H Y P E R C A L C E M I A

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Despite its frequent occurrence and recognition, hypercalcemia continues to be an intriguing problem. Because of its many etiologies, this condition has embraced many disciplines: various hormonal, nutritional, genetic and neoplastic factors have been implicated for its pathogenesis. Its clinical presentation varies considerably. While it may present as a medical emergency, it may not often be associated with any clear-cut symptomatology. Therapeutic modalities for the control of hypercalcemia have been very numerous, a situation probably reflecting the complexity of the disease process.

Recently, some progress has been made toward the understanding of the causes for the hypercalcemia and development of reliable diagnostic criteria. It has therefore been possible to begin to construct a rational basis for therapy of hypercalcemia, wherein treatment is directed at correcting the underlying disorder.

DEFINITION OF HYPERCALCEMIA

A clear understanding of the physicochemical state of calcium in blood and of calcium homeostatic control is required before hypercalcemia may be properly defined.

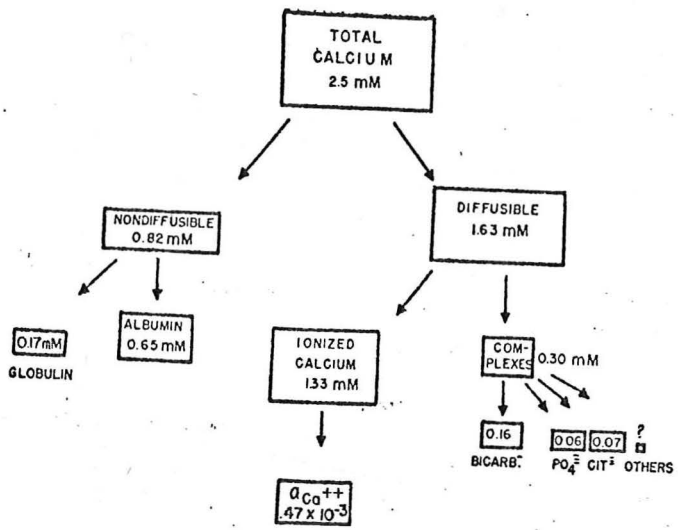
State of Ca in Plasma

The total serum Ca (Ca_T) is the sum of free ionized Ca (Ca^{++}) and complexed Ca (CaX) (Fig. 1).

$$Ca_T = Ca^{++} + CaX \qquad \text{Fig. 1}$$

The complexed Ca_1 is composed of diffusible and non-diffusible components (Fig. 2). The diffusible component, comprising approximately 1/8 of Ca_T, represents formation of soluble complexes, principally with phosphate, citrate and bicarbonate. The non-diffusible component, accounting for about 1/3 of Ca_T, reflects binding to proteins, principally albumin. Critical factors which affect the complexation of Ca is the pH and concentration of ligands, particularly of albumin and phosphate.[2] The reduction in pH inhibits complexation and thereby increases free ionized Ca, and vice versa. A change in albumin concentration of 1 g% may alter Ca_T by as much as 1 mg%.

The critical fraction which is important in pathophysiology is Ca^{++}. Unfortunately, few reliable techniques are available for its direct analysis. Two approaches allow indirect measurement of Ca^{++}. The diffusible component, comprising approximately 75% of Ca_T, may be obtained by ultrafiltration.[3] The Ca^{++} may then be determined by "subtracting" from ultrafiltrable Ca, soluble complexes of Ca (obtained by means of a computer program). Alternatively, the calcium



—The state of calcium in normal serum as calculated from ultrafiltration data and formation constants. In ignoring possible ion competition—with Mg^{++}, for example—the amount of calcium estimated to be complexed may be in error (too high). This error could hardly affect the estimated ionized calcium by more than 2 or 3 per cent, however. *mM* designates mM/l.

Fig. 2

ion activity ($^{\alpha}Ca^{++}$) may be determined with the Ca ion electrode[4] (Fig. 3).

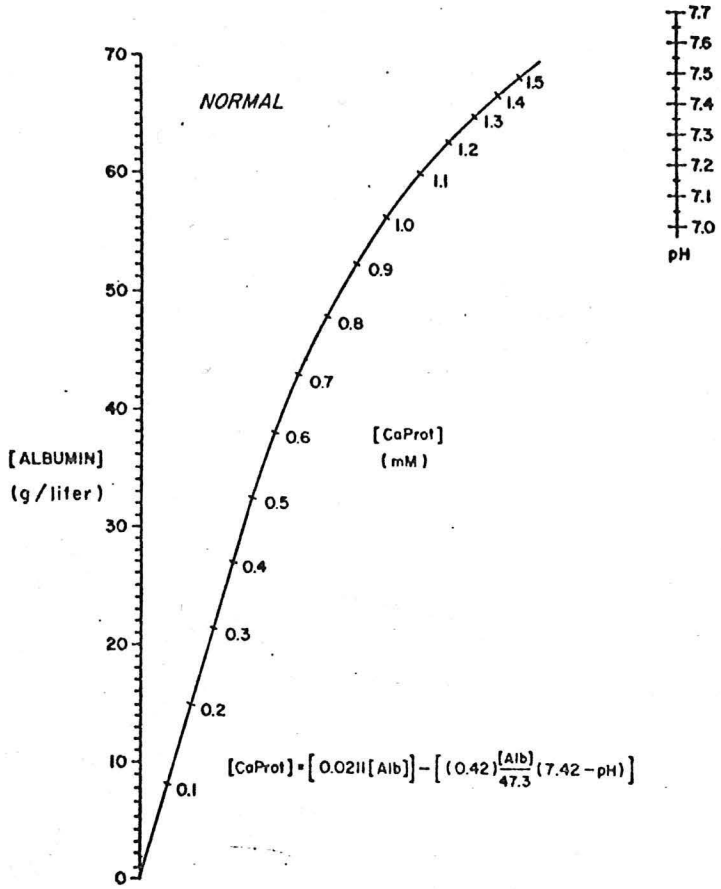
$$^{\alpha}Ca^{++} = \gamma_{Ca^{++}} \cdot C_{Ca^{++}} \qquad \text{Fig. 3}$$

Since the ionic strength of serum approximates .15, the activity coefficient of Ca (γ) may be assumed to be constant at approximately .36. The standard curve may be drawn from values of $^{\alpha}Ca^{++}$ (electrode potential) at various Ca^{++} concentration in artificial solutions of constant ionic strength (of 0.15). The concentration of Ca^{++} ($C_{Ca^{++}}$) may be obtained by extrapolation from the standard curve.

When neither of the above methods are available, protein bound Ca may be determined from the following nomogram of Moore[4] (Fig. 4).

Ca Homeostatic Mechanisms

Under normal circumstances, the circulating concentration of Ca^{++} is maintained within a narrow range by various homeostatic mechanisms.



Nomogram for estimating protein-bound calcium levels [CaProt] in normal subjects. [CaProt] is obtained by connecting observed albumin and pH values with a ruler; [CaProt] is then read from the curve. Derivation of the equation is given in the text.

Fig. 4

Three types of homeostatic control mechanisms are probably involved in the maintenance of plasma Ca concentration,-one hormonal, another physicochemical, and the third physiological.

(a) Hormonal regulation. Parathyroid hormone (PTH) is recognized as the most important factor in Ca homeostasis. The secretion of this hormone is carefully regulated by the plasma concentration of Ca^{++} (Fig. 5).[5] When plasma Ca^{++} is depressed, the secretion of PTH is stimulated. The stimulation of PTH restores plasma Ca^{++} to normal by increasing bone resorption, intestinal Ca absorption, and/or renal tubular reabsorption of Ca. Conversely, when plasma Ca^{++} is increased, the secretion of PTH is suppressed; plasma Ca^{++} is thereby reduced toward normal.

Three other factors,-1,25-dihydroxycholecalciferol (1,25-DHCC), calcitonin (CT) and gastrin, have been implicated in Ca homeostasis. These hormones are each capable of altering plasma Ca^{++} concentration; their secretion may be modified by the circulating concentration of Ca^{++}.

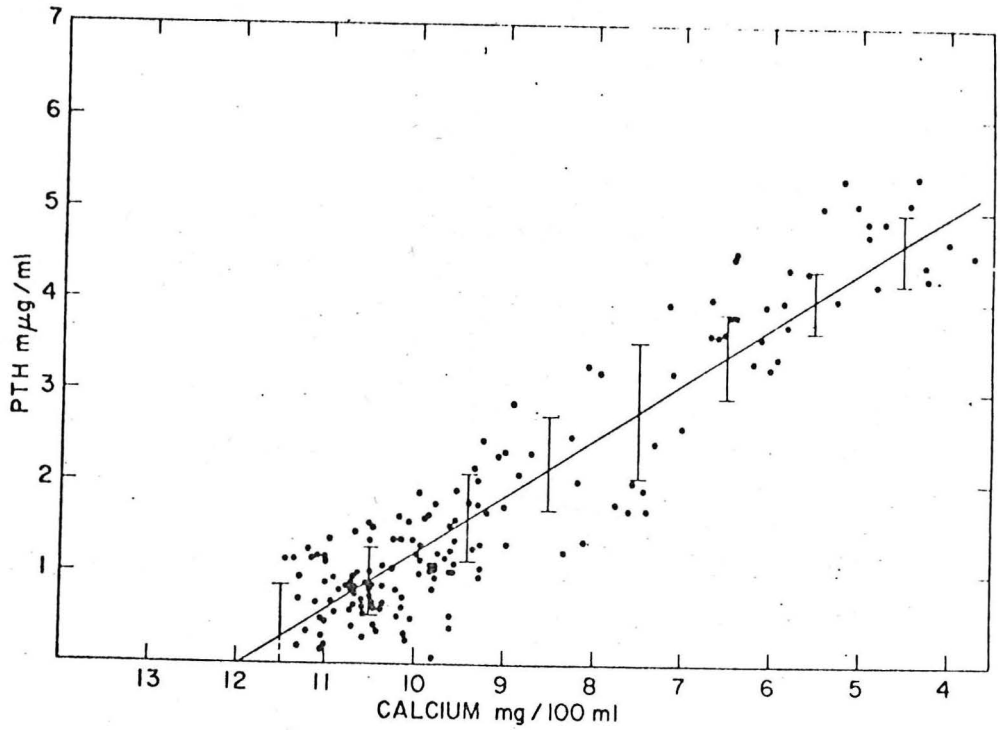

PTH mμg/ml
7
6
5
4
3
2
1
13
12
11
10
9
8
7
6
5
4
CALCIUM mg/100 ml

Fig. 5

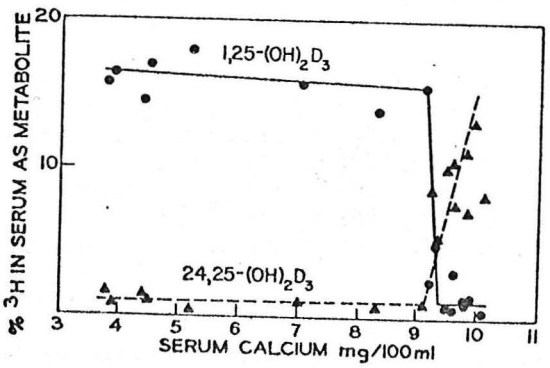

% ³H IN SERUM AS METABOLITE
20
10
1,25-(OH)₂D₃
24,25-(OH)₂D₃
3
4
5
6
7
8
9
10
11
SERUM CALCIUM mg/100ml

Fig. 6

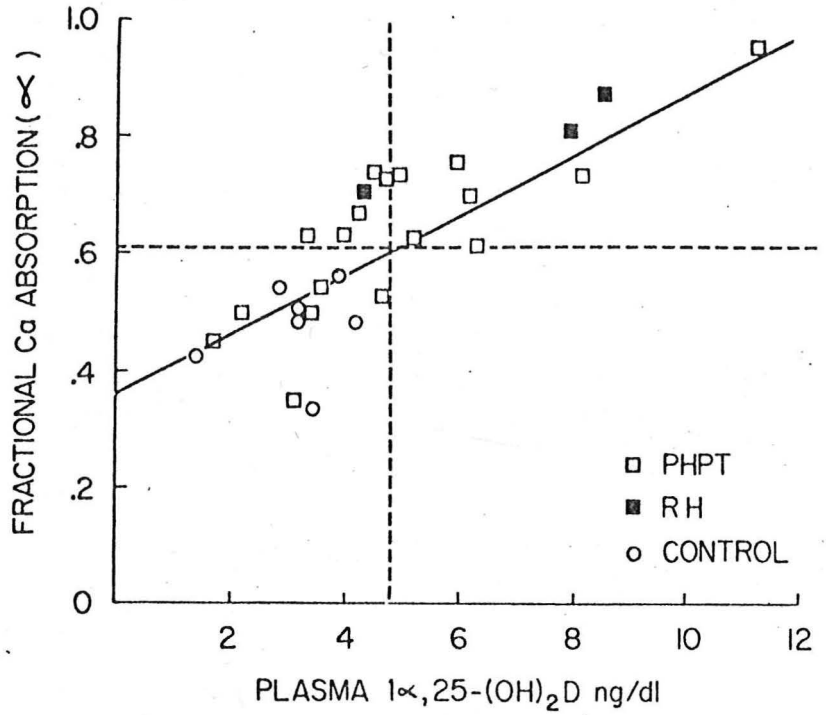


Fig. 7

As with PTH, the secretion of 1,25-DHCC is stimulated by low plasma Ca^{++}, and suppressed by high plasma Ca^{++} (Fig. 6) [6]. The importance of 1,25-DHCC in Ca homeostasis appears irrefutable. The synthesis and function of 1,25-DHCC appears to be closely related to the state of parathyroid function.[7] Its secretion is stimulated in conditions of PTH-excess. This vitamin D metabolite may be an important mediator for the PTH-stimulated intestinal Ca absorption.[8] In primary hyperparathyroidism, for example, the increased absorption of Ca was positively correlated with the raised circulating levels of 1,25-DHCC (Fig. 7). There is evidence, though preliminary and as yet inconclusive, that the stimulation of bone resorption produced by PTH may be mediated through 1,25-DHCC.[9] While both 1,25-DHCC and PTH are effective in promoting bone resorption, physiologic amount of 1,25-DHCC has been shown to exert this action *in vitro* whereas, larger amounts of PTH are required.

The secretion of CT and gastrin is also dependent on plasma concentration of Ca^{++},[10,11] though opposite in direction to that of PTH

and 1,25-DHCC. Unlike the latter hormones, CT and gastrin lower the circulating concentration of Ca^{++}. The CT does so by inhibiting bone resorption[12] and promoting renal Ca loss;[13] gastrin's action may be direct or may be indirect via stimulation of CT secretion.[14] Thus, when plasma Ca^{++} is increased, the enhanced secretion of CT and gastrin may serve to lower plasma Ca^{++} towards normal. Unfortunately, the biological significance of CT and gastrin in health has been questioned.[15] When the endogenous production of CT is largely eliminated by thyroidectomy, there is no evidence that a major disturbance of Ca homeostasis ensues.

Magnesium ion is also probably involved in the regulation of PTH secretion.[16] The importance of this regulatory mechanism in the pathogenesis of hypercalcemia is not known.

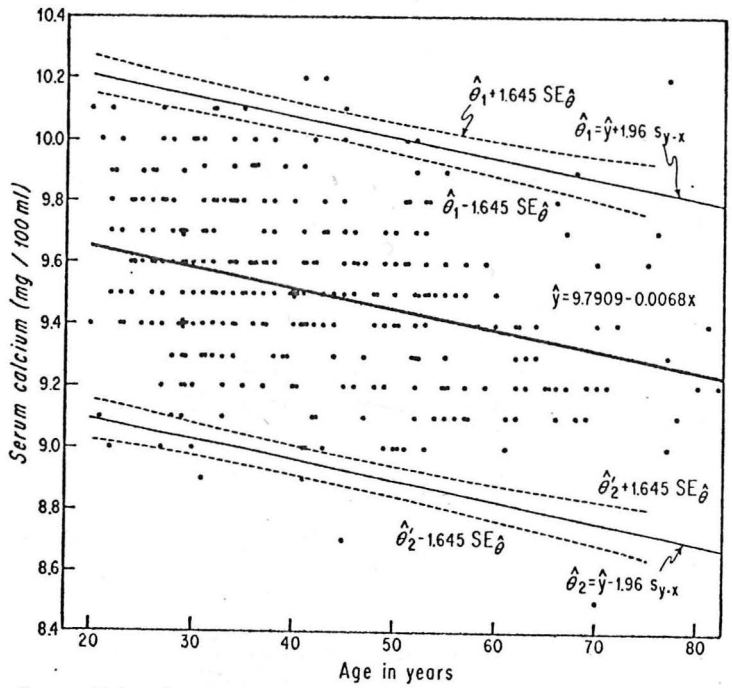
(b) Physicochemical regulation.[1] It has been hypothesized that plasma concentrations of Ca^{++} and phosphate reflect the solubility of the bone mineral. This hypothesis assumes that circulating concentrations of Ca^{++} and phosphate are maintained at a constant product, representing saturation with respect to a particular phase of calcium phosphate in bone. This scheme could explain the decline in plasma Ca^{++} which ensues from the rise in plasma phosphate. The circulating concentration of Ca^{++} is expected to be maintained in a narrow range, in so far as the plasma concentration of phosphate does not fluctuate widely.

Unfortunately, various physicochemical studies have failed to identify the particular phase of calcium phosphate with which plasma Ca^{++} and phosphate might be in steady state. They have shown the extracellular fluid to be supersaturated with respect to hydroxyapatite, the predominate mineral phase in bone, and undersaturated with respect to brushite ($CaHPO_4 \cdot 2H_2O$),[1] the "precursor" phase of hydroxyapatite.[17-19] The results suggest that the interstitial fluid of bone, which is in steady state with bone mineral, is not equivalent to the extracellular fluid in ionic composition. It has therefore been postulated that a barrier or ion gradient exists between these two fluid compartments. The action of PTH, CT and 1,25-DHCC, for example, may be assumed to involve the regulation of this ionic gradient.

(c) Physiological regulation. When the plasma level of Ca^{++} is abruptly increased, the excess Ca load may be removed by intestinal secretion and renal excretion.[20] While the intestinal Ca secretion is limited, the kidneys may remove as much as 800 mg Ca/day, while maintaining plasma Ca^{++} in the normal range. These mechanisms restore the plasma concentration of Ca^{++} towards normal, even when the hormonal regulation is lost.

Normal Serum Ca Concentration

The normal range for serum Ca has become more refined consequent to the improved methods for the analysis of Ca_T. Extensive studies by Keating et al.[21] indicate that serum Ca_T level declines with age and



Serum calcium in normal men, with main regression line against age and limits encompassing 95% of frequency and 90% confidence intervals for the limits.

Fig. 8

is lower in normal women than in normal men (Fig. 8). We find this nomogram to be useful, provided that there are no significant abnormalities in pH or in protein concentrations.

The most reliable means for defining normocalcemia, especially in states of disturbed acid-base balance or protein metabolism, is by the determination of plasma Ca^{++}. If Ca ion electrode is not available, Ca^{++} may be estimated from the ultrafiltrable Ca, obtained from the nomogram of Moore (Fig. 4).

Hypercalcemia: Loss of Ca Homeostatic Control

Hypercalcemia may be viewed as the sequela of the loss of Ca homeostatic control. For it to develop, there must be first, a sufficient, unabated "input" of calcium into the circulating fluid, as might occur from a continued excessive rate of bone resorption or of intestinal Ca absorption. Such a situation might result from the loss of hormonal regulation, as in primary hyperparathyroidism (PHPT) or from

other causes, as in neoplastic invasion of bone. Secondly, the extent of the input of Ca in the circulating fluid must exceed the capacity of the kidneys (and of intestines) to remove the Ca load. Hypercalcemia develops more quickly when the ability of the kidneys to excrete Ca is embarrassed, as in metabolic alkalosis.

Since methods for Ca^{++} determination are generally unavailable, hypercalcemia is usually defined with serum Ca_T, e.g. as values exceeding the normal range in the nomogram of Keating et al. (Fig. 8).[21]

CAUSES OF HYPERCALCEMIA

Hypercalcemia may be classified according to three main routes of Ca "entry" into the circulating fluid (Fig. 9).

Fig. 9

Classification of Hypercalcemia

(a) Increased Bone Resorption

- Primary Hyperparathyroidism
- Neoplasm with
  - Ectopic PTH Production
  - Ectopic Prostaglandin Production
  - OAF
  - Sterol?
- Neoplasm with Osteolytic Metastasis
- Thyrotoxicosis
- Others: (Vit D Toxicity, Sarcoidosis)

(b) Increased G-I Ca Absorption

- Vit D Toxicity
- Sarcoidosis
- Idiopathic Hypercalcemia of Infancy
- (Milk-Alkali Syndrome)
- (Primary Hyperparathyroidism)
- (P Depletion?)

(c) Increased Renal Tubular Reabsorption of Ca

- (Alkalosis)
- (Primary Hyperparathyroidism)
- (Volume Depletion)
- (Thiazide Therapy)

Certain conditions affect Ca entry at several sites. Parentheses indicate that the Ca entry at the particular site probably plays a minor role in the development of hypercalcemia. Some of these conditions will now be described in detail.

Primary hyperparathyroidism

Primary hyperparathyroidism is a disorder resulting from the loss of Ca homeostatic control involving PTH.[22] Thus, PTH is secreted by adenomatous or hyperplastic parathyroid tissue in amounts which are inappropriately high for the level of circulating Ca^{++}. Hypercalcemia develops from the combined effects of PTH-induced stimulation of bone resorption, intestinal Ca absorption, and of renal tubular reabsorption of Ca (Fig. 10). Hypercalciuria is often found. Even though PTH augments the renal tubular reabsorption of Ca, this action of the hormone is usually insufficient to overcome the increased renal filtered load of Ca associated with hypercalcemia (Fig. 11).

The major symptoms of primary hyperparathyroidism may be ascribed to the PTH-induced resorption of bone, hypercalciuria or hypercalcemia (Fig. 12). The severity or the type of bone disease probably depends to some extent on the degree of PTH secretion. Brown tumor, osteitis fibrosa cystica or extensive subperiosteal resorption is usually associated with high circulating levels of PTH and large glandular size. Osteoporosis, particularly in postmenopausal white women, may result from moderate stimulation of PTH for a prolonged period.[23]

There is ample evidence that PTH is required for the development of osteoporosis.[24,25] Osteoporosis is rarely encountered in hypoparathyroidism.[26] Osteoporosis of disuse[27] and low Ca intake[28] does not develop in the absence of parathyroid glands. The bone cell metabolism in osteoporosis resembles that in primary hyperparathyroidism.[29] As mentioned before, osteoporosis may be the clinical presentation of

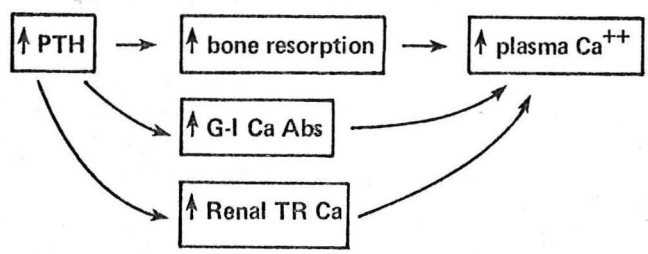


Fig. 10

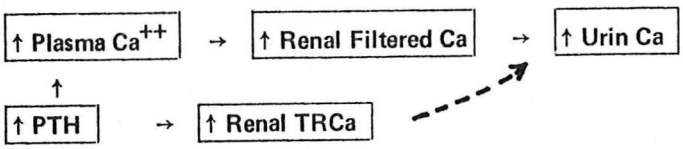


Fig. 11

PATHOGENESIS

Symptom		Probable Cause
Bone Disease	—	↑ Bone Resorption
Nephrolithiasis	—	Hypercalciuria ↑ Urin pH
Peptic Ulcer D CNS signs Fatigue Mental Disorders	}	Hypercalcemia

Fig. 12

primary hyperparathyroidism.

The association of osteoporosis in postmenopausal state emphasizes the important relationship between estrogen and PTH in the genesis of osteoporosis. Estrogen is believed to antagonize the action of PTH on bone.[30,31] It has been shown to inhibit the PTH-induced resorption of bone *in vitro*.[30] It reduces plasma concentration of Ca_T as well as renal excretion of Ca and hydroxyproline when given to man.[32,33] The consequent stimulation of PTH probably contributes to the increased intestinal Ca absorption and development of hypophosphatemia. The loss of the "protective" action of estrogen against the PTH-mediated bone resorption may account for the osteoporosis in postmenopausal state.

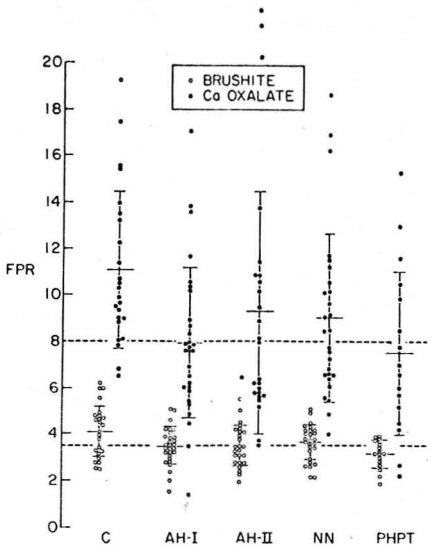
Hypercalciuria is an important, though not the sole factor concerned with renal stone disease.[18,34] Nephrocalcinosis is much less commonly encountered than nephrolithiasis. When it is present, nephrocalcinosis is usually associated with renal tubular acidosis. The renal tubular acidosis may occur in PHPT probably from the PTH-dependent renal bicarbonate loss.[35] The clinical presentation of nephrolithiasis in PHPT may be indistinguishable from that of absorptive hypercalciuria. However, the stone analysis may yield a higher frequency of predominantly Ca phosphate stones than those composed predominantly of Ca oxalate.

Hypercalciuria probably contributes to stone formation by rendering urine supersaturated with respect to brushite ($CaHPO_4 \cdot 2H_2O$) and Ca oxalate.[18,34] However, it is not the sole factor since certain patients with PHPT do not form stones despite hypercalciuria and a supersaturated state of urine with respect to Ca salts. Recent studies suggest that there is in PHPT an increased renal excretion of a certain substance, which facilitates spontaneous precipitation of Ca phosphate and Ca oxalate (Fig. 13).[34] This "promoter" of nucleation has not yet been characterized.

Hypercalcemia is probably the cause for various disturbances of the central nervous system. Peptic ulcer disease may be the consequence of Ca-dependent stimulation of the secretions of gastrin and hydrochloric acid.[11] This explanation is inadequate, since not all patients with PHPT demonstrate gastric acid hypersecretion despite hypercalcemia.

There has been a major change in the clinical presentation of PHPT during the past decade. While only 1% of cases were considered to be asymptomatic by Cope in his report in 1965,[36] 20% of our cases had no symptoms normally attributed to the disease (Fig. 14).[22] This changing trend is probably the result of earlier detection from routine determination of serum Ca and from improved diagnostic techniques.

Biochemically, the diagnosis of PHPT may be made from determinations of serum Ca, P, immunoreactive PTH (iPTH) and urinary cyclic AMP.[37,38] Serum Ca_T is almost always elevated, but is seldom greater than 14 mg%. When it is normal, it may be increased above normal by



The formation product ratio (FPR) of brushite and Ca oxalate. The upper horizontal dashed line indicates FPR of Ca oxalate for synthetic solution (devoid of inhibitors of nucleation). The lower horizontal line represents FPR of brushite for synthetic solution.

Fig. 13

CLINICAL PRESENTATION

Presenting Feature	Cope (n=343)	Authors (n=79)
	% of total cases	
Overt Bone Disease	23	14
Nephrolithiasis	57	32
Peptic Ulcer Disease	8	9
Hypertension	2	43
Asymptomatic	1	20

Fig. 14

certain provocative procedures, such as oral administration of Ca, thiazide[39] or P-binding antacids.[40] Serum P is sometimes low, but may be within the normal range. The immunoassay for serum PTH may be very helpful, particularly when the antiserum directed against the carboxy-terminal end of the PTH molecule is utilized and the values for iPTH are corrected for serum Ca.[41] Since PTH provides the most potent stimulus to the renal excretion of cyclic AMP,[42] urinary cyclic AMP may be significantly elevated in PHPT.[37,43] When it is obtained from urine samples collected for 24-hours under controlled diet and environment, it may provide an "integrated" measure of parathyroid function.[37] Urinary cyclic AMP may be normal despite parathyroid stimulation in renal disease (GFR < 40 ml/min). It may be elevated in certain conditions other than PHPT, such as in diabetes mellitus,[44] pheochromocytoma, inappropriate ADH syndrome, thyroxicosis,[45] and secondary hyperparathyroidism of renal hypercalciuria[38] and osteomalacia. Recent studies indicate that the determination of "nephrogenous" cyclic AMP (exclusive of filtered component) may yield a better measure of parathyroid function.

The serum Cl:P ratio,[46-48] though increased in some cases of PHPT,[49] has a limited value because of the wide overlap into the control range.

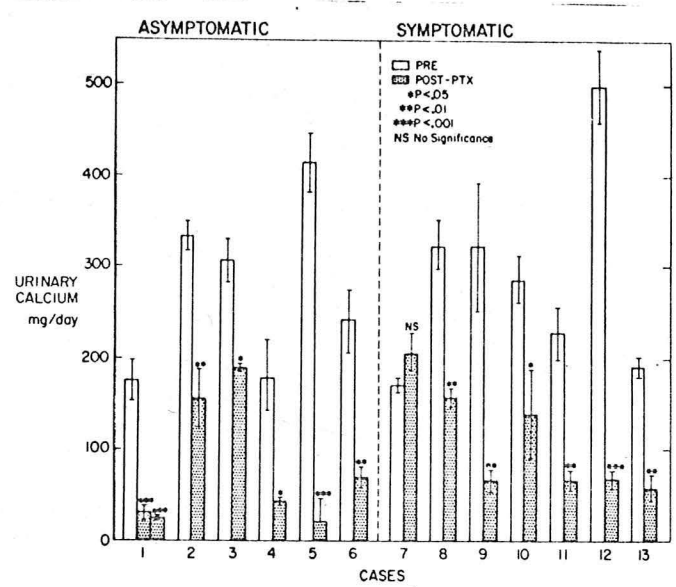
Certain physiologic derangements of Ca metabolism may occur in PHPT.[50] They include: hypercalciuria, which predisposes to nephrolithiasis; evidence for negative Ca balance, which may be demonstrated by high fasting urinary Ca, urinary Ca exceeding absorbed Ca, and low bone density; and reduced glomerular filtration rate of less than 65 ml/min. These "deleterious sequelae of PTH-excess" may be present even in asymptomatic PHPT, and may be restored towards normal following parathyroidectomy (Fig. 15).

The above physiologic derangements may be utilized to define indications for parathyroid exploration, especially in asymptomatic PHPT. Surgical removal of the abnormal parathyroid tissue is clearly indicated in symptomatic PHPT. Where surgery is contraindicated or refused, treatment with orthophosphate,[51] cellulose phosphate,[52] calcitonin,[13] or estrogen[33] may be considered. Adrenal corticosteroids[53] and inhibitors of prostaglandin synthesis (indomethacin and aspirin) have been shown to be largely ineffective.

The PHPT may be associated with multiple endocrine neoplasia[54] and may coexist in Paget's disease of bone[55] and thyrotoxicosis.[56-59]

Ectopic PTH Production

In 1941, Albright first described a case of renal cell carcinoma with hypercalcemia and hypophosphatemia.[60] The chemical finding of hypercalcemia was reversed by radiotherapy to solitary bony metastasis and reappeared with recurrence of metastasis. He postulated that the neoplastic tissue was producing a substance, which was biologically similar to PTH. Thus, the concept of "ectopic PTH production" was



. Twenty-four hour urinary calcium excretion before and after parathyroidectomy. The open blocks represent pre-PTX values, and closed blocks the post-PTX values.

Fig. 15

introduced several decades before the chemical characterization of PTH. Although the description of this condition has been customarily attributed to Plimpton and Gellhorn, Albright's report predated that of latter workers by 15 years. In 1956, Plimpton and Gellhorn reported the case of a 49-year-old man with renal cell carcinoma with hypercalcemia, in whom nephrectomy restored the serum Ca to normal.[62] Unlike the case of Albright, this patient did not have skeletal metastasis. Since there was no direct destruction of bone to produce the hypercalcemia, this case more clearly documented the humoral etiology for the hypercalcemia. These cases provide a reminder that the presence of osteolytic metastasis need not necessarily exclude a humoral mechanism for the hypercalcemia.

Since then, a wide variety of neoplasias have been associated with ectopic PTH production.[62-65] While most were "solid" tumors, some were "soft" (lymphosarcoma, Hodgkin's disease). Most common were renal cell carcinoma and squamous cell carcinoma of the lung.

The hormone production by neoplasia has now been documented by

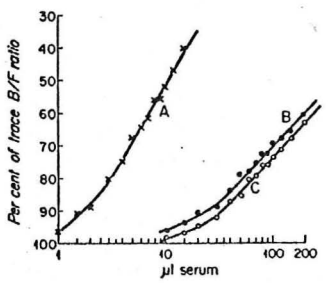
the demonstration of immunoreactive PTH in neoplastic tissue by immunoassay, immunofluorescent localization and by autoradiography.[66] The ectopic PTH hormone is probably not identical structurally to the native hormone produced by parathyroid glands, since it has been shown to be not as reactive immunologically as the native hormone[65] (Fig. 16). However, the ectopic PTH probably possesses the same biological activity, since it promotes bone resorption, causes phosphaturia and hypercalcemia, and probably stimulates renal adenyl cyclase.

The presentation of ectopic PTH production differs from PHPT in the following respects: (a) the onset of hypercalcemia is much more sudden and progressive, (b) the degree of hypercalcemia and hypercalciuria is more marked, often exceeding 14 mg% and 600 mg/day, respectively, (c) hypophosphatemia is usually present, (d) serum Cl/P is usually less than 33, whereas it may be greater than this value in the majority of cases with PHPT,[46,49] (e) symptoms of peptic ulceration, skeletal fractures and renal stones are usually absent, a situation probably reflecting the acute course of the disease, and (f) serum alkaline phosphatase activity is more frequently elevated.

Treatment usually consists of anti-tumor therapy and correction of acute hypercalcemia (see Section on Treatment).

Ectopic Prostaglandin (PG) Production

In 1960, Goldhaber discovered hypercalcemia in the mouse with fibrosarcoma.[67] The extract of the tumor tissue was found to cause bone



Plots of log of dilution of serum used in assay system (antiserum GP-1 M) versus corresponding bound-to-free ratio for standard hyperparathyroid serum (A) and for sera from two patients (B and C) with ectopic hyperparathyroidism who had relatively high PTH immunoreactivity with antiserum GP-1 M. To control possible nonspecific effects, sufficient hypoparathyroid serum was added so that all tubes had an equal serum content. Slopes of fitted straight lines for dilutional curves B and C were significantly ($P < 0.001$) less than slope of dilutional curve A ($b = -56.3$, $SE = 3.3$).

Fig. 16

resorption in tissue culture. Subsequently, Tashjian et al. demonstrated production of prostaglandin F_2 (PGE_2) by the mouse fibrosarcoma.[68] Inhibition of PGE_2 synthesis by indomethacin restored serum Ca to normal, commensurate with decreased levels of circulating PGE_2. It is now known that prostaglandin E_1 and E_2 stimulate skeletal adenyl cyclase and cause bone resorption *in vitro*.[69]

The possibility that there might be a parallel to this animal model in man was suggested by Powell et al.[70] They found in tumor extracts of patients with hypercalcemia, bone-resorbing activity in tissue culture, but no immunoassayable PTH.[70] It is now recognized that certain human neoplasias are capable of producing prostaglandins. Prostaglandin-like substance and immunoreactive prostaglandins (E, A and F) have been identified in tumor tissue.[71] Elevated levels of immunoreactive prostaglandins in serum[71] and high renal excretion of the major urinary metabolite of PGE have been demonstrated.[72] Treatment with indomethacin or aspirin has been shown to ameliorate hypercalcemia, commensurate with the decline in serum immunoreactive prostaglandins and urinary prostaglandin metabolite.[71,72] As in the case of ectopic PTH production, it is reasonable to speculate that prostaglandin (probably E) produced by neoplastic tissue is carried via hematogenous circulation to bone, where it stimulates resorption, thereby causing hypercalcemia.

The presentation of ectopic PG production resembles that of ectopic PTH production, with the following exceptions:[72] (a) serum iPTH is suppressed, (b) Serum P is usually normal, and (c) it is invariably caused by solid tumors. The renal excretion of cyclic AMP has not been measured, but is probably depressed. Unlike ectopic PTH production, the hypercalcemia of ectopic PG production is responsive to indomethacin or aspirin.

Osteoclast-Activiting Factor (OAF)

In 1971, Raisz became intrigued with the problem of localized resorption of bone associated with chronic inflammation (such as periodontal disease), while he was on a sabattical leave at the National Institute of Dental Research. He then initiated his classic studies concerned with the delineation of OAF. It was found that lymphocytes, upon stimulation by antigens to which the donor has developed cellular immunity or by nonspecific mitogens (solubilized dental plague or phytohemagglutinin), produce soluble substance which stimulates bone resorption in organ culture.[73] The substance was termed osteoclast-activating factor because the treated bone showed numerous active osteoclasts. The OAF could be distinguished from PTH, PGE_2 and 1,25-DHCC from dose-response curves (in terms of ^{45}Ca release from bone).[74] Moreover, OAF-stimulated bone resorption was inhibited more effectively by cortisol than was PTH stimulation. The chemical identification of OAF has not yet been completed.[75]

The clinical importance of OAF was realized when it was shown that this substance could also be produced by neoplastic cells as part of the cellular immune response to neoplasia.[74] Lymphoid cell lines from patients with myeloma, Burkitt's lymphoma and malignant lymphoma were

shown to elaborate OAF. The supernatant fluid from short-term cultures of bone marrow from patients with multiple myeloma was shown to contain OAF.[76] The OAF produced by these soft tumors may cause hypercalcemia by stimulating osteoclastic bone resorption. Unlike in ectopic PTH or PG production, the effect of OAF is probably confined to bone. It is probably formed in bone upon invasion by tumor, and causes bone destruction locally.

The hypercalcemia from excessive OAF production is resistant to indomethacin, but is probably responsive to adrenal corticosteroids.

Neoplasm with Synthesis of Sterol

It is theoretically possible that hypercalcemia in certain neoplasia may be the consequence of increased synthesis of 1,25-DHCC by the tumor tissue.[77] The vitamin D metabolite may then cause hypercalcemia by promoting skeletal resorption and stimulating intestinal Ca absorption. Although increased synthesis of 1,25-DHCC has not yet been demonstrated in any neoplasm, Gordan et al. reported the production in breast cancer of a certain sterol which stimulated bone resorption.[78] This sterol has not yet been identified chemically. It is noteworthy that the hypercalcemia of breast cancer is fairly responsive to treatment by adrenal corticosteroids,[79] as in vitamin D intoxication.

The frequency of involvement of various humoral mechanisms (e.g. ectopic PTH or PG, OAF, or sterol) in cancer is not known.

Osteolytic Metastasis

When certain neoplasia invade bone, they may cause hypercalcemia by direct destruction of bone without involving humoral substances. Destruction of only 1% of bone over a 12 day period may be sufficient to cause hypercalcemia in a 70-kg man, since it may release from bone into the circulation more than 800 mg Ca each day. As in ectopic PTH production, serum and urinary Ca may be markedly increased. However, serum P is usually normal and both serum iPTH and urinary cyclic AMP are suppressed. As mentioned before, the presence of osteolytic metastasis need not exclude the operation of humoral mechanisms for the hypercalcemia.

The hypercalcemia of osteolytic metastasis is more responsive to adrenocorticosteroids than that of ectopic PTH or PG production.

Sarcoidosis

Hypercalcemia of sarcoidosis is probably vitamin D-dependent.[80,81] It may be provoked by low doses of vitamin D, and ameliorated by adrenal corticosteroids as in vitamin D toxicity. Although hypersensitivity to vitamin D had been previously invoked, recent studies suggest that there may be an increased synthesis of 1,25-DHCC.[82] Hypercalcemia is probably the consequence of either vitamin D-dependent intestinal hyperabsorption

of Ca or excessive skeletal Ca mobilization, or both.

When a low Ca diet and avoidance of sunlight fail to ameliorate the hypercalcemia, steroids (e.g. Prednisone 10 mg qid) may be tried.

Milk-Alkali Syndrome

In 1949, Burnett et al. described hypercalcemia developing following prolonged intake of milk and absorbable alkali.[83] Characteristic features were: hypercalcemia without hypercalciuria or hypophosphatemia, mild metabolic alkalosis, normal serum alkaline phosphatase activity, marked renal insufficiency, and calcinosis. Improvement ensued upon avoidance of milk and alkali.

The primary pathogenetic event is the absorption of large amounts of Ca and alkali. The ensuing alkalosis promotes renal tubular reabsorption of Ca. Hypercalcemia probably develops from the increased Ca absorption and impaired renal Ca excretion. Renal insufficiency further contributes to hypercalcemia by limiting renal Ca excretion. As might be expected, parathyroid function is suppressed.

Dent postulates that patients who develop Milk-Alkali Syndrome are probably those who initially had an intestinal hyperabsorption of Ca.[84] This hypothesis could explain the apparent predilection for the syndrome in a minority of cases exposed to milk and alkali ingestion, and correction of hypercalcemia by limitation of intestinal Ca absorption with cellulose phosphate.

The situation in Milk-Alkali Syndrome contrasts strikingly with that of absorptive hypercalciuria,[37] in which hypercalcemia rarely develops despite intestinal hyperabsorption of Ca. The results suggest that in the absence of enhanced bone mobilization or renal tubular reabsorption of Ca, the increased delivery of Ca from the intestinal tract may be handled adequately by physiologic compensatory mechanisms.

The Milk-Alkali Syndrome has become infrequent with the decreasing popularity of absorbable antacids and with wider usage of non-absorbable alkali.

When withdrawal of alkali and milk is ineffective, cellulose phosphate (5 g tid) or steroids (e.g. Prednisone 10 mg qid) may be considered.

P-Depletion Syndrome

Non-absorbable antacids may also cause hypercalcemia by a different mechanism.

Mild hypercalcemia (up to 11 mg%) and marked hypophosphatemia may ensue from dietary P restriction and ingestion of P-binding antacids.[40,85] Urinary Ca is typically high and urinary P unusually low. Parathyroid

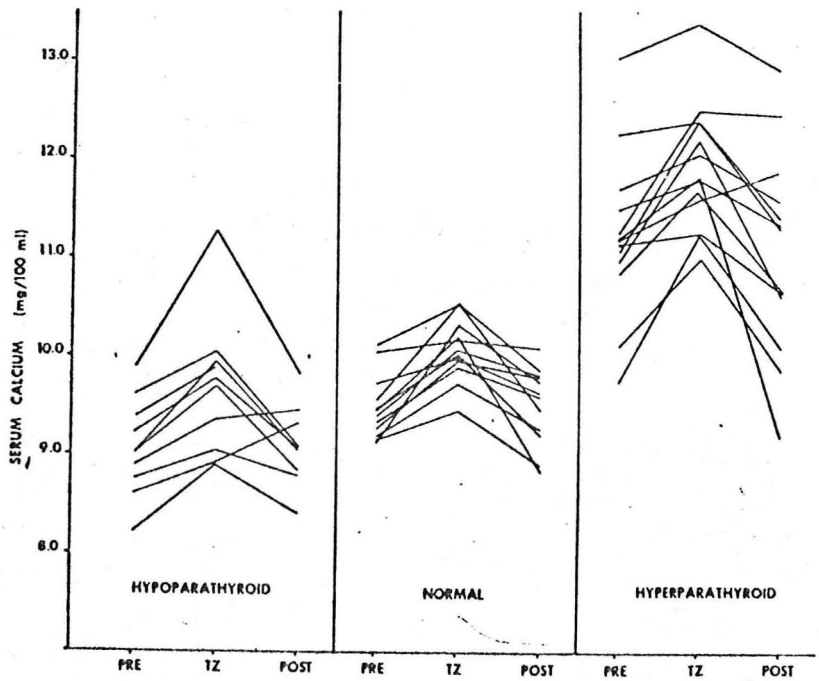
function is suppressed.

Hypercalcemia is partly the consequence of an increased intestinal Ca absorption. Although the synthesis of 1,25-DHCC has been shown to be stimulated in hypophosphatemic experimental animals,[86] the circulating concentration of 1,25-DHCC is not altered by P-deprivation in man.[87] On the other hand, P deprivation increases the available Ca for absorption, by limiting the amount of intraluminal phosphate. Thus, the increased Ca absorption occurring in P deprivation in man is probably the result of an increased available Ca pool, rather than a change in the Ca absorptive mechanism. The enhanced mobilization of Ca from bone, associated with hypophosphatemia,[88] probably contributes to the development of hypercalcemia.

Treatment consists of cessation of antacids or low-P diet, and oral orthophosphates (e.g. Neutra Phos 0.5 g P tid) when necessary.

Thiazide Therapy

Thiazide is unique among diuretics in stimulating renal tubular reabsorption of Ca.[89] Although it was believed to stimulate bone resorption via parathyroid glands,[90] conclusive evidence for this contention is



The levels of total serum calcium during the control period (PRE), hydrochlorothiazide administration (TZ), and the post-treatment period (Post) in normals and patients with hypoparathyroidism and hyperparathyroidism. Each line represents a single subject and connects the mean value of four to nine determinations made during each period.

Fig. 17

lacking. Thiazide effect on intestinal Ca absorption has not been clearly defined. In normal man, the intestinal Ca absorption is not altered or is slightly increased during treatment.

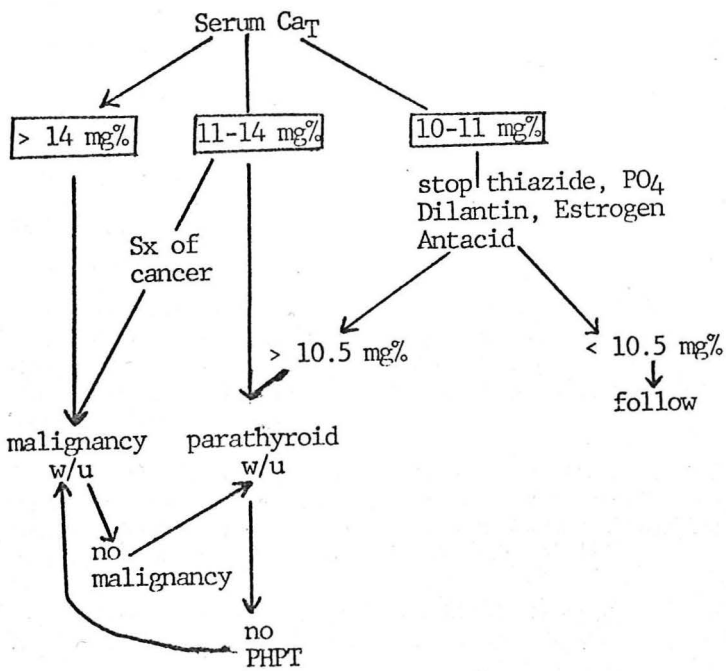
Mild hypercalcemia (up to 10.6 mg%) may ensue during thiazide therapy in normal man (Fig. 17).[91] Part of this rise in serum Ca_T probably reflects the increased protein-bound Ca; the reduction in extracellular fluid volume augments the circulating concentration of proteins and probably causes increased Ca binding. The circulating Ca^{++} is probably also increased slightly from the inhibition of renal Ca loss. The latter mechanism may be predominant in conditions characterized by an excessive skeletal mobilization of Ca,[39] such as PHPT. Under such circumstances, true hypercalcemia, reflected by a rise in plasma Ca^{++}, may be found. The total serum Ca may reach moderately high levels.

Thiazide diuretic should be avoided when significant hypercalcemia (> 11 mg%) develops.

GENERAL DIAGNOSTIC CONSIDERATIONS

In the preceding section, the diagnostic criteria and therapy for specific conditions associated with hypercalcemia were discussed. This section considers general guidelines in the evaluation of hypercalcemia, particularly that due to PHPT or associated with neoplasm.

Fig. 18



The initial evaluation should include repeated determinations of serum Ca_T (Fig. 18).

If hypercalcemia is marked (> 14 mg%), work-up (w/u) for malignancy should be initiated. Skeletal roentgenogram or bone scan should be obtained to exclude osteolytic metastasis. In the absence of osteolytic lesions, a search should be made for the various humoral mechanisms associated with hypercalcemia.

The following classification might be helpful (Fig. 19).

Fig. 19

Differential Diagnosis of Hypercalcemias

	Primary Hyperpara-thyroidism	Ectopic "PTH" Production	Ectopic PGE Production	OAF Production
Renal Stones, Skel Frx, Peptic Ulcer	Frequent	Rare	Rare	Rare
Weight Loss	Rare	Frequent	Frequent	Frequent
Onset	Slow	Rapid	Rapid	Rapid
Localizing Sx of Malignancy	Rare	Frequent	Frequent	Frequent
Carcinoma	Rare	"Solid">"Soft"	"Solid"	"Soft"
Treatment	PTX		Indomethacin ASA	Steroids
Serum Ca	↑	↑↑	↑↑	↑↑
Serum P	↓,N	↓,N	N	N
Serum Cl	N,↑	N	N	N
Urin Ca	↑,N	↑↑	↑↑	↑↑
PTH	↑↑	↑	↓	↓
Urin cAMP	↑	↑	↓	↓

When no malignancy is found, an appropriate parathyroid evaluation for PHPT is indicated. We find the following protocol to be useful[37,38] (Fig. 20), since it provides not only a biochemical measure of parathyroid function, but also an assessment of physiologic derangements which may result from PTH-excess.

If the hypercalcemia is mild-moderate (11-14 mg%), we suggest parathyroid evaluation unless there are symptoms of carcinoma. Malignancy work-up should be instituted if neoplasm is suspected or if parathyroid evaluation does not disclose the presence of PHPT.

When serum Ca is only slightly elevated, it is important to be certain that a true hypercalcemia is present. An estimate of plasma

	Diet	α	BD	SMA20	PTH	1,25-DHCC	Urinary Ca	Urinary P	Urinary cAMP	Urinary Cr
Day 1	LSD	√	√	√			√	√	√	√
2	LSD			√	√	√	√	√	√	√
3	LSD			√			√	√	√	√
4	Fast				√		√		√	√
	Load				√		√		√	√

Abbrev: LSD, liquid synthetic diet; α, fractional Ca absorption; BD, bone density; cAMP, cyclic AMP; Cr, creatinine.

Fig. 20

Ca^{++} should be made; the extent of protein binding of Ca should be estimated. If patients are maintained on thiazide, phosphates, Dilantin, estrogen or antacid, their serum Ca_T should be interpreted appropriately, by a careful consideration of the potential effects of these drugs on Ca_T. Whenever possible, these drug should be withdrawn temporarily and serum Ca_T redetermined. If true hypercalcemia is present, parathyroid evaluation may be undertaken.

GENERAL THERAPEUTIC CONSIDERATIONS

Treatment of Acute Severe Hypercalcemia

Hypercalcemia, when it is acute and severe, may present as a medical emergency. Customary therapy is intravenous saline and furosemide, as recommended by Suki.[92] This regimen does not alter the basic disease process; it lowers serum Ca by promoting renal Ca loss. Thiazide diuretic and phosphates should be avoided. Oral Ca intake should be restricted.

If significant hypercalcemia persists, a more specific therapy may be required. Mithramycin may be very effective in those conditions in which the primary cause for the hypercalcemia is the excessive skeletal resorption.[93-96] At the recommended dosage for the hypercalcemia (25 mg/kg each), it has been met with few side-effects. We would regard mithramycin as the drug of choice for severe hypercalcemia of PHPT and solid neoplasia.

Steroid (e.g. Prednisone 10 mg qid) might be useful in hypercalcemia associated with vitamin D toxicity, sarcoidosis,[80] soft tumors,[97] breast carcinoma,[79] and osteolytic metastasis.

Treatment of Chronic Hypercalcemia

Many patients with hypercalcemia may be relatively stable and alert. The treatment should be directed at correcting the underlying cause for the hypercalcemia. If such treatment is ineffective or cannot be undertaken, a decision must be made regarding the need for the correction of hypercalcemia. The following guidelines might be useful in the treatment of chronic hypercalcemia.

Indomethacin (25 mg tid) or aspirin (600 mg qid) might be considered for solid tumors without osteolytic metastasis. Prednisone (5 tid) might be tried in soft tumors, sarcoidosis, and osteolytic metastasis. Larger doses might be required in breast carcinoma. Ethinyl estradiol (0.1 mg qd) might be considered for postmenopausal women with PHPT. Neutra-Phos (500 mg P tid) might be effective in all forms of hypercalcemia; however, it might elicit soft-tissue calcification.

CONCLUDING REMARKS

A considerable progress has been made toward the definition of hypercalcemia, and delineation of Ca homeostatic mechanism and pathogenetic factors leading to hypercalcemia. The understanding of these concepts should allow construction of a rational mode of therapy for the hypercalcemia.

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