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# Refractory Hypercalcemia in Sarcoidosis: Exacerbation by thiazide diuretics, differentiation from primary hyperparathyroidism, and possible role of prolactin

A. M. Parfitt, MD\*

*Hypercalcemia in a patient with sarcoidosis was made worse by a thiazide diuretic initially given to control hypercalciuria alone. The hypercalcemia was unusually resistant to corticosteroid treatment during the summer even after the thiazide diuretic had been discontinued. Lack of response to corticosteroid together with decreased tubular reabsorption of phosphate and increased tubular reabsorption of calcium suggested associated primary hyperparathyroidism, but PTH was undetectable by immunoassay, and nephrogenous cyclic AMP excretion was zero. Amenorrhea, galactorrhea and hyperprolactinemia were found to be due to a pituitary tumor which was removed. The experience with this patient suggests that: 1) exacerbation of hypercalcemia by thiazides does not discriminate between its different causes; 2) finding low values for plasma parathyroid hormone (PTH) and nephrogenous cyclic AMP is the most certain way of excluding primary hyperparathyroidism in patients with hypercalcemia from other causes; 3) prolactin excess, by increasing the synthesis of 1,25 dihydroxycholecalciferol, may have intensified the calcium metabolism disorder.*

**H**YPERCALCURIA leading to nephrolithiasis and hypercalcemia leading to nephrocalcinosis are well recognized complications of sarcoidosis.<sup>1</sup> In most instances, the disordered calcium metabolism is readily controlled by dietary calcium restriction and corticosteroids,<sup>2</sup> but occasionally these measures are relatively ineffective. Such a case is the subject of this paper.

## Case Report

A white woman, born in 1943, was first seen at Henry Ford Hospital in November, 1975 at the age of 33 for recurrent kidney stones associated with sarcoidosis. In 1961, at age 18, a normal pregnancy was followed by amenorrhea. She did not want more children and the cause was not established, but thyroid medication was given for good measure. In 1967, at age 24, a routine chest x-ray was abnormal; tuberculosis was suspected, but not confirmed. The pulmonary infiltration progressed, and three years later, in 1970, a biopsy of a lymph node in the neck showed sarcoidosis. Corticosteroids were given for six weeks with inconclusive results. Apart from a skin rash on the legs, she remained well without further treatment for the next three years. In June, 1973, however, the first sign of disordered calcium metabolism abruptly appeared. This was a severe attack of left-sided ureteric colic which required a ureterolithotomy. Similar attacks of pain, but lasting only 12-24 hours and always on the left side, recurred every few months. In March, 1975 a more severe attack occurred on the right side and required litholopaxy via cystoscopy.

Two months later her family physician referred her to the Baylor College of Medicine in Houston. Two stones were found in the left kidney and one in the right, all of which were removed surgically. The stones were composed of a mixture of calcium oxalate and calcium phosphate. The plasma calcium was normal at 9.2 mg/dl, but urinary calcium excretion was increased to 428 mg/24 hours on a regular diet, decreasing to 169 mg on a low calcium diet. Renal function was normal with a plasma creatinine of 1.0 mg/dl and a creatinine clearance of 101 ml/minute. The diagnosis of sarcoidosis was confirmed by positive biopsies of a skin lesion on the leg and of a para-aortic lymph node. There was diffuse interstitial infiltration in the lungs with a combined restrictive and obstructive defect in ventilation. Concerning the amenorrhea, morning and evening plasma cortisol, insulin tolerance test, including growth hormone and cortisol response and plasma levels of luteinizing

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hormone, triiodothyronine, thyroxine, and thyroid stimulating hormone were all normal. The exogenous thyroid was stopped, and she was discharged on a thiazide diuretic, a low calcium diet, and a low sodium diet, all given to lower urinary calcium excretion. Potassium phosphate was given as additional treatment for the kidney stones, but was discontinued after a few months and replaced by a nonphosphate containing potassium supplement. Although there were no further attacks of ureteric colic, urinary tract infections resumed and serial x-rays showed regrowth of the stones.

The patient was first seen at Henry Ford Hospital six months after leaving Houston in November, 1975. There was no abnormality on physical examination apart from the abdominal scars. In particular, there was no enlargement of liver, spleen or lymph nodes, no ocular calcification, and the blood pressure was normal. The plasma calcium was higher (10.5 mg/dl) and the urinary calcium lower (162 mg/24 hours) than previously, most likely a result of the thiazide diuretic therapy. The plasma creatinine was 1.9 mg/dl and creatinine clearance only 50 ml/minute. The chest x-ray showed persistent pulmonary infiltration which had not changed during the previous year. X-ray of the renal tract showed several small stones on the left and a single large stone on the right, which had progressively increased in size, although the projections were not precisely comparable (Figure 1). The recurrence of stones after the surgery in 1975 could have been due to the administration of supplemental phosphate to a patient with recurrent urinary tract infection, but the stones continued to grow even after the phosphate supplement had been discontinued. Despite worsening renal

function and inadequate control of stone formation, no improvements could be made in her treatment.

However, in April 1976, hypercalcemia was noted for the first time, the plasma calcium having risen to 11.6 mg/100 ml and the 24-hour urinary calcium excretion to 306 mg. The dietary intake of calcium, determined by accurate record of food consumption for a week, was only 330 mg. The plasma parathyroid hormone (PTH) level was at the lower limit of detectability. The thiazide diuretic was discontinued, and the plasma calcium fell to 10.2 mg/100 ml. Thiazides were started again, and several weeks later the plasma calcium had risen again to 11.9 mg/100 ml. Progress over the next several months is shown in Figure 2; all the plasma calcium values in this and subsequent figures are corrected for protein.<sup>3</sup> Although the hypercalcemia was evidently precipitated in part by thiazides, the need to maintain effective suppression of urinary calcium excretion was critical. Consequently, the thiazide was continued and a trial of corticosteroids was begun, indicated also because of persistently abnormal ventilatory function tests. Allopurinol was given for hyperuricemia, a drug which may also be helpful in the control of calcium nephrolithiasis.<sup>4</sup> The initial dose of prednisone was 60 mg daily, then reduced to 30 mg, but the hypercalcemia persisted. Although hydrocortisone has occasionally been more effective than prednisone in the hypercalcemia of sarcoidosis,<sup>5</sup> it did not prove so in this case. Only when the thiazide diuretic was discontinued did the hypercalcemia show some response to the corticosteroid treatment. Note that the period of refractory hypercalcemia occurred during the summer months, a point which will be taken up later.

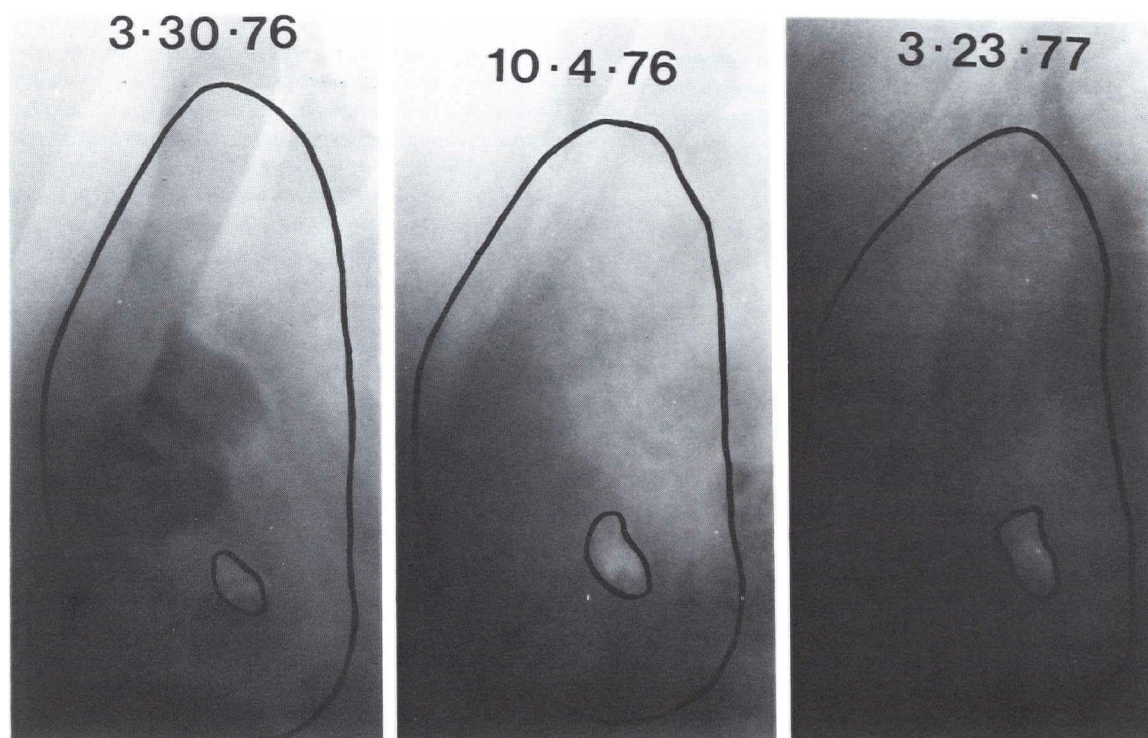


Fig. 1  
Serial plain films of renal tract over one-year period showing increase in size of stone and decrease in size of kidney.

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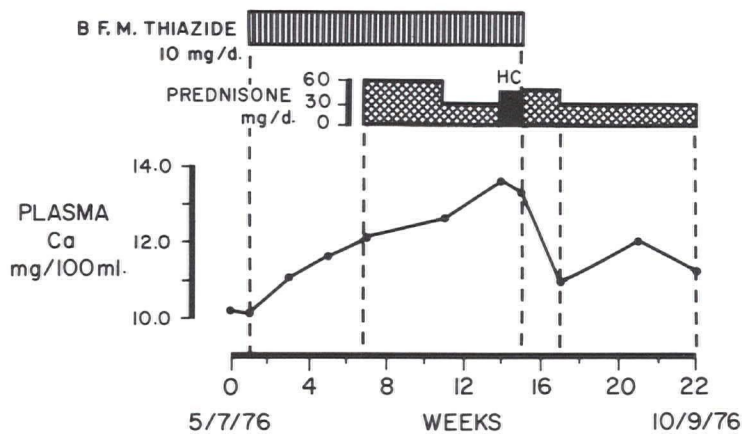


Fig. 2

Serial values for plasma calcium. Bendroflumethiazide worsened hypercalcemia and blocked the response to corticosteroid; normocalcemia was not restored even after the thiazide was discontinued. Note that the progressive rise in plasma calcium occurred during the summer. All values for total calcium in this and subsequent figures are corrected for protein.<sup>3</sup>

Despite the low PTH level, hypercalcemia refractory to corticosteroids in a patient with sarcoidosis suggested co-existing primary hyperparathyroidism, and in November, 1976 the patient was admitted to the hospital for further study. Other possible causes of hypercalcemia were ruled out by appropriate tests. Looking for further evidence of possible hyperparathyroidism, a bone biopsy was performed which showed an increase in the proportion of the trabecular surface covered by osteoclasts. Although this was consistent with hyperparathyroidism, other features of the bone biopsy were against this diagnosis. The bone mineral content of the radius measured by photon absorptiometry was normal. While these studies were proceeding, the dietary intake of calcium was further reduced to 150 mg/day, and the plasma calcium fell slowly to 10.1 mg/100 ml, a normal value. The ionized calcium was only marginally raised at 4.7 mg/100 ml (4.6 being the upper limit of normal).

Rigorous dietary calcium restriction and prednisone 30 mg on alternate days were continued at home. Plasma calcium remained normal for the next six months; in May, 1977 it was 9.8 mg/100 ml and the serum creatinine had fallen to 1.3. The patient was concerned about her Cushingoid facies and a weight gain of 26 pounds. For this reason and also because there had been no improvement either in the chest x-ray or in ventilatory function tests, prednisone was gradually withdrawn. This was quickly followed by a recurrence of severe hypercalcemia requiring hospital admission. As in the previous year this episode occurred during the summer months. The creatinine clearance had fallen to 24 ml/minute, the tubular reabsorption of phosphate was decreased, and the tubular reabsorption of calcium was increased (Table 1). Although both of these findings are consistent with increased PTH secretion, the PTH measured by radio-immunoassay was undetectable and the nephrogenous cyclic adenosine monophosphate (Nc'AMP) excretion, a more specific test of renal

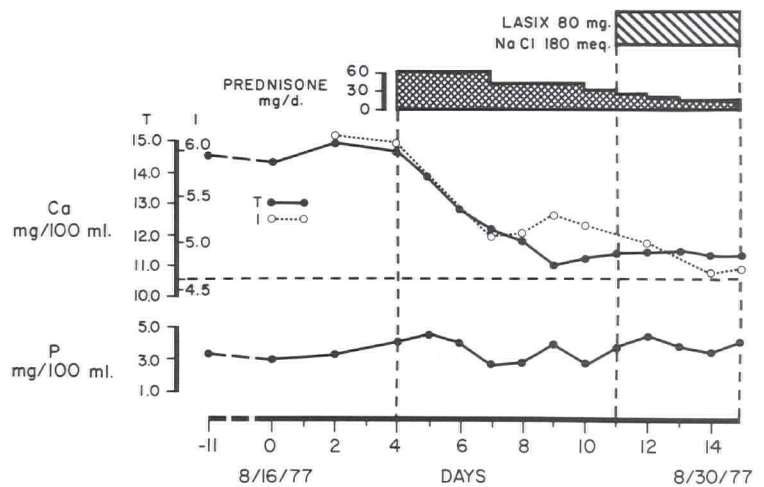


Fig. 3

Serial values for plasma calcium and inorganic phosphate while in hospital. There was a rapid fall in both total and ionized calcium, but mild hypercalcemia persisted. The combination of lasix and sodium chloride produced no further significant change.

tubular responsiveness to PTH,<sup>6</sup> was zero. The patient reluctantly agreed to the reinstatement of prednisone, which produced a rapid fall in plasma calcium to nearly normal (Figure 3). Two hundred mEq of sodium chloride combined with furosemide 80 mg daily was then given in the hope that increasing the urinary excretion of sodium would also increase urinary calcium excretion and further lower the plasma calcium. There was no further change in total calcium although there was a suggestive fall in ionized calcium.

The possibility of a pituitary or hypothalamic cause for amenorrhea was reconsidered despite the previously negative investigations, because galactorrhea was detected for the first time. Since sarcoid granulomas can occur in the central nervous system, the amenorrhea could have been the first symptom of the disease. Thyroid and adrenal function were again normal. The plasma prolactin level was 720 ng/ml, which was very high, and both the LH and FSH levels were abnormally low. Laminograms of the pituitary fossa indicated the presence of a tumor which was removed on February 20, 1978 by trans-sphenoidal hypophysectomy; the plasma prolactin fell to 44.6 ng/ml. The excess prolactin may have accounted for some of the unusual aspects of the disordered calcium metabolism as well as for amenorrhoea and galactorrhea.

## Discussion

This patient has sarcoidosis, hypercalciuria, nephrolithiasis, and hypercalcemia exacerbated by thiazides but responding eventually to corticosteroids, associated with a prolactin secreting pituitary tumor. Three aspects of the case will be discussed; first, the various diagnostic procedures which indicated that the patient did not have hyperparathyroidism as well as sarcoidosis; second, the pathophysiology of the calcium disturbances in sarcoidosis and in thiazide diuretic

therapy and their possible relationship to prolactin; and third, the difficult problems in treating this patient.

### Differentiation between sarcoidosis with hypercalcemia and hyperparathyroidism

There is no doubt that the patient had sarcoidosis, but in this disease there is an increased prevalence of primary hyperparathyroidism.<sup>7</sup> This rarely causes rapidly changing hypercalcemia,<sup>8</sup> but in patients with both diseases the hypercalcemia does not respond to corticosteroids, so that exclusion of primary hyperparathyroidism was of particular importance in this patient. Figure 4 shows the effect of a standard cortisone test, 150 mg daily for 10 days, in three patients, one with primary hyperparathyroidism who showed no change in plasma calcium, one with sarcoidosis showing a fall in plasma calcium to normal, and one with both diseases in whom the effect was the same as in primary hyperparathyroidism alone. As a general rule, when a patient has both primary hyperparathyroidism and some other disease which can cause hypercalcemia, the hypercalcemia is due entirely to the hyperparathyroidism. Only very rarely does the second disease make an independent contribution.

Although the obvious way of excluding overactivity of an endocrine gland is to measure the relevant hormone in the blood, this is much more complex for PTH than for almost any other hormone. PTH is an 84-amino-acid polypeptide with biologic activity residing in the first 34 amino-acids at the amino terminus. Like other peptide hormones, PTH is measured by radio-immunoassay; in the absence of pure human hormone, antibodies are raised by immunizing animals with bovine PTH, which resembles the human hormone sufficiently for antibodies to crossreact. There are

at least three separate immunogenic sites along the PTH molecule, and different antisera may react with any combination of these. The PTH molecule is broken up into shorter fragments both in the liver and in the kidney. The major component of immuno-assayable PTH in the circulation is a C terminal fragment (molecular weight about 7,000 daltons) which has a long half-life and is biologically inert. Cleavage at a different site may also produce a biologically active fragment and a shorter inactive fragment. Because of these complexities no one really knows what they are measuring by a particular radio-immunoassay. Fortunately, the interpretation of a negative result is more certain. In this patient the PTH level was low or undetectable with four different assays in four different laboratories at various times.

PTH reduces the tubular reabsorption of phosphate, and tests based on this action have been used in diagnosis for the last 20 years. From simultaneous measurements of the concentrations of phosphate and creatinine in plasma and urine it is possible to calculate the percentage of the filtered load of phosphate which is reabsorbed. It is physiologically more accurate to use the same data to calculate the mean threshold of phosphate excretion, which is numerically equal to the maximum reabsorptive capacity corrected for glomerular filtration rate or  $TmP/GFR$ .<sup>9</sup> This quantity is almost always low in hyperparathyroidism, but there are many other influences on phosphate excretion so that the test is nonspecific. Low values can occur with any form of hypercalcemia, as in the present case.

PTH also increases the tubular reabsorption of calcium, which is best shown by relating urinary calcium excretion/100 ml of creatinine clearance to the simultaneously measured plasma calcium. In primary hyperparathyroidism the urinary calcium is less than would be expected for the same degree of hypercalcemia produced by calcium infusion, indicating increased tubular reabsorption.<sup>10</sup> This test is nonspecific because the tubular reabsorption of calcium, as of phosphate, is influenced by many other factors. One in particular is sodium balance. Sodium depletion and contraction of the extracellular fluid volume lead to increased tubular reabsorption of sodium and also of calcium. Patients with severe hypercalcemia of whatever etiology are frequently dehydrated because of vomiting and polyuria so that salt depletion and increased tubular reabsorption of calcium are to be expected. For this reason, correction of salt depletion is an important component of the treatment of severe hypercalcemia.<sup>8</sup> The tubular reabsorption of calcium in this patient when assessed in this manner was normal when she was first seen, and increased during the second episode of severe hypercalcemia, but this increase was the result of dehydration, not of increased PTH secretion.

Another test based on the action of PTH on the renal tubule is the excretion of cyclic adenosine monophosphate

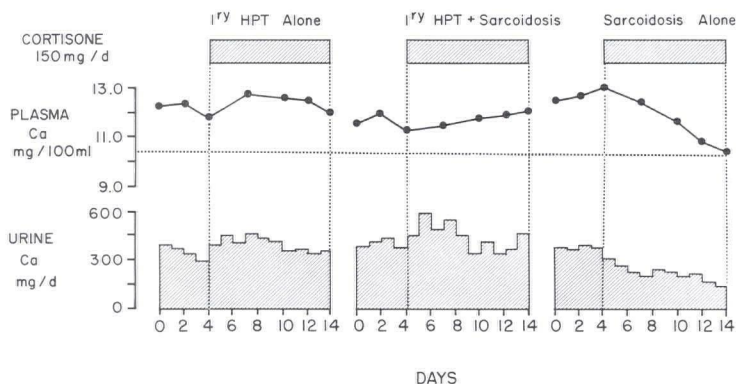


Fig. 4

Response of plasma calcium and inorganic phosphate and 24-hour urinary calcium to standard cortisone test. Note the fall of plasma calcium to normal in sarcoidosis alone, and no significant change in primary hyperparathyroidism with or without sarcoidosis.

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(c'AMP). PTH, like many other peptide hormones, initiates its biologic effects by binding to a receptor at the cell membrane. This leads to activation of the membrane-bound enzyme adenylate cyclase which catalyzes the conversion of ATP to c'AMP. In the renal tubule cell this action occurs at the base or antiluminal pole. Some of the c'AMP enters the cell and travels to the luminal pole where it leads to inhibition of the entry of phosphate from the tubular lumen. The c'AMP then passes out of the cell into the lumen and is eventually excreted in the urine. The urinary excretion of c'AMP is also derived from two other sources unrelated to the action of PTH. First, c'AMP is produced in many tissues by the action of catecholamines, glucagon and other hormones, and the surplus c'AMP is excreted in the urine. Second, antidiuretic hormone also acts on the renal tubule by activating adenylate cyclase. By measuring the plasma level of c'AMP and the creatinine clearance, the filtered load of c'AMP can be determined and subtracted from the total urinary excretion to give the nephrogenous component. In order to suppress ADH secretion, water diuresis is induced so that the nephrogenous c'AMP is then a reflection solely of endogenous PTH secretion. A further refinement is to express nephrogenous c'AMP excretion/100 ml creatinine clearance. This is a measure of the tubular response to PTH per unit of functioning renal tissue and can be used to assess parathyroid function in renal failure. Nephrogenous c'AMP is somewhat less sensitive than tests based on the tubular reabsorption of phosphate or of calcium, in that normal values occur more commonly in patients with proven hyperparathyroidism. But it is more precise in that elevated values more certainly indicate hyperparathyroidism and abnormally low values more certainly indicate its absence. In this patient the nephrogenous c'AMP was undetectable.

Patients with hyperparathyroidism may have changes in the bones, usually characterized by an increase in the proportion of bone surface undergoing both resorption and formation. Bone resorption is indicated microscopically by the presence of scalloped erosions of the bone surface known as Howship's lacunae. If these contain osteoclasts, which are large multinucleated cells, it is reasonable to infer that resorption was active at the time of the biopsy, but frequently Howship's lacunae contain other kinds of cell or no cells at all, indicating that resorption was probably not active. Normally, Howship's lacunae occupy about 5% of the total trabecular bone surface, but only about 10% of the Howship's lacunar surface is lined by osteoclasts. In the present case (Table I), there was a substantial increase in both the total resorption surface and the active or osteoclast-lined resorption surface, but a paradoxical decrease in the extent of the bone forming surface, in contrast to the increase usually observed in hyperparathyroidism. There was also a marked discrepancy between the iliac trabecular surface

where osteoclastic resorption was increased, and the iliac cortex where there were no osteoclasts at all. Like the change in tubular reabsorption of calcium and phosphate, an increase in the extent of surface resorption is not specific for hyperparathyroidism but occurs in several other conditions causing hypercalcemia, including vitamin D poisoning and sarcoidosis.

**TABLE I**  
**Diagnostic Information For and Against Concomitant Hyperparathyroidism (HPT)**

	<b>For HPT</b>	<b>Against HPT</b>
History	nephrolithiasis	initial normocalcemia
TmP/GFR (mg/100 ml)	2.2 (NR 2.8-4.2)	
Tubular reabsorption of Ca <sup>1</sup>	increased	
Response to thiazides (TZ)	plasma Ca rose	
Bone mineral content		normal
Response to corticosteroids (on TZ)	no change	
Response to corticosteroids (off TZ)		plasma Ca fell
Nephrogenous c'AMP		zero
PTH		undetectable

<sup>1</sup> Based on relationship between calcium excretion (0.61 mg/100 ml C<sub>Cr</sub>) and plasma calcium (14.2 mg/100 ml) in comparison with normal values.<sup>10</sup>

A final point concerning the state of the bones is the measurement of the bone mineral content of the radius by photon absorptiometry. The scans are made with the Norland-Cameron instrument across the forearm at two sites: a proximal site about one-third of the distance from the styloid process to the olecranon, where the bone is almost entirely cortical; and a more distal site about one-tenth of the distance from the olecranon, where there is a higher proportion of trabecular bone. In hyperparathyroidism the values tend to be reduced at both sites, but there is a relatively greater reduction at the distal site. In our patient both values and the relationship between them were normal.

The rapid response of the hypercalcemia to corticosteroids on the second occasion when the patient was not taking thiazide diuretics is very strong evidence against hyperparathyroidism. Typical responses to steroids are shown in Figure 4. Although steroid responsive hypercalcemia has been recorded in a few patients with primary hyperparathyroidism, they all had a more rapidly progressive form of the disease than usual, characterized by a short history, large tumors, and frequent presence of osteitis fibrosa. Slowly progressive hyperparathyroidism without overt

bone disease is never responsive to corticosteroids.<sup>8</sup>

Table II summarizes the results of the various diagnostic tests and their bearing on the presence or absence of concomitant hyperparathyroidism in this patient. Although exacerbation of hypercalcemia with thiazides is characteristic of primary hyperparathyroidism, it may also occur in other conditions. Each of the other test results tending to favor the diagnosis of hyperparathyroidism is nonspecific and susceptible of alternative interpretations. On the other hand, the combination of undetectable PTH, zero nephrogenous cyclic AMP, and suppression of hypercalcemia by prednisone is conclusive evidence against hyperparathyroidism.

**TABLE II**  
**Measurements on Iliac Bone Biopsy After**  
**Double Tetracycline Labelling**

Quantity	Normal Range	Present Case
Total bone volume (%TMT)*	20.2 ± 4.0	12.1
Total formation surface (%TS)**	12.9 ± 5.8	2.2
Osteoblast surface (%TS)	5.0 ± 3.3	1.6
Total resorption surface (%TS)	5.8 ± 2.0	29.2
Osteoclast surface (%TS)	1.0 ± 0.5	6.3
Osteoid seam width (um)	12.0 ± 3.4	6.7
Appositional rate (um/d)	0.75 ± 0.12	0.4

\* TMT = total marrow tissue

\*\* TS = total surface

### The calcium disorder in sarcoidosis and its relationship to hyperprolactinemia and thiazide diuretic administration

In sarcoidosis the metabolic state resembles closely that of vitamin D intoxication. There is increased gastrointestinal absorption of calcium, increased bone turnover, hypercalciuria, and hypercalcemia, all of which are reversed by the administration of corticosteroids, just as in vitamin D poisoning.<sup>2</sup> Even in patients whose calcium metabolism appears to be normal there may be increased urinary hydroxyproline excretion and suppressed PTH levels, so that the calcium disorder probably affects all patients with the disease, although the intensity varies considerably from one patient to another.<sup>11,12</sup> Vitamin D (or cholecalciferol), whether ingested as such in the diet or synthesized in the skin in response to irradiation by ultraviolet light, is biologically inactive. It is converted in the liver to 25-hydroxycholecalciferol (25HCC), which in turn is converted in the kidney either to 1,25-dihydroxycholecalciferol (1,25DHCC) or to 24,25-dihydroxycholecalciferol (24,25DHCC). 25HCC is active in high dose, but 1,25DHCC is much more potent and is the main physiologically active metabolite. Patients with sarcoidosis are abnormally sensitive to vitamin D, in that small oral doses, such as 0.25 mg or 10,000 units

daily, or exposure of the skin to ultraviolet light may induce hypercalcemia,<sup>2</sup> although these procedures have no effect in a normal person. This abnormal sensitivity explains the spontaneous disappearance of hypercalcemia which may follow hospital admission<sup>1</sup> as well as the seasonal variation in the intensity of the calcium disorder. In a study at Duke University some years ago,<sup>13</sup> all plasma calcium estimations in patients with sarcoidosis for a whole year were examined. They showed a significant increase during the summer months, whereas all the other values accumulated during the same period showed no change. In our patient, a seasonal fluctuation was clearly evident, and in retrospect, it was a mistake to withdraw corticosteroids at the beginning of the summer.

Another consequence of the increased sensitivity to sunlight is the pronounced geographic variation in the prevalence of the calcium disorder. In Washington DC, where summer is short and many patients are dark skinned, hypercalcemia is rare and occurs only in patients with extensive and severe disease.<sup>14</sup> By contrast, in Queensland, Australia, with a predominantly light-skinned population exposed to tropical sunlight for the entire year, hypercalciuria is almost universal and hypercalcemia occurs in 30% of patients. This is so even in asymptomatic persons whose only manifestation of the disease is enlarged hilar lymph nodes discovered by compulsory annual chest x-ray.

The precise nature of the disorder of vitamin D metabolism in sarcoidosis remains to be determined.<sup>15</sup> The plasma level of 25HCC is normal and rises to the same extent as in normal subjects in response to vitamin D administration or to ultraviolet irradiation of the skin; thus, there is no increase in the conversion of vitamin D to its first metabolite in the liver. Plasma levels of 1,25DHCC have been measured only in a few patients, and values to date have been either normal or only marginally raised. Since the calcium hyperabsorption of sarcoidosis leads to suppression of PTH, and since PTH is one of the factors which stimulates the formation of 1,25DHCC by the kidney, the plasma levels of this metabolite should be low. A normal value, therefore, may reflect a failure to suppress the process of renal 1-hydroxylation. However, the levels in the blood are lower than are found in idiopathic hypercalciuria, in which increased intestinal absorption of calcium is accompanied by a normal plasma calcium.<sup>16</sup> It is therefore unlikely that the hypercalcemia of sarcoidosis can be attributed solely to increased production of 1,25DHCC. Finally, when patients with sarcoidosis are given 1,25DHCC they show the same increase in intestinal absorption and urinary excretion of calcium as normal persons. The increased sensitivity to vitamin D in sarcoidosis cannot be explained within the framework of current knowledge of vitamin D metabolism, which suggests that another, as yet unidentified, metabolite of vitamin

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D may be produced in excessive amounts in this disease.

In some experimental animals prolactin is a potent stimulus to the formation of 1,25DHCC,<sup>17</sup> which may explain the increased intestinal absorption of calcium that occurs during lactation. Enhancement by prolactin of the synthesis of 1,25DHCC is an attractive explanation for the unusual refractoriness to treatment in this patient, but plasma levels of 1,25DHCC are not yet available. If this explanation is correct, her hypercalcemia should be much less of a problem during future summers.

The undoubted relationship between hypercalcemia and thiazide diuretic administration in this patient is noteworthy. In normal subjects thiazides reduce the urinary excretion of calcium but plasma calcium corrected for protein does not change.<sup>18</sup> In primary hyperparathyroidism thiazides characteristically cause further elevation of the plasma calcium but may have the same effect in patients receiving high doses of vitamin D either for osteoporosis<sup>19</sup> or for hypoparathyroidism.<sup>20</sup> It is therefore not surprising that thiazide-induced hypercalcemia should also occur in sarcoidosis; evidently, precipitation of hypercalcemia by thiazide diuretics does not necessarily indicate hyperparathyroidism.

### Treatment of the calcium disturbance in sarcoidosis

In patients with hypercalciuria alone urinary calcium should be reduced if possible in order to minimize the risk of nephrolithiasis. Thiazide diuretics are effective and may lower urinary calcium without raising plasma calcium, as in hypercalciuria from other causes. It is not known why hypercalcemia occurs in some patients but not in others. Corticosteroids are unsatisfactory because any beneficial effect due to reversal of the abnormality caused by the disease may be nullified by the direct hypercalciuric effect of the medication itself. Cellulose phosphate binds calcium and magnesium in the gut and is a useful adjunct to a low calcium diet,<sup>21</sup> but unfortunately it is not yet available in the United States.

Corticosteroids are the most effective treatment for hypercalcemia in sarcoidosis<sup>2</sup> and may be beneficial for other manifestations of the disease. Urinary calcium falls rapidly in parallel with the plasma calcium, in contrast to the lack of effect of corticosteroids on urinary calcium in patients with hypercalciuria alone. Nevertheless, an alternative which avoided the long-term harmful effects of corticosteroids would be valuable. Some years ago chloroquine was found to be effective in a few patients, possibly by minimizing in some way the effect of sunlight on the skin.<sup>22</sup> My own experience with this agent is limited to a single case in which the administration of chloroquine was followed by a gradual correction of the hypercalcemia. However, since the disease activity was also subsiding, it is quite possible

that the chloroquine was given coincidentally at the time of a spontaneous remission. If refractory hypercalcemia recurs in the summer despite a return of the plasma prolactin level to normal, chloroquine might be used in this patient.

### Acknowledgments

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