Management of Postmenopausal Osteoporosis

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During the consideration of metabolic bone diseases at Medical Grand Rounds held on January 3, 1980, a seemingly rational and physiologically sound approach to osteoporosis was taken. Various hormonal and metabolic derangements were identified, such as estrogen deficiency, parathyroid hormone excess, and altered vitamin D and calcium metabolism. It was assumed that these defects were pathogenetically important in osteoporosis, and that their restoration would be therapeutically useful.

One particular approach seemed particularly promising. It entailed the use of 25-hydroxyvitamin D (25-OHD) to restore normal intestinal calcium absorption and thiazide to reduce urinary calcium, in order to produce calcium accretion in bone. However, the available evidence suggests that this approach as well as other physiologically sound treatment programs may have a limited value in the management of osteoporosis. While these therapies were often useful in halting the progression of bone disease, they were generally ineffective in increasing the mass of bone. Because so much bone had already been lost, patients remained at risk for further fractures.

From the above considerations, the full pathogenetic significance of various hormonal or metabolic disturbances identified in osteoporosis may be questioned. It is also clear that new therapies designed to augment bone mass must be formulated. These circumstances led us to initiate a new treatment study, the "coherence" therapy of osteoporosis to be described below.

In order to provide an appropriate background, we shall review briefly normal bone cell metabolism and the disturbed bone cell metabolism encountered in postmenopausal osteoporosis. A brief discussion of clinical presentation and laboratory examination will follow. Past treatment approaches will then be considered with particular reference to rationale and responsiveness. The remainder of the discussion will be devoted to the coherence therapy of osteoporosis.

GENERAL COMMENTS

Postmenopausal osteoporosis symptomatically affects 4 million women in the United States. It begins 4-5 years after menopause and increases in frequency thereafter. It is estimated that 25% of Caucasian women over 60 years of age suffer from osteoporosis. It is responsible for 700,000 new fractures yearly. The annual cost of hip fractures alone is approximately $1 billion.[1]

The primary abnormality is the reduced amount of bone mass (osteopenia), resulting from bone resorption which is proportionately greater than formation. The loss of bone affects bone mineral and matrix equally. The remaining bone is grossly normal. When the bone mass has decreased to a point where it is insufficient to maintain the normal structural integrity of the skeleton, fractures and skeletal symptoms appear. The trabecular bone is more severely affected than cortical bone. Thus, bones which are rich in trabecular bone and/or which are responsible

for weight bearing, are prime targets for fractures. Thus, common sites of fractures are the vertebra, ribs, proximal femur, pelvis and distal radius.

NORMAL BONE CELL METABOLISM

Bone tissue may be depicted schematically as a block, composed of osteoid (non-mineralized matrix) and calcified bone. It is a dynamic tissue undergoing continuous remodelling. The remodelling entails three processes: (a) matrix (collagen) synthesis by osteoblasts, (b) mineralization of collagen (or deposition principally of calcium phosphate) to form calcified bone, and (c) bone resorption, or destruction of calcified bone by osteoclasts. In its customary usage, bone formation refers to matrix synthesis. The formation of calcified bone is therefore the sum of bone formation and mineralization.

These processes occur principally at bone surfaces,--endosteal surface covering trabecular (cancellous) bone, periosteal surface, and Haversian system within the cortical bone.[2] Each surface, called cell envelope, is covered by mesenchymal cells, thought to be precursor cells for osteoclasts, osteoblasts and osteocytes.

At the cellular level, bone undergoes continual breakdown and repair in discrete areas called "bone remodelling units" or basic multicellular units.[3] In periosteum and in trabecular bone, these units are spread out over the surface, and are supplied by blood from the periosteal and medullary vessels. In cortical bone, the remodelling units are parallel to the long axis of the Haversian system; they are supplied by Haversian vessels.

Each unit has areas of resorption and formation. The resorption is initiated by osteoclasts that resorb calcified bone, forming a cavity of about 50-250 μ in diameter. The osteoclasts in the areas of resorption are followed by osteoblasts which form osteoid. After the osteoid grows to a thickness of 10-15 μ, it becomes mineralized. Thus, the creation of a new basic multicellular unit, normally occurring over 4 months, is represented by:

Appearance of Osteoclasts ⟶ Resorption ⟶ Appearance of Osteoblasts ⟶ Formation

Central to the remodelling process is the concept of "coupling" between bone resorption and bone formation. To explain how osteoblastic matrix synthesis quickly follows osteoclastic resorption, Bordier and Rasmussen introduced the hypothesis of cellular continuity, where osteoclasts derive their origin from osteoprogenitor cells, and osteoblasts form by transformation of osteoblasts.[4] However, the validity of this hypothesis has been questioned by recent studies suggesting separate cellular origin for osteoclasts and osteoblasts, osteoblasts derived from monocytes and macrophages and osteoblasts from fibroblasts.[5]

There may be internal remodelling as well. After osteoblasts form collagen, they become incorporated into matrix, and become osteoid osteocytes. These cells are believed to be responsible for the mineralization of the matrix by an elaboration of matrix vesicles.[6] When mineralization is completed, the cells become enclosed within calcified bone as mature osteocytes. These osteocytes are connected to each other and with surface osteocytes (cell envelope) by protoplasmic extensions pas-

sing through canaliculi. This system, comprising minicirculation of bone, provides a functional boundary between blood and bone. There is some evidence that mature osteocytes may participate in bone remodelling, involved in "osteocytic osteolysis" allowing a rapid skeletal mobilization of calcium.

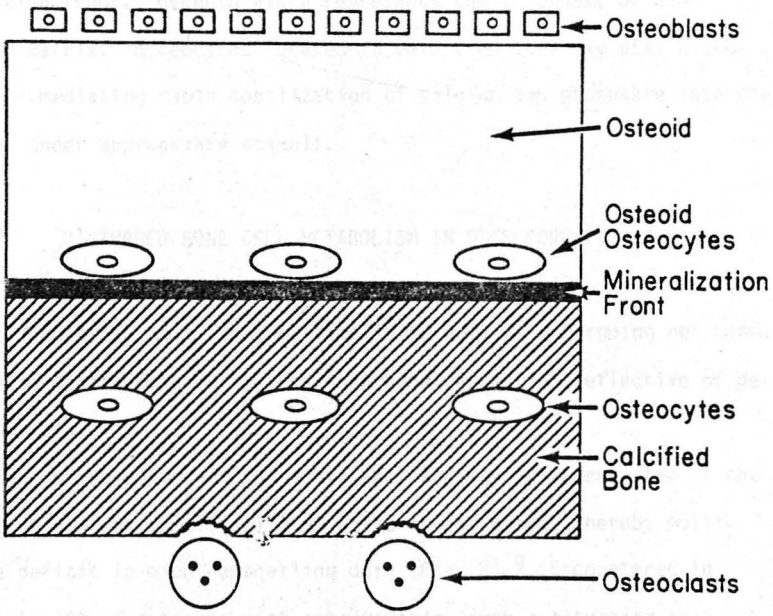

Figure 1.

In Fig. 1, the functional role of four principal cell types are schematically presented.[7] As previously described, osteoclasts resorb calcified bone, and osteoblasts synthesize the matrix. Osteoid osteocytes,

located over osteoid lamella may be responsible for the initiation of mineralization by elaborating membrane-bound extracellular matrix vesicles.[8] These vesicles are rich in alkaline phosphatase and are believed to be the initial site of mineralization. A sharp line of calcification separating the osteoid and calcified bone is called mineralization front. Osteoid width represents the thickness of non-mineralized matrix. Osteocytes located in calcified bone may play a crucial role in mediating rapid mobilization of calcium and phosphate into the circulation under appropriate stimuli.

DISTURBED BONE CELL METABOLISM IN OSTEOPOROSIS

In osteoporosis, each basic multicellular unit is undergoing net bone loss, because bone formation is less than bone resorption reflective of defective coupling.

The rate of bone loss of the whole skeleton may be accentuated if the birth rate of new basic multicellular units is increased, thereby multiplying the deficit in each remodelling unit (Fig. 2).[9] Encountered in approximately 10% of patients with osteoporosis, such a situation is characterized by a high remodelling state, with high resorption and formation surfaces and normal osteoblastic matrix synthesis.[9] Some of these patients present with a high serum PTH and urinary hydroxyproline.

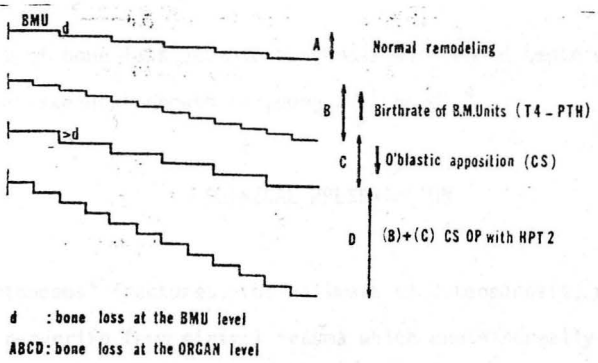

Figure 2 - Diagrammatic representation of the loss of bone tissue in normal aging (A), in high remodeling osteoporoses induced by thyroid hormones or parathyroid hormone (B), in osteoporoses with osteoblastic depression such as corticosteroid induced osteoporosis (C), and in situations where B and C are combined, as in corticosteroid osteoporosis with high PTH.

Alternatively, the rate of bone loss may be increased if there is a depression of osteoblastic activity beyond that expected from normal ageing, even when osteoclastic resorptive activity is normal (Fig. 2). Thus, the tissue deficit of each basic multicellular unit may be magnified. This state of low bone turnover is encountered in approximately 33% of patients with osteoporosis.

The remaining patients show no evidence of increased remodelling or depressed osteoblastic activity (compared to normal), except for a reduced amount of trabecular bone. Thus, their rate of bone loss is probably equivalent to that of control women of similar age without bone disease. It has been speculated they represent the lower fringe of physiological osteopenia, where a significant reduction in bone mass occurred despite a

normal rate of bone loss because bone mass was low to begin with (at the end of their skeletal growth in young adulthood).[9]

CLINICAL PRESENTATION

"Spontaneous" fractures, the hallmark of osteoporosis, represents fractures occurring from minimal trauma which could normally be sustained without incurring damage. Common sites of involvement are the vertebrae, ribs, proximal femur and distal radius-ulna. Fractures may occur from a minor fall (from ground level) or bending to pick up an object.

Pain is the most common symptomatology of vertebral fracture. It is generally localized to the area of involvement, but may radiate laterally. It may be associated with paravertebral muscle spasm and localized tenderness. The severity and duration of pain vary considerably among patients. It may last for 1-2 months.

Skeletal deformity may develop from anterior wedging and collapse of vertebrae. "Dowager's hump" may occur from fractures of thoracic and lumbar vertebrae. Loss of height is common. Patients often complain of chronic back pain, occurring probably on a mechanical basis. When the length of spine becomes severely contracted by fractures, abdominal and pulmonary function may be embarrassed.

LABORATORY EXAMINATION

Serum concentrations of calcium, phosphorus and alkaline phosphatase are normal in patients with postmenopausal osteoporosis. The serum concentration of PTH is usually normal, but it may be high in a minority of patients.[10] Serum 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$) and intestinal calcium absorption are generally reduced.[11] Urinary calcium is normal or low in most patients; it may be elevated in a minority of patients particularly if they suffer from renal hypercalciuria.

Radiologically, early signs include loss of the trabecular pattern on vertebrae and femoral neck. The trabecular bone which is not parallel to the line of weight bearing is lost first by the osteoporotic process, and accounts for the prominence of vertical striations in the vertebrae, and serves as the basis for the trabecular pattern index for the staging of osteoporosis.[12] The cortical thickness of metacarpal bone or radius may be reduced in osteoporosis.[13] In the long bones, there is an accelerated bone loss endosteally with menopause, whereas the bone continues to be deposited externally (periosteally) though at a slower rate. Thus, the total width of bone may be greater, but the cortical bone thickness may be less than in the premenopausal state. Other roentgenologic signs include prominence of vertebral end plates, Schmorl's nodes, vertebral collapse, fractures of rib and femoral neck and kyphoscoliosis.

The skeletal roentgenologic examination is inadequate to quantitate the extent of bone loss in osteoporosis because up to 40% of bone mineral may be lost before it can be detected roentgenologically. A more sensitive measure of bone density may be obtained from photon absorptiometric an-

alysis. Such an analysis of the shaft of the radius has revealed low bone density in some patients with osteoporosis[14] (Fig. 3). The measurement of bone density in the axial skeleton by dual photon absorptiometry may provide a better discrimination[15] (Fig. 4).

Bone histologic examination has revealed a heterogeneity of the morphologic picture, including low- and high remodelling activity.[9,16] Unfortunately, the exact histomorphometric picture cannot be accurately predicted from biochemical presentation.[16]

PAST TREATMENT PROGRAMS

Therapies Designed to Arrest Further Bone Loss

Much of past approaches for the management of osteoporosis may be characterized as incoherence treatment programs,[17] which were continuously administered and aimed at replacement or correction of hormonal and metabolic deficiencies or derangements (Table 1). It was assumed that these defects were pathogenetically important and their restoration would be therapeutically useful. These treatments were considered to be incoherent, because they were given continuously and since no concerted effort was made to synchronize the bone remodelling process of activation, resorption and formation.

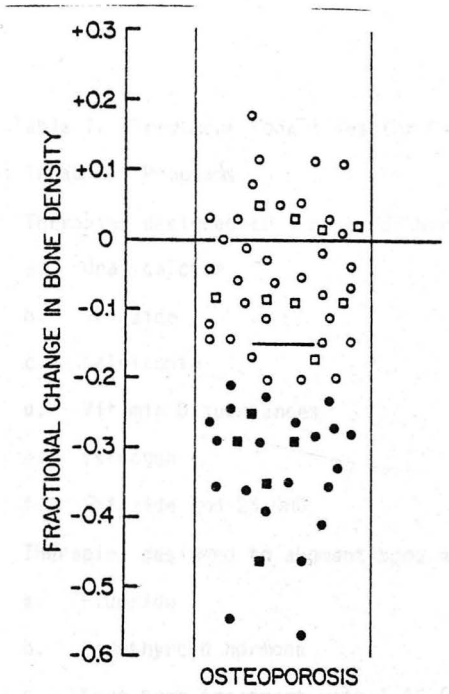

Figure 3.

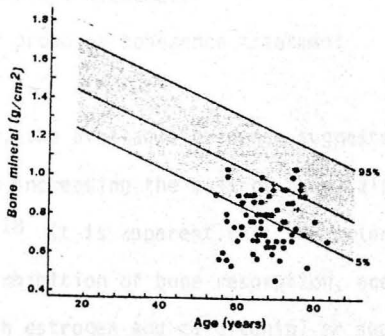

FIGURE 4. Individual values for BMD of lumbar spine in 76 women with osteoporosis and one or more vertebral-compression fractures (●). Center line denotes age regression for normal women and upper and lower lines represent 90% confidence limits.

Table 1. Treatment Modalities for Osteoporosis

I. Past Treatment Programs
   1. Therapies designed to arrest further bone loss
      a. Oral calcium
      b. Thiazide
      c. Calcitonin
      d. Vitamin D substances
      e. Estrogen
      f. Thiazide and 25-OHD
   2. Therapies designed to augment bone mass
      a. Fluoride
      b. Parathyroid hormone
      c. Long-term treatment with $1,25\text{-}(OH)_2D$

II. New Treatment Approach
   1. Coherence treatment
   2. Our proposed coherence treatment

Unfortunately, the available evidence suggests that these treatments are ineffective in increasing the mass of bone, although they may prevent further bone loss.[18] It is apparent that the principal effect of these treatments is an inhibition of bone resorption, occurring by antagonism of PTH action (as with estrogen and calcitonin) or suppression of PTH secretion (as with calcium and vitamin D preparations). With continued therapy, bone formation also declined (probably due to coupling), nullifying the beneficial effect of inhibited bone resorption.

Oral Calcium

An important nutritional factor in the pathogenesis of osteoporosis is the amount of calcium intake required to maintain balance. There is evidence that this requirement for calcium increases with advancing age.[19] This finding may reflect the continued decline in intestinal calcium absorption reported with ageing,[20] and the apparent loss of intestinal adaptation to varying calcium intake in older women.[11] Calcium intake is lower in women than in men. Reduced calcium intake has been associated with a higher fracture rate.[21] Intestinal lactase deficiency has been reported to be more common in osteoporosis.[22] The consequent avoidance of calcium-rich dairy products has been implicated in the development of bone disease.

The rationale for oral calcium supplementation is to overcome inadequate calcium absorption resulting from low calcium intake and defective intestinal calcium transport. The total amount of calcium absorbed may be increased substantially by higher calcium intake (probably by the operation of passive absorption), even though the fractional calcium absorption remains subnormal.[23] By enhancing calcium absorption, oral calcium supplements may inhibit parathyroid function and thereby suppress PTH-dependent bone resorption. The rate of bone remodelling or the birth rate of new basic multicellular units is therefore reduced. Thus, this form of therapy may retard loss but is not expected to augment bone mass.

Available studies indicate that oral calcium supplements may improve calcium balance,[19] and prevent further loss of bone.[24-26] Calcium supplements have been provided as calcium gluconate, calcium carbonate or calcium lactate, at a dosage of 500-1500 mg calcium/day. A total calcium intake (supplemental and dietary) of 1.5 g/day is often recommended for patients with postmenopausal osteoporosis.

Thiazide.

Our preliminary studies indicate that certain patients with postmenopausal osteoporosis may present with renal hypercalciuria (impaired renal tubular reabsorption of calcium) with secondary hyperparathyroidism. However, unlike patients with renal stones,[27] patients with osteoporosis suffering from renal hypercalciuria do not have a compensatory intestinal hyperabsorption of calcium.

The use of thiazide in osteoporosis is based on the ability of this diuretic to reduce renal calcium excretion. This action has been ascribed to the direct stimulation of calcium reabsorption in the distal tubule,[28] and to the enhancement of proximal tubular reabsorption by causing extracellular volume depletion.[29]

In patients with renal hypercalciuria and nephrolithiasis, thiazide has been shown to correct the "renal leak" of calcium and restore normal parathyroid function. However, the state of calcium balance probably did not change since the ensuing suppression of $1,25\text{-}(OH)_2D$ caused a decline in intestinal calcium absorption.[27] Thus, thiazide is expected to reduce

bone resorption by inhibition of PTH secretion and thereby prevent further loss of bone. However, this effect is not likely to be sustained because of compensatory fall in calcium absorption. It may be indicated in the minority of patients with postmenopausal osteoporosis presenting with renal hypercalciuria and secondary hyperparathyroidism. An adequate hypocalciuric response may be obtained with hydrochlorothiazide 25-50 mg twice/day or trichlormethiazide 2-4 mg/day.

The suggested use of thiazide in osteoporosis would seem paradoxical and contraindicated, since thiazide has been believed to accentuate PTH-dependent bone resorption,[30] cause parathyroid glandular enlargement[31] and induce or accentuate hypercalcemia in primary hyperparathyroidism[32] and secondary hyperparathyroidism of chronic renal failure.[33] However, the findng of parathyroid stimulation by thiazide in the dog could not be confirmed in the rat.[34] In patients with renal hypercalciuria and secondary hyperparathyroidism (and probably in normal subjects), thiazide suppresses parathyroid function via reduction of calcium excretion, and does not cause true hypercalcemia (reflected by increased ionized calcium).[35] Thiazide may potentiate osteocytic resorption.[36] This action could explain the development of true hypercalcemia during thiazide therapy of primary hyperparathyroidism and vitamin D-treated hypoparathyroidism, --conditions in which osteocytic activity may already have been stimulated. There is no conclusive evidence that thiazide stimulates osteoclastic resorption. Thiazide has been shown to reduce hydroxyproline excretion,[37] Vo- (radiocalcium efflux from bone),[38] and to retard the decline in bone density (in primary hyperparathyroidism).[39]

The effect of long-term thiazide treatment in postmenopausal women was evaluated in a randomized controlled study.[40] Thiazide was shown to prevent the decline in bone density (of the midshaft of forearm bones) during the first six months of treatment. Thereafter, the bone density declined at the same rate as in the control group. The transient effect observed probably reflects the time required for the compensatory fall in intestinal calcium absorption to take place.

Calcitonin

The rationale for the use of calcitonin is based on the finding that the secretory response of calcitonin to calcium infusion may be impaired in patients with postmenopausal osteoporosis[41] and on the knowledge that calcitonin is a well-recognized inhibitor of PTH-induced bone resorption.[42] Unfortunately, calcitonin given alone may cause secondary hyperparathyroidism by decreasing serum calcium concentration. The ensuing stimulation of PTH secretion may negate the inhibition of bone resorption by calcitonin.[43] Moreover, even if calcitonin inhibits bone formation, this treatment probably will not increase the mass of bone because of the commensurate decline in bone formation.

The above view is supported by available studies which indicate variable effects of calcitonin therapy on bone resorption, formation, calcium balance and total body calcium.[43,44] The concurrent administration of calcium averted the development of secondary hyperparathyroidism and caused a reduction in bone formation.[45] However, no increment in bone mass was

found. Moreover, the effect of calcitonin and calcium was found to be qualitatively the same as that of calcium or calcium plus vitamin D.

Vitamin D Substances

Serum 1,25-$(OH)_2D$ has been shown to be reduced in osteoporosis.[11,46] Slovik et al. found that patients with postmenopausal osteoporosis had an impaired 1,25-$(OH)_2D$ synthesis following stimulation by exogenous PTH, compared to young (<45 years) men and women.[47] However, Riggs et al. were unable to find any difference in the responsiveness of osteoporotic patients from that of postmenopausal control women matched for age.[48] Although our preliminary report had indicated the ability of patients with postmenopausal osteoporosis to increase serum 1,25-$(OH)_2D$ following 25-OHD therapy,[46] a further study disclosed failure of such a response in some patients. There is good evidence that estrogen lack may cause an inhibition of 1,25-$(OH)_2D$ synthesis, as will be discussed.[11] These results indicate that 1,25-$(OH)_2D$ synthesis is reduced in the postmenopausal state. Recently, it has been reported that this impairment is more severe in osteoporotic women than in postmenopausal women without bone disease.

Our preliminary study indicates that some patients with postmenopausal osteoporosis may have a reduced circulating concentration of 25-OHD and 24,25-dihydroxyvitamin D (24,25-$(OH)_2D$). However, another group found a high serum concentration of 25-OHD.[49]

The use of vitamin D substances in postmenopausal osteoporosis would seem logical because of evidence for vitamin D deficiency and low calcium absorption previously enumerated.[11,46] The treatment should increase intestinal calcium absorption, suppress PTH secretion and inhibit bone resorption. Certain vitamin D metabolites (25-OHD and 24,25-$(OH)_2D$) may stimulate bone formation by affecting osteoblast function, as previously discussed.

The treatment with vitamin D or 1,25-$(OH)_2D$ in osteoporosis has been shown to lower serum PTH and bone resorption.[45,50,51] However, bone formation declined following vitamin D treatment, probably because of the coupling response to the decline in bone resorption.[50] During 1,25-$(OH)_2D$ therapy, no improvement in calcium balance occurred despite stimulation of calcium absorption, because of a rise in urinary calcium.[51] Moreover, 1,25-$(OH)_2D$ treatment was ineffective in preventing the decline in bone density of appendicular bone occurring in patients with postmenopausal osteoporosis.[52] Similarly, long-term trials with vitamin D indicated no effect on bone loss or the occurrence of new fractures.[24,53]

Although 25-OHD is capable of stimulating the synthesis of 24,25-$(OH)_2D$ and 1,25-$(OH)_2D$,[46] our preliminary study indicates that this treatment does not always stimulate the intestinal calcium absorption in postmenopausal osteoporosis. As in the situation with 1,25-$(OH)_2D$ therapy, the increased calcium absorption was negated by the rise in urinary calcium excretion.

Estrogen

The potential pathogenetic role of estrogen lack in osteoporosis has gained renewed emphasis from recent studies by Riggs et al.[11,54]

The estrogen lack theory assumes that estrogen plays a critical role in bone metabolism. There is considerable evidence which suggests that estrogen might modify the PTH-induced bone resorption. The PTH-induced loss of bone, as measured from decreases in bone content of calcium and hydroxyproline, is accentuated by oophorectomy.[55] In postmenopausal women with hypoparathyroidism, the age-related loss of bone does not develop.[56] In our experience, the bone density, as measured by ^{125}I-photon absorption of the distal third of the radius,[57] is significantly reduced in the majority of white postmenopausal women with primary hyperparathyroidism, unlike in male patients of comparable age with this condition.

When estrogens are given to patients with postmenopausal osteoporosis or primary hyperparathyroidism, the following changes are usually found:[58-64] retention of calcium and phosphorus; decreases in serum and urinary calcium and phosphorus, urinary hydroxyproline, fasting urinary calcium and bone resorption (by histomorphometry); and an increase in serum immunoreactive PTH. Thus, despite stimulation of parathyroid function (presumably from the decline in serum calcium), bone resorption is inhibited. These findings support the concept that estrogens decrease the responsiveness of bone to endogenous PTH. Indeed, estrogen has been shown to inhibit the PTH-induced release of calcium from mouse calvaria in

vitro,[65] although this action of estrogen has not been confirmed.[66] Thus, the development of bone disease in the postmenopausal state may be associated at least in part with the loss of the protective effect of estrogens against parathyroid hormone action.

Because of the enhanced mobilization of calcium from bone, parathyroid function may be suppressed in postmenopausal osteoporosis. Reduced serum PTH has been reported in the majority of patients with this disease.[9,10] Further, since PTH may be involved in the mediation of 1,25-$(OH)_2D$ synthesis,[67,68] a low serum concentration of 1,25-$(OH)_2D$ might be expected, and could explain reduced intestinal Ca absorption found in some patients with postmenopausal osteoporosis.[11]

The following pathogenetic scheme may therefore to constructed: estrogen lack $\longrightarrow$ $\uparrow$PTH-induced bone resorption $\longrightarrow$ $\uparrow$skeletal Ca mobilization $\longrightarrow$ $\downarrow$ PTH secretion $\longrightarrow$ $\downarrow$ 1,25-$(OH)_2D$ synthesis $\longrightarrow$ $\downarrow$intestinal Ca absorption. Two other factors may contribute to impaired 1,25-$(OH)_2D$ production during estrogen lack. Though controversial, estrogen is believed to stimulate renal 1α-hydroxylase activity.[69] Estrogen lack could then cause a reduced 1,25-$(OH)_2D$ synthesis. Moreover, serum P may rise from an increased mobilization from bone and from reduced renal excretion of P (associated with parathyroid suppression). This rise may then inhibit 1,25-$(OH)_2D$ synthesis.[70] The validity of this scheme has been supported by the findings of reduced circulating concentrations of PTH and 1,25-$(OH)_2D$, and of low intestinal Ca absorption.[11] Moreover, a short-term treatment with estrogen was found to restore these values towards normal.[54]

The pathogenetic role of estrogen lack in osteoporosis is further supported by the finding of accelerated bone loss with the onset of menopause.[71,72] Such a temporal relationship has been shown for "cortical" bone[15,57,72] as well as trabecular bone,[9] although a recent densitometometric analysis of axial skeleton has disclosed a linear decline in bone density occurring before menopause.[9]

Despite its attractiveness, the estrogen lack theory has certain drawbacks. First, although the increased sensitivity of bone to PTH could explain bone loss, it cannot adequately explain the defective coupling[73] and the frequent occurrence of low bone remodelling[9] previously discussed. Thus, a disturbance in osteoblastic function from estrogen lack or ageing is necessary. Secondly, despite a few reports to the contrary,[74,75] it has not been possible to document that the estrogen deficiency was more severe in the patient with bone disease than in comparable women without bone disease.[76-78] Third, it is unlikely that there is an impaired responsiveness of target tissues to estrogen action, since the concentration of estrogen receptors in the cytosolic fraction of cervical tissue was not found to be different.[79] Finally, no estrogen receptors have been demonstrated in bone.[80]

From above considerations, estrogen replacement would seem rational in postmenopausal osteoporosis since it should inhibit PTH-induced bone resorption,[18] and it may restore normal osteoblast function.

Indeed, estrogen therapy has been shown to restore much of the biochemical abnormalities[11] encountered in many patients with post-

menopausal osteoporosis. Thus, it has been reported that estrogen treatment decreased serum calcium, increased serum PTH and 1,25-$(OH)_2D$ and augmented intestinal calcium absorption.[54] Moreover, it has been shown to inhibit bone resorption.[63] During short-term therapy (<6 months), no change in bone formation was found.[63,64] However, with continued therapy, bone formation declined probably as a result of coupling response to the decreased bone resorption.[64] Thus, in patients with established bone disease with fractures, estrogen therapy does not create new bone,[25] even though it may inhibit the rate of bone loss.[24]

In healthy postmenopausal and oophorectomized women, the institution of estrogen therapy shortly after the onset of estrogen lack has been shown to prevent bone loss (Fig. 5).[81] When the treatment was given 2-6 years after menopause or oophorectomy, a significant rise in bone density in the appendicular skeleton of 1-3% per year occurred.[82-84] The rise was observed only during the first three years of therapy; no further change occurred thereafter.[82] Moreover, estrogen therapy was shown to prevent the occurrence of spinal[81] and hip fractures.[85] Thus, there is emerging evidence that estrogen may have a prophylactic value in the prevention of age-related bone loss and fractures.

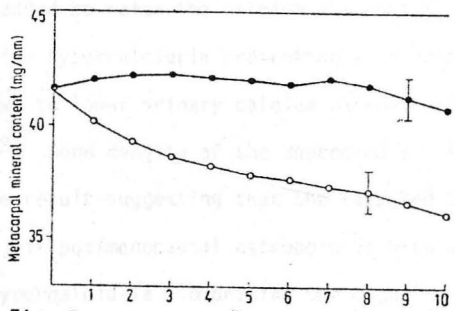

Fig. 5
Bone mineral content in the two groups of patients.
Maximum SE shown. Upper line represents those treated with oestrogen; lower line those treated with placebo.

In considering estrogen therapy, potential side effects should be carefully considered.[86] The usual effective dose is equine estrogen 0.625 mg/day or ethinyl estradiol 0.05-0.1 mg/day given intermittently (on treatment for three weeks and withdrawal for one week). A careful gynecological examination is mandatory.

Thiazide and 25-OHD

Our own therapeutic program, entailing the use of thiazide and 25-hydroxyvitamin D (25-OHD) was a logical extension of studies in nephrolithiasis.[27,87] An apparently new clinical presentation of postmenopausal osteoporosis was disclosed, characterized by renal hyper-

calciuria, secondary hyperparathyroidism and high bone remodelling, but without a compensatory intestinal hyperabsorption of calcium. Thiazide was used to correct the renal leak of calcium and parathyroid stimulation,[87] and 25-OHD was added to raise the calcium absorption.

In absorptive hypercalciuria presenting with nephrolithiasis, thiazide therapy was shown to lower urinary calcium without affecting the high calcium absorption.[87] Bone density of the appendicular skeleton increased,[88] the result suggesting that the retained calcium was accreted in bone. Thus, in postmenopausal osteoporosis with low calcium absorption without renal hypercalciuria (comprising the majority of patients with osteoporosis), 25-OHD was given to increase calcium absorption (to simulate absorptive hypercalciuria), and thiazide was added when hypercalciuria developed. The use of 25-OHD was based on the previous finding that it increased the circulating concentration of all three active vitamin D metabolites.[46] It was hoped that the augmented production of $1,25\text{-}(OH)_2D$ would activate osteoclasts, $24,25\text{-}(OH)_2D$ would stimulate osteoblasts[7] and the positive bone mineral balance would promote mineralization.

Unfortunately, in some patients with postmenopausal osteoporosis, 25-OHD was ineffective in raising serum $1,25\text{-}(OH)_2D$ and calcium absorption. Moreover, thiazide was found to lower serum $1,25\text{-}(OH)_2D$ and calcium absorption.

Therapies Designed to Augment Bone Mass

This approach is designed to increase the total mass of bone by interventions which may not be considered "physiological." On the one hand, an unnatural compound (fluoride) may be administered to provide marked stimulation of osteoblastic activity. On the other hand, bone-resorbing agents (e.g. PTH and large amounts of $1,25\text{-}(OH)_2D$) may be given to activate the osteclasts and to accelerate the birth rate of new bone remodelling units.

An incoherent use of these agents, involving continuous administration, will now be discussed.

Fluoride

Fluoride has been recommended for osteoporosis because of its ability to stimulate osteoblastic matrix synthesis.[89,90] When it is given alone, an abundance of poorly mineralized osteoid may be found, a finding indicating that the newly formed osteoid does not undergo an adequate calcification.[89,91] Moreover, there may be an increased resorption as well. However, the addition of vitamin D and calcium to fluoride has been shown to augment the amount of mineralized bone, reduce osteoid volume, and to prevent increased resorption (Fig. 6, Fig. 7).[89,92,93] An increased total bone mass has been reported during long-term treatment with this combined regimen.[1,93,94]

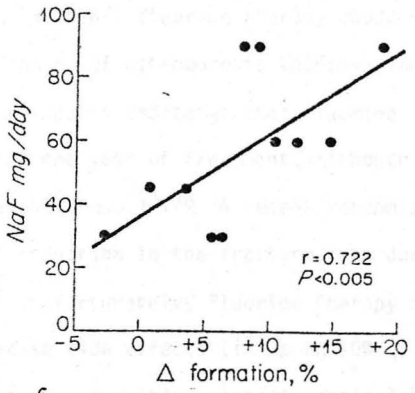

Figure 6. Relationship between daily dose of sodium fluoride (NaF) and increase in bone formation.

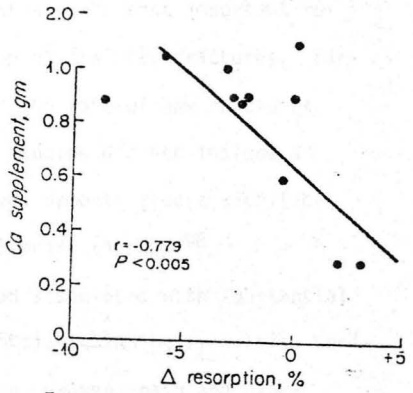

Figure 7. Relationship between daily dose of calcium (Ca) supplement and change in bone resorption.

The available evidence suggests that fluoride therapy may increase the mass of bone by markedly stimulating matrix synthesis. Even if fluoride were to exert this effect, this action must be short-lived, since the osteoblastic activity becomes markedly reduced after two years of therapy.[93]

It has been argued that the new bone forming occurring under the influence of fluoride may not confer much benefit to the patients, since the newly formed bone is abnormal in chemical composition and morphology. The "fluoridic" bone is rich in fluoroapatite which has a higher crystallinity and reduced solubility than normally occurring hydroxyapatite.[95] Moreover, it is composed of mosaic rather than lamellar bone with decreased elasticity.[96] Thus, the increase in bone mass occurring after fluoride therapy may not indicate that the bone has been strengthened.

However, fluoride therapy appears to satisfy the most important requirement of osteoporosis therapy--inhibition of skeletal fractures. Earlier reports indicated that fluoride reduced the rate of new fractures after one year of treatment, although these studies did not include a placebo group.[93,98] A recent randomized study demonstrated a significant reduction in the fracture rate during fluoride therapy.[98]

Unfortunately, fluoride therapy has been associated with substantial adverse side effects (in up to 40% of patients), including synovitis, periarticular fascitis, gastrointestinal bleeding, nausea, pain and diarrhea.[93,98] The recommended dose of sodium fluoride is 25 mg twice/day, with oral calcium supplements (600-1500 mg calcium/day), with or without vitamin D (50,000 units once or twice/week).

Parathyroid Hormone

There is some evidence that PTH excess may contribute to the development of osteoporosis. Osteoporotic picture may be encountered in primary hyperparathyroidism. Serum PTH concentration may be increased in some patients with high remodelling osteoporosis.[9] The pathogenetic importance of PTH excess in osteoporosis is further shown by the failure of the development of immobilization osteoporosis in parathyroid deficiency,[99] and the lack of osteoporosis in hypoparathyroidism, and the frequent occurrence of osteoporosis in primary hyperparathyroidism.[100]

Thus, the use of a potent bone resorbing agent such as PTH in the treatment of a bone-wasting disease such as osteoporosis would seem para-

doxical. However, there is sound theoretical basis for the assertion that a judicious use of PTH may augment the mass of bone. First, PTH is the only substance who so far has been shown to activate osteoclasts, accelerate the birth rate of new bone remodelling units and secondarily stimulate osteoblasts via coupling.[101] Second, the active life of osteoblasts is several fold longer than that of osteoclasts.[102]

The above contention is supported by substantial experimental animal and clinical data, particularly when small amounts of PTH involving minor changes in calcium fluxes were implicated. In young rats, repeated injections of PTH has been shown to augment trabecular bone mass.[103] In human subjects with mild primary hyperparathyroidism or with secondary hyperparathyroidism of renal failure, osteosclerosis may develop.[104-106]

Encouraging results have already emerged from the treatment of patients with postmenopausal osteoporosis with daily injections of human parathyroid hormone (1-34 fragment) at subhypercalcemic dosage.[107-111] A marked increase in bone turnover was observed by radiocalcium kinetic analysis and bone histology. Both bone formation and resorption increased; however, the increment in formation exceeded the change in resorption. These changes affected principally the trabecular bone. Thus, the most notable change in bone histology was a marked increase in trabecular bone volume (of mean 92% from baseline) (Fig. 8).[109] The intestinal calcium absorption rose, probably consequent to the PTH-dependent stimulation of $1,25\text{-}(OH)_2D$ synthesis.

Unfortunately, calcium balance for the whole group did not change. Moreover, there was a reduction in cortical bone mass probably due to continued exposure to PTH.[111]

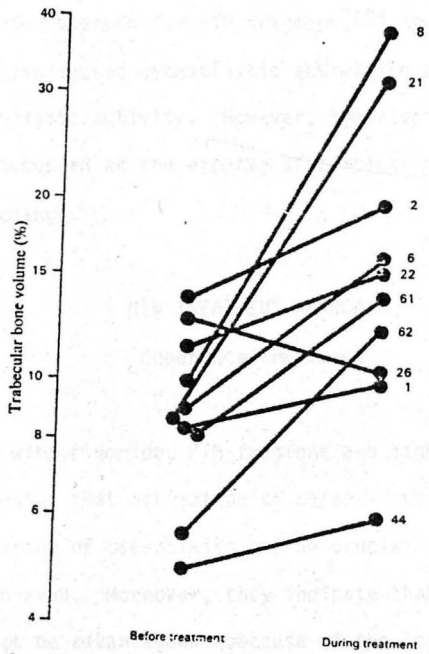

Fig. 8. *Percentage improvements in trabecular bone volume shown on a logarithmic scale (mean of two independent measurements per biopsy)*

Long-term treatment with 1,25-$(OH)_2D$

Gallagher et al.[112] treated 12 patients with postmenopausal osteoporosis with 1,25-$(OH)_2D$ 0.5 µg/day for 2 years. They found a rise in both bone formation and resorption as well as in trabecular bone volume. However, calcium balance did not change significantly. The results are comparable to those observed for PTH fragment,[109] and suggest that 1,25-$(OH)_2D$ may have caused osteoclastic activation and secondarily stimulated osteoblastic activity. However, the rise in trabecular bone volume may have occurred at the expense of cortical bone, since calcium balance did not change.

NEW TREATMENT APPROACH

Coherence Treatment

The studies with fluoride, PTH fragment and high doses of 1,25-$(OH)_2D$ suggested that activation of osteoclasts and primary or secondary stimulation of osteoblasts may be crucial if an increase in bone mass is to be achieved. Moreover, they indicate that long-term continued treatments may not be advantageous because of the loss of the stimulatory effect of fluoride on bone formation and sustained destruction of bone from continued administration of PTH or 1,25-$(OH)_2D$.

The coherence therapy is an innovative approach, designed to augment bone mass, which obviates some of the negative effects of treatments enumerated above.

This formulation, as initially proposed by Frost,[113] is based on the following observations.

First, bone remodelling occurring in basic multicellular units follows the sequence of activation followed by resorption and then by formation. Since this sequence appears to be invariant, no new bone remodelling units may be formed without activation. The remodelling process in these units account for most of the lamellar bone turnover in adults. Thus, the skeletal balance of the whole body ultimately depends on activation.

Second, the activity of individual bone remodelling units is normally out of phase with each other, some undergoing resorption and others formation. In other words, there is temporal incoherence among basic multicellular units.

Third, the activity of bone remodelling units may be synchronized or made coherent by intermittent "activation pulse" by purposeful short-term administration of agents capable of stimulating osteoclasts.

Fourth, once an activation pulse has been given, the depression of osteoclastic activity by certain inhibitors of bone resorption should not interfere with the stimulation of osteoblasts.

Fifth, since the active life of osteoblasts is much longer than that of osteoclasts, osteoblastic bone formation should be sustained for some period following withdrawal of suppressive influence.

Sixth, the bone remodelling units should be responsive to repeated pulsing of activation and depression. Thus, the birthrate of new remodelling units may be accelerated and the duration of the life of bone remodelling units could be manipulated.

The actual mode of coherence therapy, as recommended by Frost,[113] entails a timed sequence of activation, depression, free and repeat (ADFR) treatment (Fig. 9 and Fig. 10).[18] Initially, an activating pulse is given for approximately 5 days, e.g. with PTH or a vitamin D metabolite. A drug is then given to depress the osteoclasts (e.g. oral calcium or diphosphonate) over about one month period corresponding to the duration of active osteoclastic resorption. During the subsequent 2-3 months, when no drug is given, the osteoblasts stimulated by activation would be allowed to form new bone. The cycle is repeated by reactivation.

This treatment should increase the whole skeletal mass, because more bone remodelling units would have been created (Fig. 10), and since bone formation should exceed the resorption in each unit (Fig. 9). The latter condition prevails because of the depression phase during which the extent of osteoclastic resorption would be reduced. Thus, the coherence therapy should obviate some of the negative effects of treatment with fluoride (reduced bone formation with prolonged treatment)[93] or with PTH (sustained destruction of bone from continued administration).[111]

No published report of the use of ADFR treatment in postmenopausal osteoporosis is available. The concepts embodied in coherence treatment could explain our results of calcium infusion therapy.[114,115] In idiopathic osteoporosis with high bone turnover, a two-week course of calcium infusion caused a sustained increased bone formation and improved calcium balance.[114,115] In contrast, no effect was observed in postmenopausal osteoporosis with low bone turnover.[116] The findings could be explained

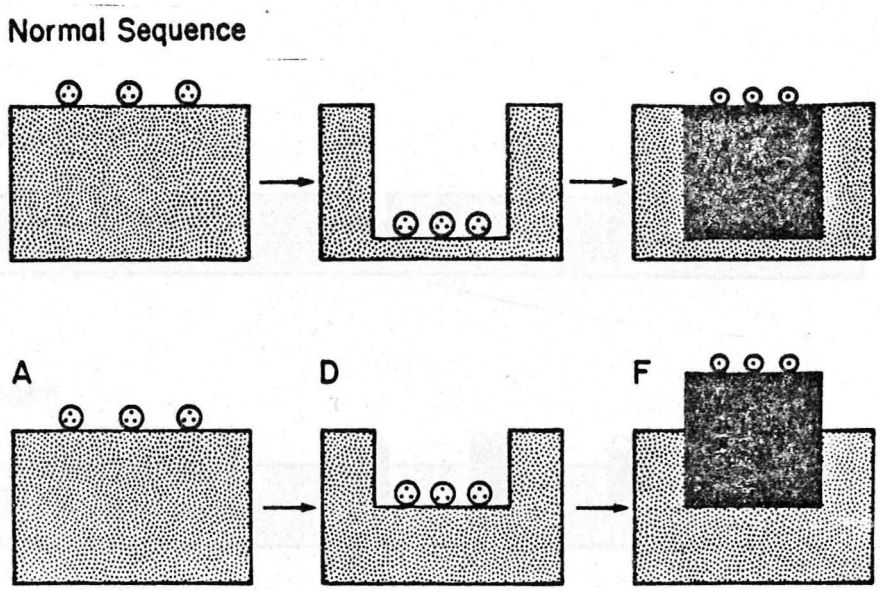

Figure 9.

Depiction of coherence treatment in an individual basic multicellular unit. Without ADFR sequence (top), the amount of bone destroyed (top middle) by osteoclasts is considered to be equal to the amount formed (top right) by osteoblasts. During depression phase (D) of coherent treatment (bottom middle), less bone is destroyed by osteoclasts than without depression (top middle). Thus, the total amount of bone left is larger following ADF sequence than without (compare bottom right with top right), assuming an equal amount of new bone formation (shaded areas).

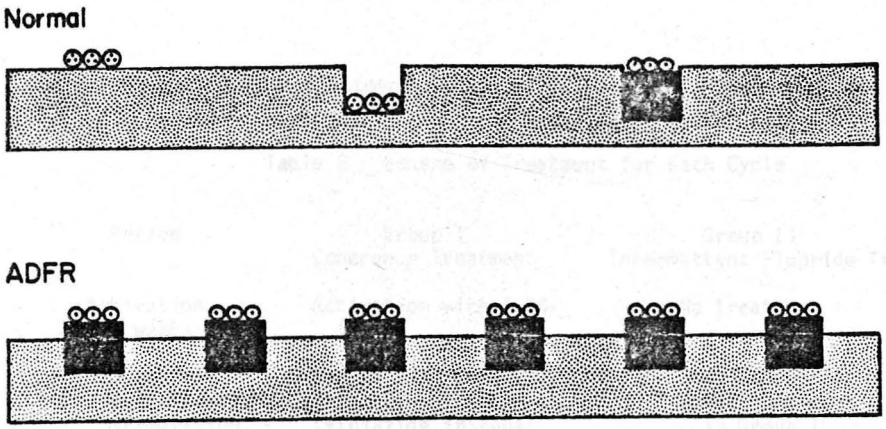

Figure 10.

Effect of coherence treatment on total bone. Normally, various basic multicellular units are out of phase (top), some undergoing activation or resorption, and others formation. Followng a successful ADFR treatment (bottom), there are more basic multicellular units which are in phase, all of them completing formation.

if idiopathic osteoporosis with high bone turnover were assumed to represent a naturally-occurring state of osteoclastic activation. The calcium infusion treatment could have depressed osteoclastic resorption without interfering with osteoblastic stimulation.

Our Proposed Coherence Treatment (Table 2)

Table 2. Scheme of Treatment for Each Cycle

Period	Group I Coherence Treatment	Group II Intermittent Fluoride Treatment
Activation, 2 weeks	Activation with 1,25-$(OH)_2D$	No treatment
Depression-Osteoblastic Stimulation, 3 months	Sodium fluoride, Ca and 25-OHD (+Thiazide in renal hypercalciuria)	Sodium fluoride Other treatment as in Group I
Free, 6 weeks	Ca and 25-OHD (+Thiazide in renal hypercalciuria)	Same treatment as in Group I

Our recently initiated proposal involves activation of osteoclasts by a short-term 1,25-$(OH)_2D$ administration in order to stimulate osteoblasts "naturally" via coupling. Fluoride is then used to further stimulate osteoblasts, recognizing the probable occurrence of defective coupling in osteoporosis. In patients with renal hypercalciuria, thiazide will be added to inhibit PTH-induced bone resorption. A fluoride-free period, in order to permit "normal" bone remodelling, will complete each sequence

which is to be repeated in successive fashion. This treatment is coherent, since the process of bone remodelling may be synchronized by sequential treatments involving osteoclastic activation followed by osteoblastic stimulation.

To the best of our knowledge, the particular sequential treatment proposed, involving 1,25-$(OH)_2D$, fluoride and thiazide has not been attempted in man before, although each has been extensively used. The uniqueness of our approach and departures from the classic coherence treatment of Frost[113] are discussed below.

By providing potent agents for osteoclastic activation and osteoblastic stimulation sequentially for defined periods, we are attempting to purposely manipulate the life time of bone remodelling units, possibly to considerably shorten it, from up to 2 years encountered in postmenopausal osteoporosis to approximately 5 months.

The treatment is initiated by activation with 1,25-$(OH)_2D$ for 2 weeks. By placing patients on a low calcium diet, it is hoped that a sufficient amount of 1,25-$(OH)_2D$ (2-4 µg/day) may be given in order to cause osteoclastic activation without provoking hypercalcemia. The time period of two weeks chosen is a compromise between the expected time required for activation and the presumed life-time of osteoclastic resorption (approximately 1 month normally). The duration of this period should be less than the duration of osteoclastic activity in order to permit a sufficient time for depression. The evidence that 1,25-$(OH)_2D$ may cause activation is derived from findings that this metabolite stimulated bone resorption in

vitro,[117,118] released lysosomal enzymes in bone culture,[119] augmented synthesis of skeletal coupling factor,[120] and restored skeletal responsiveness to PTH in vivo.[121]

The second step is osteoblastic stimulation and osteoclastic depression initiated simultaneously over a 3 month period with fluoride, calcium supplements, and a modest dose of 25-OHD (50 µg twice/week). The ability of fluoride to augment osteoblastic matrix synthesis is well established.[92] It is therefore hoped that fluoride would stimulate osteoblasts newly formed by coupling as well as recruit new osteoblasts (thereby correcting presumed coupling defect). A limited duration of fluoride treatment may reduce occurrence of adverse side effects and may potentially confine the formation of abnormal bone by allowing normal bone remodelling during its withdrawal period. Moreover, the intermittent administration of fluoride may minimize the loss of its effect on osteoblastic bone formation.[93] The duration of this period corresponds to the approximate normal life time of osteoblasts.

Calcium supplements and 25-OHD are given with sodium fluoride in order to depress PTH-induced osteoclastic resorption,[50] to prevent development of osteomalacia and promote mineralization of newly formed matrix during fluoride therapy.[89]

The third step is the fluoride-free period of 6 weeks which corresponds to the Free period of ADFR treatment of Frost.[113] Although fluoride treatment is stopped, calcium and 25-OHD are continually given in order to facilitate "normal bone remodelling", and to "correct" any mineralization defect which may have developed during fluoride therapy.

The above description conforms to the treatment for osteoporosis of low turnover,[9] the most common presentation of postmenopausal osteoporosis. Our proposal acknowledges the existence of osteoporosis of renal hypercalciuria, secondary hyperparathyroidism and high skeletal turnover. The above treatment program will be modified slightly to accommodate the treatment of this variant of osteoporosis. During the fluoride-treated and fluoride-free periods, thiazide will be added to correct renal leak of calcium and secondary hyperparathyroidism.[27] During the activation period, no thiazide will be given, so that secondary hyperparathyroidism would be manifest and add to the activation produced by $1,25\text{-}(OH)_2D$.

CONCLUSION

The ultimate goal of therapy is to augment mineralized bone volume, rather than simply to retard the rate of bone loss. To do so, it may be necessary to (a) increase bone turnover thereby raising the number of active bone remodelling units, and (b) augment osteoblastic matrix synthesis, so that formation would outweigh resorption. Most of the past treatment programs have been disappointing. However, an innovative approach entailing synchronized sequential osteoclastic activation followed by osteoblastic stimulation may potentially meet the above objective.

References

1. Riggs, B.L. 1979 Postmenopausal and senile osteoporosis: current concepts of etiology and treatment. Endo. Japan 1:31.
2. Frame, B. and A.M. Parfitt. 1978. Osteomalacia: current concepts. Ann. Int. Med. 89:966.
3. Frost, H.M. 1973. Bone Remodelling and Its Relation to Metabolic Bone Disease. Springfield, Charles C. Thomas.
4. Rasmussen, H. and P.J. Bordier. 1974. The Physiological and Cellular Basis of Metabolic Bone Disease. Baltimore, Williams and Wilkins.
5. Jaworski, Z.F.G. 1981. Physiology and pathology of bone remodelling. Orthop. Clin. N. Am. 12:485-512.
6. Anderson, H.C. 1978. Introduction to the 2nd Conference on Matrix Vesicle Calcification. Metab. Bone Dis. Rel. Res. 1:83.
7. Rasmussen, H. and P. Bordier. 1978. Vitamin D and bone. Metab. Dis. Rel. Res. 1:7.
8. Howell, D., J.C. Pita, and J. Alvarez. 1976. Possible role of extracellular matrix vesicles in initial calcification of healing rachitic cartilage. Fed. Proc. 35:122.
9. Meunier, P.J., P. Courpron, C. Edouard, C. Alexandre, C. Bressot, P. Lips, and B.F. Boyce. 1979. Bone histomorphometry in osteoporotic states, In: Osteoporosis II, U.S. Barzel (Ed.) Grune and Stratton, p. 27.
10. Riggs, B.L., C.D. Arnaud, J. Jowsey, R.S. Goldsmith, and P.J. Kelly. 1973. Parathyroid function in primary osteoporosis. J. Clin. Invest. 52:181.

11. Gallagher, J.C., B.L. Riggs, J. Eisman, A. Hamstra, S.B. Arnaud, and H.F. DeLuca. 1979. Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients. J. Clin. Invest. 64:729.

12. Singh, M., B.L. Riggs, J.W. Beabout, and J. Jowsey. 1973. Femoral trabecular pattern index for evaluation of spinal osteoporosis. Mayo Clin. Proc. 48:184.

13. Meema, S. and H.E. Meema. 1973. Age trends of bone mineral mass, muscle width, and subcutaneous fat in normals and osteoporotics. Calc. Tiss. Res. 12:101.

14. Lawoyin, S., S. Sismilich, R. Browne, and C.Y.C. Pak. 1979. Bone mineral content in patients with primary hyperparathyroidism, osteoporosis, and calcium urolithiasis. Metabolism. 28:1250.

15. Riggs, B.L., H.W. Wahner, W.L. Dunn, R.B. Mazess, K.P. Offord, and L.J. Melton, III. 1981. Differential changes in bone mineral density of the appendicular and axial skeleton with aging. J. Clin. Invest. 67:328.

16. Whyte, M.P., M.A. Bergfeld, W.A. Murphy, L.V. Avioli, and S.L. Teitelbaum. 1982. Postmenopausal osteoporosis. A heterogeneous disorder as assessed by histomorphometric analysis of iliac crest bone from untreated patients. Am. J. Med. 72:193.

17. Recker, R.R. 1981. Continuous treatment of osteoporosis: current status. Orthoped. Clin. N. Am. 12:611.

18. Pak, C.Y.C. Postmenopausal osteoporosis. In: Clinical Perspectives in Obstetrics and Gynecology. Vol. I The Menopause. Springer-Verlag.

19. Heaney, R.P., R.R. Recker, and P.D. Saville. 1978. Menopausal changes in calcium balance performance. J. Lab. Clin. Med. 92:953.

20. Ireland, P. and J.S. Fordtran. 1973. Effect of dietary calcium and age on jejunal calcium absorption in humans studied by intestinal perfusion. J. Clin. Invest. 52:2672.

21. Matkovic, V., K. Kostial, J. Simonvic, et al. 1979. Bone status and fracture rates in two regions of Yugoslavia.Am. J. Clin. Nutr. 32:540.

22. Birge, S.J., H.T. Keutmann, P. Cuatrecasas, and G.C. Whedon. 1967. Osteoporosis, intestinal lactase deficiency and low dietary calcium intake. N. Engl. J. Med. 276:445.

23. Vergne-Marini, P., T.F. Parker, C.Y.C. Pak, A.R. Hull, H.F. DeLuca, and J.S. Fordtran. 1976. Jejunal and ileal calcium absorption in patients with chronic renal disease. Effect of 1α-hydroxycholecalciferol. J. Clin. Invest. 57:861.

24. Nordin, B.E.C., A. Horsman, R.G. Crilly, et al. 1980. Treatment of spinal osteoporosis in postmenopausal women. Brit. Med. J. 280:451.

25. Recker, R.R., P.D. Saville, and R.P. Heaney. 1977. Effect of estrogens and calcium carbonate on bone loss in postmenopausal women. Ann. Int. Med. 87:649.

26. Riggs, B.L., P.J. Kelly, V.R. Kinney, et al. 1967. Calcium deficiency and osteoporosis. J. Bone Joint Surg. 49A:915.

27. Zerwekh, J.E. and C.Y.C. Pak. 1980. Selective effect of thiazide therapy on serum 1α,25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hypercalciurias. Metabolism 29:13.

28. Sutton, R.A.L. and J.H. Dirks. 1977. Renal handling of calcium: overview, In: Phosphate Metabolism, eds. S.G. Massry and E. Ritz, Plenum Publishing Co., New York, vol. 81, p. 15.

29. Porter, R.H., B.G. Cox, D. Heaney, T.H. Hostetter, B.J. Stinebaugh, and W.N. Suki. 1978. Treatment of hypoparathyroid patients with chlorthalidone. N. Engl. J. Med. 298:577.

30. Parfitt, A.M. 1969. Chlorothiazide-induced hypercalcemia in juvenile osteoporosis and hyperparathyroidism. N. Engl. J. Med. 281:55.

31. Pickleman, J.R., F.H. Straus, II, M. Forland, and E. Paloyan. 1969. Thiazide-induced parathyroid stimulation. Metabolism 18:867.

32. Brickman, A.S., S.G. Massry, and J.W. Coburn. 1972. Changes in serum and urinary calcium during treatment with hydrochlorothiazide: Studies on mechanisms. J. Clin. Invest. 51:945.

33. Koppel, M.H., S.G. Massry, J.H. Shinaberger, D.L. Hartenbower, and J.W. Coburn. 1970. Thiazide-induced rise in serum calcium and magnesium in patients on maintenance hemodialysis. Ann. Intern. Med. 72:895.

34. Hahn, T.J. and L.V. Avioli. 1970. Effects of parenteral thiazide administration on parathyroid function. Clin. Res. 18:31A.

35. Yendt, E.R. and M. Cohanim. 1978. Prevention of calcium stones with thiazides. Kid. Int. 13:397.

36. Malluche, H.H., W.A. Meyer, F.R. Singer, and S.G. Massry. 1979. Thiazide induced increased density of osteocytes: a mechanism for the rise in serum calcium by thiazides. Am. Soc. Nephrol. Abstracts. December, p. 57A.

37. Yendt. E.R. 1970. Renal calculi. Can. Med. Assoc. J. 102:479.

38. Gursel, E. 1970. Effects of diuretics on renal and intestinal handling of calcium. N.Y. State J. Med. 70:399.

39. Palayan, E., M. Forland, and J.R. Pickleman. 1969. Hyperparathyroidism coexisting with hypertension and prolonged thiazides administration. J. Am. Med. Assoc. 210:1243.

40. Transbol, I., M.S. Christensen, G.F. Jensen, C. Christiansen, and P. McNair. 1982. Thiazide for the postponement of postmenopausal bone loss. Metabolism. 31:383.

41. Taggart, H.M., J.L. Ivey, K. Sisom, C.H. Chestnutt, III, D.J. Baylink, M.B. Huber, and B.A. Roos. 1982. Deficient calcitonin response to calcium stimulation in postmenopausal osteoporosis. Lancet Feb. 27:475.

42. Aliapoulios, M.A., P. Goldhaber, and P.L. Munson. 1966. Thyrocalcitonin inhibition of bone resorption induced by parathyroid hormone in tissue culture. Science 151:330.

43. Jowsey, J., B.L. Riggs, R.S. Goldsmith, P.J. Kelly, and C.D. Arnaud. 1971. Effects of prolonged administration of porcine calcitonin in postmenopausal osteoporosis. J. Clin. Endocrinol. Metab. 33:752.

44. Wallach, S., S.H. Cohn, H.L. Atkins, et al. 1977. Effect of salmon calcitonin on skeletal mass in osteoporosis. Curr. Ther. Res. 22:556.

45. Jowsey, J., B.L. Riggs, P.J. Kelly, and D.L. Hoffman. 1978. Calcium and salmon calcitonin in treatment of osteoporosis. J. Clin. Endocrinol. Metab. 47:633.

46. Lawoyin, S., J.E. Zerwekh, K. Glass, and C.Y.C. Pak. 1980. Ability of 25-OH-vitamin D_3 therapy to augment serum 1,25-$(OH)_2D$ and 24,25-$(OH)_2$ vitamin D in postmenopausal osteoporosis. J. Clin. Endocrinol. Metab. 50:593.

47. Slovik, D.M., J.S. Adams, R.M. Neer, M.F. Holick, J.T. Potts. 1981. Deficient production of 1,25-dihydroxyvitamin D in elderly osteoporotic patients. N. Engl. J. Med. 305:372.

48. Riggs, B.L., A. Hamstra, H.F. DeLuca. 1981. Assessment of 25-hydroxyvitamin D 1α-hydroxylase reserve in postmenopausal osteoporosis by administration of parathyroid extract. J. Clin. Endocrinol. Metab. 53:833.

49. Lore, F., G. DiCairaro, A.M. Signorini, and A. Caniggia. 1981. Serum levels of 25-hydroxyvitamin D in postmenopausal osteoporosis. Calc. Tiss. Res. 33:467.

50. Riggs, B.L., J. Jowsey, P.J. Kelly, D.L. Hoffman, and C.D. Arnaud. 1976. Effects of oral therapy with calcium and vitamin D in primary osteoporosis. J. Clin. Endocrinol. Metab. 42:1139.

51. Davies, M., E.B. Mawer, and P.H. Adams. 1977. Vitamin D metabolism and the response to 1,25-dihydroxycholecalciferol in osteoporosis. J. Clin. Endocrinol. Metab. 45:199.

52. Christiansen, C., M.S. Christensen, P. Rodbro, C. Hagen, and I. Transbol. 1981. Effect of 1,25-dihydroxyvitamin D in itself or combined with hormone treatment in preventing postmenopausal osteoporosis. Europ. J. Clin. Invest. 11:305.

53. Wandless, I., S. Jarvis, and J.G. Evans. 1980. Vitamin D_3 in osteoporosis. Brit. Med. J. 280:1320.

54. Gallagher, J.C., B.L. Riggs, and H.F. DeLuca. 1980. Effect of estrogen on calcium absorption and serum vitamin D metabolites in postmenopausal osteoporosis. J. Clin. Endocrinol. Metab. 51:1359.

55. Orimo, H., T. Fujita, and M. Yoshikawa. 1972. Increased sensitivity of bone to parathyroid hormone in ovariectomized rats. Endocrinol. 90:760.

56. Hossain, M., D.A. Smith, and B.E.C. Nordin. 1970. Parathyroid activity and postmenopausal osteoporosis. Lancet 1:809.

57. Pak, C.Y.C., A. Stewart, R. Kaplan, H. Bone, C. Notz, and R. Browne. 1975. Photon absorptiometric analysis of bone density in primary hyperparathyroidism. Lancet 2:7.

58. Reifenstein, E.C., Jr., and F. Albrigt. 1947. Metabolic effects of steroid hormone in osteoporosis. J. Clin. Invest. 26:24.

59. Wallach, S. and P.H. Henneman. 1959. Prolonged estrogen therapy in postmenopausal women. J. Am. Med. Assoc. 171:1637.

60. Canniggia, A. and C. Gennari. 1972. Sites and modes of action of an estrogen-gestagen combination of calcium and phosphate metabolism in postmenopausal osteoporosis. Clin. Orthop. 85:187.

61. Aitken, J.M., D.M. Hart, and D.A. Smith. 1971. The effect of long-term mestranol administration on calcium and phosphorus homeostasis in oophorectomized women. Clin. Sci. 41:233.

62. Young, M.M., C. Jasani, D.A. Smith, and B.E.C. Nordin. 1968. Some effects of ethinyl oestradiol on calcium and phosphorus metabolism in osteoporosis. Clin. Sci. 34:411.

63. Riggs, B.L., J. Jowsey, P.J. Kelly, J.D. Jones, and F.T. Maher. 1969. Effect of sex hormones on bone in primary osteoporosis. J. Clin. Invest. 48:1065.

64. Riggs, B.L., J. Jowsey, R.S. Goldsmith, P.J. Kelly, D.L. Hoffman, and C.D. Arnaud. 1972. Short- and long-term effects of estrogen and synthetic anabolic hormone in postmenopausal osteoporosis. J. CLin. Invest. 51:1659.

65. Atkins, D., J.M. Zanelli, M. Peacock, and B.E.C Nordin. 1972. The effect of oestrogens on the respone of bone to parathyroid hormone in vitro. J. Endocrinol. 54:107.

66. Caputo, C.B., D. Meadows, and L. Raisz. 1976. Failure of estrogen and androgen to inhibit bone resorption in tissue culture. Endocrinol. 98:1065.

67. Kaplan, R.A., M.R. Haussler, L.J. Deftos, H. Bone, and C.Y.C. Pak. 1977. The role of 1α,25-dihydroxy vitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J. Clin. Invest. 59:756.

68. Garabedian, M., M.F. Holick, H.F. DeLuca, and I.T. Boyle. 1972. Control of 25-hydroxycholecalciferol metabolism by parathyroid glands. Proc. Nat. Acad. Sci. U.S.A.

69. Tanaka, Y., L. Castillo, and H.F. DeLuca. 1976. Control of renal vitamin D hydroxylases in birds by sex hormones. Proc. Natl. Acad. Sci. 73:2701.

70. Hughes, M.R., P.R. Brumbaugh, M.R. Haussler, J.E. Wergedal, D.J. Baylink. 1975. Regulation of serum 1α,25-dihydroxyvitamin D_3 by calcium and phosphate in the rat. Science 190:578.

71. Cohn, S.H., A. Vaswani, I. Zanzi, et al. 1976. Effect of aging on bone mass in adult women. Am. J. Physiol. 230:143.

72. Smith, D.M., M.R.A. Khairi, J. Norton, et al. 1976. Age and activity effects on rate of bone mineral loss. J. Clin. Invest. 58:716.

73. Ivey, J.L. and D.J. Baylink. 1981. Postmenopausal osteoporosis: proposed roles of defective coupling and estrogen deficiency. Metab. Bone and Res. 3:3.

74. Lindsey, R., J.R.T. Coutts, and D.M. Hart. 1977. The effect of endogenous oestrogen on plasma and urinary calcium and phosphate in oophorectomized women. Clin. Endocrinol. (Oxford) 6:87.

75. Marshall, D.H., R.G. Crilly, and B.E.C. Nordin. 1977. Plasma androstenedione and oestrone levels in normal and osteoporotic postmenopausal women. Brit. Med. J. 2:1177.

76. Avioli, L.V. 1981. Postmenopausal osteoporosis: prevention versus cure. Federat. Proc. 40:2418.

77. Riggs, B.L., R.J. Ryan, H.W. Wahner, N.S. Jiang, and V.R. Mattox. 1973. Serum concentrations of estrogen, testosterone and gonadotropins in osteoporotic and nonosteoporotic postmenopausal women. J. Clin. Endocrinol. Metab. 36:1097.

78. Adlin, E.V. and S.G. Korenman. 1980. Endocrine aspects of aging. Ann. Int. Med. 92:429.

79. Davidson, B.J., B.L. Riggs, C.B. Conlam, and D.O. Toft. 1978. Concentration of cytosolic estrogen receptors in patients with postmenopausal osteoporosis. Clin. Res. 26:678A.

80. Van Paassen, H.C., J. Poortman, I.M.C. Borgart-Creutzburg, J.H.H. Thijssen, and S.A. Duursma. 1978. Oestrogen binding proteins in bone cell cytosol. Calc. Tiss. Res. 25:249-254.

81. Lindsay, R., D.M. Hart, C. Forrest, and C. Baird. 1980. Prevention of spinal osteoporosis in oophorectomised women. Lancet November 29, p. 1151.

82. Lindsay, R., J.M. Aitken, J.B. Anderson, D.M. Hart, E.B. MacDonald, and A.C. Clarke. 1976. Long-term prevention of postmenopausal osteoporosis by oestrogen. Lancet, May 15, p. 1038.

83. Christiansen, C., M.S. Christensen, and I. Transbol. 1981. Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet, February 28, p. 459.

84. Christiansen, C., R.B. Mazess, I. Transbol, and G.F. Jensen. 1981. Factors in response to treatment of early postmenopausal bone loss. Calcif. Tiss. Int. 33:575.

85. Hutchinson, T.A., J.M. Polansky, and A.R. Feinstein. 1979. Postmenopausal oestrogens protect against fractures of hip and distal radius. Lancet 2:705.

86. Weinstein, M.C. 1980. Estrogen use in postmenopausal women--costs, risks, and benefits. N. Engl. J. Med. 303:308.

87. Pak, C.Y.C. 1979. Physiological basis for absorptive and renal hypercalciurias. Am. J. Physiol. 237:F415.

88. Pak, C.Y.C., M.J. Nicar, and C. Northcutt. 1981. The definition of the mechanism of hypercalciuria is necessary for the treatment of recurrent stone formers. In: Issues of Nephrology. Accepted.

89. Jowsey, J., R.K. Schenk, and F.W. Reutter. 1968. Some results of the effect of fluoride on bone tissue in osteoporosis. J. Clin. Endocrinol. Metab. 28:869.

90. Rich, C., and J. Ensinck. 1961. Effect of sodium fluoride on calcium metabolism of human beings. Nature 191:184.

91. Cass, R.M., J.D. Croft, Jr., P. Perkins, W. Nye, C. Waterhouse, and R. Terry. 1966. New bone formation in osteoporosis following treatment with sodium fluoride. Arch. Intern. Med. 118:111.

92. Jowsey, J., B.L. Riggs, P.J. Kelly, and D.L. Hoffman. 1972. Effect of combined therapy with sodium fluoride, vitamin D and calcium in osteoporosis. Am. J. Med. 53:43.

93. Briancon, D. and P.J. Meunier. 1981. Treatment of osteoporosis with fluoride, calcium, and vitamin D. Ortho. Clin. N. Am. 12:629.

94. Harrison, J.E., K.G. McNeill, W.C. Sturtridge, T.A. Bayley, T.M. Murray, C. Williams, C. Tam, and V. Fornasier. 1981. Three-year changes in bone mineral mass of postmenopausal osteoporotic patients based on neutron activation analysis of the central third of the skeleton. J. Clin. Endocrinol. Metab. 52:751.

95. McCann, H.G. 1968. The solubility of fluorapatite and its relationship to that of calcium fluoride. Arch. Oral. Biol. 13:987.

96. Wolinsky, I., A. Simkin, and K. Guggenheim. 1972. Effects of fluoride on metabolism and mechanical properties of rat bone. Am. J. Physiol. 223:46.

97. Riggs, B.L., S.F. Hodgson, D.L. Hoffman, P.J. Kelly, K.A. Johnson, and D. Taves. 1980. Treatment of primary osteoporosis with fluoride and calcium. Clinical tolerance and fracture occurrence. J. Am. Med. Assoc. 243:446.

98. Riggs, B.L., E. Seeman, S.F. Hodgson, D.R. Taves, and W.M. O'Fallon. 1982. Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. N. Engl. J. Med. 306:446.

99. Burkhart, J.M. and J. Jowsey. 1967. Parathyroid and thyroid hormones in the development of immobilization osteoporosis. Endocrinol. 81:1053.

100. Bone, H.G., III, W.H. Snyder, and C.Y.C. Pak. 1977. Diagnosis of hyperparathyroidism. Ann. Rev. Med. 28:111.

101. Ashton, B.A., M.R. Owen, C.C. Eagleson, and J.A. Parsons. 1981. In: Endocrinology of Calcium Regulating Hormones. Eds. D.V. Cohn and R.V. Talmage. Excerpta Medica, Amsterdam.

102. Frost, H.M. 1979. Treatment of osteoporosis by manipulation of coherent bone cell populations. Clin. Orthop. 143:227.

103. Kalu, D.N., J. Pennock, F.H. Doyle, and G.V. Foster. 1970. Parathyroid hormone and experimental osteosclerosis. Lancet 1:1363.

104. Genant, H.K., J.M. Baron, E. Paloyan, and J. Jowsey. 1975. Osteosclerosis in primary hyperparathyroidism. Am. J. Med. 59:104.

105. Kaye, M., J.E. Pritchard, G. Halpenny, and W. Wright. 1960. Bone disease in chronic renal failure with particular reference to osteosclerosis. Medicine (Balt.) 39:157.

106. Teitelbaum, S.L., M.A. Bergfeld, J. Freitag, K.A. Hruska, and E. Slatopolsky. 1980. Do parathyroid hormone and 1,25-dihydroxyvitamin D modulate bone formation in uremia J. Clin. Endocrinol. Metab. 51:247.

107. Reeve, J., D. Williams, R. Hesp, P. Hulme, L. Klenerman, J.M. Zanelli, A.J. Darby, G.W. Tregear, and J.A. Parsons. 1976. Anabolic effect of low doses of a fragment of human parathyroid hormone on the skeleton in postmenopausal osteoporosis. Lancet 1035.

108. Slovik, D.M., R.M. Neer, and J.T. Potts. 1981. Short-term effects of synthetic human parathyroid hormone-(1-34) administration on bone mineral metabolism in osteoporotic patients. J. Clin. Invest. 68:1261.

109. Parsons, J.A., P. Meunier, R. Podbesek, J. Reeve, and R.W. Stevenson. 1981. Pathological and therapeutic implications of the cellular and humoral response to parathyroin. Biochm. Soc. Trans. 9:383.

110. Reeve, J., M. Arlot, M. Bernat, S. Charhon, C. Edouard, D. Slovik, F.J.F.E. Vismans, and P.J. Meunier. 1981. Calcium-47 kinetic

measurements of bone turnover compared to bone histomorphometry in osteoporosis: the influence of human parathyroid fragment (hPTH 1-34) therapy. Metab. Bone Dis. Rel. Res. 3:23.

111. Reeve, J., P. Meunier, J.A. Parsons, et al. 1980. Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicenter trial. Brit. Med. J. 2:1340.

112. Gallagher, J.C., C.M. Jerpbak, W.S.S. Jee, K.A. Johnson, H.F. DeLuca, and B.L. Riggs. 1982. 1,25-Dihydroxyvitamin D_3: Short- and long-term effects on bone and calcium metabolism in patients with post-menopausal osteoporosis. Proc. Natl. Acad. Sci. 79:3325.

113. Frost, H.M. 1981. Coherence treatment of osteoporosis. Orthop. Clin. N. Am. 12:649.

114. Pak, C.Y.C., E. Zisman, R. Evens, J. Jowsey, C. Delea, and F.C. Bartter. 1969. Treatment of osteoporosis with calcium infusion. Am. J. Med. 47:7.

115. Jowsey, J., F.C. Hoye, C.Y.C. Pak, and F.C. Bartter. 1969. The treatment of osteoporosis with calcium infusion. Evaluation of bone biopsies. Am. J. Med. 27:17.

116. Walton, J., M. Dominquez, and F.C. Bartter. 1975. Effects of calcium infusion in patients with postmenopausal osteoporosis. Metab. 24:849.

117. Reynolds, J.J., H.F. Holick, and H.F. DeLuca. 1973. The role of vitamin D metabolites on bone resorption. Calcif. Tiss. Res. 12:295.

118. Raisz, L.G., C.L. Trummel, M.F. Holick, and H.F. DeLuca. 1972. 1α,25-dihydroxycholecalciferol, a potent stimulator of bone resorption in tissue culture. Science 175:768.

119. Lerner, U. and G.T. Gustafson. 1982. Inhibition of 1α-hydroxy-vitamin D_3 stimulated bone resorption in tissue culture by the calcium antagonist verapamil. Europ. J. Clin. Invest. 12:185.

120. Farley, J.R., A.K. Taylor, and D.J. Baylink. 1982. PTE and $1,25\text{-}(OH)_2D_3$ can modulate the effects of a putative skeletal coupling factor in vitro. In: The American Society for Bone and Mineral Research. Abstracts of the Fourth Annual Scientific Meeting. p. 38.

121. Massry, S.G., S. Kua, J. Garty and R.M. Friedler. 1978. Role of uremia in the skeletal resistance to the calcemic action of parathyroid hormone. Min. Elect. Metab. 1:172.