# H Y P O P A R A T H Y R O I D I S M

Medical Grand Rounds
Southwestern Medical School
University of Texas Health Science Center at Dallas

May 18, 1978

Although hypoparathyroidism has long been recognized, the metabolic or hormonal basis for its diverse etiologies is only now beginning to be elucidated. This development has paralleled the recent advances in research concerning parathyroid hormone (PTH), vitamin D and cyclic AMP.

## PATHOGENESIS OF HYPOPARATHYROIDISM-GENERAL CONSIDERATIONS

Hypoparathyroidism may result from defects at any point in the parathyroid gland-end organ axis[1] (Fig. 1). There may be a

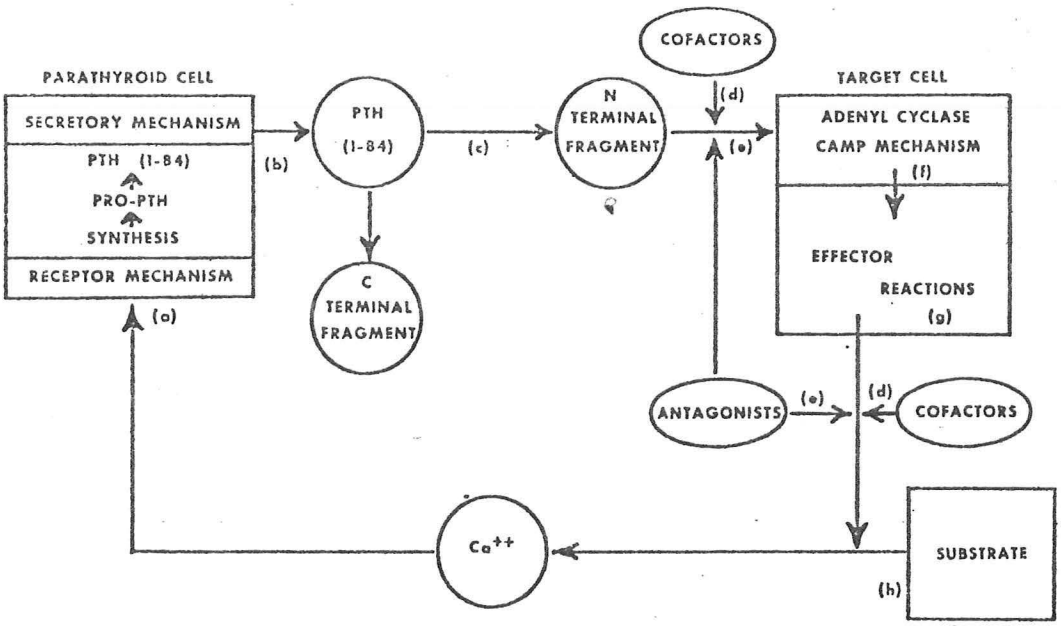



Figure 1

deficient production of PTH, from an impaired secretory response to hypocalcemia or from a reduced glandular mass (a and b in Figure). The circulating form of PTH may be physiologically ineffective, due to impaired production of active PTH fragments (c). Finally, the target tissue may be resistant to the action of PTH, because of a defective synthesis of cyclic AMP, an impaired expression of cyclic AMP (f and g) or an inherent abnormality of the target and tissue (h). The ultimate result, irrespective of mechanism, is a reduced parathyroid hormone action on target organs, principally bone, kidney and gut.

### Requirement of Disturbed Vitamin D Metabolism

Much of the biochemical and metabolic derangements of hypoparathyroidism may be ascribed to reduced parathyroid hormone action. However, it is becoming increasingly clear

that the full expression of hypoparathyroid state requires the concurrent deficiency of 1α,25-dihydroxycholecalciferol (1,25-DHCC), the renal metabolite of vitamin D.[2]

Several reports have already indicated that the circulating concentration of 1,25-DHCC is reduced in hypoparathyroidism (Fig. 2).[3-7] The decreased synthesis of 1,25-DHCC may be explained by the absence of two recognized stimuli for 1α-hydroxylase, - PTH and hypophosphatemia.[8] Moreover, there is some evidence that the synthesis of this vitamin D metabolite may be "primarily" affected in pseudohypoparathyroidism, as will be discussed later.

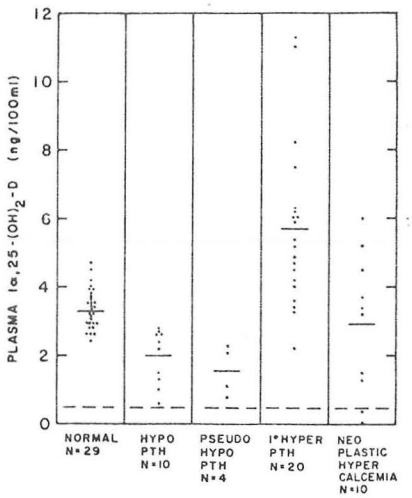



Figure 2

Normal Actions of PTH and 1,25-DHCC (Fig. 3)

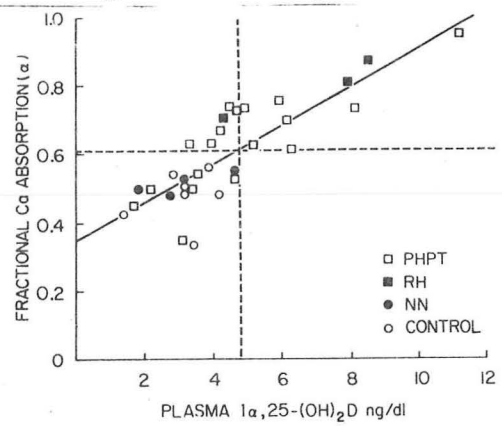
An understanding of the normal physiological action of PTH and 1,25-DHCC on bone, kidney and gut is critical to the delineation of pathogenetic mechanisms in hypoparathyroidism. In bone, PTH stimulates osteoclastic bone resorption and osteocytic calcium transfer.[9] Osteoclastic resorption, probably mediated independently of 1,25-DHCC, causes destruction of mineralized matrix, and is responsible for osteitis fibrosa. Osteocytic calcium transfer

NORMAL ACTIONS OF PTH AND 1,25-DHCC

| | PTH | 1,25-DHCC | PTH + 1,25-DHCC |
|---|---|---|---|
| Osteocytic calcium transfer | — | ↑(high conc.) | ↑ |
| Osteoclastic bone resorption | ↑ | ↑(high conc.) | ↑ |
| Bone mineralization | — | ↑(?) | ? |
| Renal P reabsorption | ↓ | ↑ | ↓ |
| Renal Ca reabsorption | ↑ | ↑ | ↑ |
| Intestinal Ca absorption | — | ↑ | ↑ |
| Skeletal and renal adenyl cyclase (urinary cyclic AMP) | ↑ | — | ↑ |

Figure 3

involves principally mineral phase and allows a rapid mobilization of calcium from bone. This process, apparently requiring the presence of 1,25-DHCC, accounts for the rapid rise in serum calcium following PTH administration. In the kidney, PTH inhibits tubular reabsorption of phosphate and augments net calcium reabsorption, independently of vitamin D metabolites.[10] These actions of PTH on bone and kidney are believed to be mediated via hormone-stimulated adenyl cyclase. In the gut, PTH augments intestinal absorption of calcium indirectly by stimulating the renal synthesis of 1,25-DHCC (Fig. 4);[11] the latter is believed to be responsible for the increased calcium absorption.




Dependence of fractional Ca absorption ($\alpha$) on plasma concentration of $1\alpha,25\text{-}(OH)_2D$ in PHPT and in RH. The horizontal dashed line indicates upper range of normal for $\alpha$ (4) and the vertical dashed line represents the upper limit of normal for plasma $1\alpha,25\text{-}(OH)_2D$. The upper range of normal for $1\alpha,25\text{-}(OH)_2D$ is given by mean+SD for values in control subjects in Tucson, Ariz. The diagonal line represents regression for the combined group of PHPT, RH, NN, and control.

Figure 4

The 1,25-DHCC is also capable of stimulating osteoclastic bone resorption and osteocytic calcium transfer.[9] At high concentrations of the vitamin D metabolite, these effects may be found in the absence of PTH. At more physiologic concentrations, the presence of PTH may be necessary for the osteocytic calcium transfer. The role of 1,25-DHCC on mineralization process (calcium phosphate deposition in organic matrix) is not known. Recent studies suggest that 25-hydroxycholecalciferol or 24,25-dihydroxycholecalciferol, but not 1,25-DHCC, may directly promote bone mineralization.[12] However, 1,25-DHCC may cause mineralization of bone indirectly by altering the circulating concentration of calcium and phosphate, or by "shifting" these ions from areas of resorption to areas of formation. Moreover, 1,25-DHCC may be required for normal bone matrix synthesis. This scheme could explain the development of osteomalacia in 1,25-DHCC deficiency.

In the kidney, 1,25-DHCC (as well as 25-hydroxycholecalciferol) increases renal tubular reabsorption of both calcium and phosphate, independently of PTH.[13] However, these effects probably play a minor role in calcium and phosphate homeostasis.

Sequelae of Reduced PTH Action and 1,25-DHCC Deficiency

(1) Hypocalcemia. Hypocalcemia is invariably found in hypoparathyroidism, and is the result of: (a) reduced PTH-dependent osteoclastic resorption, (b) decreased osteocytic calcium transfer consequent to 1,25-DHCC deficiency and/or reduced PTH action, (c) low renal tubular reabsorption of calcium from reduced PTH action, and (d) impaired intestinal calcium absorption from 1,25-DHCC deficiency.

(2) Hyperphosphatemia ensues primarily from the impaired renal phosphate clearance consequent to reduced PTH action.

(3) Bone Disease. In PTH-deficient or ineffective hypoparathyroidism and in PTH-resistant hypoparathyroidism with total skeletal resistance, bone disease is uncommon. However, osteomalacia may develop if there is a severe 1,25-DHCC deficiency. Defective mineralization of bone with increased osteoid width has been reported in a patient with PTH-deficient (idiopathic) hypoparathyroidism with very low serum concentration of 1,25-DHCC[7] (Fig. 5). Similar finding has also been reported in PTH-resistant hypoparathyroidism (pseudohypoparathyroidism).[5,6,14]

Quantitative microradiography of bone biopsy in patient with idiopathic hypoparathyroidism

| | Patient | Normals (age 15–19) |
|---|---|---|
| Resorption (%) | 3.6 | 5.0 ± 1.7* |
| Formation (%) | 1.3 | 5.0 ± 3.4* |
| Osteoid width ($\mu$) | 41.5 ± 15.3* | 14.8 ± 1.5* |

* $\bar{X}$ ± 1 SD.

Figure 5

Another form of bone disease is osteitis fibrosa, associated with certain forms of PTH-resistant hypoparathyroidism, to be described more fully later. In pseudohypoparathyroidism with osteitis fibrosa, osteoclastic bone resorption is responsive to PTH action, despite resistance to the hormone in the kidney and in osteocytic calcium transfer. Osteitis may develop from increased PTH action alone.[9] When either osteomalacia or osteitis fibrosa is present, serum alkaline phosphatase may be elevated.

(4) Symptomatology of hypoparathyroidism.[15-23] Much of the symptoms common to most forms of hypoparathyroidism may be ascribed to hypocalcemia and hyperphosphatemia. Hypocalcemia is responsible for neuromuscular irritability and frequently causes carpopedal spasm, paresthesias of the face, fingers and toes, and occasionally muscle cramps. Latent tetany may be revealed by Chovstek's sign and Trousseau's sign. However, both signs, particularly the former, may be present in normal persons, and may be absent in patients with hypocalcemia. Hypocalcemia may indirectly cause lenticular opascities, by disturbing cation transport in the lens.[18] A prolonged Q-T

interval may be found in hypocalcemia. However, cardiac disease is uncommon, although congestive heart failure has been reported in severe hypocalcemia, probably consequent to decreased inotropic activity of the heart.[22] Partial insensitivity to digoxin has been reported.[23]

Soft tissue calcification may occur, probably consequent to hyperphosphatemia. When there is a basal ganglion calcification, dysfunction of the extrapyramidal-motor system may be found, such as Parkinsonism and chorea. Parkinsonism of hypoparathyroidism is resistant to L-dopa therapy,[20] but may be responsive to restoration of normal serum calcium and phosphate.

Various ectodermal changes may be found, including dry rough skin and mild trophic changes of fingernails.

There are certain clinical presentations which are specific for the particular form of hypoparathyroidism. They will be discussed later.

Albright's Osteodystrophy

Since the report by Albright et al.[24] of the association between PTH-resistant hypoparathyroidism (pseudohypoparathyroidism) and characteristic somatic features, it has been customary to relegate these features to the PTH-resistant state and to its genetically-related condition of pseudopseudohypoparathyroidism. These somatic features include short stature, round face, short neck, shortening of metacarpals and shortening of metatarsals. However, it is now recognized that this characteristic body habitus may not be found in some cases of PTH-resistant (pseudo-) hypoparathyroidism,[1] and may be present, albeit rarely in PTH-deficient hypoparathyroidism.[25] Thus, Albright's hereditary osteodystrophy is not a prerequisite for the PTH-resistant (pseudo-) hypoparathyroidism, and its presence does not exclude PTH-deficient hypoparathyroidism. It is always present in pseudopseudohypoparathyroidism (to be discussed later).

## CLASSIFICATION OF HYPOPARATHYROIDISM

From the preceding discussion of pathogenetic mechanisms, it is clear that a more "rational" classification of hypoparathyroidism could be formulated on the basis of specific hormonal or metabolic derangements. A simple and useful classification was proposed by Moses et al.[25] according to PTH deficiency, ineffectiveness or resistance (Fig. 6). In a more elaborate categorization, Nusynowitz et al.[1] suggested division into two

Classification of disorders of or related to PTH deficiency or unresponsiveness

| Category | Old terminology | Proposed terminology |
|---|---|---|
| PTH-deficient hypocalcemia | | |
| 1. lack of hormone | Hypoparathyroidism | Hormone-deficient hypoparathyroidism |
| 2. ineffective hormone | Pseudoidiopathic hypoparathyroidism (16) | Hormone-ineffective hypoparathyroidism<br>A. Without skeletal changes<br>B. With Albright's osteodystrophy |
| PTH-resistant hypocalcemia | Pseudohypoparathyroidism | Hormone-resistant hypoparathyroidism<br>A. Without skeletal changes<br>B. With Albright's osteodystrophy |
| Normocalcemia | Pseudopseudohypoparathyroidism | Albright's osteodystrophy |

Hormone-ineffective hypoparathyroidism with Albright's osteodystrophy has not yet been described.

Figure 6

broad groups, hormonopenic (PTH deficiency) or hormonoplethoric (PTH excess). The latter group includes PTH-ineffective and PTH-resistant hypoparathyroidism.

Each cause will now be discussed separately, with special emphasis on various etiologic factors, unique pathogenetic mechanisms and clinical features.

## PTH-DEFICIENT HYPOPARATHYROIDISM

### Unique Pathogenetic Mechanisms

This condition is characterized by a reduced or absent synthesis of PTH; the target tissues are responsive to the action of PTH. Thus, the serum concentration of PTH is low or undetectable,[7] and the basal renal excretion of urinary cyclic AMP is low.[26-28] When challenged by an exogenous PTH, PTH-dependent adenyl cyclase in bone and kidney are stimulated, as shown by marked increase in the renal excretion of cyclic AMP[29] and in phosphate clearance. The circulating concentration of 1,25-DHCC is low[3,7] (as discussed before); the reduced synthesis of this vitamin D metabolite accounts for the subnormal intestinal calcium absorption.

During exogenous PTH challenge, urinary hydroxyproline increases,[30] a finding indicating that PTH dependent osteoclastic remodelling is intact. However, serum calcium also rises,[7] despite reduced initial circulating of 1,25-DHCC. This calcemic response to PTH seems paradoxical, since it is believed to be secondary to 1,25-DHCC-dependent osteocytic calcium transfer. Though unproven, there is probably a rapid synthesis of 1,25-DHCC during PTH administration.

The causes for PTH-deficient hypoparathyroidism are:

1. Postoperative
   a. Thyroid surgery
   b. Radical neck surgery
   c. Parathyroid surgery
2. Idiopathic
   a. Familial
   b. Sporadic (? Autoimmune)
3. Replacement
   a. Infiltration-hemochromatosis
   b. Invasion-metastatic cancer
4. Developmental
   a. Branchial dysembryogenesis-DiGeorge Syndrome
5. Postirradiation-$^{131}$I

Figure 7

Postoperative Hypoparathyroidism

This condition, probably representing the most common form of hypoparathyroidism, results from an inadvertent removal of parathyroid glands during thyroid surgery or from an overly aggressive parathyroid surgery for hyperparathyroidism. The incidence of hypoparathyroidism following thyroid surgery has substantially decreased consequent to improved recognition and surgical technique. Recent reports indicate an incidence of less than 4.5% following thyroidectomy for benign thyroid disease, and somewhat higher incidence following surgery for thyroid cancer of 3-17%, depending on the extent of surgery.[31-33]

The postoperative hypoparathyroidism is much more common following "liberal" approach to parathyroid surgery for primary hyperparathyroidism, where at least two glands are routinely removed, 3 1/2 glands are removed when more than one gland is enlarged, and where biopsy is liberally taken.[34] Symptomatic hypocalcemia requiring treatment may occur in as many as 1/4 of patients. In the "conservative" approach, where only grossly enlarged glands are removed, the incidence of hypoparathyroidism is negligible.

Idiopathic Hypoparathyroidism

This condition is a relatively rare condition, with less than 100 reported cases.[1,35] It results from either absent, or fatty replacement or atrophy, of parathyroid glands.[35] In familial form, it may be inherited as a sex-linked recessive character, autosomal recessive or autosomal dominant with variable penetrance. Sporadic form, occurring at any time in life, may

occur alone or in combination with pernicious anemia, Addison's disease or moniliasis. Hypoadrenalism[36] and moniliasis may also occur in the familial form,[37] though less commonly than in the sporadic form. This association has led to the suggestion that idiopathic hypoparathyroidism is a form of an autoimmune disease.

The association of moniliasis is unique to this form of hypoparathyroidism.

Other Causes of PTH-Deficient Hypoparathyroidism

Rarely, hypoparathyroidism may result from infiltration of parathyroid glands by iron in hemochromatosis[38] or from invasion by malignant metastasis.[39] In DiGeorge Syndrome,[40] there is a congenital absence of parathyroid glands; it is associated with immunologic deficiencies, cardiovascular anomalies and unusual facial features. Though extremely rare, hypoparathyroidism may develop following $^{131}I$ therapy.[41] In contrast, x-radiation of the neck has not been shown to cause parathyroid deficiency.

## PTH-INEFFECTIVE HYPOPARATHYROIDISM
## (Pseudoidiopathic Hypoparathyroidism)

This condition is characterized by an elaboration of PTH, which is biologically inactive; the target tissues are responsive to the action of PTH. One case of this condition has been described.[42] A young man, with hypocalcemia, hyperphosphatemia with normal renal function, was found to have normal or high serum immunoreactive PTH in several different assay systems. Infusion of exogenous PTH elicited normal phosphaturic and cyclic AMP responses. He had no somatic features of Albright's osteodystrophy.

## PTH-RESISTANT HYPOPARATHYROIDISM

Pseudohypoparathyroidism represents the hallmark of PTH resistance and will be discussed in detail. This term will be loosely used here to denote PTH-resistant hypoparathyroidism with or without Albright's osteodystrophy, but exclusive of acquired causes such as hypomagnesemia and chronic renal failure.

This form of hypoparathyroidism is believed to result from resistance of target tissues to the action of PTH. The physiological control of PTH secretion is apparently intact.

Thus, the serum concentration of immunoreactive PTH is high,[43] probably consequent to parathyroid stimulation by hypocalcemia. Normalization of serum calcium has been shown to suppress PTH secretion.[14] The resistance to PTH may be partial or complete, and is represented by a defect in (a) osteocytic calcium transfer, (b) osteoclastic resorption, (c) renal cyclic AMP generation, (d) physiological expression of renal cyclic AMP, and in (e) intestinal calcium absorption. The resistance may be shown from the measurement following exogenous PTH administration of changes in (a) serum calcium, (b) urinary hydroxyproline, (c) urinary cyclic AMP, (d) urinary phosphorus and calcium, and in (e) radiocalcium absorption, respectively (Fig. 8).

PTH RESISTANCE

| | Types (Defect in:) | Methods of Measurement (Blunted response to exogenous PTH with respect to:) | Dependence |
|---|---|---|---|
| 1. | Osteocytic calcium transfer | Increment in serum calcium | 1,25-DHCC |
| 2. | Osteoclastic bone resorption | Increment in urinary hydroxyproline | Skeletal adenyl cyclase |
| 3. | Renal cyclic AMP generation | Increment in urinary cyclic AMP | Renal adenyl cyclase |
| 4. | Renal cyclic AMP expression | Increment in urinary phosphate<br>Decrement in urinary Ca/Na clearance | Calcium |
| 5. | Intestinal calcium absorption | Radiocalcium absorption | 1,25-DHCC |

Figure 8

(1) Dependence of PTH resistance on adenyl cyclase system. Some of above types of PTH resistance may be represented by an inability of PTH to stimulate adenyl cyclase in kidney and bone.

Normally, PTH may bind to specific membrane receptors in kidney and bone and activates adenyl cyclase. The cyclic AMP so-formed in turn binds to specific intracellular receptor proteins which mediate the hormone effects. These effects, reproducible by exogenous dibutyryl cyclic AMP,[44] are represented by hyperphosphaturia, reduced renal Ca/Na clearance, and osteoclastic bone resorption (increased urinary hydroxyproline).

The resistance to PTH, involving inability of PTH to stimulate adenyl cyclase, would be manifested by a blunted increment (upon challenge by exogenous PTH) in urinary cyclic AMP

(Fig. 9),[29] phosphorus and hydroxyproline, and a less prominent

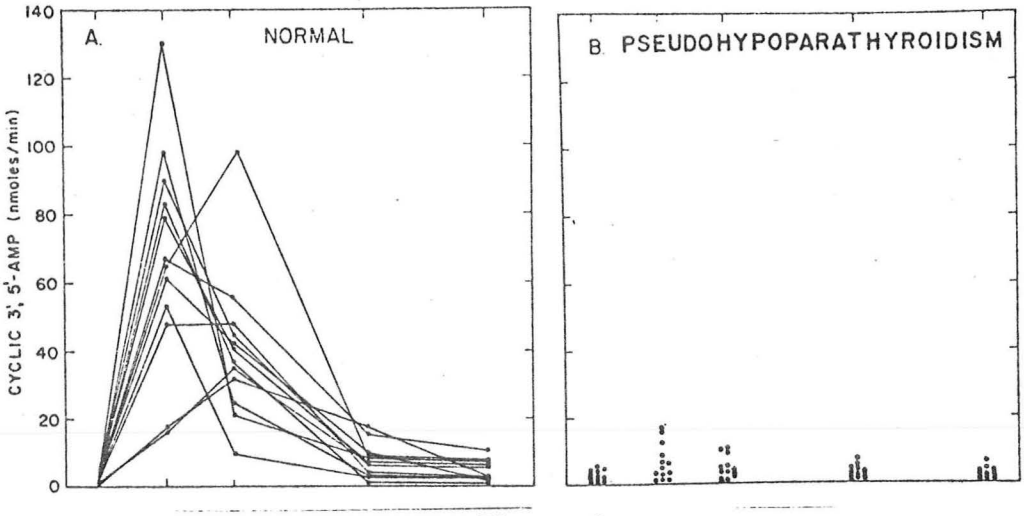


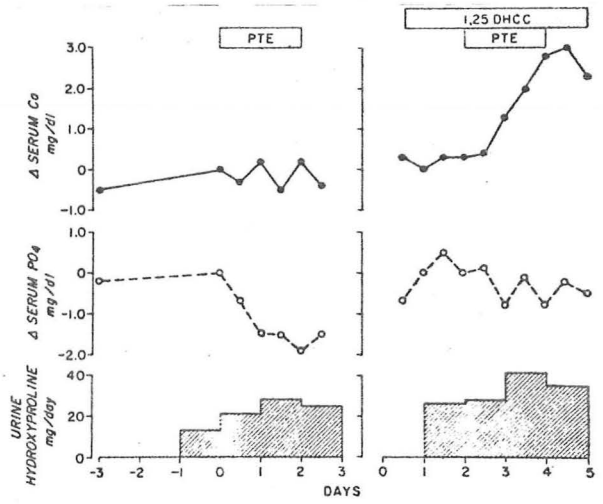

Figure 9

decrement in urinary Ca/Na clearance.[45] The subnormal stimulation of skeletal adenyl cyclase may partly account for the blunted calcemic response by affecting osteoclastic resorption.

(2) Dependence of PTH resistance on reduced 1,25-DHCC synthesis. Since PTH is known to provide one of the stimuli for 1,25-DHCC synthesis,[8] it has been suggested that the reduced serum concentration of 1,25-DHCC in pseudohypoparathyroidism may represent another form of PTH resistance in the kidney.[46] However, there is some evidence that the synthesis of 1,25-DHCC may be primarily deranged in pseudohypoparathyroidism.[6] Thus, the reported serum concentration of 1,25-DHCC is generally lower,[3] and reports of osteomalacia more frequent in pseudohypoparathyroidism than in PTH-deficient hypoparathyroidism (Fig. 2). There is a dichotomy between PTH resistance involving insufficient stimulation of renal adenyl cyclase and that involving subnormal 1,25-DHCC synthesis. Thus, a very low serum concentration of 1,25-DHCC was reported in a patient with pseudohypoparathyroidism with a normal renal responsiveness.[6] Moreover, the defective 1,25-DHCC synthesis apparently is not causally related to hyperphosphatemia, since the low serum concentration of 1,25-DHCC persisted despite restoration of normal serum concentration of phosphate with vitamin D therapy.[6]

The above hypothesis assumes that the subnormal production of 1,25-DHCC in pseudohypoparathyroidism may not be corrected by an exogenous PTH or by a restoration of normal serum phosphate, unlike in PTH-deficient hypoparathyroidism. This presumed inherent

defect in the renal synthesis of 1,25-DHCC could account for the blunted calcemic response to exogenous PTH in pseudohypoparathyroidism. The impaired calcemic response to PTH may be explained by (a) subnormal osteocytic calcium transfer, (b) defective stimulation of osteoclastic bone resorption, and/or by (c) "osteoid-rich" bone, which is resistant to PTH action.[47] The recent study of Metz et al.[6] suggests that the first factor largely accounts for the poor calcemic response to PTH in pseudohypoparathyroidism (Fig. 10). A patient with pseudohypoparathyroidism with normal renal responsiveness had a very low circulating concentration of 1,25-DHCC, and a blunted calcemic response to PTH. When 1,25-DHCC was given exogenously to achieve normal serum concentration of 1,25-DHCC, at a dose and duration insufficient to significantly alter serum calcium concentration, the calcemic response to PTH was restored. The data suggested that the 1,25-DHCC deficiency, and the failure of PTH to correct it, accounted for the blunted calcemic response, probably by affecting osteocytic calcium transfer. This situation in pseudohypoparathyroidism clearly contrasts with that of PTH-deficient (idiopathic hypoparathyroidism),[7] as previously discussed.




**Responses of Serum Calcium (Ca) and Serum Phosphate ($PO_4$) and Urinary Hydroxyproline to Prolonged Administration of Parathyroid Extract (PTE), without and with Pretreatment with 1,25-Dihydroxycholecalciferol (1,25 DHCC).**

**Base-line total serum calcium levels at the start of day zero and one, respectively, were 8.1 and 8.7 mg per deciliter, respectively. Serum phosphate was 5.2 and 4.2 mg per deciliter.**

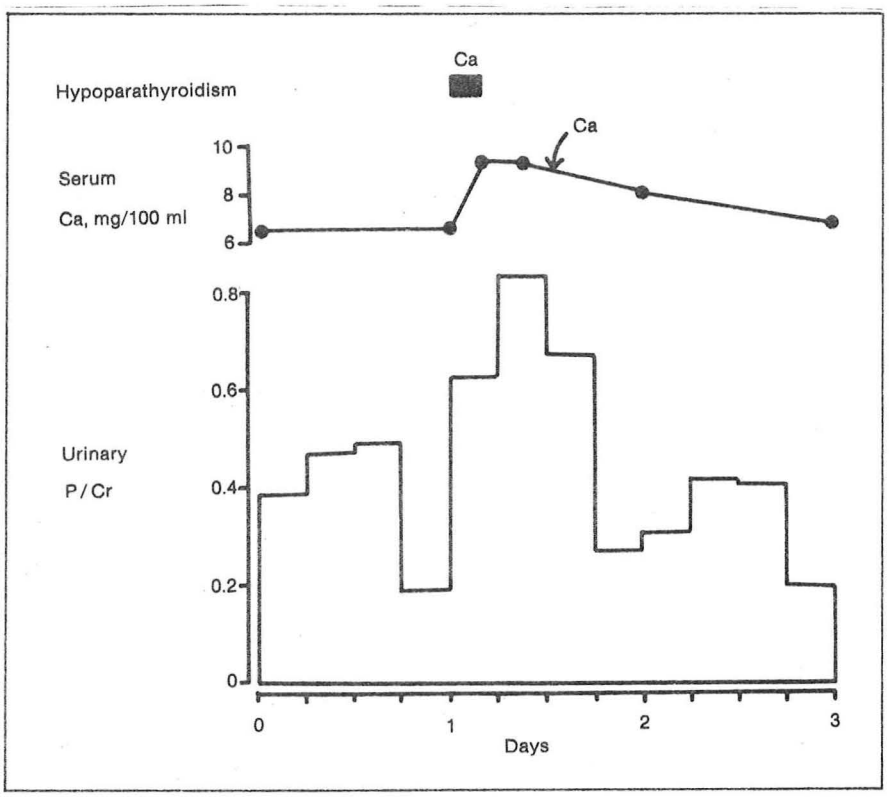
Figure 10

The subnormal production of 1,25-DHCC and the failure of PTH to correct it could also explain the resistance of intestinal calcium transport to PTH in pseudohypoparathyroidism. Though seldom measured, the intestinal calcium absorption is low,[48] and cannot be restored to normal by exogenous PTH in pseudohypoparathyroidism.[14]

(3) Dependence of PTH resistance on vitamin D therapy or calcium infusion. Some types of PTH resistance may be corrected by prior vitamin D or calcium therapy.[45,49,50] Before vitamin D therapy, patients had subnormal calcemic and phosphaturic response to exogenous PTH. When normal serum calcium and phosphorus

concentrations were restored by pharmacologic amounts of vitamin D, they showed normal calcemic and phosphaturic responses. However, the exogenous PTH could not stimulate the renal excretion of cyclic AMP, or the renal tubular reabsorption of Ca.[45]

Though unproven, the restoration of calcemic response by vitamin D therapy could be explained by the production of sufficient amount of 1,25-DHCC to stimulate osteocytic calcium transfer, healing of osteomalacia permitting bone more sensitive to PTH action, or by synthesis of other vitamin D metabolites which might participate in osteocytic calcium transfer. The restoration of phosphaturic response may represent a sequela of increases in serum calcium concentration and in renal filtered load of calcium. In patients with postsurgical hypoparathyroidism, induced hypercalcemia has long been known to augment renal phosphate clearance (Fig. 11).[51,52]




*Effect of calcium infusion in a patient with postoperative hypoparathyroidism. The level of urinary excretion of phosphorus (expressed as mg phosphorus per mg creatinine, P/Cr) throughout the day of calcium infusion was considerably greater than that of the corresponding time periods of the control day.*

Figure 11

There is some evidence, though inconclusive, that restoration of normal serum calcium by calcium infusion could "unmask" the physiologic expression of cyclic AMP, and cause hyperphosphaturia upon PTH challenge, in situation where the cyclic AMP response to PTH is normal but its expression is defective (to be described later under pseudohypoparathyroidism Type II).

The foregoing discussion permits a comparison between pseudohypoparathyroidism and PTH-deficient hypoparathyroidism, with respect to their pathogenetic mechanisms (Fig. 12).

COMPARISON OF PATHOGENETIC MECHANISMS BETWEEN PTH-RESISTANT AND PTH-DEFICIENT HYPOPARATHYROIDISM

| | PTH-Resistant (Complete) | PTH-Deficient (Idiopathic) |
|---|---|---|
| Basal | | |
| Serum Ca | ↓ | ↓ |
| Serum P | ↑ | ↑ |
| Serum 1,25-DHCC | ↓↓ | ↓ |
| Serum PTH | ↑ | ↓ |
| Urinary cyclic AMP | ↓ | ↓ |
| Intestinal Ca absorption | ↓ | ↓ |
| PTH Challenge | | |
| Urinary cyclic AMP | — | ↑ |
| Serum 1,25-DHCC (postulated) | — | ↑ |
| Serum Ca | — | ↑ |
| Urinary P | — | ↑ |
| Serum P | — | ↓ |
| Urinary Ca/Na clearance | — | ↓ |
| Intestinal Ca absorption | — | ↑ |
| PTH Challenge post Vit D Therapy | | |
| Urinary cyclic AMP | — | ↑ |
| Serum 1,25-DHCC | ↑(?) | ↑ |
| Serum Ca | ↑ | ↑ |
| Urinary P | ↑ | ↑ |
| Serum P | ↓ | ↓ |
| Urinary Ca/Na clearance | — | ↓ |
| Intestinal Ca absorption | ↑ | ↑ |

Figure 12

(4) Other unique features of pseudohypoparathyroidism. Hypocalcemia is not the consequence of excessive secretion of calcitonin, since the removal of the endogenous source of

calcitonin by thyroidectomy does not correct the hypocalcemia.[43,53] Serum concentration of 25-hydroxycholecalciferol is normal.[6] The subnormal calcemic response to PTH therefore cannot be attributed to the deficiency of this vitamin D metabolite. The resistance to PTH could also be demonstrated with exogenous 1-34 PTH peptide (biologically active).[54] Thus, it is unlikely that the resistance is caused by a defect in PTH metabolism. A deficient production of thyrotropin[30] or prolactin[55] has been reported in some patients with pseudohypoparathyroidism. The significance of these findings is uncertain.[56] Even though prolactin is believed to be a "secretogogue" of 1,25-DHCC in experimental animals,[57] it remains a pure speculation to implicate a causal relationship between prolactin deficiency and reduced synthesis of 1,25-DHCC.

Mental retardation and Albright's osteodytrophy may be present. Although they may be absent in some patients, they are more frequently associated in pseudohypoparathyroidism, than in PTH-deficient or PTH-ineffective hypoparathyroidism.

Classification of PTH-Resistant Hypoparathyroidism

Various forms of PTH-resistant hypoparathyroidism may be classified on the basis of specific types of PTH resistance discussed previously. The resistance may be complete or partial. If the defective synthesis of 1,25-DHCC is ubiquitous, as may be assumed, all forms of PTH-resistant hypoparathyroidism will present with at least two types of PTH resistance,- an impaired calcemic response and a subnormal increment in intestinal calcium absorption.

(1) Pseudohypoparathyroidism Type I (skeletal and renal resistance to PTH). Exogenous PTH causes subnormal increments in serum Ca, and in urinary cyclic AMP, phosphate and hydroxyproline. Serum alkaline phosphatase may be normal.

(2) Pseudohypoparathyroidism with osteitis fibrosa (renal resistance and skeletal responsiveness). A total or partial skeletal responsiveness causes osteitis fibrosa by permitting PTH-dependent stimulation of osteoclastic resorption. Serum alkaline phosphatase may be elevated.

(3) Pseudohypoparathyroidism Type II (abnormal expression of renal cyclic AMP). Drezner et al.[58] described a patient with hypocalcemia, who had high basal values for serum PTH and urinary cyclic AMP. Exogenous PTH caused a marked rise in urinary cyclic AMP, without provoking a phosphaturic or a calcemic response. In another patient with this condition, Rodriguez et al.[59] was able to restore the phosphaturic response to PTH by calcium infusion.

Calcium administration alone was unable to alter either cyclic AMP or phosphate excretion.

(4) Pseudohypoparathyroidism with skeletal resistance and renal responsiveness.[6] Serum alkaline phosphatase activity was normal. Exogenous PTH elicited a normal response with respect to cyclic AMP and phosphate excretion. However, serum 1,25-DHCC was very low, and caused a blunted calcemic response to PTH.

(5) Pseudopseudohypoparathyroidism.[60-62] This condition may represent an incompletely expressed form of genetically determined abnormality of which pseudohypoparathyroidism is the complete clinical syndrome. Pseudopseudohypoparathyroidism is often found in near relatives of pseudohypoparathyroidism. The same patients may express features of both pseudopseudo- or pseudohypoparathyroidism during the course of their disease.[60] Pseudopseudohypoparathyroidism is always associated with Albright's osteodystrophy.

## OTHER CAUSES OF PTH-RESISTANT HYPOPARATHYROIDISM

### Hypomagnesemia

Hypocalcemia is a frequent complication of hypomagnesemia. Three causes have been implicated: an impaired PTH responsiveness,[63] a subnormal PTH secretion,[64] and a defective Ca-Mg exchange in bone.[65,66] The last cause, occurring independently of PTH, probably coexists with either one of the other causes of hypocalcemia of Mg deficiency. The first cause represents a form of PTH-deficient hypoparathyroidism.

In hypomagnesemia of steatorrhea or chronic alcoholism, hypocalcemia may result from PTH resistance. The exogenous PTH has been shown to elicit a subnormal calcemic response, a blunted osteoclastic bone resorption (reduced increment in urinary hydroxyproline) and in some cases an impaired phosphaturic response. The correction of hypomagnesemia has been shown to restore the normal PTH responsiveness. The exact mechanism by which hypomagnesemia leads to PTH resistance is not known.

### Chronic Renal Failure

Renal osteodystrophy resembles in many respects pseudohypoparathyroidism with osteitis fibrosa.[15,47] Similarities include: hypocalcemia, hyperphosphatemia, high serum alkaline phosphatase activity, parathyroid hyperplasia, high serum PTH, reduced intestinal calcium absorption, and bone biopsy evidence of osteomalacia and osteitis fibrosa. In chronic renal failure, the serum concentration of 1,25-DHCC may also be reduced,[3] from low renal parenchymal mass. This low serum 1,25-DHCC may be responsible for the PTH resistance.

Thus, exogenous PTH elicits a subnormal calcemic response,[67] a finding suggesting a defect in osteocytic calcium transfer. There is probably a resistance to PTH with respect to intestinal calcium transport, since calcium absorption is reduced despite high circulating concentration of PTH. However, the osteoclastic bone resorption is responsive to PTH since osteitis fibrosa develops.

## TREATMENT OF HYPOPARATHYROIDISM

### Conservative Management

Since most of the symptoms of hypoparathyroidism are results of hypocalcemia and hyperphosphatemia, the initial aim of therapy is the restoration of normal circulating concentration of calcium and phosphate. The following regimens serve as useful adjuncts to therapy with vitamin D or its metabolites.

(1) Oral calcium supplementation. Directed at increasing the amount of absorbed calcium, oral calcium alone is rarely sufficient to restore normocalcemia. Used in conjunction with vitamin D or its metabolites, usual dose is approximately 1-1.5 g calcium/day in divided doses. Commercial preparations include: OsCal, 250 mg Ca/tablet; calcium lactate, 84 mg Ca/600 mg tablet; calcium gluconate, 89 mg Ca/1 g tablet; NeoCalglucon, 89 mg Ca/4 ml. Milk is not desirable as a source of dietary calcium because of its high phosphate content.

(2) Phosphate-binding antacids. Again used in conjunction with vitamin D or its metabolites, P-binding antacids may increase intestinal calcium absorption, by "removing" phosphate which may normally complex calcium, and thus making more calcium available for absorption. Moreover, by reducing the circulating concentration of phosphate, these antacids may stimulate the renal synthesis of 1,25-DHCC,[8] at least in PTH-deficient hypoparathyroidism; in so doing, intestinal calcium absorption may be promoted. Whether the restoration of normal serum phosphate by antacids can directly ameliorate the hypocalcemia through operation of physicochemical solubility considerations is not known. Commerical preparations include Amphojel or Gelusil, 1 oz with each meal.

(3) Chlorthalidone with dietary sodium restriction. Porter et al.[68] have recently shown that chlorthalidone, a thiazide-like sulfonamide diuretic, used in conjunction with a low-sodium diet (< 100 meq/day), may permit a maintenance of normal serum calcium concentration, without the use of vitamin D, in certain patients with PTH-deficient or PTH-resistant (pseudo-) hypoparathyroidism. The rise in serum calcium involved both total and ionized fraction. Urinary calcium decreased by approximately 100 mg/day; however, this decrease was considered to be insufficient to account for

the rise in serum calcium (of 1.1 mg/dl) alone. Thus, they suggested that chlorthalidone and low sodium diet may augment the intestinal calcium absorption. The exact mechanisms need to be elucidated. It should be emphasized that most of these patients who responded to above therapy probably did not have a severe hypoparathyroidism, since the mean serum concentration of calcium prior to treatment was 8.2 mg/dl.

Unlike chlorthalidone or thiazide, furosemide may augment renal calcium excretion and lower serum calcium in hypoparathyroidism.[69] Furosemide should be avoided.

(4) Ammonium chloride therapy.[70] Certain patients with hypoparathyroidism may manifest mild metabolic alkalosis (increased arterial pH and high arterial $pCO_2$). In one such patient, Barzel[70] has shown that ammonium chloride therapy may restore normal serum calcium and phosphate concentrations. This form of therapy should not be undertaken without a careful consideration of long-term effects, particularly on bone.

(5) Acetozolamide.[71] A recent report suggests that acetozolamide may augment serum calcium concentration and reduce serum phosphate in pseudohypoparathyroidism with renal resistance to PTH. It is presumed that this action is mediated by effects on bone.

Vitamin D Therapy

Commercially available preparations are dihydrotachysterol and vitamin $D_2$. Customary dosages are 50,000-100,000 units (1.25-2.5 mg)/day for vitamin $D_2$ and 0.2-0.6 mg/day for dihydrotachysterol. Because of a presumed impairment in the synthesis of 1,25-DHCC in hypoparathyroidism, the treatment with these compounds probably does not substantially increase the circulating concentration of 1,25-DHCC. The biological activity following treatment probably results from the action of 25-hydroxycholecalciferol or of 25-hydroxydihydrotachysterol (formed by hepatic 25-hydroxylation).

The treatment with dihydrotachysterol or vitamin $D_2$ augments the intestinal calcium absorption. Whether these compounds promote calcium mobilization from bone is not known, although such skeletal effect must be present in vitamin D toxicity. They may cause healing of osteomalacia and osteitis fibrosa.

These compounds have prolonged onset and duration of action (1-2 weeks for dihydrotachysterol and 2-4 weeks for vitamin $D_2$),

probably owing to tissue storage or lag period for conversion to active metabolites. Another major disadvantage of treatment with these compounds is the unpredictable development of vitamin D toxicity. There is a wide overlap between the maintenance dose and the dose which produces vitamin D intoxication. Toxicity may develop suddenly after years of adequate maintenance, without a change in dosage.

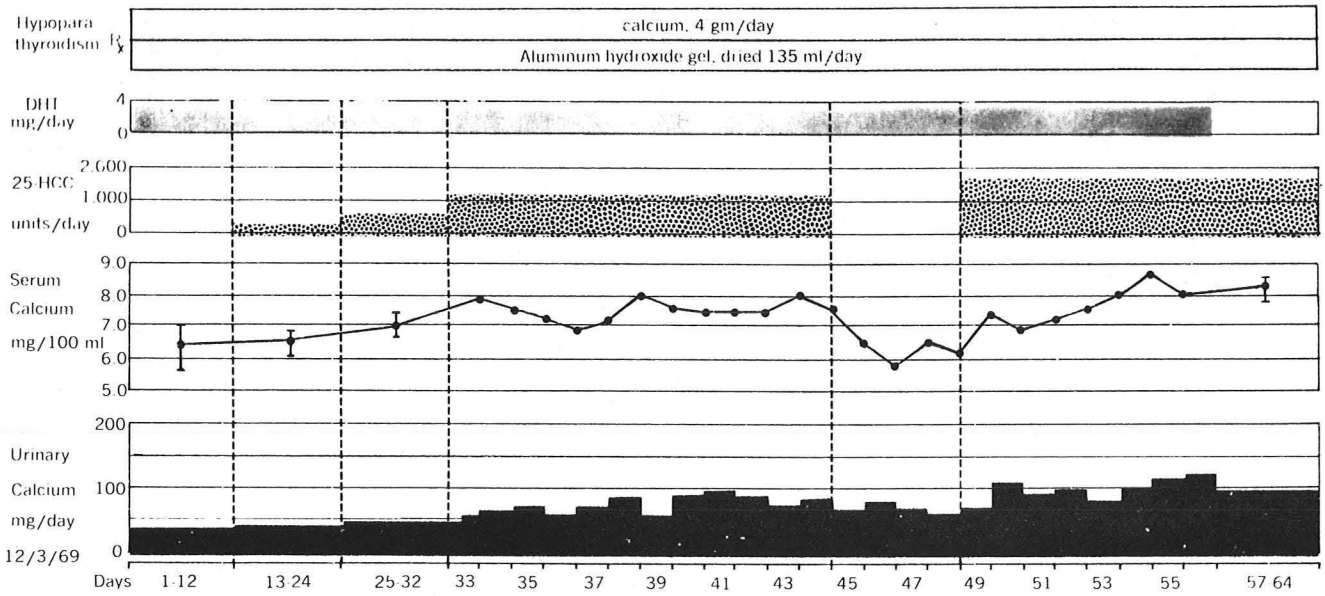
Our practice is to provide routinely calcium supplements and antacids (e.g. OsCal 1 tab qid and Amphojel or Maalox 1 oz tid or qid) and give a minimum amount of dihydrotachysterol (usually 0.2 mg/day) to achieve normal serum concentration. The change in dosage of dihydrotachysterol is made no more often than every 2-3 weeks. The patients should be followed at least every 6 months, even if they are stable. Phenobarbital, diphenylhydantoin, and furosemide should be avoided. Adequate treatment should be provided for concurrent hypomagnesemia or hypothyroidism.[30]

Vitamin D Metabolites

Active metabolites of vitamin D,- 25-hydroxycholecalciferol[72] and 1,25-DHCC,[73,74] may eventually prove to be more useful than the currently available preparations in the management of hypoparathyroidism. Advantages of these investigational agents are: (a) effectiveness in cases who are resistant to the action of dihydrotachysterol or vitamin D, (b) shorter onset of action (1 day for 1,25-DHCC and < 1 week for 25-hydroxycholecalciferol, and (c) lower dose required (1-2 ug/day for 1,25-DHCC and 20-50 ug/day for 25-hydroxycholecalciferol).

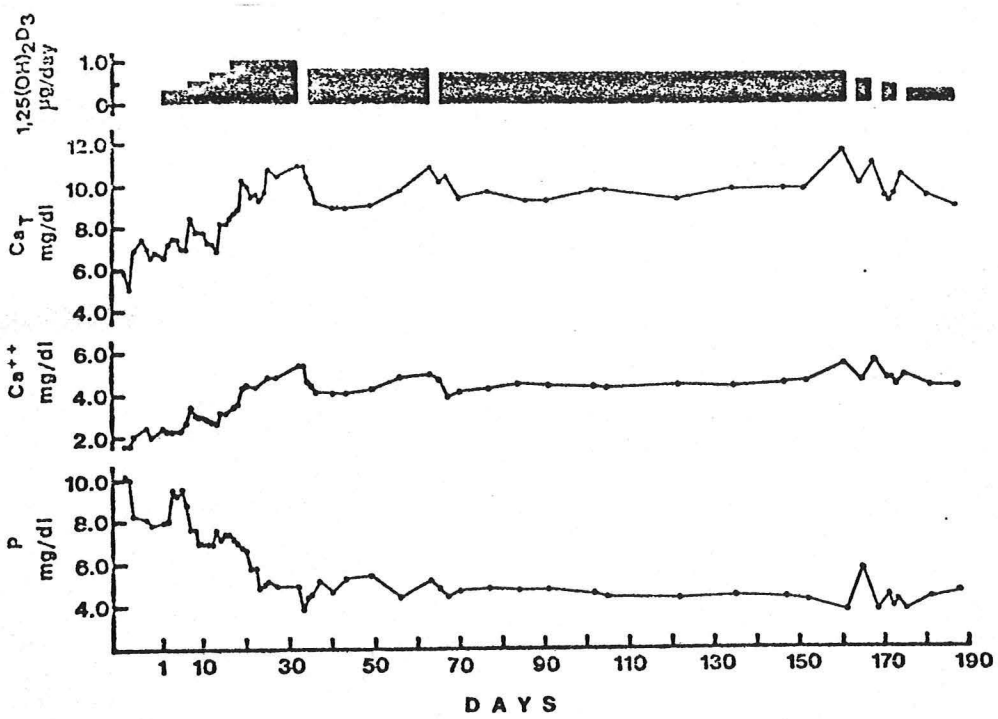
Certain patients with hypoparathyroidism may have a marked resistance to treatment with vitamin D (1 million units or 25 mg/day) or dihydrotachysterol (4 mg/day),[72] for poorly defined reasons. In such a patient, the treatment with 25-hydroxycholecalciferol has been shown to be effective (Fig. 13). 25-hydroxycholecalciferol may be particularly useful in the treatment of renal osteodystrophy.[12]

In most cases of hypoparathyroidism, 1,25-DHCC is probably superior to 25-hydroxycholecalciferol (Fig. 14). A lower dose is needed and the onset of action is faster.[73] 1,25-DHCC provides a potent stimulus to intestinal calcium absorption. It may restore the normal calcemic response to PTH by permitting osteocytic calcium transfer in patients with PTH-resistant (pseudo-) hypoparathyroidism. If defective synthesis of 1,25-DHCC is pathogenetically important in hypoparathyroidism as has been postulated, 1,25-DHCC therapy would seem logical physiologically. A long-term satisfactory control of hypoparathyroidism has been reported.[73,74] Unfortunately, resistance to this drug




*Effect of 25-HCC in patient 1 (first course) on serum and urinary calcium levels. During first 32 days of study, serum calcium concentration presented as mean ± range, and urinary calcium excretion as mean of each period.*

Figure 13




Case 3: The effects of $1,25(OH)_2D_3$ on serum levels of total calcium, ionized calcium and inorganic phosphate. The total daily dose of $1,25(OH)_2D_3$, given orally, is indicated at the top of the figure.

Figure 14

has been reported in a patient with PTH-deficient (idiopathic) hypoparathyroidism.[75]

## CONCLUSION

Recent advances in the understanding of metabolism and physiological action of PTH and vitamin D have permitted an elucidation of certain aspects of pathogenetic mechanisms, and provided the basis for improved classification and a more rational approach to management of hypoparathyroidism. Central to pathogenesis and categorization is the recognition that hypoparathyroidism may result from a PTH deficiency, ineffectiveness or resistance, with a resultant aberration in adenyl cyclase activity in target tissues. Also critical is the subnormal production of 1,25-DHCC occurring primarily or as a secondary process. This reduced synthesis of the vitamin D metabolite may influence calcium and skeletal metabolism by a direct action or via a modification of PTH response. The anticipated availability of 1,25-DHCC in the near future promises to provide an effective and physiologically meaningful mode of therapy for hypoparathyroidism.

## REFERENCES


1. Nusynowitz, M.L., B. Frame, and F.O. Kolb. 1976. The spectrum of the hypoparathyroid state: a classification based on physiological principles. Medicine 55:105-119.
2. Holick, M.D. and H.F. DeLuca. 1973. The role of vitamin D metabolites in bone resorption. Calc. Tiss. Res. 12:295-301.
3. Haussler, M.R., D.J. Baylink, M.R. Hughes, P.F. Brumbaugh, J.E. Wergedal, F.H. Shen, R.L. Nielsen, S.J. Counts, K.M. Bursac, and T.A. McCain. 1976. The assay of 1$\alpha$,25-dihydroxy vitamin $D_3$: physiologic and pathologic modulation of circulating hormone levels. Clin. Endocrinol. 5:151s-165s.
4. Rosen, J.F., A.R. Fleischman, L. Finberg, J. Eisman, and H.F. DeLuca. 1977. 1,25-dihydroxycholecalciferol: Its use in the long-term management of idiopathic hypoparathyroidism in children. J. Clin. Endocrinol. Metab. 45:457-468.
5. Drezner, M.K., F.A. Neelon, M. Haussler, H.T. McPherson, and H. E. Lebovitz. 1976. 1,25-Dihydroxycholecalciferol deficiency: the probable cause of hypocalcemia and metabolic bone disease in pseudohypoparathyroidism. J. Clin. Endocrinol. Metab. 42:621-628.
6. Metz, S.A., D.J. Baylink, M.R. Hughes, M.R. Haussler, and R.P. Robertson. 1977. Selective deficiency of 1,25-dihydroxycholecalciferol. A cause of isolated skeletal resistance to parathyroid hormone. New Engl. J. Med. 297:1084-1090.
7. Drezner, M.K., F.A. Neelon, J. Jowsey, and H.E. Lebovitz. 1977. Hypoparathyroidism: A possible cause of osteomalacia. J. Clin. Endocrinol. Metab. 45:114-122.
8. Hughes, M.R., P.F. Brumbaugh, M.R. Haussler, J.E. Wergedal, and D.J. Baylink. 1975. Regulation of serum 1$\alpha$,25-dihydroxyvitamin $D_3$ by calcium and phosphate in the rat. Science 190:578-580.
9. Parfitt, A.M. 1976. Progress in endocrinology and metabolism: The actions of parathyroid hormone on bone: relation to bone modelling and turnover, calcium homeostasis, and metabolic bone diseases. Part II of IV Parts: PTH and bone cells: bone turnover and plasma calcium regulation. Metabolism 25:909-955.
10. Czekalski, S., N. Loreau, F. Paillard, R. Ardaillou, J.-P., and Mallet, E. 1974. Effect of bovine parathyroid hormone 1-34 fragment on renal production and excretion of adenosine 3',5'-monophosphate in man. Europ. J. Clin. Invest. 4:85.
11. Kaplan, R.A., M.R. Haussler, L.J. Deftos, H. Bone, and C.Y.C. Pak. 1977. The role of 1$\alpha$,25-dihydroxy vitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J. Clin. Invest. 59:756-760.
12. Bordier, P., H. Rasmussen, P. Marie, L. Miravet, J. Gueris, and A. Ryckwaert. Vitamin D metabolites and bone mineralization in man. J. Clin. Endocrinol. Metab. 46:284-294.

13. Puschett, J.B., P.C. Fernandez, I.T. Boyle, R.W. Gray, J.L. Omdahl, and H.F. DeLuca. 1972. The acute renal tubular effects of 1,25-dihydroxycholecalciferol. P.S.E.B.M. 141: 379-384.
14. Birkenhager, J.C., H.F. Seldenrath, W.H.L. Hackeng, A.P.M. Schellekens, A.L.J. VanderVeer, and F. Roelfsema. 1973. Calcium and phosphorus metabolism, parathyroid hormone, calcitonin and bone histology in pseudohypoparathyroidism. Europ. J. Clin. Invest. 3:37-34.
15. Schneider, A.B. and L.M. Sherwood. 1975. Pathogenesis and management of hypoparathyroidism and other hypocalcemic disorders. Metabolism 24:871-898.
16. Dimich, A., P.B. Bedrossian, and S. Wallach. 1967. Hypoparathyroidism. Clinical observations in 34 patients. Arch. Int. Med. 120:449-458.
17. Fourman, P., K. Rawnsley, R.H. Davis, K.H. Jones, and D.B. Morgan. 1967. Effect of calcium on mental symptoms in partial parathyroid insufficiency. Lancet 2:914-915.
18. Ireland, A.W., J.W. Hornbrook, F.C. Neale, and S. Posen. 1968. The crystalline lens in chronic surgical hypoparathyroidism. Arch. Int. Med. 122:408-411.
19. Bajandas, F.J. and J.L. Smith. 1976. Optic neuritis in hypoparathyroidism. Neurology 26:451-454.
20. Klawans, H.L., M. Lupton, and L. Simon. 1976. Calcification of the basal ganglia as a cause of levodopa-resistant parkinsonism. Neurology 26:221-225.
21. J.E. Adams and M. Davies. 1977. Paravertebral and peripheral ligamentous ossification; an unusual association of hypoparathyroidism. Postgraduate Med. J. 53:167-172.
22. Falks, J.M., C.A. Bush, M. Tzagournis, and F.B. Thomas. 1976. Congestive heart failure complicating the hungry bone syndrome. Amer. J. Med. Sci. 271:85-89.
23. Chopra, D., P. Janson, and C.T. Sawin. 1977. Insensitivity to digoxin associated with hypocalcemia. New Engl. J. Med. 296:917-918.
24. Albright, F., C.H. Burnett, P.H. Smith, and W. Parson. 1942. Pseudohypoparathyroidism - an example of "Seabright-Bantam Syndrome". Endocrinology 30:922.
25. Moses, A.M., K.J. Rao, R. Coulson, and M. Miller. 1974. Parathyroid hormone deficiency with Albright's hereditary osteodystrophy. J. Clin. Endocrinol. Metab. 39:496-500.
26. Murad, F. and C.Y.C. Pak. 1972. Urinary excretion of adenosine 3',5'-monophosphate and guanosine 3',5'-monophosphate. New Engl. J. Med. 286:1382-1387.
27. Drezner, M.K., F.A. Neelon, H.B. Curtis, and H.E. Lebovitz. 1976. Renal cyclic adenosine monophosphate: An accurate index of parathyroid function. Metabolism 25:1103-1112.
28. Broadus, A.E., J.E. Mahaffey, F.C. Bartter, and R.M. Neer. 1977. Nephrogenous cyclic adenosine monophosphate as a parathyroid function test. J. Clin. Invest. 60:771-783.

29. Chase, L.R., G.L. Melson, and G.D. Aurbach. 1969. Pseudohypoparathyroidism: defective excretion of 3',5'-AMP in response to parathyroid hormone. J. Clin. Invest. 48: 1832-1844.
30. Zisman, E., M. Lotz, and M.E. Jenkins. 1969. Studies in pseudohypoparathyroidism. Am. J. Med. 46:464.
31. Hans, S.S. and P.T. Lee. 1976. Post-thyroidectomy hypoparathyroidism. Am. Surgeon 2:930-933.
32. Andersson, A., L. Bergdahl, and L. Boquist. 1977. Thyroid carcinoma in children. Am. Surgeon 1:159-163.
33. Perzik, S.L. 1976. The place of total thyroidectomy in the management of 909 patients with thyroid disease. Am. J. Surg. 132:480-483.
34. Edis, A.J., O.H. Beahrs, J.A. VanHeerden, and O.E. Akwari. 1977. "Conservative" versus "liberal" approach to parathyroid neck exploration. Surgery 82:466-473.
35. Bronsky, D., D.S. Kushner, A. Dublin, and I. Snapper. 1958. Idiopathic hypoparathyroidism and pseudohypoparathyroidism: case reports and review of the literature. Medicine 37:317.
36. Hooper, M.J., J.N. Carter, and J.N. Stiel. 1973. Idiopathic hypoparathyroidism and idiopathic hypoadrenalism occurring separately in two siblings. Med. J. Aust. 1:990-993.
37. Pisanty, S. and A. Garfunkel. 1977. Familial hypoparathyroidism with candidiasis and mental retardation. Oral Surg. 44:374-383.
38. Sherman, L.A., A. Pfefferbaum, and E.B. Brown, Jr. 1970. Hypoparathyroidism in a patient with longstanding iron storage disease. Ann. Int. Med. 73:259-261.
39. Horwitz, C.A., L.W.P. Myers, and F.W. Foote. 1972. Secondary malignant tumors of parathyroid glands: report of two cases with associated hypoparathyroidism. Am. J. Med. 52:797.
40. DiGeorge, A.M. 1968. Congenital absence of the thymus and its immunologic consequences: concurrence with congenital hypoparathyroidism. Birth Defects 4:116.
41. Townsend, J.D. 1961. Hypoparathyroidism following radioactive iodine therapy for intractable angina pectoris. Ann. Intern. Med. 55:662.
42. Nusynowitz, M.L. and M.H. Klein. 1973. Pseudoidiopathic hypoparathyroidism. Hypoparathyroidism with ineffective parathyroid hormone. Am. J. Med. 55:677-686.
43. Lee, J.B., A.H. Tashjian Jr., J.M. Streeto, and A.G. Frantz. 1968. Familial pseudohypoparathyroidism. Role of parathyroid hormone and thyrocalcitonin. New Engl. J. Med. 279:1179-1184.
44. Bell, N.H., S. Avery, T. Sinha, C.M. Clark, Jr., D.O. Allen, and C. Johnston, Jr. 1972. Effects of dibutyryl cyclic adenosine 3'5'-monophosphate and parathyroid extract on calcium and phosphorus metabolism in hypoparathyroidism and pseudohypoparathyroidism. J. Clin. Invest. 51:816-823.

45. Moses, A.M., N. Breslau, and R. Coulson. Renal responses to PTH in patients with hormone-resistant (pseudo) hypoparathyroidism.
46. Rasmussen, H. and P. Bordier. 1974. The physiological and cellular basis of metabolic bone disease. Williams and Wilkins, Baltimore, pp. 234-249.
47. Frame, B. and A.M. Parfitt. 1973. The syndromes of parathyroid hormone resistance. Clinical Aspects of Metabolic Bone Disease. Frame, B., A.M. Parfitt, and A. Duncan, eds. Excerpta Medica, Amsterdam, p. 454.
48. Pak, C.Y.C., H.F. DeLuca, J.M. ChavezdelosRios, T. Suda, B. Ruskin, and C. Delea. 1970. Treatment of vitamin D resistant hypoparathyroidism with 25-hydroxycholecalciferol. Arch. Int. Med. 126:239-247.
49. Stogmann, W. and J.A. Fischer. 1975. Pseudohypoparathyroidism. Disappearance of the resistance to parathyroid extract during treatment with vitamin D. Am. J. Med. 59: 140-144.
50. Suh, S.M., D. Fraser, and S.W. Kooh. 1970. Pseudohypoparathyroidism: Responsiveness to parathyroid extract induced by vitamin $D_2$ therapy. J. Clin. Endocrinol. 30:609-614.
51. Pak, C.Y.C., D. East, L. Sanzenbacher, B.S. Ruskin, and J. Cox. 1972. A simple and reliable test for the diagnosis of hyperparathyroidism. Arch. Int. Med. 129:48-55.
52. Eisenberg, E. 1965. Effect of serum calcium level and parathyroid extract on phosphate and calcium excretion in hypoparathyroid patients. J. Clin. Invest. 44:942.
53. Suh, S.M., S.W. Kooh, A.M. Chan, D. Fraser, and A.H. Tashjian, Jr. 1969. Pseudohypoparathyroidism: No improvement following total thyroidectomy. J. Clin. Endocrinol. 29:429-439.
54. Neer, R.M., G.W. Tregear, and J.T. Potts, Jr. 1977. Renal effects of native parathyroid hormone and synthetic biologically active fragments in pseudohypoparathyroidism and hypoparathyroidism. J. Clin. Endocrinol. Metab. 38:420-423.
55. Spanos, E., K.W. Colston, I.M.S. Evans, L.S. Galante, S.J. Macauley, and I. Macintyre. 1976. Effect of prolactin on vitamin D metabolism. Molec. Cel. Endocrinol. 5:163-167.
56. Carlson, H.E. and A.S. Brickman. 1977. Effect of hypocalcemia on hormonal responses to thyrotropin-releasing hormone. J. Clin. Endocrinol. Metab. 45:209-214.
57. Carlson, H.E., A.S. Brickman, and G.F. Bottazzo. 1977. Prolactin deficiency in pseudohypoparathyroidism. New Engl. J. Med. 296:140-144.
58. Drezner, M., F.A. Neelon, and H.E. Lebovitz. 1973. Pseudohypoparathyroidism Type II: A possible defect in the reception of the cyclic AMP signal. New Engl. J. Med. 289: 1056-1060.

59. Rodriquez, H.J., H. Villarreal, S. Klahr, and E. Slatopolsky. 1974. Pseudohypoparathyroidism Type II. Restoration of normal renal responsiveness to parathyroid hormone by calcium administration. J. Clin. Endocrinol. 39:693.
60. Mautalen, C.A., J.F. Dymling, and M. Horwith. 1967. Pseudohypoparathyroidism 1942-1966: a negative progress report. Am. J. Med. 42:977-985.
61. DeSwiet, J. 1973. Pseudo-pseudo-hypoparathyroidism with coarctation of the aorta-a clinical syndrome? Postgrad. Med. J. 49:598-600.
62. Jewelewica, R. and L.E. Nachtigall. 1971. Pseudo-pseudo-hypoparathyroidism and pregnancy. A case report. Ob. Gyn. 37:396-401.
63. Estep, H., W.A. Shaw, C. Watlington, R. Hobe, W. Holland, and S.G. Tucker. 1969. Hypocalcemia due to hypomagnesemia and reversible parathyroid hormone unresponsiveness. J. Clin. Endocrinol. Metab. 29:842.
64. Suh, S.M., A.H. Tashjian, Jr., N. Matsuo, D.K. Parkinson, and D. Fraser. 1973. Normal end-organ responsiveness to parathyroid hormone, impaired parathyroid gland function. J. Clin. Invest. 52:153, 1973.
65. Chase, L.R. and E. Slatopolsky. 1974. Secretion and metabolic efficacy of parathyroid hormone in patients with severe hypomagnesemia. J. Clin. Endocrinol. Metab. 38: 363-371.
66. Pak, C.Y.C. and E.C. Diller. 1969. Ionic interaction with bone mineral. V. Effect of $Mg^{2+}$, $citrate^{3-}$, $F^{-}$, and $SO_4^{2-}$ on the solubility, dissolution and growth of bone mineral. Calc. Tiss. Res. 4:69-72.
67. Massry, S.G., J.W. Coburn, D.B.N. Lee, J. Jowsey, and C.R. Kleeman. 1973. Skeletal resistance to parathyroid hormone in renal failure. Ann. Int. Med. 78:357, 1973.
68. Porter, R.H., B.G. Cox, D. Heaney, T.H. Hostetter, B.J. Stinebaugh, and W. Suki. 1978. Treatment of hypoparathyroid patients with chlorthalidone. New Engl. J. Med. 298:577-581.
69. Gabow, P.A., T.J. Hanson, M.M. Popovtzer, and R.W. Schrier. 1977. Furosemide-induced reduction in ionized calcium in hypoparathyroid patients. Annals of Internal Medicine 86:579-581.
70. Barzel, U.S. 1976. Treatment of hypoparathyroidism. N.Y. State J. Med. 1:579-581.
71. Baran, D.T., R. Shires, S. Klahr, E. Slatopolsky, and L.V. Avioli. 1978. Effect of acetozolamide (AC) in Type I pseudohypoparathyroidism (PHP). Clin. Res. 26: 410A.
72. Pak, C.Y.C. 1970. 25-hydroxycholecalciferol. J. Am. Med. Assoc. 213:1480-1482.

73. Rosen, J.F., A.R. Fleischman, L. Finberg, J. Eisman, and H.F. DeLuca. 1977. 1,25-Dihydroxycholecalciferol: Its use in the long-term management of idiopathic hypoparathyroidism in children. J. Clin. Endocrinol. Metab. 45:457-468.
74. Davies, M., C.M. Taylor, L.F. Hill, and S.W. Stanbury. 1977. 1,25-Dihydroxycholecalciferol in hypoparathyroidism. Lancet 1:55-59.
75. Chesney, R.W., S.D. Horowitz, B.E. Kream, J.A. Eisman, R. Hong, and H.F. DeLuca. 1977. Failure of conventional doses of 1α,25-dihydroxycholecalciferol to correct hypocalcemia in a girl with idiopathic hypoparathyroidism. New Engl. J. Med. 297:1272-1275.