hyperparathyroidism may have had a "renal leak" of calcium.

The six patients with normocalciuric nephrolithiasis had normal values for serum PTH, urinary cAMP, and serum concentrations of Ca and P, indicating normal parathyroid function. The urinary Ca was less than 200 mg/day and the fractional Ca absorption was usually within the normal range. The value of $Ca_A - Ca_{UV}$ was positive, and fasting urinary Ca and bone density were within the normal range. Thus, as in absorptive hypercalciuria, there was no evidence for excessive skeletal mobilization of calcium.

However, urinary Ca was significantly higher than in the control group, and the mean value for fractional Ca absorption was greater than that for the control group, though less than that for absorptive hypercalciuria. Thus, these patients with normocalciuric nephrolithiasis may have a borderline abnormality of intestinal Ca absorption. However, this group had a reduced creatinine clearance (69 ± 9 ml/min). It is therefore possible that some of the patients may have had absorptive hypercalciuria, but are no longer excreting large amounts of calcium in their urine because they have developed renal disease.

Among patients who were previously diagnosed as idiopathic hypercalciuria, 22 had absorptive hypercal-

ciuria and only 2 probably had renal hypercalciuria. This finding differs from that of Coe et al. (6), who reported that the majority of patients with idiopathic hypercalciuria presented with secondary hyperparathyroidism. However, these workers did not use a controlled diet and relied mainly on a radioimmunoassay of serum PTH (11).

In contrast, our diagnoses were established by several independent measures of parathyroid function as well as by an assessment of the state of calcium metabolism under a carefully controlled dietary regimen. Parathyroid function was measured directly by the determination of immunoreactive serum PTH by two different techniques, including that employed by Coe et al. (6, 11), and indirectly by an analysis of urinary cAMP, which has been shown to be highly correlated with serum PTH. Calcium metabolism was evaluated by assessments of quantitative bone density and of skeletal mobilization of calcium (from fasting urinary calcium), and by comparison of absorbed calcium with urinary calcium. The results from these independent techniques were complementary.

This study, therefore, provides reliable diagnostic criteria for the various forms of hypercalciuria and of normocalciuric nephrolithiasis, and support for the proposed mechanisms for the pathogenesis of hypercalciuria.

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