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Estrogen therapy in postmenopausal osteoporosis

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ESTROGEN THERAPY

IN

POSTMENOPAUSAL OSTEOPOROSIS

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I. INTRODUCTION.

A relatively newly recognized metabolic disease was recently described by Fuller Albright of the Harvard Medical School and was named postmenopausal osteoporosis. This entity had been considered under the general headings of senile osteoporosis and idiopathic osteoporosis for many years. Due to experimental and clinical analysis of osteoporosis it was found that a large segment of these cases had one characteristic in common, i. e., the postmenopausal state, either physiological or artificial. It was but a step from this finding to the consideration and the successful use of estrogen in the treatment of this condition. Although still in the investigative stage, estrogen therapy shows great promise in arresting the progression of postmenopausal osteoporosis and in promoting the deposition of new bone. The subject of the present paper will be largely concerned with the evidence relating to the effects of estrogen on bone metabolisms in postmenopausal osteoporosis.

There are several things that make postmenopausal osteoporosis of great clinical interest: (1) it clearly delineates the etiology of the majority of cases of osteoporosis, which were formerly lumped into the general groups of senile and idiopathic osteoporosis; (2) it provides an interesting concept of the action of the gonadal hormones on skeletal tissue, skin and other tissues; (3) the clarification of the etiology of this type of osteoporosis has resulted in the establishment of a new type of therapy--estrogen administration--for this disorder; and (4) it opens vast realms of theoretical possibilities for treating rarefying bone disorders and stimulating the healing of fractures in

in the aged, prevention of progression of rarefying bone disorders, and, indeed, even of prevention of the disorders themselves. It hardly needs to be pointed out that the trend is toward a larger percentage of the population to live longer and thus, with women, to live many years in the postmenopausal state. For the medical profession, therefore, there is a large job ahead in the study of diseases and treatment of diseases of people in the autumn of life. In the more distant future, it is conceivable that prophylaxis will take its rightful place, but until geriatric disorders are recognized and understood clearly, this will have to remain a vision.

II. THE NATURE OF CERTAIN METABOLIC RAREFYING BONE DISEASES.

There are three types of metabolic diseases in which too little calcified bone is found. These are osteoporosis, osteomalacia, and osteitis fibrosa generalisata or hyperparathyroidism. They can be characterized according to the underlying disorder that causes them.

(1) Osteomalacia is a deficiency disease in which bone formation and resorption continue normally but calcification of the newly-formed osteoid tissue is defective. Many reasons have been listed for the deficient absorption of calcium and phosphorus from the gastro-intestinal tract. These can be found elsewhere. In laboratory studies a high serum alkaline phosphatase level and low serum calcium and phosphorus levels are found. In summary, it is a failure of mineralization of bone due to a deficient supply of calcium and phosphorus.

(2) In osteitis fibrosa generalisata (or cystica) the primary disturbance is increased bone destruction. There is a loss of bony tissue because of the increased activity on the part of the osteoclasts, the cells that seem to be involved in bone resorption. Hyperparathyroidism is the commonest cause and, when present, high serum alkaline phosphatase, low serum phosphorus and high serum calcium levels are found.

(3) Osteoporosis is primarily a disorder of tissue metabolism, i. e., the osteoblasts lay down too little bony matrix but the matrix which is laid down is normally calcified. Osteoporosis is only secondarily a disease of calcium and phosphorus metabolism, therefore, as expected, the serum calcium and phosphorus levels are normal. Since the alkaline phosphatase level of the serum is presumably an indication of osteoblastic activity, it is rather surprising to note that the serum level of alkaline phosphatase is normal; especially so, when it is realized that the total amount of osteoid tissue is greatly reduced. The normal level that is found is an indication of a rather low over-all osteoblastic activity.

Another way of looking at this is to recall that bone is a living tissue. All living tissue is subject to anabolism and catabolism. Adult bone is composed of an organic matrix in which a complex of calcium, phosphorus, and carbonate is imbedded. Two processes, formation and resorption, occur continually and simultaneously. In normal bone these are balanced and the skeleton is sufficiently rigid to withstand stresses and strains to which it is subjected. According to physical-chemical laws, this organic-mineral tissue is constantly being remodelled with new bone formation occurring to meet the demands of the skeleton; and resorption of unneeded tissue removes that tissue that is not needed. A person doing heavy work over long periods of time is likely to acquire a more massive skeleton than a sedentary worker. In the above-named rarefying bone disorders, however, the skeleton cannot respond normally to stresses and strains due to underlying metabolic disorders. In osteoporosis, as mentioned above, there is too little skeletal mass to provide rigid support. The bone that is formed is calcified normally, but there is just too little organic matrix available to hold enough of the calcium-phosphorus-carbonate complex in an amount to make a bone of normal size and strength.

III. CLINICAL CONDITIONS ASSOCIATED WITH OSTEOPOROSIS.

Osteoporosis is associated with a number of clinical conditions (35).

a. Disuse atrophy (1, 2, 3, 5, 35), such as occurs with orthopedic immobilization, occurs due to the aforementioned lack of the normal stimulus of stresses and strains for osteoblastic activity.

b. Senility, where the bony tissue atrophies as do other tissues (skin, hair, and muscle) probably causes atrophy due to the general slowing down of the vital processes of anabolism which may be explained partly on a hormonal basis (6).

c. Malnutrition and other conditions such as starvation, nephrosis, hyperthyroidism, and certain cases of pregnancy, may cause osteoporosis due to the lack of sufficient protein "building blocks" necessary for the formation of bone matrix (3, 5, 6, 12, 35).

d. Excess of adrenal cortical "S" hormone, the 11-oxysteroid hormone of the adrenal cortex, causes osteoporosis due to inhibition of anabolism of protoplasm and bone matrix in particular. This is seen in a number of conditions including Cushing's syndrome, the adaptation syndrome of Selye (e.g., burns and shock), and in the administration of adrenocorticotropic hormone (6, 9, 35).

e. Acromegaly has been cited as another cause of osteoporosis (35). The cause of the osteoporosis in this condition is unknown for certain, but has been postulated variously to be due to: (1) inadequate nitrogen intake to keep in nitrogen balance; (2) an overproduction of adrenocorticotropic hormone with resultant overproduction of the adrenal cortical "S" hormone; or (3) a lack of gonadal hormones secondary to the destruction of the gonadotrophic hormones by the pituitary tumors.

f. The post-menopausal state is the commonest of all forms of osteoporosis according to Reifenstein and Albright (35). The difficulty underlying this entity is a deficiency of estrogen which results in failure to stimulate the osteoblasts.

g. Idiopathic osteoporosis includes those cases in which the etiology is obscure and which cannot be accounted for on other bases.

IV. THE NATURE OF POSTMENOPAUSAL OSTEOPOROSIS.

a. The Clinical Findings.

The usual history of postmenopausal osteoporosis is that a woman about 8 to 10 years past the menopause (either physiological or artificial) notices weakness, fatigue or a dull ache in the lower part of the back, and has a general feeling of inability to accomplish her daily work (1, 3, 5, 12, 15). Sometimes the backache may become so severe that she seeks medical aid before the osteoporosis is developed to the extent that it is possible to demonstrate it roentgenographically. This early stage may last several years before the true nature of the condition is known. Cobey (15) notes that in this early stage, fatigue causes the patients to have poor posture but not the round-back deformity that comes with collapse of vertebrae. There is no great degree of muscle spasm with motion and the pain and tenderness are usually not acute.

Some time later after receiving a slight jar or a fall, or while lifting or bending, the woman experiences a sudden snap or acute pain in the back. This is due to collapse of one or more vertebrae. The pain that occurs with this is severe and often forces her to go to bed for a few days or weeks. The type of back pain may be varied but is characteristically aggravated by movement even of the slightest degree such as lifting, coughing, sneezing, turning, jarring, or bending. Typically, therefore, she walks with short, careful steps to avoid jarring. The pain occurs chiefly in the lower part of the thoracic region and in the lumbar region. A multitude of referred pains projected along nerve roots may be seen frequently, causing pain in the neck and shoulders, down the arms, along the ribs, over the precordium, in the epigastrium, in both flanks and over the iliac crests, or there may be associated sciatica (3, 12, 18, 21, 24, 35, 40).

With progress of the atrophy of the bone the patients become round shouldered and seem to lose stature. There is usually marked limitation of motions of the spinal column due to muscle spasm. Brown, Ghormley, and Camp note that pressure on the spinous processes does not elicit more than moderate tenderness and is not well localized, but jarring or bending (as mentioned above) causes severe pain. Eaton, however, feels that the best diagnostic test is to find tenderness on pressure on subcutaneous bone. The pain in the back and the root pain gradually become worse and finally compel the patient to go to bed for relief (12).

b. Laboratory Findings.

In various metabolic studies done on patients with postmenopausal osteoporosis, determinations of the serum levels of calcium, phosphorus and alkaline phosphatase have consistently shown values within normal limits (1, 2, 3, 6, 12, 18, 21, 35). Black, Ghormley and Camp (12) at the Mayo Clinic found an average value of 9.8 mgm. per cent. of serum calcium in 92 determinations carried out on 68 cases. The calcium levels in these cases varied from 7.8 to 12.7 mgm. per cent. with the majority being between 9 and 11 mgm. per cent. Serum inorganic phosphorus determinations in 58 cases had a mean value of 3.4 mgm. per cent. with values ranging from 2.1 to 6.5 mgm. per cent. In a similar manner the results of serum alkaline phosphatase determinations done in 47 cases had a mean value of 3.8 Bodansky units with a range from 2.0 to 13.4 units. Furthermore, in 6 of their cases that had abnormally high or low phosphatase levels, normal values were found on later determinations.

Albright and his colleagues (1, 2, 3, 5, 6, 35) emphasize repeatedly that osteoporosis is a disorder of tissue metabolism and only secondarily one of calcium metabolism. They report many cases of osteoporosis including postmenopausal osteoporosis, and observe that the serum calcium and phosphorus levels in the latter are usually normal. "Furthermore, since the phosphatase level of the

serum is presumably an index of osteoblastic activity one would not expect it to be elevated; if anything one would expect the opposite. As a matter of fact the level in osteoporosis is usually normal." (2)

In looking at the marked loss of calcium from the bones one would almost expect to find an increased serum calcium level. Albright, Burnett, Cope, and Parsons (2), however, state that hypercalcinemia is not a feature of postmenopausal osteoporosis but is probably met with only in the osteoporosis of previously active young individuals suddenly having a large part of the skeleton immobilized as by infantile paralysis or by a plaster cast. Eaton (18) further explains this lack of hypercalcinemia as being due to such a slow chronic loss that there is not enough calcium mobilized into the blood at any one time to raise the serum level, but it is sufficient over a long period of time to result in considerable loss of calcium from the bones.

In spite of normal serum calcium levels hypercalcinuria is seen in the early stages of osteoporosis (2, 3, 27) just as in hyperparathyroidism and in fractures, and may lead to kidney complications. Albright, Smith and Richardson (3) found urinary calculi in 5 of 40 patients with postmenopausal osteoporosis. Immobilization following fractures, which are so common with this disorder, may further increase the urinary output of calcium. Howard, Parsons, and Bigham (27) in studies on fracture patients found that there is a steady rise in the urinary content of calcium for the first month after fractures and that the peak excretion was maintained until mobilization was allowed. The combination of the basic osteoporosis and immobilization for the fractures may, therefore, result in a dangerous amount of calcium excretion and kidney damage. This factor is an important consideration in therapy which will be discussed later. As will be seen (vide infra) Albright attempts the minimum of immobilization to prevent this cause of loss of calcium.

c. Pathologic and Roentgenological Findings.

The osteoporosis characteristic of the menopausal state has a predilection for bones of the spine and pelvis (1, 3, 5, 12, 15, 18, 24, 40). The long bones are involved only in the more severe cases (1, 3, 5, 15, 18, 40) and the skull (1, 3, 5, 18, 40), in contradistinction to osteitis fibrosa generalisata, shows little or no involvement. Albright (2, 5) notes that the lamina dura, which is the lamina of bone in the jaws bordering the tooth sockets, is readily visible on x-ray. This is a characteristic constant in postmenopausal osteoporosis and in the severe cases of decalcification is a critical differential point from the generalized decalcification due to hyperparathyroidism.

Schmorl's classic description (3, 12) of the vertebral changes in senile osteoporosis applies in every detail to those seen in postmenopausal osteoporosis which is understandable since the latter entity previously was classified under senile osteoporosis and has similar pathological findings. The cortical bone of the vertebrae is much thinner than normal and the marrow spaces and the medullary cavity are enlarged. Vascular rather than osteoclastic resorption occurs as evidenced by clean smooth trabeculae. Also the trabeculae are thinner and less numerous than normal. The gradual progress of the osteoporosis results in weak vertebrae that are unable to stand up under normal stresses and strains of the body and the internal pressure of the intervertebral disks. Eventually the central part of the vertebral body collapses and the nucleus pulposus and disk balloon. Schmorl likened the appearance of the narrowed vertebrae with intervening ballooned disks to "fish vertebrae". If, however, the disks have lost their expansibility through degenerative processes, this narrowing will not occur. "Schmorl's nodes" are herniations of the nucleus pulposus through fissures or cracks in the cartilaginous plates into the vertebral body. These may be caused in the normal daily activity or from even very slight trauma

(vide supra). The same minimum of trauma may cause compression fractures of the anterior portion of the osteoporotic vertebral bodies with collapse of the vertebrae.

The intervertebral disks most frequently involved are those in the lower thoracic and the lumbar region and the vertebrae here are the ones most commonly compressed (12). In these regions the disks maintain their expansibility longer and are normally more expansible than in the upper thoracic regions. Degenerative changes in the disks, however, occur in the upper thoracic region and dorsal kyphosis and hypertrophic changes about the anterior margins of the vertebral bodies result from the thinning of the disks. It is the dorsal kyphosis that is usually seen in older persons. The amount of ballooning of the disks and the number of vertebrae compressed depends on the grade of the osteoporosis. In slight osteoporosis there is no ballooning, whereas in extreme grades of osteoporosis nearly all or all of the disks may show ballooning (12). The backache and the sharp radiating pain may conceivably be caused by nerve root pressure, but Black, Ghormley and Camp failed to find evidence of pressure of the disks on the nerves and believe, instead, that the pain is of reflex nature arising from recently compressed vertebrae and referred along the nerve roots. They note that there may be severe osteoporosis and many ballooned disks and compressed vertebrae without pain. Albright, Smith and Richardson (3) likewise report that there may be no back symptoms and an x-ray examination taken for some other condition may be the first evidence of osteoporosis.

As was said above, the long bones are involved to a lesser extent than the pelvis and spine. The femur seems to be fractured more commonly than other long bones in these cases (1, 3, 5, 15, 18, 40). Cobey (15) makes the interesting observation that "fractures of the neck of the femur and spine in old people are probably due more to osteoporosis than trauma". He avers that in-

stead of actually falling and breaking the hip as is so commonly stated, the sequence should be that the hip breaks and then the patient falls. This, according to Cobey, is "surely most often the case in regard to fractures in the neck of the femur, or the so-called cervical fractures."

The difficulty of detecting early cases of osteoporosis by roentgenological examination can be appreciated if it is realized that there must be a 40 percent. loss of the calcium with an equal loss of the matrix from the bone before a diagnosis of osteoporosis can be made roentgenographically (15). It is perhaps because of this technical difficulty that the first x-ray evidence of the disease is often compression fractures of the vertebrae or fractures of the femur (vide supra). Cobey notes further that the redeposition of new bony matrix and its recalcification takes a period of six months to six years to make itself evident on the x-ray film.

Dr. Mary S. Sherman's very interesting case of a fifty-eight year old woman with Paget's disease complicated by severe postmenopausal osteoporosis shows the extremes to which this disease may go, especially when complicating Paget's disease. In her case the decalcification of the right leg bones was so severe that "when the right foot was elevated, the entire right lower extremity hung between the foot and the pelvis like a piece of rubber hose, and that extremity could easily be twisted in any direction." (40) Albright, likewise, has reported cases in which Paget's disease had superimposed postmenopausal osteoporosis (3) and the latter so modified Paget's disease that the sclerosing aspect of Paget's disease was missing. In the case of Mrs. M. L. (3) "the skull was flat and soft and the pulsations of the brain could be felt and seen!" Roentgenological examinations showed none of the increased bone density that is typically seen in Paget's disease. It was felt that the same factor that caused postmenopausal osteoporosis had similarly inhibited the osteoblastic activity in Paget's disease.

A point to be constantly borne in mind, therefore, is that postmenopausal osteoporosis can complicate other diseases as indicated above. For a further example, a case presented before the Medical Grand Rounds of the Massachusetts General Hospital (21) presents a possibility of osteomalacia complicating postmenopausal osteoporosis.

V. EXPERIMENTAL EVIDENCE OF THE EFFECTS OF ESTROGENS ON OSTEOGENESIS.

Instead of a chronological account of various work done on the effects of estrogenic hormones on the skeletal system and on the calcium and phosphorus metabolism, it is believed that it will be more understandable to treat the matter according to species. This approach will be used because of the wide species differences and in turn the differences between lower animals and man.

a. Fish and Amphibia.

The cod, puffer and the toad Xenopus all lay eggs without shells but with a high calcium content. Females of all three species show higher serum calcium levels during the development of eggs than males (22, 40). The cod and puffer have blood calcium levels of 29 mgm. per cent. when developing eggs compared to a level of 9 to 12.5 mgm. per cent. in males. The male toad Xenopus always has a lower calcium level than the female. The female of this species in addition has a higher calcium level in the egg-laying season than in the non-breeding season (22). The serum inorganic phosphate is decreased during the breeding season and after the injection of progesterone and estradiol benzoate. Gonadectomy in this species has no effect on the phosphorus metabolism; no study of the effect on calcium metabolism has been made.

The dogfish shark and other viviparous fish have identical values in the male and female and the serum calcium levels do not vary with gestation in the female (22, 40). This corresponds with the lack of variation in blood chemistry during gestation in mammals.

b. Birds.

(1) Pigenons.

In 1926 Riddle and Reinhart (36) made the observation that the blood calcium in the female pigeon shows large increases at each ovulation period to about twice the normal value. Male doves and pigeons, however, show no marked fluctuations of the serum calcium level in the various stages of the reproductive cycle. They believed that this variation was "probably first of all an expression of a newly found relation which the parathyroids bear to reproduction in the female bird."

Laying hens have been shown to have a much greater serum calcium level than for sexually inactive females. In addition the calcium level has been correlated with the ovum size (22).

Kyes and Potter in 1934 (30) found structural variations in the long bones of the leg of the female pigeon that were not found in the male and further correlated these changes with the maturation of the ovarian follicle. The marrow cavity of the female pigeons showed no ossification where there was no follicle of a diameter greater than 2 mm. However, when there was an ovarian follicle of more than 4.5 mm. in diameter, there was always some degree of ossification. Extreme ossification of the marrow was found when a 10 mm. follicle was present.

In 1936 Riddle and Dotti demonstrated that a rise in serum calcium can be caused by injections of estrogens similar to the rise in serum calcium seen when the ovary contains a large ovum. A similar rise in the serum calcium was noted by Pfeiffer and Gardner in 1938 and in addition they showed that injected estrogens also could produce hyperossification of medullary bone (22). Bloom, Bloom, and McLean in 1941 (13) also noted the cyclic changes in formation of medullary bone correlated with maturation of ovarian follicles. Intense destruction of the bone was found during calcification of the egg shell. They discussed the relation of hormones to these phenomena and emphasized that the hypercalcemia

differs from that of hyperparathyroidism chiefly in that during the physiological hypercalcemia in pigeons the concentration of ionized calcium is not increased.

Bloom, McLean, and Bloom in 1942 (14) found that estrogens would not induce medullary bone formation in castrates or males with inactive testes. They found that androgens (testosterone) as well as estrogens were essential to the formation of medullary bone in castrates. They also separated the two phenomena of hypercalcemia and hyperossification in pigeons.

Riddle, Rauch and Smith in 1945 (37) successfully showed that estradiol benzoate could raise the serum calcium of completely parathyroidectomized pigeons to the same level as in normal controls. Endosteal bone formation in these parathyroidectomized pigeons was as effectively brought about by estrogen as in normal birds. This would seem further to indicate a direct action of estrogens on bone and calcium metabolism and that it is not mediated through the parathyroid gland as inferred by Riddle and Reinhart (36).

Riddle and McDonald (38) noted that estrogens increase the plasma calcium and inorganic phosphorus of normal, parathyroidectomized, and hypophysectomized pigeons. McDonald, Riddle and Smith (32) found that while thyroxin seemed to inhibit estrogen-induced increases in plasma calcium, inorganic phosphorus and protein phosphorus, it does not prevent the formation of endosteal bone which follows estrogen administration. They concluded that the inhibition of estrogen-induced increases in plasma constituents by thyroxin is probably a secondary effect associated with an increased metabolism and excretion of calcium, phosphorus and nitrogen.

(2) Chickens.

A hypercalcemia during the laying period was noted in hens and was found by Benjamin and Hess to be in the non-filtrable fraction of thecalcium whereas the filtrable fractions remained practically unchanged (11). Injected estrogens in small amounts (8) or in amounts normally found in the body (34) are not able to

significantly raise the serum calcium level in pullets. Massive doses, however, were observed (8, 34) to increase the serum calcium level.

(3) Ducks and Sparrows.

These two species both show increases of the serum calcium level and increased ossification in the medullary canals with estrogen administration (22).

c. Mammals.

(1) Mice.

Estrogens injected into mice of the C3H strain resulted in increase of endosteal bone in the femur but this effect was not seen in the CHI strain. In the C3H strains a deficiency of Vitamin D did not prevent the typical changes in the femur (39).

The Silberbergs (44) found that in some species and strains of mice there was an overproduction of bone but in others the effects of estrogens was merely to inhibit resorptive processes. McLean (33) and Urist, Budy and McLean (46) found that large doses of estrogens produced spectacular results in mice with obliteration of the marrow cavity within 1 to 3 months with the speed of hyperossification depending on the size of the dose. In addition, bone resorption was markedly inhibited (46). Estradiol was inhibited in its action on bone when injected with testosterone propionate in both male and female mice. Estradiol injected into male and testosterone injected into female mice both caused increases of bone and of bone ash. The effects in the females was only slightly greater than in the controls while the estrogen-treated males showed greatly increased bone and ash weights over those of untreated control animals. The conclusion might be drawn that estrogens in mice have a definite stimulating effect on ossification.

(2) Rats.

Ely and Phillips (19) concluded that physiologic amounts of estradiol had

no demonstrable effect on skeletal development. Likewise, Lippman and Saunders (31) felt that any change produced by high doses of estrogens was relative rather than absolute and was due to a loss of water and organic material rather than a real stimulus to hyperossification.

On the contrary Day and Follis (17) found a decrease in normal destruction of bony trabeculae and some increase in osteoblastic activity at the cartilage shaft junction. Bell and Cuthbertson (10) noted that estradiol caused formation of slightly heavier and stronger bones than normal in rats. Armstrong, et al. (7) using orchidectomized rats found that estradiol dipropionate reduced the bony atrophy which resulted from this operation. McLean (33) and Urist, Budy and McLean (46) find that estrogens, even in small doses, inhibit the normal resorption of spongy bone laid down in the process of growth in length of the long bones. The increase in density of the bones was roughly proportional to the dose of estrogen. It is the belief of McLean that estrogen acts "not by promoting calcification or increased density of already formed bone or bone matrix but by the formation of new bone."

Serum phosphorus and phosphatase levels in rats were studied by Tuba, Baker, and Cantor (45). They found no significant difference in the effect of estrogens on the serum phosphorus or phosphatase of either males or females that had previously been castrated.

Riddle and Dotti (22) found an increase in serum calcium in intact, hypophysectomized or gonadectomized rats after the injection of several different estrogens.

(3) Rabbits, Dogs, Hamsters, Kittens, and Guinea Pigs.

In hamsters, guinea pigs, rabbits, kittens, and puppies (46) proliferation of epiphyseal cartilage and new bone formation were suppressed by injections of as large doses of estrogens as the animals would tolerate. The result was a

stunting in the growth of long bones to one-fourth or one-half normal length. A reduction in the number of osteoblasts and bone trabeculae was found in immature rabbits. In many species there were degenerative changes in the bone marrow with cyst formation. In general, there seemed to be a non-specific repression of all cellular activity when large doses of estrogens were used in these species (46). The Silberbergs (42, 43) described estrogen administration in the immature guinea pig as causing premature aging of the skeleton. Ovariectomy, on the other hand, causes an initial proliferation of cartilage at the epiphyses and a retardation of calcification and ossification. Maturation of the osseous system is delayed.

The serum calcium level is decreased in rabbits both with crude ovarian extract and large amounts of estrone (22). In the dog small amounts of estrogens are reported variously to have no effect (33) and to cause a slight rise in the serum calcium level (22).

In general, it is seen that there is a great species difference in the effects of estrogen on bone and on the calcium and phosphorus metabolism. In certain cases, i. e., pigeons, chickens, ducks, sparrows, mice and rats, there seems to be well-substantiated evidence of stimulation of osteogenesis or of inhibition of normal destructive tendencies. Rabbits, dogs, hamsters, kittens, and guinea pigs, however, seem to show a non-specific repression of cellular activity.

VI. EVIDENCE OF THE ROLE OF ESTROGEN THERAPY IN POSTMENOPAUSAL OSTEOPOROSIS.

a. Relationship of Age and the Menopause to Osteoporosis.

As stated above, Albright examined all of the cases of so-called idiopathic generalized osteoporosis that were found in the records of the Massachusetts General Hospital and found that in those under the age of 65 years, there was an almost constant occurrence of the postmenopausal state (1, 3). He was able

to find 42 cases of unexplained generalized osteoporosis in the hospital records between 1931 and 1940 and found that 40 of these were women. Of these women, 30 had undergone physiological menopause and 10 had experienced artificial menopause (1, 3). There was no explanation for the osteoporosis in the two men. Furthermore, it was found that there were no cases of generalized osteoporosis occurring in women before the menopause that could not be explained on some other basis.

Although Albright (3) would not entirely rule out age as a factor in the causation of this disorder, it was noted that one of his cases was a woman who was only 42 years of age at the time of onset of the symptoms (35). He tried to eliminate the factor of senility by excluding cases over 65 years of age at the onset of symptoms. Others, however, have cited cases that indicate that this condition may occur in even younger women. Cobey (15) cites two cases in which the condition developed after artificial menopause, one of whom was only 23 and the other 39 years old at the time of onset of symptoms. It should be emphasized that these are unusual cases and merely tend to support the contention of Albright that the menopause rather than age is the important factor. As would be expected on a statistical basis, most of the cases occur in older women and usually past the age of 50 (1, 3, 12, 18), since this is the age at which the majority of women have undergone spontaneous menopause.

Varney, Kenyon, and Koch in 1942 reported on a syndrome of ovarian dwarfism. They asked Albright, Smith, and Fraser to prepare a paper on the cases that had come to the Massachusetts General Hospital that similarly showed the syndrome of primary ovarian insufficiency and decreased stature (4). Among the various things characteristic of this syndrome was osteoporosis of the spine and the pelvis which was quite similar to that seen in the postmenopausal woman. Another point in common with the postmenopausal woman was a tendency of some to develop

atrophy of the skin. In this group of patients with a life-long ovarian insufficiency, these conditions found strongly suggest a direct connection etiologically between estrogen and bone metabolism. That the osteoporosis did occur in these patients at a relatively early age (the second to fourth decades) seems to be further evidence that age alone is not the most important factor in the etiology of osteoporosis in women.

In addressing the American College of Physicians in 1947, Albright (6) declared that there are two steps in the cessation of hormonal stimulation of the osteoblasts in the female. The first of these is the cessation of the estrogen hormones, the menopause, and the second stage is the cessation of 17-ketosteroid production by the adrenal, which he calls the "adrenopause". Since both of these hormones are premised to be concerned with stimulation of osteoblasts, the relatively early disappearance in the female of one of them, estrin, accounts for the fact that osteoporosis is much more common in females. This is in accordance with the findings of Ghormley and his associates at the Mayo Clinic (12, 24), in that they found osteoporosis afflicted women four times as frequently as men and that by inference from their statistics it could be seen that the average age of onset in women was about 9 to 10 years following the menopause.

b. Effect of Estrogens on the Calcium and Phosphorus Metabolism.

A second finding that supports the conclusion that this type of osteoporosis is due to an hormonal deficiency consequent to the postmenopausal state is that estrogens have the power when administered to these women of placing them in a markedly positive calcium and phosphorus balance and that this effect continues as long as the estrogen is administered. The effect seems to be evident in about 6 days, and the maximum effect is reached about 20 to 30 days after the therapy is commenced (35). Following the cessation of the treatment there is

little change for about 15 days, and then there is found a slow reversal to the original balance. A second course of therapy will again cause the calcium and phosphorus balance to become positive (1, 3, 5, 6, 18, 21, 26, 35, 40). Reifenstein and Albright (35, 41) noted that the positive calcium balance remained for 30 to 50 days after the cessation of therapy. The phosphorus balance together with the nitrogen balance, however, had a more rapid reversal. Shorr and Carter (41) noticed a much more rapid fall in the calcium balance and that it seemed to parallel the fall in the phosphorus and nitrogen balance.

At variance with the above findings, Johnston (28) found that the effect of giving estrogens in doses of from 12,000 to 36,000 rat units to apparently normal girls at puberty resulted in a depression of the calcium balance with increased excretion in both the urinary and fecal fractions. In addition the nitrogen balance was depressed in 3 of 8 cases. It should be noticed that this was measuring the effect of giving an excess rather than that of correcting a deficit. Johnston points out that with thyroid administration there are opposite effects that result when used in deficiency states and in excessive amounts. An analogy was drawn between the possible similarity with estrogens. Reifenstein and Albright (35) found a somewhat similar effect when giving large doses of estradiol in postmenopausal osteoporosis. In one patient (case 3) the estradiol dosage was doubled during seven 5-day periods of study and it was found that not only was the calcium balance not improved with this larger dose, but that it seemed to be reduced. This would seem to indicate that the lowest dosage compatible with improvement is to be preferred.

Reifenstein and Albright (35) further observed in their metabolic studies that fecal as well as urinary calcium and phosphorus excretions were decreased by estrogens. The urinary nitrogen excretion showed a poorly-sustained decrease and the serum alkaline phosphatase levels failed to rise. The synthetic estrogen, diethylstilbestrol, appeared to be as effective as the naturally-occurring

estradiol. The ranges of dosages employed for estradiol benzoate went from a low of 1.66 mgm. every 3 days to a high of 3.32 mgm. daily intramuscularly. Diethylstilbestrol was used in dosages of 1 to 15 mgm. daily by mouth. They failed to find a significant difference between the larger and smaller doses except in the one case of an adverse effect of the large dose as mentioned above. 15 mgm. of diethylstilbestrol seemed, however, in the one case studied with it, to be slightly more effective than 1 mgm. daily.

c. Histological and Roentgenological Evidence of the Effect of estrogens on Osteoporosis.

The work of Dr. Mary S. Sherman of the University of Chicago (40) published in 1948 established a third invaluable piece of evidence concerning the value of estrogens in osteoporosis. She found in a patient with Paget's disease with superimposed severe postmenopausal osteoporosis, that estrogen therapy not only caused the bones to become palpably more firm but that bony tissue was so increased that it could be proved both histologically and by x-ray. The work is so monumental and the changes are so graphic that it will be quoted in part.

"The roentgenograms revealed spectacular changes in many bones.....There was extreme osteoporosis of the pelvis and lumbar spine with collapse of the latter. The same osteoporosis was present to an even greater degree in the femora, both of which showed multiple unhealed fractures. The left leg was relatively normal, but in the right the tibia was almost invisible.....With the use of local anaesthesia, pieces of the skull, one rib, and the right tibia were removed for microscopic examination. There was so little bone in the right leg that the needle penetrated the cortex. The bone was identifiable, but was so soft that it could be compressed by the slightest digital pressure. The specimen was scooped out with the handle of a knife.....With this diagnosis (Paget's disease with superimposed postmenopausal osteoporosis) it was decided to treat the patient with massive doses of estrogenic hormone. During this period and for three months pre-

ceding it she was given the regular house diet with no added calcium or vitamin D. She had a total of 610,000 rat units (101.3 mgm) of estradiol benzoate in twenty-eight days. Within the first three days, marked subjective improvement began. The bone pain diminished; the patient began to be active; and her general attitude, from one of extreme apathy, began to be more normal. Within a week, she could be moved without discomfort, and the spontaneous bone pain had disappeared. At the end of a month, she was able to sit in a chair and manage her meals by herself. Her limbs no longer felt soft, and there was palpable callus about many of the fractures. Roentgenograms taken at this time showed surprising changes. The right tibia was now clearly outlined, and there were definite trabeculae throughout its length. Both femora were increased in density, and about the many fractures there was exuberant, fairly dense callus. Similar increased density was evident in the pelvis, but the rest of the bones appeared unchanged. Biopsy studies were repeated with material from the same areas which had been examined before. On this occasion, the bone of the tibia was found to be sufficiently dense and resistant so that an osteotome was necessary to cut it. The bone taken from the tibia shows the generalized increase in number and thickness of the bone trabeculae. Many surfaces are completely covered by osteoblasts, while others have numerous osteoclasts."

In earlier articles Albright omitted mention of histological and roentgenological evidence of the effect of estrogens on osteoporosis. Reifenstein and Albright (35) stated that "it would be difficult to produce undisputed evidence that the bones (excluding fracture-sites) as visualized by x-ray have become more calcified than before the therapy was instituted." They did find that the most recent films of the longest treated cases showed fairly convincing evidence to support their supposition that bone was becoming more calcified (35). The case presented by Dr. Sherman is outstanding in this regard, therefore, because it is the first time in the human that indisputable histological and roentgenological

evidence was recorded that osteogenesis is stimulated and that bone actually becomes more dense under estrogen therapy. Of further interest is Cobey's observation (15) that he had a decreased number of non-unions in fractures of the neck of the femur using estrogen therapy.

VII. ADDITIONAL THERAPY IN POSTMENOPAUSAL OSTEOPOROSIS AND ITS RATIONALE.

Reference has been made to the work of Black, Ghormley and Camp (12) and Ghormley, Sutherland, and Pollock (24) of the Mayo Foundation on senile osteoporosis. It is believed that most of the cases that they classify as senile osteoporosis now can be reclassified as postmenopausal. It is noted (12) that they found improvement in 43 per cent. of cases treated for less than six months and symptomatic improvement of 70 percent of patients treated longer than six months. The regime used was essentially a diet high in calcium and phosphorus, or administration of calcium and phosphorus, supplemented by vitamin D. They used bed rest with caution to avoid atrophy of disuse. Braces and corsets to support the spinal column were considered essential in some cases (24). In addition, heat and massage were applied to the spine to relieve the pain and muscle spasm. They were not able to show x-ray evidence of improvement in any of their cases since the follow-up period extended on an average of only twenty-nine months from onset of treatment. It is rather significant that Ghormley says "such treatment must be kept up for many months to accomplish any improvement" (24).

Albright et al. (1, 3, 35) discussed the various theories of the relation of the diet to postmenopausal osteoporosis and felt that since osteoporosis is due to a deficiency in bone matrix protoplasm, a high protein diet is probably indicated, but since this condition is not one of calcium and phosphorus metabolism primarily, excessively high intakes of calcium and phosphorus and of vitamin D were probably not indicated. This view does not preclude the use of various salts of calcium and phosphorus nor of vitamin D, but suggests that the

intake should be limited to several times the minimum daily requirements.

Emerson and Beckman (20) noted a generalized rarefaction of diaphyseal bone in children with nephrosis. They attributed this to an excessive loss of calcium in the stool since the urine was almost void of calcium and the feces contained an abnormally great amount of calcium. This seems to indicate that the absorption of calcium is less during states of nitrogen deficiency. As early as 1930 Cuthbertson (16) noted a loss of nitrogen in the urine following fractures and found that vitamin D did not appear to alter the metabolism apart from a slight increase in the urinary excretion of calcium. Howard, Parsons, and Bigham (27) corroborated Cuthbertson's work on nitrogen excretion following fractures, but found further that when this occurred there followed an increased excretion of calcium in the urine. Albright et al. (3, 6, 35) likewise noted a negative calcium balance in protein deficiency states such as starvation, malnutrition, nephrosis and in certain cases of pregnancy. Using two patients with an idiopathic osteoporosis in which pregnancy made the condition much worse, Albright (6) added serum albumin intravenously at the rate of 50 grams of purified serum albumin daily for 12 days while on a constant diet and found that the urinary calcium excretion bore an inverse relationship to the serum albumin level. In a second experiment, Albright repeated the procedure except that the albumin was given orally. Instead of finding the same effect as in the experiment when serum albumin was given intravenously, there was no rise in the serum albumin level and also no fall in the urinary calcium excretion. This seems to strengthen the conclusions that with low serum albumin levels the absorption of calcium is markedly reduced and the retention of serum calcium is likewise lessened. This led Albright to conclude that serum albumin is important in bone metabolism and that it is probably a precursor to bone matrix. Cobey (15) has carried this point even farther and recommends that the protein level of the diet should be as high as the patient can tolerate and even uses protein digest orally in order

to keep a positive nitrogen balance which he feels necessary for osteoid formation.

As for the question of whether large intakes of calcium and phosphorus are indicated, it would seem elemental to say that, if there is a coincident calcium deficiency as in osteomalacia (21), an increased supply of calcium, phosphorus and vitamin D is needed and would clearly be indicated. In the postmenopausal case presented by Dr. Sherman (40) she tested the effects of calcium and vitamin D administration with and without the use of estrogen. She found when calcium and vitamin D were given with estrogen, that the excretion of calcium was only very little more than on estrogen alone, indicating that calcium actually was being absorbed and stored in a greater quantity. During a subsequent period in which calcium and vitamin D were being given, she discontinued estrogen administration and the patient went into a negative calcium balance. Within two months after cessation of estrogen therapy, or a little beyond the time that Reifenstein and Albright (35, 41) reckon for the residual effect of estrogens to be expended, the patient had a recurrence of her symptoms with such alarming rapidity that the trial on calcium and vitamin D alone had to be stopped. This is rather good evidence that the role of dietary calcium, phosphorus, and vitamin D is not one of stimulation of osteogenesis, but rather a physico-chemical role in speeding absorption of, and in supplying the inorganic material for, the calcification of bone. There does seem to be a greater utilization of calcium with simultaneous administration of estrogen, however, so the recommendation of a high calcium, high vitamin D diet is entirely justified (12, 15, 18, 21, 23, 24, 35, 41). The physiological explanation may be that since estrogen stimulates the production of more matrix, there is an increased amount of newly formed bone that needs calcification and that with these salts being deposited, according to the law of mass action, the quantity being absorbed by the blood will be and is greater. The caution of Albright (35) that excessive intakes of calcium and

phosphorus and of vitamin D are not desired is well-taken by most clinicians in light of the possibility of causing hypercalcinuria with its attendant dangers of urinary calculi and kidney damage (3, 26). It would hardly be worth the candle to treat the patient for osteoporosis and have the patient die of kidney damage. The doses used by Ghormley et al. (12, 24) were one teaspoonful of tribasic calcium phosphate three times a day and a daily total of 10,000 to 50,000 units of vitamin D. The dosage of calcium used was only slightly in excess of the actual daily requirements (0.5 to 1.0 grams a day) and the vitamin D is in the range of dosages used to correct deficiencies. In addition foods high in calcium and phosphorus are recommended (12, 15, 24).

Absolute immobilization must be avoided in osteoporotic patients to prevent a superimposed atrophy of disuse (1, 3, 5, 6, 12, 15, 24, 35, 40). Braces and corsets as used by Ghormley (24) probably do not take the entire weight off of the spine and thus may allow stresses and strains to stimulate osteoblastic activity. It seems definite that they do relieve the patient of a certain measure of pain. Coby (15) uses a more conservative approach and keeps his patients with fractures of the neck of the femur due to osteoporosis in bed for 3 or 4 months and allows only partial weight-bearing until 6 months have elapsed after the fracture. This is a great deal more rest than is given to those with spinal fractures, but the incidence of non-union is perhaps the deciding factor in the choice of amount of bed-rest. The intangible factor of the increase of a feeling of well-being that results from ambulation goes a long way toward dispelling psychoneurotic tendencies and the invalid complex seen so often in bed-fast patients.

VIII. BRIEF COMMENTS ON THE EFFECTS OF OTHER HORMONES ON OSTEOGENESIS.

a. Effects of Hormones on Osteogenesis in General.

In an address before the Laurentian Hormone Conference in 1947 Fuller Albright (5) attempted to "cover the field" in a survey of the effects of

various hormones on osteogenesis. His summary, in chart form, will be reproduced here:

HORMONE	ENDOCHONDRAL BONE	ENDOSTEAL BONE	PERIOSTEAL (MEMBRANOUS)	REMARKS
Parathyroid	No effect	No direct effect (see remarks)	No effect	Excess may lead to increased bone destruction and secondarily to compensatory increased endosteal bone formation.
Thyroid	Stimulates	No direct effect (see remark)	No effect	Excess may lead to negative nitrogen balance and secondarily to starvation osteoporosis.
"The" Growth Hormone	Stimulates	No good data (see remarks	Stimulates	Demineralization in acromegaly probably secondary phenomenon.
Testosterone Propionate and Methyl Testost.	Stimulates	Stimulates	No effect	
Estradiol Benzoate and Dipropionate	Large amount inhibit; small amounts may stimulate	Stimulates	No effect	
Progesterone	Insufficient data	Insuffic. data	Insuff. data	
Adrenal Cortical "S" hormone	Inhibits	Inhibits	Insuff. data	
Adrenal Cortical "N" hormone	Stimulates	Stimulates	No effect	

(1) Hormones stimulating osteogenesis include:

(a) Estrogens:(see above)

(b) Testosterone: (see chart above and text below).

(c) Adrenal Cortical "N" hormone, i. e., a 17-ketosteroid hormone (5, 6, 15).

(d) Thyroxin in physiological amounts (5, 28, 32) and when administered to correct a deficiency (28).

(e) "The" growth hormone of the pituitary (5, 10, 43).

(2) Hormones inhibiting osteogenesis include:

(a) Adrenal cortical "S" hormone, i. e., an 11-oxysteroid hormone (5, 6).

(b) Excess of thyroxin, by exerting an unfavorable effect on the nitrogen balance (5, 10, 28, 32).

(c) Adrenocorticotropic hormone (ACTH) of the pituitary, by causing increasing production of adrenal cortical "S" hormone (5, 6, 9).

(3) The parathyroid hormone is not listed above as either stimulating or inhibiting osteogenesis. This is omitted because the secretion of the parathyroid is assumed to have an action primarily on the calcium and phosphorus metabolism (2, 5, 13, 29, 37, 38) and only secondarily on bone. It is noticed that there is no lack of bone matrix in osteitis fibrosis generalisata but a definite demineralization of bone. The demineralization by weakening bone causes an increase of stresses and strains on the bone. These are felt to be the stimulus for increased osteoid formation, not any direct action by the parathyroid. This view is held by the group at the Harvard Medical School including Aub and Albright, whereas Collip of Montreal believes there is a direct action of the parathyroid on bone. It must be admitted that there are points in favor of each thesis, but the former seems to be better substantiated.

Experimental work concerning estrogens and their effects on bone indicates that the effects of estrogen are not mediated through the parathyroid (vide supra). For the present discussion, therefore, the role of the parathyroids will be dropped summarily.

b. <u>The Role of Androgens in Bone Metabolism</u>.

Orchidectomy was found to increase the degree of bony atrophy in the male rat, an effect which was prevented by the administration of large doses of testosterone propionate (7). Bloom, McLean, and Bloom (14) found that androgens, as well as estrogens, are essential for the formation of medullary bone in male pigeons with inactive testes. Riddle and McDonald (38), however, could not

produce an increase in the calcium or phosphorus level with androgens in normal pigeons. In animals it may be assumed, therefore, that when a deficiency is present, androgens have a definite effect in bone formation.

In the human, testosterone likewise has a definite role in bone metabolism. It has been found to stimulate protoplasmic anabolism with retention of nitrogen, phosphorus, potassium and sulfur in the proportions in which they are found in protoplasm (5, 6, 21, 35, 41). Stimulation of protoplasmic anabolism in osteoporotic diseases means stimulation of the osteoblasts to lay down osteoid tissue (5).

In the adaptation syndrome of Selye and Cushing's syndrome testosterone gives beneficial results by overcoming the anti-anabolic effect of the adrenal cortical "S" hormone by the introduction of an anabolic effect (5, 6, 35). Even in Addison's disease where there is a decrease or absence of adrenal cortical tissue and of adrenal cortical hormones testosterone has been found to cause nitrogen and phosphorus retention (6).

In postmenopausal osteoporosis testosterone, likewise, reduces the calcium, phosphorus, and nitrogen excretion (6, 33, 35, 41). Shorr and Carter (41) noted an initial increase and a later decrease of the storage of nitrogen with continued administration of testosterone. Reifenstein and Albright (35), however, flatly state that in their cases the decrease in the urinary nitrogen excretion was marked and prolonged.

The effect of androgens used in conjunction with estrogens in postmenopausal osteoporosis has been studied (5, 35, 40, 41) and the combination has been reported to have a greater effect on the calcium, phosphorus, and nitrogen metabolism than either alone (5, 35, 41). Dr. Mary S. Sherman (40) administered 100 to 125 mgm. of testosterone propionate daily with estrogens to her patient but could find no perceptible change in the clinical or roentgenographic picture. However, since she used androgens only after estrogens had caused amelioration

of the clinical symptoms and the bones had become more dense to x-ray, this only means that no dramatic changes in these two factors were observed. At least there was no neutralizing effect noted in the six weeks trial in her case.

This brings up the observation of Halvorsen (25). He noticed that when estradiol benzoate and testosterone propionate were injected simultaneously in mice they seemed to neutralize each other in their effects on bone. In normal humans (41) the same neutralization of the effects of estrogens by androgens as measured by vaginal smears was noted when the ratio of testosterone to estradiol was 50 to 1 by weight. It may be that in deficiency states that the dosages as used are not in the same ratio and that this partly accounts for the synergistic effect on the calcium, phosphorus, and nitrogen metabolism.

Dosages of androgens employed by Reifenstein and Albright (35) in the treatment of osteoporotic diseases were 25 to 50 mgm. testosterone propionate daily intramuscularly and 40 to 100 mgm. methyl testosterone daily by mouth. Methyl testosterone appeared to be as effective as testosterone propionate. They usually give some form of testosterone for the first 6 to 12 weeks in postmenopausal and senile osteoporosis. Coby (15) notes that the only methods clinically available at present for the production of new bone matrix is by using estrogenic and/or androgenic therapy coupled with a high nitrogen (protein) intake to achieve a positive nitrogen balance.

In summary, testosterone exerts a synergistic effect with estrogens on the calcium, phosphorus, and nitrogen metabolism in postmenopausal osteoporosis. Since it has a greater effect than estrogens in causing nitrogen retention and developing a positive nitrogen balance, it may be valuable as a supplementary agent in treating postmenopausal osteoporosis and may be necessary in the more recalcitrant cases to be used continuously, or until a favorable result has been assured.

IX. SUMMARY.

1. Postmenopausal osteoporosis is a metabolic disease in which hormonal deficiencies occurring in certain women as a consequence of the postmenopausal state produces an osteoporosis chiefly of the spine and pelvis. This osteoporosis is caused by too little bone formation due to failure of stimulation of the osteoblasts to lay down sufficient bone matrix. The matrix laid down is adequately calcified, thus it is only secondarily a disorder of mineral metabolism. The clinical, laboratory, pathological, and x-ray findings in postmenopausal osteoporosis are discussed.

2. Estrogens induce a retention of calcium and phosphorus and place patients with postmenopausal osteoporosis in a positive calcium and phosphorus balance as long as the estrogens are administered. There is some residual effect lasting 30 to 50 days after estrogens are discontinued, but thereafter an exacerbation of the disease is noted if estrogens are not continued.

3. Doses of estradiol benzoate sufficient to produce a positive calcium and phosphorus balance range from 1.66 mgm. every 3 days to a high of 3.32 mgm. daily intramuscularly. Evidence is cited that the lower dosage is as effective as the higher dose. Diethylstilbestrol, a synthetic estrogen, in doses ranging from 1 to 15 mgm. daily by mouth is as effective as the natural estrogens in producing a positive calcium and phosphorus balance. The smaller doses of diethylstilbestrol appear, similarly, to be nearly as effective as the larger doses.

4. Histological and roentgenological evidence that estrogens increase bone formation is mentioned.

5. The action of estrogens in relieving subjective symptoms of pain and discomfort rather promptly was noted.

6. Additional therapy recommended in postmenopausal osteoporosis includes

a high protein, high calcium diet with added vitamin D. The dangers of absolute immobilization are stressed and recommendation is made that bed rest, braces, and corsets be used cautiously to avoid superimposed atrophy of disuse.

7. Androgens stimulate protoplasmic anabolism and in postmenopausal osteoporosis cause retention of nitrogen, phosphorus, potassium and sulfur in the proportions found in protoplasm. They reduce calcium excretion, like estrogens, but to a lesser extent.

8. Androgens used with estrogens have a synergistic effect and the combination has a greater effect on the calcium, phosphorus, and nitrogen metabolism than either used alone. The possibility that androgens may be valuable as a supplement to estrogen therapy in postmenopausal osteoporosis is mentioned.

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