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DRUG TREATMENT OF THE OSTEOPOROSES

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INTRODUCTION

Until very recently it was extremely difficult to evaluate the efficacy of various treatments proposed for osteoporosis. Previous criteria included production of positive calcium balance, reduction of frequency of fractures, prevention of loss of height, and subjective endpoints such as relief of pain. The advent of a number of reliable noninvasive methods for quantitation of bone mineral mass has made objective evaluation practicable. Tracer kinetics and microradiography of bone biopsy material have added valuable information on mode of action though interpretation of such data without consideration of effects on bone mass has led to some serious misconceptions.

Terminology

A serious source of confusion has been the imprecise use of the word *osteoporosis.* This is a time-honored word meaning decreased bone mass. What bone remains is normally mineralized; there is just too little bone. Because this term was widely misused for nonspecific radiolucency of any cause (from artifact to metastatic cancer), Göran Bauer introduced the alternate term *osteopaenia* from the Greek for poverty of bone. Predictably, this term has been similarly misused. A current term, *age-related bone loss,* correctly indicates that bone mass eventually decreases with age in all races and in both sexes. It fails to note that bone loss is far greater in women than in men; that bone mass is quantitatively preserved in women until the menopause when it declines precipitously; that the fragility of the skeleton thereafter frequently leads to fractures of the vertebrae, wrists, and hips in women but only rarely and at a later age in men; and that in women the bone loss which follows loss of ovarian function is preventable by rather small doses of estrogens. For this condition, therefore, the term *postmenopausal osteoporosis,* coined by Albright in 1940 (1), now seems better descriptive and more appropriate.

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Causes of Osteoporosis

Osteoporosis also occurs commonly in immobilization ("disuse atropy of bone"); as a result of an excess of osteolytic agents (endogenous or exogenous adrenal glucocorticoids, thyroid hormones, heparin, cytotoxic chemotherapeutic agents), in liver diseases (alcoholic or biliary cirrhosis, hemochromatosis), in young people of either sex with hypogonadism; and rarely for no apparent reason, "idiopathic osteoporosis." Many of the last-named category are probably the result of previous immobilization, alcoholism, or other known causes of osteoporosis, no longer present or obvious when the disease is first recognized. Osteoporosis also occurs rarely as a transient, self-limited disease in children; in scurvy; in protein-calorie malnutrition; and as a result of weightlessness in space flight. Clinically, radiologically, by tracer kinetics, and, most important, in their response to treatment, these various osteoporoses are quite different from each other and at different stages in each disease. Much confusion has resulted from extrapolating results observed in one form of osteoporosis to others. Osteoporosis can result from too little bone formation or too much bone breakdown, usually known as resorption, catabolism, or osteolysis. Normally, these two processes—formation and resorption—are homeostatically linked to each other. As will be seen, pharmacologic agents can primarily affect either or both of these processes. It should be noted that osteoporosis is quite different from osteomalacia (deficient mineralization), osteitis fibrosa (hyperparathyroid bone disease), and many other diseases of bone causing radiolucency and fragility of the skeleton.

POSTMENOPAUSAL OSTEOPOROSIS

This condition constitutes a serious public health problem affecting many millions of ethnically predisposed postmenopausal or oophorectomized women. In contrast, it is rare for men to have symptomatic osteoporosis before age 70 unless they have been immobilized (e.g. by paralysis or fracture), or have been exposed to large doses of corticoids or alcohol, or have liver disease, long-standing diabetes mellitus, or intestinal malabsorption, e.g. after gastrectomy. Treatment has not been studied for any of these except those forms caused by immobilization and corticoid overdose (see below). Blacks, of either sex, are rarely affected (2). Osteoporotic fractures occur commonly in women of Oriental or Latin-American ancestry though the exact frequency has not been ascertained. Bone mineral mass measurements in a California community show black>yellow>white (3). Present data indicate that the most frequently affected woman is the postmenopausal or oophorectomized white woman. She has usually lost a significant amount of bone (>2 standard deviations) by age 65 (Figure 1) when 26% of untreated white women have vertebral fractures (4), increasing to 50% by age 75 (5). Hip fractures double in frequency in white women every 5 years after age 60, causing considerable morbidity and mortality (6). In contrast, hip fractures are one tenth as frequent in men and are uncommon in black women (7). Asymptomatic age-related bone loss is often called *physiologic* while osteoporotic fractures are clearly *pathologic*. Measurements of bone mass

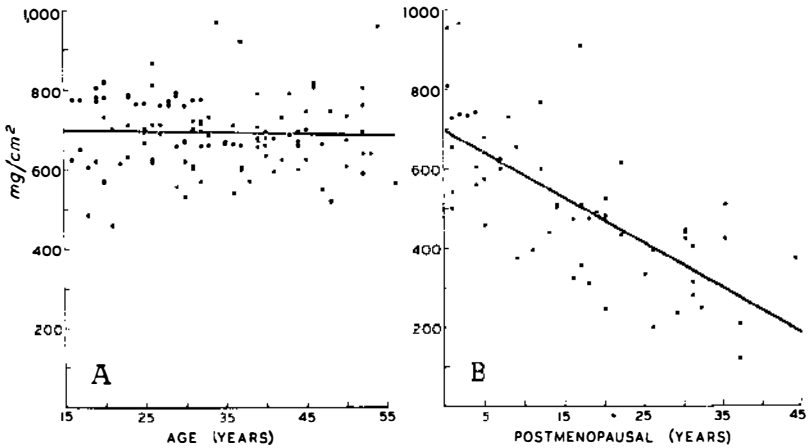

Figure 1 Bone mineral mass in normal premenopausal women according to age (*A*) and in normal postmenopausal women in relation to number of postmenopausal years (*B*). [Reprinted with permission from (8).]

show that vertebral and hip fractures (9) are associated with significantly greater bone loss than normal. Therefore, pathologic osteoporosis can be regarded as a complication of advanced physiologic, age-related bone loss.

Postmenopausal osteoporosis is probably the most frequent of the symptomatic osteoporoses, causing more disability and affecting more people than any other form. More is known of the etiology, pathogenesis, clinical and roentgen characteristics, epidemiology, prevention, and complications of this entity than any of the other osteoporoses. Fragility of the skeleton of the aging woman has existed from ancient times and the responsible bone loss is evident in paleopathologic specimens studied today (10, 11). It is therefore surprising that this sexual dimorphorism was not described until 1882 when Bruns noted that hip fractures after age 50 are much more frequent in women than in men (12). This difference was then assumed to reflect the result of tripping over long skirts, but current data show that the same female preponderance of hip fractures still persists in England (13) and Scandinavia (6) today where the long-skirt hypothesis is no longer tenable.

Relation to Estrogens

Albright first related osteoporosis to the menopause (1, 14, 15) and shortly after to congenital ovarian deficiency (16). He showed that 1 mg of stilbestrol reversed the negative calcium and phosphate balances of such women. Henneman & Wallach, in a retrospective study of Albright's patients, found that estrogen therapy for menopausal symptoms prevented loss of height and that estrogen therapy for advanced postmenopausal osteoporosis with vertebral factures and loss of height, in most cases, prevented further shrinkage (17, 18). (The few who continued to fracture may have received an inadequate dose.) Hernberg reported a similar series in 1960

with confirmatory results (19). In a 25-year prospective study, Gordan, Picchi & Roof (20) found that women treated with androgenic-anabolic steroids (fluoxymesterone, oxandrolone, oxymetholone, norethandrolone, anvene, methyltestosterone, methylandrostenediol, testosterone enanthate, nandrolone phenopropionate), which were poorly tolerated because of their androgenicity, had a fracture rate of 40 per 1000 patient-years, not significantly different from the 50–70 normally sustained by untreated osteoporotic women (21, 22). In contrast, full-dose estrogen replacement therapy (conjugated estrogens USP 1.25 mg daily for 20–25 consecutive days each month) virtually abolished further fractures in women with advanced postmenopausal osteoporosis who, on estrogen treatment, sustained only three fractures per 1000 patient-years. In the estrogen-treated group, reduction or cessation of the dose of estrogen was promptly followed by recurrent fractures; the rate rose to 25 per 1000 patient-years. When these women resumed their full replacement dose of estrogen, fractures ceased.

Reduction of the fracture rate in estrogen-treated oophorectomized women was reported in 1976 by Burch, Byrd & Vaughn (23). In 14,318 patient-years of estrogen treatment, 40 wrist fractures were expected; only 12 occurred. In this very large series, no hip fractures occurred at all! (J. Burch, personal communication, June 10, 1976). Both in the series of Gordan et al, whose 220 osteoporotic women received 1864 patient-years of estrogen therapy, and in that of Burch, Byrd & Vaughn, whose 1000 hysterectomized women received 14,318 patient-years of estrogen therapy, cancer incidence and mortality were less than expected from actuarial data. A very large number of reports, reviewed by Gordan & Vaughan (24) in 1976, shows that cyclically administered estrogens in doses corresponding to ethynyl estradiol or mestranol 50 μg, stilbestrol 1 mg or conjugated estrogens USP 1.25 mg daily for 20–25 consecutive days each month does not increase the incidence of cancer, thrombophlebitis, heart disease, or stroke. These doses can cause salt and water retention, aggravate fibroids or migraine, and are associated with an increased incidence of gall bladder disease.

Prevention of bone loss by estrogen replacement after oophorectomy or the menopause has been well described in retrospective studies by the Meemas (8, 9, 25–27) and in well-controlled prospective studies by Aitken et al and Lindsay et al (28–30), and by Heaney, Recker, and their co-workers (31–33). It has also been shown that women taking oral contraceptives containing 100 μg of mestranol daily have increased bone mass compared to women of the same age, ethnic group, and area of residence (34). Lindsay et al measured bone mass by photon absorptiometry at two sites in 120 oophorectomized young women (Figure 2). Using the double-blind technique, they gave 63 women mestranol 20–25 μg daily while 57 received a lactose placebo. There was a linear loss of bone in the placebo-treated women. The estrogen-treated women not only were protected against bone loss but actually showed a significant gain in bone, maximal at 3 years and maintained throughout the 5 years of the study (still in progress). In a nonmanipulative study, Heaney & Recker (31) measured calcium balance and kinetics in 160 perimenopausal white women. Bone resorption increased significantly in untreated women at the menopause but not in 25 who had been given estrogen replacement therapy by their

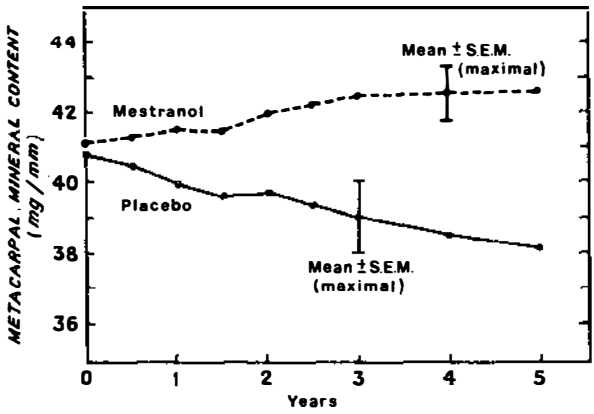

Figure 2 Mean metacarpal mineral content during five-year follow-up of group observed from three years after bilateral oophorectomy (zero time). [From Lindsay et al (1976) with kind permission of the authors and the editor of *Lancet.*]

physicians (usually conjugated estrogens USP 0.625 mg daily). Heaney, Recker & Saville (32) then carried out prospective, controlled studies measuring bone mass by two techniques (cortical thickness and photon absorptiometry) in three groups of women going through a natural menopause: the first, untreated; the second, treated with a combination of conjugated estrogens USP 0.625 mg and methyltestosterone 5 mg daily; and third, a group treated with calcium carbonate 2.6 g daily (33). The untreated women lost bone throughout the two years of study while neither treated group showed any bone loss at all. These exacting studies [Aitken et al, Lindsay et al, and Heaney et al (28–33)] confirm the Meemas' earlier demonstration (8, 9, 25–27) that bone loss (*a*) rapidly follows loss of ovarian function (oophorectomy or the menopause); (*b*) can be prevented by an estrogen-androgen combination or by a calcium salt; and (*c*) can be prevented and actually reversed by low-dose estrogens. It should be noted that 2.6 g of calcium carbonate provides 1040 mg of calcium ion in addition to the dietary calcium so that these women received a total of approximately 1.4 g of calcium daily. Urinary calcium increased, in contrast to the hormone-treated women whose urinary calcium excretion decreased (33). A similar amount of calcium, given as the lactate-gluconate or glycerophosphate was reported ineffective in preventing bone loss by D. A. Smith et al (35). The reason for the divergent results with the different calcium salts in the different patient population can only be guessed at present.

Mechanism of Action of Sex Hormones

The mode of action of estrogens on bone metabolism is now reasonably well agreed upon. Albright had suggested in 1940 that estrogens stimulate bone formation, thus providing maternal calcium reservoirs for the needs of the fetal skeleton. He had good reason for this belief based on the knowledge then available. In birds and mice,

estrogens do indeed increase endosteal bone mass (36), so much so that they can crowd out the marrow and cause anemia. Other tissue-building (anabolic) hormones such as testosterone also corrected the calcium and phosphate losses of osteoporotic women. In postmenopausal osteoporosis, bone biopsy specimens do not show the gross excess in numbers of osteoclasts that characterizes the rapid bone destruction of osteitis fibrosa. But in concluding from these data that estrogens stimulate bone formation, Albright was wrong. Increased bone mass does not require increased bone formation; it can also result from a decrease in bone breakdown. Conversely, as Albright himself pointed out in 1940: "One can have too little bone, either because bone resorption is too great or because deposition is too little." In 1963, Gordan & Eisenberg showed that estrogens, androgens, and anabolic steroids, all of which induced positive calcium balance and reduced calcium excretion of osteoporotic women, did *not* increase the bone accretion rate as shown by a bone-seeking tracer (37). In all cases, the accretion rate actually fell. If a compound increases calcium balance without increasing the bone formation rate, it can only be reducing bone resorption. These compounds, therefore, are not anabolic for bone but are anticatabolic. Using an entirely different technique, Riggs et al in 1969 came to an identical conclusion (38). Iliac crest biopsies showed that 11 of 12 osteoporotic patients had an increased bone resorption surface by microradiography. Administration of an estrogen or an androgen reduced the bone resorption surface to normal. In agreement with the earlier work of Gordan & Eisenberg, Riggs et al concluded that, "the major effect of sex hormones in osteoporosis is an inhibition of bone resorption." As noted above, this conclusion is further supported by the subsequent direct measurements of the bone resorption rate by Heaney & Recker in 1976 and also by Hansen, Gordan & Prussin in 1973 (39).

The fact that these compounds reduce the bone accretion rate as shown by kinetic studies, and the bone formation surface as shown by microradiography, must be interpreted in the context of the total effect on bone mass. If reduced bone formation were the primary and only effect of estrogens on bone, bone mass would fall. It does not; estrogen prophylaxis or therapy in oophorectomized or postmenopausal women is accompanied by an actual increase in bone mass (8, 30). The primary effect of these agents is to reduce bone breakdown; the fall in bone formation rate is the predictable homeostatic response to reduced bone destruction since the two processes are necessarily linked to each other (40). Women given long-term estrogen therapy for advanced postmenopausal osteoporosis usually stop fracturing and resume normal or near normal physical activity, continued so far in the series of Gordan et al for 29 years (20). Clearly, the estrogen-induced fall in the bone formation rate has not been deleterious to the patients or to their bone.

The mechanisms by which estrogens inhibit bone destruction have received inadequate attention. Albright in 1940 pointed out correctly that thin bones are accompanied by parchment-like thin skin in postmenopausal osteoporosis and in many other conditions, e.g. Cushing's syndrome, hyperthyroidism, osteogenesis imperfecta, and old age. Albright suggested in 1941 that the common denominator is probably loss of the collagen protein matrix of both tissues. This hypothesis has been directly confirmed in the rat by Igarashi et al (41) who found that estriol inhibits

bone collagen loss in experimental osteoporosis, by Katz & Kappas (42, 43) who found that estrogen reduces urinary hydroxyprolinuria in women, and by Laitinen who found that collagen in bone plays an active role in the regulation of bone formation and resorption in the rat (44). All these data suggest that estrogens normally inhibit some collagenolytic system in skin and bone and that loss of this inhibition at the menopause permits this collagenase to break down these tissues. Recently, Cruess & Hong (45) found that estrogen administration in vivo reduces the collagenolytic activity of rat bone measured in vitro. Estrogen in vitro had no such effect. A recent report from the same laboratory indicates absence of estrogen receptors in bone (46), and several studies describe failure of estrogens and androgens to inhibit bone resorption in vitro (47, 48). A possible solution to this dilemma has been suggested by Klotz and his co-workers (49, 50) who suggest that estrogens may affect bone indirectly by stimulating calcitonin production since calcitonin is known to inhibit bone resorption in vitro. They found that 33 postmenopausal women had low serum calcitonin levels; estrogen administration to 13 raised the level to the premenopausal norm. Oophorectomy in the rat also lowered serum calcitonin levels. These data, while highly promising, must be looked upon as preliminary since the levels reported are all at the lower end of the sensitivity of the radioimmunoassay. Estrogens and calcitonin alike are established antiosteolytic agents in vivo. Whether estrogen works through calcitonin remains to be seen. Estrogens also increase 25-hydroxyvitamin D 1-α hydroxylase (51), at least in birds, a mechanism that may explain how they increase calcium absorption (52) and stimulate calcitonin secretion. A rise in serum calcium levels after oral administration of calcium carbonate may also explain its osteotrophic activity. This mechanism would require a rise in serum calcium and a decline of serum parathyroid hormone levels, neither of which occurs in estrogen-treated osteoporotic women.

Calcitonin

This antiosteolytic agent, discovered by Copp in 1961, is the antihypercalcemic peptide hormone elaborated by the "C" or parafollicular cells of the mammalian thyroid gland or the ultimobranchial glands of birds, fish, and reptiles. While its other effects remain in dispute, its ability to inhibit bone resorption is universally agreed upon. It therefore seemed reasonable to try it in osteoporosis. Numerous early studies, however, showed no beneficial effects. Two reasons are probable: (*a*) the rather large *doses* used lowered serum calcium levels, induced secondary hyperparathyroidism, and caused bone breakdown; (*b*) *antibody production* is frequent with salmon calcitonin, the preparation most commonly used in the United States. Recently, Milhaud et al, using small doses of porcine calcitonin (1 MRC unit intramuscularly three times weekly), showed by kinetic techniques an increase in intestinal calcium absorption and bone formation and a reduction in bone resorption and calciuria in 20 osteoporotic women (53). Bone pain was relieved but is hard to evaluate since Solomon, Dickerson & Eisenberg showed in 1960 that placebos can also relieve pain in postmenopausal osteoporosis (54). No antibody formation was found in the women treated with porcine calcitonin. In another study, Wallach et al ingeniously prevented the hypocalcemia and secondary hyperparathyroidism of

calcitonin therapy by simultaneously administrating calcium and found a 4% increase in "bone mass" in six months of treatment (55). What was actually measured was total body calcium by neutron activation analysis so that it cannot be certain that the retained calcium was in the bones. Bone mass measurements were not recorded.

Prophylaxis and Treatment

From the foregoing, it now seems justified to conclude that postmenopausal bone loss and pathologic osteoporosis are preventable. If one assumes, not unreasonably, that postmenopausal bone loss and pathologic fractures are a continuum (Figure 3), there are now three proved effective ways to prevent bone loss and to prevent further fractures in postmenopausal osteoporosis: (*a*) low dose estrogen replacement upon loss of ovarian function in ethnically predisposed women; (*b*) low dose porcine calcitonin therapy; or (*c*) calcium carbonate 2.6 g daily by mouth (but not equivalent doses of calcium lactate-gluconate or glycerophosphate). For predisposed women, therefore, low dose estrogen replacement (mestranol or ethynyl estradiol 20 μg daily or conjugated estrogens USP 0.625 mg daily) and low dose porcine calcitonin or calcium carbonate (minimum dose not yet determined) are reasonable for *prophylaxis;* for *treatment* of pathologic osteoporosis, the estrogen dose should probably be doubled, e.g. mestranol or ethynyl estradiol 50 μg or conjugated estrogens USP 1.25 mg or stilbestrol 1 mg or methallanestril 6 mg daily for 20–25 consecutive days each month. Porcine calcitonin 1 MRC unit 3 times weekly by intramuscular

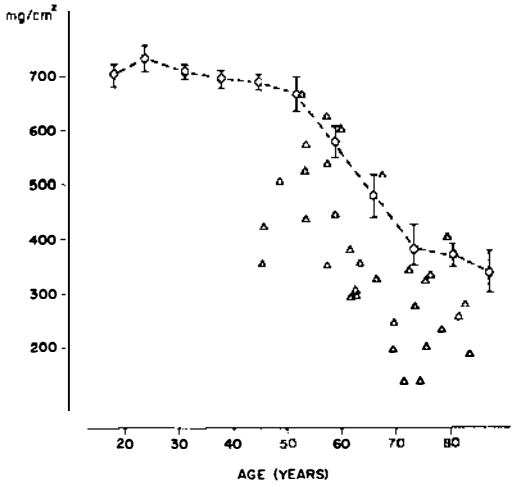

Figure 3 Bone mineral mass of the radius in 33 women with osteoporotic vertebral compression (Δ) compared with values in the normal female of population (0), according to age. The lower limit of normal in the 21- to 49-year age range is 500 mg/cm². Bars indicate the SE of the mean. [From (8) by permission.]

injection appears to suffice and calcium carbonate 2.6 g daily is the minimal dose shown to be effective at this time. Lower doses of the proved effective agents have not yet been tested.

Unproved Remedies

A number of other treatments have been proposed for postmenopausal osteoporosis including fluorides, phosphates, diphosphonates, anabolic-androgenic steroids, vitamin D and 1,25-dihydroxy-vitamin D. All of these have serious undesirable effects; some produce abnormal bone or are otherwise unacceptably toxic; none has been shown effective in preventing fractures or restoring bones with normal architecture. Two peptide hormones are currently under study, both too early for definitive evaluation at this time: human growth hormone (hGH) and—surprisingly—synthetic human parathyroid peptide fragment 1–34 (containing the first 34 amino acid residues of the amino terminal fragment of the native parathyroid hormone molecule). While growth hormone causes bone growth in rats and dogs (56), it produced no beneficial effect on bone mass in seven women and one man measured by total body neutron activation analysis, photon absorptiometry, calcium tracer kinetics, microradiography, or hydroxyprolinuria (57). In fact, bone mineral mass decreased and hyperglycemia, hypertension, arthralgias, and carpal tunnel syndrome were encountered. hPTH 1–34 in vitro induced anabolic effects in both osteoblasts and cartilage cells of cultured embryonic mouse radii in organ culture (58). In a preliminary report of four women with "primary" osteoporosis and vertebral fractures, intramuscular injection of 100 μg of hPTH 1–34 increased the bone accretion rate more than it did resorption as shown by tracer kinetics, calcium balance, and microradiography (59). Bone mass measurements in the femur, however, showed no significant change. At the Sixth Parathyroid Conference in Vancouver June 12–17, 1977, several discussants suggested that most of the kinetic data are consistent with the production of hyperparathyroid bone disease rather than an anabolic effect. The positive calcium balance is not, however, consistent with this explanation. An expanded study is in progress.

In this reviewer's opinion, the demonstration of effective treatments besides estrogen is of great importance since estrogen therapy is unsuitable for some women, e.g. with endometriosis, large fibroids, or shortly after mastectomy for breast cancer. For such patients, calcium carbonate or calcitonin may be more acceptable. Whether anabolic steroids may be useful requires further investigation. Their failure to prevent fractures has already been noted (20). Since then, a carefully conducted prospective study using the double-blind technique showed significant improvement in total body calcium content and calcium balance in ten osteoporotic women treated with methandrostenolone as compared to six receiving placebos over a 26-month period of observation (60).

CORTICOID OSTEOPOROSIS

Unlike the osteoporosis of postmenopausal women, corticoid-induced osteoporosis is characterized not only by fractures of the vertebrae but also of the ribs (which

are rarely fractured in postmenopausal osteoporosis), by a pathognomonic X-ray appearance of eburnation of the vertebral cortex ("pseudocallus" or marginal condensation), by a transient rise in bone accretion (37, 39, 61), followed by a prolonged and severe fall (62), by a profoundly reduced bone formation surface by microradiography (63), and greatly reduced bone mass, shown by total body calcium content (64). No good method of treatment is presently established; the best approach is prevention by use of minimal doses for the shortest period of time required. Most human studies are complicated by having been carried out in patients with rheumatoid arthritis, which itself causes severe osteoporosis (65), and a low accretion rate (66) or in asthma where bone involvement is less frequent (67).

Pathogenesis

The mode of action of corticoids on bone is complicated and not completely understood. Three established actions of glucocorticoids probably acount for the severe osteoporosis these compounds can produce. Corticoids inhibit bone formation (68), accelerate bone resorption (69), and stimulate the secretion of parathyroid hormone in vivo (70) and in vitro (71). They also inhibit intestinal active transport of calcium (72), inhibit prolyl hydroxylase activity in a number of rat tissues (73), and profoundly disturb collagen synthesis and catabolism (44). Corticoid receptors have been identified in bone (74).

Some of the apparently contradictory effects of corticoids on bone can be reconciled as follows: in temporal sequence, both man and the rat first show excessive osteolysis and increased urinary excretion of calcium and hydroxyproline. At this stage, accretion is high, probably as a transient homeostatic response. Later, accretion is very low, reflecting the antianabolic effect of corticoids, probably exerted directly on bone collagen. Since increased parathyroid secretion occurs early, it is tempting to assume that it plays a role in the increased turnover, resorption, and accretion at this stage. On the other hand, bone damage was as severe in thyroparathyroidectomized rats as in intact controls (75). Corticoids somehow lower serum calcium levels acutely (76, 77), providing a reasonable basis for an early stimulus to parathyroid secretion. Perhaps the absence of osteitis fibrosa may be rationalized by the well-known ability of glucocorticoids to inhibit fibroblastic activity and protein synthesis. Other manifestations consistent with parathyroid hormone actions are a low serum phosphate level, a low rate of tubular reabsorption of phosphate (78), and hypercalciuria. These are not specific for parathyroid hormone and may be direct effects of corticoids on the renal tubule.

Prophylaxis and Treatment

Since spontaneous Cushing's disease is rare, most corticoid-induced osteoporosis is iatrogenic. The best prevention is to minimize the insult by keeping the dose and duration of corticoid therapy minimal. In some situations, of course, high dose, long-term treatment cannot be avoided, e.g. in lupus erythematosus, pemphigus, or after renal transplantation. A hopeful approach is based on the single recent report that alternate-day corticoid administration to normal children was less damaging than daily treatment as shown by urinary hydroxyproline excretion (79).

Henneman et al in 1955 (80) showed that administration of estrogen to women and androgens to men asthmatics receiving large doses of corticoids reduced urinary calcium excretion. Several fragmentary reports suggest that anticatabolic ("anabolic") steroids may be similarly useful (80–84). Failure of these agents to protect against osteoporosis in corticoid-treated animals (85) or patients (86) in well-designed studies indicates the uncertain nature of this proposed treatment. In the rabbit, calcitonin has been reported effective (87); calcium salts, estrogens, and androgens were ineffective (88). Considering the extent, frequency, and serious nature of this condition, it is sad that so little is known of how to prevent or treat it.

IMMOBILIZATION OSTEOPOROSIS

If one includes the local effects of short-term immobilization, this form of osteoporosis could, at least technically, be the most common of the osteoporoses. The local type is usually asymptomatic and requires no treatment. Generalized osteoporosis which follows paralysis or whole body casting, by contrast, can be a serious symptomatic disease. Deitrick (89) showed in 1948 that partial immobilization of normal young men caused bone breakdown as shown by negative calcium and phosphate balances. When the United States space program started, a number of repetitions of Deitrick's experiment were carried out and conclusively confirmed bone loss by direct and indirect methods. These data were worrisome; if weightlessness can be equated with immobilization, bone loss, hypercalciuria, kidney stones, and perhaps hypercalcemia might occur in space flight. The report of Whedon et al (90) in 1974 on the increased urinary calcium excretion and negative calcium balance of astronauts in actual flight confirmed these fears. Direct measurement of bone density (os calcis) in the Gemini 4 and 5 and Apollo 8 missions showed what was thought to be serious bone loss. Vogel & Whittle (91) have recently recalculated these data and concluded that the loss was overestimated because of technical problems. The revised loss should be 2.9% and 3% for Gemini 4 and 9.2% for Gemini 5. These amounts are probably not dangerous in relatively short flights but could become serious if maintained in longer flights. Fortunately, data from three subsequent Apollo missions showed no significant bone loss in 13 of 15 crewmen and only slight losses in 2 others. Curiously, the bed rest immobilization studies showed no loss of bone in the radius or ulna in contrast to the os calcis.

Pathogenesis

It has long been known that serum alkaline phosphatase levels fall in immobilization and it had therefore been assumed that loss of the stress-and-strain stimulus on the osteoblasts results in decreased bone formation. Kinetic studies by Heaney (92) in 1962, however, showed that accretion actually increases. The microradiographic studies of Minaire (93) in 1974 have helped to clarify this apparent contradiction. In a study of 96 immobilized patients, 22 of whom had suffered spinal cord injury, the first period of 25 weeks was marked by increased osteoclastic and osteocytic activity. In this time, trabecular bone decreased 33%. Later, osteoblastic bone forma-

tion declined. Early increased resorption and later decreased bone formation, of course, resulted in a highly rarified bone. The early increased accretion is doubtless a secondary homeostatic response to increased resorption. Unfortunately, increased formation does not persist to compensate for bone loss.

Treatments

The pioneering studies of Deitrick in 1948 showed that mechanical stimulation by an oscillating bed reduced calcium losses by approximately 50%. Obviously minimizing loss of mechanical stress is important both in prophylaxis and treatment. When possible, standing is more effective than tilting the bed (94, 95). Prophylactic isometric exercises probably account, at least in part, for the reduced loss of bone in the Gemini 7 astronauts.

An "anabolic" (really anticatabolic) steroid, norethandrolone, was found effective in reducing the hypercalciuria of immobilization in paralytic poliomyelitis by Plum & Dunning (96) in 1958. This approach has been little studied since then, perhaps because of disappointing results reported in bedfast children by Keele & Vose (97) in 1971 and in immobilized rabbits treated with nandrolone phenproprionate by Levin (98) in 1972. Fluoride and glucagon have likewise been disappointing in immobilized cats and rats (99–101). Singh & Jowsey (102) found no effect of calcitonin on the bone of immobilized rabbits.

CONCLUSION

The most hopeful information is the very recent demonstration in properly designed and executed studies that postmenopausal bone loss in ethnically predisposed women can be prevented and fracture incidence reduced by low dose estrogens, calcitonin, or large doses of calcium carbonate. Less is known of how to prevent or minimize the other osteoporoses other than to use long-term, high dose corticoids sparingly and only when necessary and to avoid immobilization insofar as possible. Recent fragmentary data suggest that alternate-day administration of corticoids may be less deleterious than daily use. There is also some evidence that the anabolic-androgenic steroids, which are really anticatabolic for bone, may be beneficial both in corticoid osteoporosis and for disuse atrophy of bone. The most obvious lesson of recent experience is the need for more and better studies of the prevention and treatment of the osteoporoses induced by corticoids or by immobilization using recently developed and validated methods of measuring bone mineral mass. Bone mass measurements accurately reflect mechanical strength of bone (103, 104) and bone loss correlates well with increased risk of fracture. In the opinion of this reviewer, the time has come to attack the serious public health problem posed by preventable fractures, especially in postmenopausal women.

Literature Cited[1]

1. Albright, F., Bloomberg, E., Smith, P. H. 1940. Post-menopausal osteoporosis. *Trans. Assoc. Am. Physicians* 55:298–305
2. Cohn, S. H., Abesamis, C., Yasumura, S., Aloia, J. F., Zanzi, I., Ellis, K. J. 1977. Comparative skeletal mass and radial bone mineral content in black and white women. *Metabolism* 26: 171–78
3. Goldsmith, N. F., Johnston, J. O., Picetti, G., Garcia, C. 1973. Bone mineral in the radius and vertebral osteoporosis in an insured population. *J. Bone Jt. Surg.* 55–A:1276–93
4. Urist, M. R., Mazet, R., Bechtol, C. O. 1959. Senile osteoporosis as a disorder influencing treatment and end results of fractures of the hip: With a preliminary report on the use of collapatite. *Am. Surg.* 25:883–90
5. Gallagher, J. C., Aaron, J., Horsman, A., Marshall, D. H., Wilkinson, R., Nordin, B. E. C. 1973. The crush fracture syndrome in post-menopausal women. *Clin. Endocrinol. Metab.* 2:293–314
6. Alffram, P. 1964. An epidemiologic study of cervical and trochanteric fractures of the femur in an urban population. *Acta Orthop. Scand. Suppl.* 65, pp. 9–109
7. Gyepes, M., Mellins, H. Z., Katz, I. 1962. The low incidence of fracture of the hip in the Negro. *J. Am. Med. Assoc.* 181:133–34
8. Meema, S., Meema, H. E. 1976. Menopausal bone loss and estrogen replacement. *Isr. J. Med. Sci.* 12:601–6
9. Meema, H. E., Meema, S. 1974. Involutional (physiologic) bone loss in women and the feasibility of preventing structural failure. *J. Am. Geriatr. Soc.* 22:443–52
10. Armelagos, G. J. 1969. Disease in ancient Nubia. Changes in disease patterns from 350 B.C. to A.D. 1400 demonstrate the interaction of biology and culture. *Science* 163:255–59
11. Perzigian, A. J. 1973. The antiquity of age-associated bone demineralization in man. *J. Am. Geriatr. Soc.* 21:100–5
12. Bruns, P. 1882. Die allgemeine Lehre von den Knochenbrüchen. *Dtsch. Chir.* 27:1–400
13. Gallagher, J. C., Nordin, B. E. C. 1973. Oestrogens and calcium metabolism. *Front. Hormone Res.* 2:98–117
14. Albright, F., Smith, P. H., Richardson, A. M. 1941. Postmenopausal osteoporosis: Its clinical features. *J. Am. Med. Assoc.* 116:2465–74
15. Albright, F. 1947. Osteoporosis. *Ann. Int. Med.* 27:861–82
16. Albright, F., Smith, P. H., Fraser, R. 1942. A syndrome characterized by primary ovarian-insufficiency and decreased stature. *Trans. Assoc. Am. Physicians* 57:219–24
17. Henneman, P. H., Wallach, S. 1957. A review of the prolonged use of estrogens and androgens in postmenopausal and senile osteoporosis. *Arch. Int. Med.* 100:715–23
18. Wallach, S., Henneman, P. H. 1959. Prolonged estrogen therapy in postmenopausal women. *J. Am. Med. Assoc.* 171:1637–42
19. Hernberg, C. A. 1960. Treatment of postmenopausal osteoporosis with oestrogens and androgens. *Acta Endocrinol.* 34:51–59
20. Gordan, G. S., Picchi, J., Roof, B. S. 1973. Antifracture efficacy of long-term estrogens for osteoporosis. *Trans. Assoc. Am. Physicians* 86:326–32
21. Iskrant, A. P. 1962. The epidemiologic approach to accident causation. *Am. J. Public Health* 52:1708–11
22. Iskrant, A. P., Smith, R. W. 1969. Osteoporosis in women 45 years and over related to subsequent fractures. *Public Health Rep.* 84:33–38
23. Burch, J. C., Byrd, B. F., Vaughn, W. K. 1976. Results of estrogen treatment in one thousand hysterectomized women for 14,318 years. In *Consensus on Menopause Research,* ed. P. A. van Keep, R. B. Greenblatt, M. Albeaux-Fernet, pp. 164–69. Lancaster, England: MTP Press (and personal communication June 10, 1976)
24. Gordan, G. S., Vaughan, C. C. 1976. *Clinical Management of the Osteoporoses,* pp. i–ix, 1–207. Acton, Mass.: Publ. Sci. Group
25. Meema, H. E., Bunker, M. L., Meema, S. 1965. Loss of compact bone due to menopause. *Am. J. Obstet. Gynecol.* 26:333–43

[1]A more complete bibliography can be found in (24).

26. Meema, H. E., Meema, S. 1968. Prevention of postmenopausal osteoporosis by hormone treatment of the menopause. *Can. Med. Assoc. J.* 99:248–51
27. Meema, S., Bunker, M. L., Meema, H. E. 1975. Preventive effect of estrogen on postmenopausal bone loss. *Arch. Int. Med.* 135:1436–40
28. Aitken, J. M., Hart, D. M., Anderson, J. B., Lindsay, R., Smith, D. A., Speirs, C. F. 1973. Osteoporosis after oophorectomy for nonmalignant disease in premenopausal women. *Br. Med. J.* 2:325–28
29. Aitken, J. M., Hart, D. M., Lindsay, R. 1973. Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. *Br. Med. J.* 3: 515–18
30. Lindsay, R., Aitken, J. M., Anderson, J. B., Hart, D. M., MacDonald, E. B., Clarke, A. C. 1976. Long-term prevention of postmenopausal osteoporosis by estrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. *Lancet* 1:1038–41
31. Heaney, R. P., Recker, R. R. 1975. Estrogen effects on bone remodeling at menopause. *Clin. Res.* 23:535 (Abstr.)
32. Recker, R. R., Saville, P. D., Heaney, R. P. 1976. Sex hormones or calcium supplements diminish postmenopausal bone loss. *Clin. Res.* 24:583 (Abstr.), *Ann. Int. Med.* In press
33. Recker, R. R., Saville, P. D., Heaney, R. P. Feb. 18, 1977. *Transcript of Proc. Endinocrinol. and Metab. Advis. Comm.*, US FDA Bur. Drugs, pp. 70–87
34. Goldsmith, N. F., Johnston, J. O. 1975. Bone mineral: Effects of oral contraceptives, pregnancy, and lactation. *J. Bone Jt. Surg.* 57-A:657–88
35. Smith, D. A., Anderson, J. J. B., Aitken, J. M., Shimmins, J. 1975. Effects of calcium supplementation of the diet on bone mass in women. In *Calcium Metabolism, Bone and Metabolic Bone Diseases,* ed. F. Kuhlencordt, H. P. Kruse, pp. 278–82. Berlin, Heidelberg & New York: Springer
36. Albright, F. 1947. Effect of hormones on osteogenesis in man. *Recent Prog. Horm. Res.* 1:293–354
37. Gordan, G. S., Eisenberg, E. 1963. Effect of oestrogens, androgens and corticoids on skeletal kinetics in man. *Proc. R. Soc. Med.* 56:1027–29
38. Riggs, B. L., Jowsey, J., Kelly, P. J., Jones, J. D., Maher, G. T. 1969. Effect of sex hormones on bone in primary osteoporosis. *J. Clin. Invest.* 48:1065–72
39. Hansen, J. W., Gordan, G. S., Prussin, S. G. 1973. Direct measurement of osteolysis in man. *J. Clin. Invest.* 52:304–15
40. Heaney, R. P. 1965. A unified concept of osteoporosis. *Am. J. Med.* 39:877–80
41. Igarashi, M., Hayashi, Y., Karube, S. 1974. Effect of estriol on bone collagen of rats with experimental osteoporosis. *Endocrinol. Jpn.* 21:387–91
42. Katz, F. H. 1968. Effects of oestradiol and oestriol on the disposition of injected radioactive proline, hydroxyproline and tyrosine in man. *Acta Endocrinol.* 58:664–72
43. Katz, F. H., Kappas, A. 1968. Influence of estradiol and estriol on urinary excretion of hydroxyproline in man. *J. Lab. Clin. Med.* 71:65–74
44. Laitinen, O. 1976. Relation to osteoporosis of age- and hormone-induced changes in the metabolism of collagen and bone. *Isr. J. Med. Sci.* 12:620–37
45. Cruess, R. L., Hong, K. C. 1976. Effect of estrogen on collagenolytic activity of rat bone. *Calcif. Tissue Res.* 20:317–20
46. Nutik, G., Cruess, R. L. 1974. Estrogen receptors in bone. An evaluation of the uptake of estrogen into bone cells. *Proc. Soc. Exp. Biol. Med.* 146:265–68
47. Caputo, C. B., Meadows, D., Raisz, L. G. 1976. Failure of estrogens and androgens to inhibit bone resorption in tissue culture. *Endocrinology* 98:1065–68
48. Liskova, M. 1976. Influence of estrogen on bone resorption in organ culture. *Calcif. Tissue Res.* 22:207–18
49. Klotz, H.-P. Delorme, M.-L., Ochoa, F., Aussenard, C. 1975. Hormones sexuelles et sécrétion de calcitonine. *Sem. Hop.* 51:1333–36
50. Delorme, M.-L., Digioia, Y., Fandard, J., Merceron, R., Raymond, J. Y., Klotz, H.-P. 1976. Oestrogènes et calcitonine. *Ann. Endocrinol.* 37:503–4
51. Tanaka, Y., Castillo, L., DeLuca, H. F. 1976. Control of renal vitamin D hydroxylases in birds by sex hormones. *Proc. Natl. Acad. Sci. USA* 73:2701–5
52. Caniggia, A., Gennari, C., Borrello, G., Bencini, M., Cesari, L., Poggi, C., Escobar, S. 1970. Intestinal absorption of calcium-47 after treatment with oral oestrogen-gestogens in senile osteoporosis. *Br. Med. J.* 4:30–32
53. Milhaud, G., Talbot, J.-N., Coutris, G. 1975. Calcitonin treatment of postmenopausal osteoporosis. Evaluation of efficacy by principal components analysis. *Biomedicine* 23:223–32

54. Solomon, G. F., Dickerson, W. J., Eisenberg, E. 1960. Psychologic and osteometabolic responses to sex hormones in elderly osteoporotic women. *Geriatrics* 15:46–60
55. Wallach, S. 1973. Discussion. In *Clinical Aspects of Metabolic Bone Disease,* ed. B. Frame, A. M. Parfitt, H. Duncan, p. 327. New York: Am. Elsevier
56. Heaney, R. P., Harris, W. H., Cockin, J., Weinberg, E. H. 1972. Growth hormone: The effect on skeletal renewal in the adult dog. *Calcif. Tissue Res.* 10:14–22
57. Aloia, J. F., Zanzi, I., Ellis, K., Jowsey, J., Roginsky, M., Wallach, S., Cohn, S. H. 1976. Effects of growth hormone in osteoporosis. *J. Clin. Endocrinol. Metab.* 43:992–99
58. Herrmann-Erlee, M. P. M., Heersche, J. N. M., Hekkelman, J. W., Gaillard, P. J., Tregear, G. W., Parsons, J. A., Potts, J. T. 1976. Effects on bone in vitro of bovine parathyroid hormone and synthetic fragments representing residues 1–34, 2–34, and 3–34. *Endocrinol. Res. Commun.* 3:21–35
59. Reeve, J., Williams, D., Hesp, R., Hulme, P., Klenerman, L. 1976. Anabolic effect of low doses of a fragment of parathyroid hormone on the skeleton in postmenopausal osteoporosis. *Lancet* 1:1035–38
60. Chestnut, C. H., Nelp, W. B., Baylink, D. J., Denney, J. D. 1977. Effect of methandrostenolone in postmenopausal bone wasting as assessed by changes in total bone mineral mass. *Metabolism* 26:267–77
61. Gordan, G. S., Hansen, J., Lubich, W. 1966. Effects of hormonal steroids on osteolysis. *Proc. 2nd Int. Congr. Horm. Steroids,* pp. 786–793
62. Eisenberg, E., Gordan, G. S. 1961. Skeletal dynamics in man measured by nonradioactive strontium. *J. Clin. Invest.* 40:1809–25
63. Jowsey, J., Riggs, B. L. 1970. Bone formation in hypercortisonism. *Acta Endocrinol.* 63:21–28
64. Aloia, J. F., Roginsky, M., Ellis, K., Shukla, K., Cohn, S. 1974. Skeletal metabolism and body composition in Cushing's syndrome. *J. Clin. Endocrinol. Metab.* 39:981–85
65. Saville, P. D., Kharinosh, O. 1967. Osteoporosis of rheumatoid arthritis: Influence of age, sex and corticosteroids. *Arthritis Rheum.* 10:423–30
66. Dymling, J-F. 1964. Calcium kinetics in osteopenia and parathyroid disease. *Acta Med. Scand.* 175:5–63
67. Sims, J. A., Mueller, M. N. 1975. Corticosteroid therapy effects on bone: Influence of disease being treated. *Clin. Res.* 23:332 (Abstr.)
68. Riggs, B. L., Jowsey, J., Kelly, P. J. 1966. Quantitative microradiographic study of bone remodeling in Cushing's syndrome. *Metabolism* 15:773–80
69. Raisz, L. G., Trummel, C. L., Wener, J. A., Simmons, H. 1972. Effect of glucocorticoids on bone resorption in tissue culture. *Endocrinology* 90:961–67
70. Hargis, G. K., Bowser, E. N., Henderson, W. J., Williams, G. A. 1974. Radioimmunoassay of rat parathyroid hormone in serum and tissue extracts. *Endocrinology* 94:1644–49
71. Au, W. Y. W. 1976. Cortisol stimulation of parathyroid hormone secretion by rat parathyroid glands in organ culture. *Science* 193:1015–17
72. Kimberg, D. V., Baerg, R. D., Gershon, E., Graudusius, R. T. 1971. Effect of cortisone treatment on the active transport of calcium by the small intestine. *J. Clin. Invest.* 50:1309–21
73. Cutroneo, K. R., Stassen, F. L. H., Cardinale, G. J. 1975. Anti-inflammatory steroids and collagen metabolism: Glucocorticoid-mediated decrease of prolyl hydroxylase. *Mol. Pharmacol.* 11:44–51
74. Feldman, D., Dziak, R., Koehler, R., Stern, P. 1975. Cytoplasmic glucocorticoid binding proteins in bone cells. *Endocrinology* 96:29–36
75. Kukreja, S. C., Bowser, E. N., Hargis, G. K., Henderson, W. J., Williams, G. A. 1976. Mechanisms of glucocorticoid-induced osteopenia: Role of parathyroid glands. *Proc. Soc. Exp. Biol. Med.* 152:358–61
76. Stoerk, H. C., Peterson, A. C., Jelinek, V. C. 1963. The blood calcium lowering effect of hydrocortisone in parathyroidectomized rats. *Proc. Soc. Exp. Biol. Med.* 114:690–95
77. Canas, F. M., Bergstrom, W. H., Churgin, S. J. 1967. Effects of the adrenal on calcium homeostasis in the rat. *Metabolism* 16:670–75
78. Anderson, J., Foster, J. B. 1959. The effect of cortisone on urinary phosphate excretion in man. *Clin. Sci.* 18:437–39
79. Liakakos, D., Vlachos, P., Anoussakis, C., Doulas, N. L. 1975. Urinary hydroxyproline values following continuous and intermittent administration of

prednisolone in children. *Helv. Paediatr. Acta* 30:495–99
80. Henneman, P. H., Irwin, J. W., Wang, D. M. K., Burrage, W. S. 1955. The effect of estrogen and androgen on calcium metabolism during cortisone administration. *J. Clin. Endocrinol.* 15:858 (Abstr.)
81. Sprague, R., Power, M., Mason, H., Albert, A., Mathieson, D., Hench, P., Kendall, E., Slocumb, C., Polley, H. 1950. Observations on the physiologic effects of cortisone and ACTH in man. *Arch. Int. Med.* 85:199–258
82. Laron, Z., Kowadlo, A., Arie, B. Z., Kalish, I., Kende, S. 1963. Interaction between 19 nor-androstenolone phenylpropionate (Durabolin) and 6-methylprednisolone (Medrol) on the bones of rats fed a low calcium diet. *Isr. J. Exp. Med.* 11:41–47
83. Ichiki, H., Usui, K., Hataya, M. 1966. Studies on the bone disorder of rats caused by heavy exercise. II. Effect of norandrostenolone phenylpropionate on the bone disorder caused by exercise. *Jpn. J. Vet. Sci.* 28:273–85
84. Albanese, A. A., Edelson, A. H., Lorenze, E. J., Wein, E. H. 1969. Quantitative radiographic survey technique for detection of bone loss. *J. Am. Geriatr. Soc.* 17:142–54
85. Freehafer, A. A. 1969. Effect of hydrocortisone and gonadal hormones on growing rabbit bone. *J. Surg. Res.* 9:35–41
86. Lindholm, B., Isaksson, B., Sjögren, B. 1967. Changes in body composition during long-term administration of cortisone and anabolic steroids in an asthmatic subject. *Metabolism* 16:162–75
87. Thompson, J. S., Palmieri, G. M. A., Eliel, L. P., Crawford, R. L. 1972. The effect of porcine calcitonin on osteoporosis induced by adrenal cortical steroids. *J. Bone Jt. Surg.* 54-A:1490–1500
88. Adams, P., Jowsey, J., 1967. Effect of calcium on cortisone-induced osteoporosis: A preliminary communication. *Endocrinology* 81:152–54
89. Dietrick, J. E. 1948. The effect of immobilization on metabolic and physiologic functions of normal men. *Bull. NY Acad. Med.* 24:364–75
90. Whedon, G. D., Lutwak, L., Reid, J., Rambaut, P., Whittle, M., Smith, M., Leach, C. 1974. Mineral and nitrogen metabolic studies on skylab orbital space flights. *Trans. Assoc. Am. Physicians* 87:95–110
91. Vogel, J. M., Whittle, M. W. 1976. Bone mineral changes: The second manned skylab mission. *Aviat. Space Environ. Med.* 47:396–400
92. Heaney, R. P. 1962. Radiocalcium metabolism in disuse osteoporosis in man. *Am. J. Med.* 33:188–200
93. Minaire, P., Meunier, P., Edouard, C., Bernard, J., Courpron, P., Bourret, J. 1974. Quantitative histological data on disuse osteoporosis. Comparison with biological data. *Calcif. Tissue Res.* 17:57–73
94. Issekutz, B., Blizzard, J. J., Birkhead, N. C., Rodahl, K. 1966. Effect of prolonged bed rest on urinary calcium output. *J. Appl. Physiol.* 21:1013–20
95. Birge, S. J., Whedon, G. D. 1968. Bone. In *Hypodynamics and Hypogravics,* ed. M. McNally, p. 213. New York: Academic
96. Plum, F., Dunning, M. F. 1958. Amelioration of hyercalciuria following poliomyelitis by 17-ethyl, 19-nortestosterone (Nilevar). *J. Clin. Endocrinol. Metab.* 18:860–71
97. Keele, D. K., Vose, G. P. 1971. Bone density in nonambulatory children. *Am. J. Dis. Child.* 121:204–6
98. Levin, S. M., Simkin, A., Naor, E., Robin, G. C., Goldenberg, A., Dorfman, H. 1972. A comparison of assay techniques in experimental disuse osteoporosis. *Clin. Orthop.* 82:246–52
99. Milicic, M., Jowsey, J. 1968. Effect of fluoride on disuse osteoporosis in the cat. *J. Bone Jt. Surg.* 50-A:701–8
100. Woodward, A. H., Jowsey, J. 1972. The effect of glucagon on immobilization osteoporosis in rats. *Endocrinology* 90:1399–1401
101. Fujita, T., Orimo, H., Ohata, M., Yoshikawa, M. 1968. Prevention of experimental bone atrophy by thyrocalcitonin. *Endocrinol. Jpn.* 15:8–12
102. Singh, M., Jowsey, J. 1970. Failure of calcitonin to prevent disuse osteopenia: An experimental study in rabbits. *Endocrinology* 87:183–86
103. Dalén, N., Hellström, L.-G., Jacobson, B. 1976. Bone mineral content and mechanical strength of the femoral neck. *Acta Orthop. Scand.* 47:503–8
104. Carter, D. R., Hayes, W. C. 1976. Bone compressive strength: Influence of density and strain rate. *Science* 194: 1174–75