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OSTEOPOROSIS: CURRENT CONCEPTS

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In 1900 the average life expectancy in this country was 47 years; today it is 73 years. As we live longer, however, age related diseases become an increasing problem. Osteoporosis, in its postmenopausal and senile forms, is a prime example. Characterized by a universal, gradual, and relentless reduction in bone mass, it compromises the mechanical competence of the skeleton to such an extent that even minimal trauma may result in fracture. The disease is considerably more prevalent in women than men. Figure 1 illustrates fracture incidence as a function of age in

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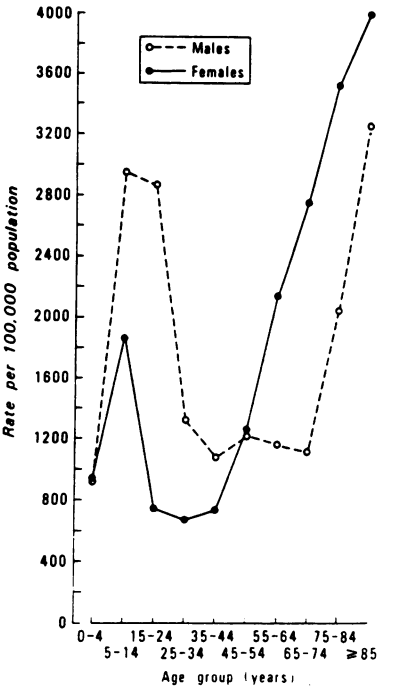

Fig. 1. Fracture incidence as a function of age in males and females. Reproduced by permission from Garroway, W. M., Stauffer, R. N., Kurland, L. T., and O'Fallon, W. M.: Limb fracture in a defined population. I. Frequency of distribution. *Mayo Clin. Proc.* *54*:701-07, 1979.

both sexes, and demonstrates the rapid rise in fracture incidence which begins in the fourth decade in women. It is estimated that by age 65, 25% of all women suffer from osteoporosis, which amounts to more than three million women in the United States alone. Black women are virtually exempt from this increase in fractures. This racial dimorphism is most probably due to a higher bone mass at skeletal maturity in black women[1] although some data conflict with this view.[2] It does appear that bone loss also occurs with aging among blacks.

The three main fracture sites associated with osteoporosis are the vertebrae (particularly lower thoracic and lumbar), distal radius (Colles fracture), and, by far the most serious, femoral neck fracture (transcervical and intertrochanteric). Vertebral crush fractures are responsible for loss of height and the familiar "dowager's hump," which is often associated with considerable morbidity (Figure 2). In severe cases the lower ribs may come to rest on the iliac crests, resulting in the cessation

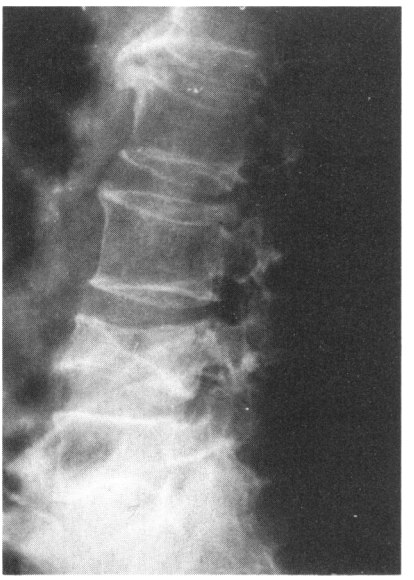

Fig. 2. Vertebral crush fracture in a female patient with established osteoporosis.

of vertebral fractures and replacement of back pain by rib pain.

The magnitude of the public health problem posed by osteoporosis can be appreciated if we consider the fact that there are almost 300,000 femoral neck fractures each year in the United States alone.[3] Moreover, approximately 10% of these patients die within three months of their fractures as a result of perioperative and postoperative complications. If we make the reasonable assumption that the fracture, and therefore osteoporosis, was the indirect cause of death, osteoporosis would then rank about 12th in the list of leading causes of death in the United States. Moreover, there is a significant financial burden on society. The acute care of hip fracture patients alone currently costs over $1 billion, mostly from Medicare funds. Recent data suggest that fracture frequency may be increasing (Figure 3). Both femoral neck and vertebral fractures have increased by 40% during the past decade. From these figures we have predicted that acute health care costs for hip fracture alone will exceed $3 billion by the end of this decade and may top $5 billion by the year 2000.[4]

Bone loss in osteoporosis is insidious, progressing asymptomatically until a fracture occurs. This, coupled with the high prevalence of the disease, has prompted description of osteoporosis as the "silent epi-

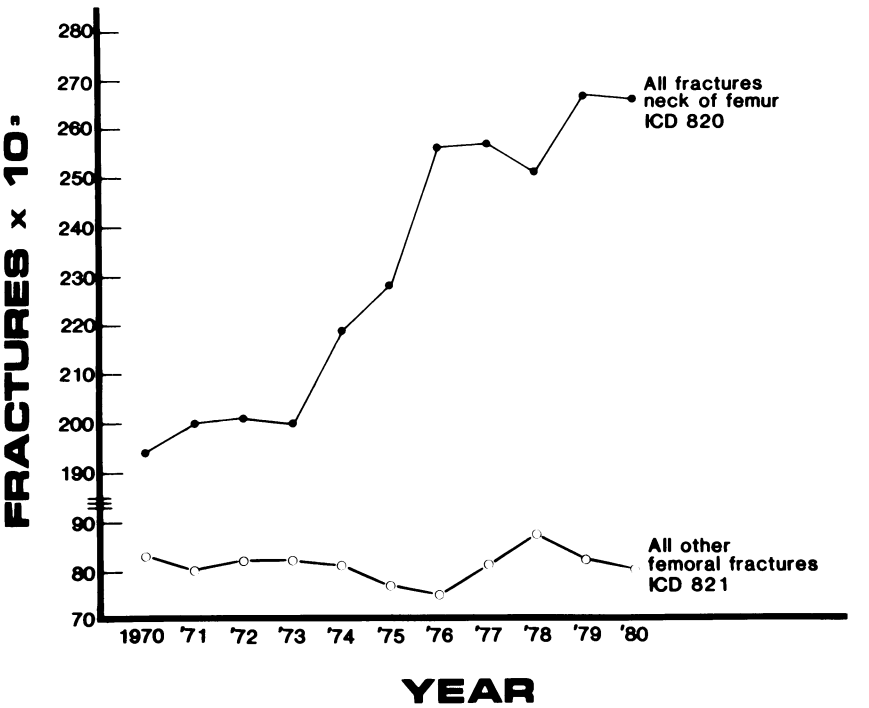

Fig. 3. Fractures of the femoral neck in the USA from 1970 through 1980. Numbers are in thousands. For comparison, all other fractures of the femur are shown (defined to be traumatic).

demic.'' Bone loss by itself is not obvious to the average physician because at present there is no widely available, simple, accurate and precise method to measure bone mass. Radiography is, by itself, insensitive, and applications of denitometric estimations to radiographic techniques tend also to be inaccurate with poor precision. Radiogrammetry, in which measurements of cortical thickness are made, yields good data in skilled hands for cross-sectional and longitudinal studies, provided the sample size is large. Single photon absorptiometry[5] is a sealed isotope technique, and is currently the most widely used technique for estimation of bone mass. Accuracy and precision are such that good cross-sectional data can be produced, and longitudinal studies may be performed on relatively small groups. Single photon absorptiometry is however applicable only to peripheral skeletal sites consisting primarily of cortical bone. Each of these techniques has only limited value in diagnosis, and treatment of individual patients because they measure only cortical bone

and changes occurring at these sites are slower, may differ from those at trabecular bone sites, and may not necessarily be representative of patterns of change at fracture sites.

Dual photon absorptiometry and computerized axial tomography can both be used to estimate bone mineral content of the spine, and the former has also been used successfully to measure bone mineral in the femoral neck, as well as total body calcium.[6,7] Current availability of both techniques is somewhat limited. In addition, no readily available non-invasive techniques can give a rapid estimate of bone turnover so that a physician can measure not only the patient's current bone status but also the rate of change. All mass measurements require repeat estimations, with a time gap of about six months before any prediction about rate of loss can be made for an individual patient.

In the absence of easy access to methods of measurement of bone mass and turnover, to give advice to his patients the clinician must estimate risk for each individual based on a number of clinical factors (see table). In our experience, family history of osteoporosis-associated fractures may be obtained in 75% of patients presenting with established disease. Whether this represents a genetic factor or other life style influences is unclear, but since inheritance of physical characteristics is common and identical twins do have essentially the same bone mass, undoubtedly genetic influences are important. We feel that the most important factors are: choosing one's parents, diet, exercise patterns throughout life, and age at menopause. It is important to emphasize that dietary factors may be important throughout life, influencing bone mass at maturity as well as perhaps reducing subsequent rate of loss. The same may be true of exercise.

Prevention

Prevention of osteoporosis, rather than cure, is not only a more desirable but probably a more realistic goal. The basis of preventive therapy lies in correcting these risk factors which the individual patient may demonstrate. Therefore, attention to diet and life style are of prime importance.

Dietary factors. Undoubtedly, the most important aspect of diet is calcium intake. The most compelling evidence that dietary calcium influences skeletal mass and fracture incidence has come from the study by Matkovic et al.,[8] who showed that Yugoslavian women with a high calcium intake (810 to 940 mg/day) had a higher metacarpal cortical area

RISK FACTORS FOR OSTEOPOROSIS

Racial factors (white, oriental)
A positive family history
Early menopause or ovariectomy
Small and slender physique
Nulliparity
Sedentary lifestyle
Poor diet, particularly low calcium intake
Excessive animal protein intake
Alcohol abuse
Cigarette smoking
Excessive caffeine intake
Hypercortisolism (endogenous or exogenous)
Thyrotoxicosis

at all ages than women from an otherwise similar region where calcium intake was low (340 to 445 mg/day). Although the rate of bone loss was the same in each group, the fracture rate for the proximal femur was much greater in the low calcium group after age 55. Apparently, adequate dietary calcium is a prerequisite for establishment of maximum skeletal status at maturity, but it is not an important factor in the prevention of subsequent loss of bone. In an elegant cohort study, Heaney and his associates[9,10] quantified the positive relationship between calcium intake and calcium balance in women. The study predicts a daily calcium intake requirement of 1,000 mg for premenopausal women to maintain zero balance (no net gain or loss of calcium). After menopause, the calcium requirement increases to 1,500 mg/day. This is almost twice the current recommended daily allowance of 800 mg/day and considerably in excess of the average dietary intake. More than 75% of American women over age 35 years have calcium intakes below the recommended allowance, and about 25% of all American women ingest less than 300 mg calcium per day.[11]

Supplementation of dietary calcium to the levels recommended by Heaney[11] may retard the rate of bone loss in postmenopausal women.[12,13] However, in both these studies calcium therapy (to give an estimated total daily intake of 1.5 g/day) was somewhat less effective than estrogen. On

the other hand, Christiansen et al.,[14] studying a group of Danish women with a relatively high daily calcium intake, failed to find a significant preventive effect of calcium. Calcium supplementation is indicated in women who are thought to be at risk from osteoporosis but who have contraindications for estrogen therapy. We generally recommend, therefore, a high calcium intake (1.5 g/day) for all women over 40 years old. Usually this requires supplementation with calcium as calcium carbonate. (A 500 mg tablet of calcium carbonate yields only 200 mg of elemental calcium.)

Physical exertion. It has been known for some time that immobilization and weightlessness promote bone loss—so-called disuse osteoporosis.[15,16] Evidence is now accumulating that the converse is also true, i.e., physical exertion may increase bone mass.[17, 18] There is a reasonable correlation between muscle mass, as estimated from total body potassium, and skeletal mass, as estimated from total body calcium.[19,20] Also, local skeletal hypertrophy corresponding to the most frequently exercised muscles has been reported in chain-saw operators, tennis players, ballet dancers, and weight-lifters.[21,22,23] However, few prospective studies have addressed the question: does exercise increase bone mass and/or reduce fracture rate in postmenopausal females? Smith et al.[24] investigated the effect of a three-year mild exercise program on the bone mineral content of the distal radius of aged female nursing home residents. They demonstrated a 4.2% increase in bone mineral content in the exercising subjects in the face of a 2% loss in the control group. Aloia and his colleagues[19] recorded a 2.6% increase in total body calcium in a group of postmenopausal women who exercised for one hour three times per week over a period of one year, and found that the daily calcium balance of the exercising subjects was significantly greater than a group of sedentary controls. However, there was no change in the bone mineral content of the distal radius.

Our present policy is to prescribe an exercise program compatible with the patient's general health and mobility. Vigorous isotonic exercises are the best. We find swimming to be most effective for patients with established disease, but, if the patient cannot swim, exercising in the therapeutic pool is also very beneficial. Many patients perform better in the pool because the risk and fear of injury are much reduced. This regimen has the additional advantage that it relieves the muscle pain, which is often the most severe problem in crush fracture syndrome. We

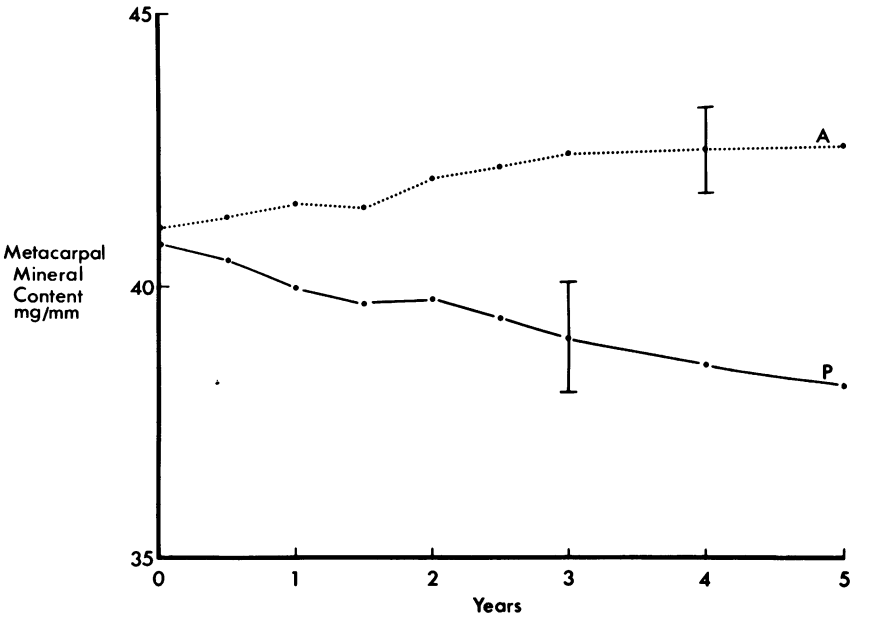

Fig. 4. Effect of mestranol (24 μg/day) and placebo on metacarpal mineral content in ovariectomized females. Reproduced by permission from Lindsay, R., Hart, D. M., Aitken, J. M., et al.: Long-term prevention of osteoporosis by estrogen. *Lancet* *1:*1038-41, 1976.

do not, however, as yet have any indication of whether or not such a program will influence bone mass.

Estrogens. There is now ample evidence from long-term prospective studies that sex hormone therapy can prevent bone loss from both peripheral and axial sites (Figures 4 and 5).[25,26,27,28] However, the primary aim of such therapy is not only to prevent bone loss per se, but also to lessen the risk of fracture. In an epidemiological study, Weiss et al.[29] found that the risk of hip and forearm fracture was more than halved among women who used estrogens for six years or longer. This decreased risk was only observed in women who were still taking estrogens at the time of survey. Taking estrogens for less than six years conferred little, if any, benefit in terms of reducing fracture risk. However, other case control and retrospective reviews have suggested that even short term estrogen exposure may somewhat reduce fracture incidence.

All of the common estrogens, when used at the appropriate dose, seem to be effective in preventing further bone loss. For conjugated equine estrogens, the most commonly prescribed estrogen preparation, the

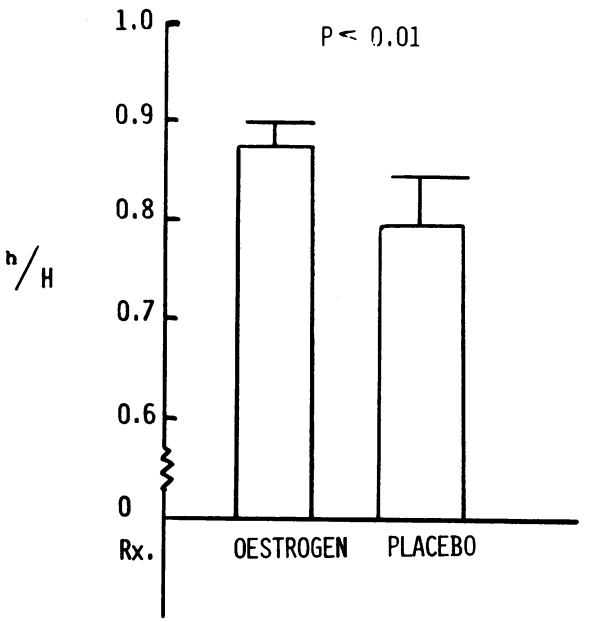

Fig. 5. Effect of estrogen treatment on the ratio of central height (h) to posterior height (H) of the second lumbar vertebra. The reduced ratio in the placebo treated group indicates the greater degree of structural failure of the vertebral body. Reproduced by permission from Lindsay, R., Hart, D. M., Aitken, J. M., et al.: Long-term prevention of osteoporosis by estrogen. *Lancet 1:*1038-41, 1976.

minimum effective dose is 0.625 mg/day (Figure 6).[30] The use of progestogens may not be as beneficial as our preliminary results with a depot compound[31] led us to believe.[32] However, OD14 (Organon, Oss, Netherlands), a synthetic progestogenic compound with mild anabolic and estrogenic activity, is apparently very effective (Figure 7),[33] and can be used in a dose that does not cause endometrial hypertrophy. One important problem with hormone replacement therapy is that, once commenced, the treatment must be maintained for a long period (probably 10 or more years). Withdrawal of estrogen therapy results in a sharp acceleration of bone loss, as though the patient had reentered the immediate postmenopausal years and bone mass falls rapidly (Figure 8).[34] This agrees with the finding from the study of Weiss et al.[28] that cessation of estrogen therapy negated any benefit that may have been gained in terms of reduced risk of fracture.

We currently only recommend hormone therapy to patients who have reduced bone mass as determined by dual photon absorptiometry early in

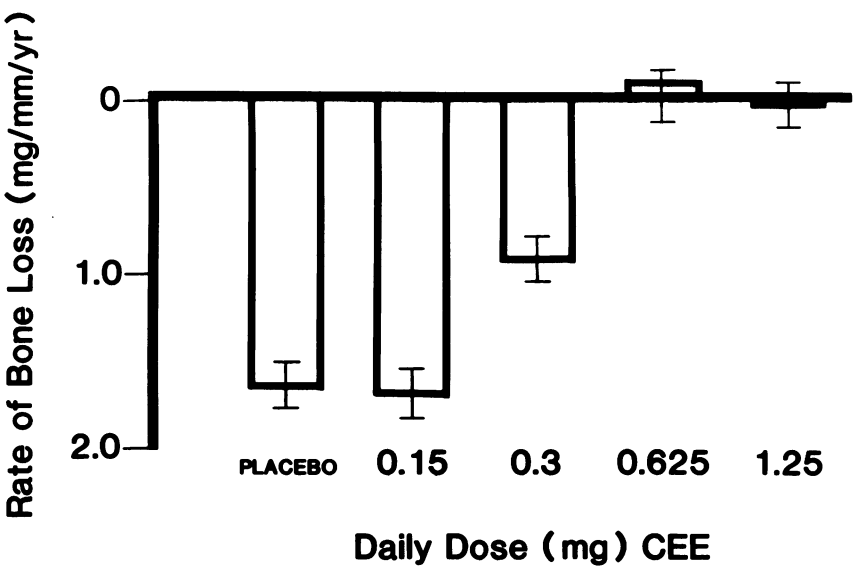

Fig. 6. Rate of bone loss, as determined by single photon absorptiometry of the metacarpal in postmenopausal women receiving four different doses of conjugated equine estrogens.

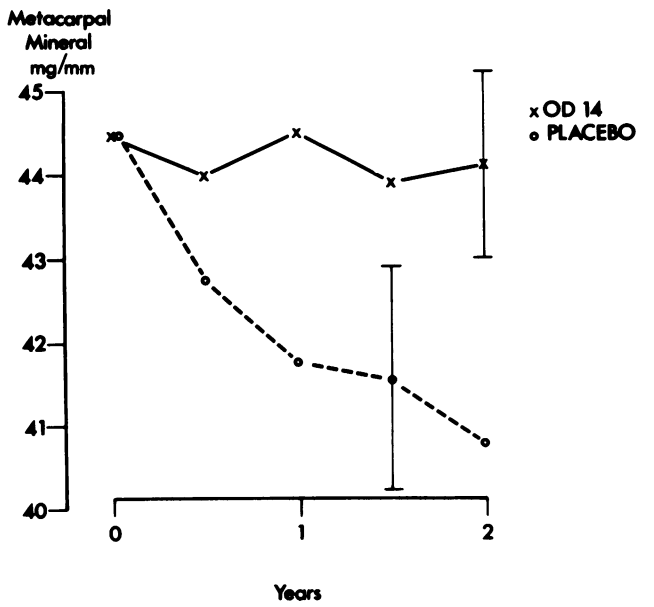

Fig. 7. Metacarpal mineral content during treatment of postmenopausal women with OD14 (Organon) or a placebo. Significant loss of bone is evident in the placebo group with no bone loss activity in the group treated with OD14.

the postmenopausal stage of their lives and if the addition of an exercise program and calcium supplementation fails to retard bone loss. The usual prescription technique provides an estrogen preparation for 21 days starting on the first day of each calendar month. If the uterus is intact, a progestogen is added from day 11 to 21. Nothing is prescribed for the remainder of the month. Although this cyclic administration of the two hormones minimizes the risk of uterine hyperplasia, we advise each patient to be reviewed at least annually by her gynecologist. The precautions and contraindications are essentially the same as those used for prescription of estrogen-containing oral contraceptives.

Treatment

It is generally agreed that once bone has been lost it is very difficult, if not impossible, to replace it. Multiple pharmacological agents have been and are currently used to treat osteoporosis, including calcium, phosphorus, magnesium, vitamin D and its metabolites, sodium fluoride, thiazide diuretics, estrogens, progestogens, androgens, anabolics, calcitonin and parathyroid hormone. Many of these agents are also used in combination. To date, the only drug that seems to stimulate new bone formation is sodium fluoride. Briancon and Meunier[35] found that combined treatment with sodium fluoride, calcium, and vitamin D over a two-year period increased the iliac trabecular bone mass in 66% of osteoporotic patients. However, restoration of trabecular bone volume to age-matched normal levels was only seen in 35% of the patients. The newly formed bone had a normal lamellar appearance and was apparently structurally competent since the study also demonstrated a significant reduction in a radiological index of vertebral deformation during the second year of therapy. Riggs and his colleagues[36] recently studied the effect of various combinations of fluoride, calcium, and estrogen on the vertebral fracture rate among osteoporotic patients. Combined therapy using all three agents was the most effective in reducing fracture recurrence, followed by calcium plus estrogen, calcium plus fluoride, and, least effective, calcium supplements by themselves. It is noteworthy that the inclusion or exclusion of vitamin D in the treatment regime made no difference to the result. However, enthusiasm over these positive results should be tempered with the knowledge that fluoride (in such high doses) is regarded as an experimental treatment for osteoporosis in this country and produces serious side effects, particularly gastrointestinal irritation and bleeding, and a painful arthropathy.

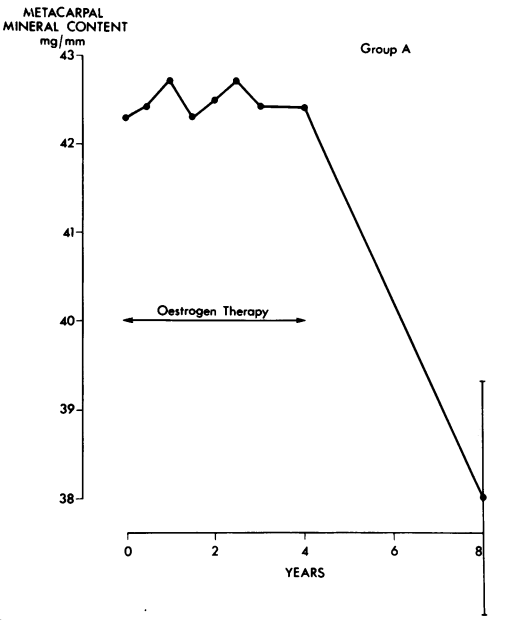

Fig. 8. Effect of withdrawal of estrogen therapy on metacarpal mineral content. Reproduced by permission from Lindsay, R., Hart, D. M., MacLean, A., et al.: Bone response to termination of estrogen treatment. *Lancet 1:*1325-27, 1978.

In treating patients with established osteoporosis primarily we offer symptomatic treatment of pain (for vertebral fractures) using hot packs, transcutaneous nerve stimulation, and pharmacological agents when required. We avoid, if possible, the use of spinal supports except for short periods when severe pain restricts mobility. To reduce further loss of bone we follow the same pharmacologic approach for prevention, relying on calcium, exercise if possible, and estrogens. If bone loss continues on this regime we then add sodium fluoride.

New Developments in Therapy

Obviously, regimes such as those described above are not universally successful. Recent understanding of bone physiology has led, however, to the development of some exciting theoretical possibilities for treatment of the disease.

Adult bone remodeling occurs in discrete units called Bone Remodeling Units (BRU), with formation coupled to resorption both in space and time (Figure 9).[37] Initially, osteoclasts appear on a certain area of bone surface and resorb a quantity of bone. These cells then disappear and after

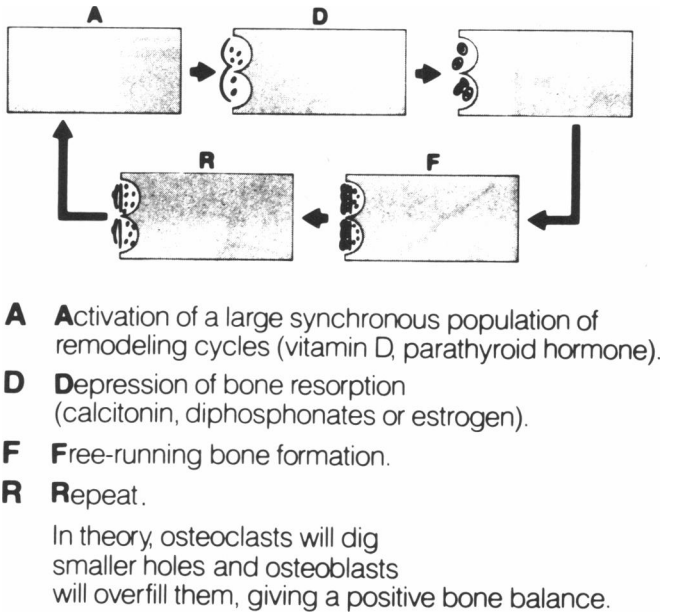

Fig. 9. Schematic representation of a bone remodeling cycle.

a finite reversal period[38] osteoblasts appear and refill the resorption cavity. When completed, the new piece of bone is referred to as a Basic Structural Unit (BSU). In cortical bone, the BSU is the familiar Haversian System; in trabecular bone it is a crescent shaped "packet" approximately 50 microns in width. Recently it has been demonstrated that the thickness of trabecular bone packets is significantly reduced in both idiopathic osteoporosis and in corticosteroid induced osteoporosis,[39,40] suggesting reduced osteoblast function. Failure of osteoblasts to refill the resorption cavities adequately could be one mechanism by which loss of bone occurs in osteoporosis. Other evidence, however, suggests that the abnormality in postmenopausal osteoporosis may result from excessive resorption by osteoclasts.[41] Whatever happens, it appears that some imbalance exists between resorption and formation such that when the resorption cavities are formed they are incompletely filled with new bone, leaving a permanent deficit.

This concept of BRUs may have important implications with regard to future therapeutic maneuvers. Frost[42] has proposed a theoretical protocol which is potentially capable of producing a substantial increase in bone mass. Briefly, the concept relies on pulsing the skeleton with an agent that

will activate a large number of BRUs simultaneously (e.g., phosphate, parathyroid hormone, 1, 25-dihydroxyvitamin D). The osteoclastic phase of the cycle could be depressed using, for example, diphosphonates, calcium, calcitonin, or even estrogen, resulting in the production of shallower than normal resorption cavities. The formation phase would then be allowed to run "free," with the hope that the osteoblasts will overfill the resorption cavities. This sequence could then be repeated as often as is necessary to restore the bone mass to normal levels. Some success with this type of approach has already been reported in both animals and man, [42,43] but much more work must be done to determine whether this theoretically sound proposal is of practical value in the treatment of postmenopausal bone loss.

Therefore, although significant advances have been made in the past 10–20 years, these are mostly in the development of sensitive, noninvasive techniques to determine bone mass, allowing the institution of preventive steps for those individuals who can be shown to be at risk. What is required now is a major campaign to educate both physicians and the general public about this disorder and the importance of prevention since our capability to treat the established disease is, as yet, severely restricted. Once crush fractures have occurred there are no techniques that can rebuild the collapsed vertebral body.

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