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Postmenopausal Osteoporosis: The evolution of our concepts of its cause*

Harold M. Frost, M.D.**

Research findings in the last 20 years concerning senile and postmenopausal osteoporosis indicate that the skeletal condition associated with these diseases arises because some systemic factor acts directly upon the bone marrow tissues. There is a secondary tendency to accelerate loss of bone greater than in the normal aging process. The loss occurs only on those surfaces in physical contact with the bone marrow tissue.

This article summarizes changes during the past decade in our thinking about the pathophysiology of postmenopausal osteoporosis which justify this rather bold and possibly even novel conclusion:

Postmenopausal osteoporosis emerges as an effect of an underlying bone marrow tissue disorder.

To set the stage for this idea we should review briefly some concepts of bone physiology and osteoporosis which enjoyed some vogue about 30 years ago. We can then appreciate best the significance of more recent developments.

The Assumptions

Approximately 30 years ago Fuller Albright's pioneer writings reflected the known facts that bone was a living tissue, one resorbed by osteoclasts and made by osteoblasts. It seemed logical then that, in the operational sense, osteoblasts throughout the skeleton probably represented one single collection of cells in the functional sense and osteoclasts another (hence the "singularity" assumption). Furthermore, they were assumed to function essentially independently of each other in re-

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sponding to systemic regulation by blood-borne messengers of chemical or hormonal nature (hence, the “independence” assumption). Further, and of particular importance here, it was assumed that this systemic regulation acted either to directly depress osteoblasts (Albright’s view), or to directly stimulate osteoclasts (a view I favored for a time, in the good company of many others), leading thereby to the deficient amount of bone tissue known to characterize the osteoporotic skeleton. Unfortunately, so far, attempts to find a medication which would selectively either stimulate the body’s osteoblasts, or inhibit its osteoclasts have been unsuccessful.

Why? I suggest that the problem may be a consequence of the way we were taught to think of the pathophysiology of the osteoporoses. Here is some evidence supporting this contention:

1) The “Independence” Assumption

While bone loss of great magnitude may occur in some adult systemic diseases, it usually proceeds only to a certain point, so that the amount of bony tissue remaining in the skeleton tends to plateau. This implies some connection between the capacities to resorb and to form bone. (Here we ignore localized processes, such as bone tumors and infections.)

In that connection, histological studies at Henry Ford Hospital eventually demonstrated a real connection between osteoclastic and osteoblastic activity in both human and animal material. Specifically, lamellar bone turnover in adult humans occurs in functionally as well as histologically distinguishable “packets” or remodeling units, which we have called Basic Multicellular Units, (BMU). These units bear several close analogies to the nephrons in the kidney. With great regularity, a typical bone remodeling BMU begins as a center of bone resorption, characterized by active osteoclastic removal of a moiety of bone amounting to approximately .05 mm$^3$ within less than a month. Osteoclastic activity then subsides, new osteoblasts materialize during the following days and proceed to fill in the eroded cavity during the next three months or so with a nearly equal amount of newly-made bone.

That sequence characterizes adult lamellar bone remodeling in man as well as in many other medium and large-sized mammals (such as dogs, goats, cats, monkeys, whales, rabbits, sheep, horses, and cows). Also, it occurs on all of the periosteal, haversian, cortical-endosteal and trabecular surfaces. Its twin properties of temporal sequence and spatial discreteness persist alike in health and in a wide variety of skeletal diseases. Within cortical bone, the remodeling sites (termed secondary osteons or haversian systems) resemble tubes some 150 to 250 microns in diameter “drilled” or oriented parallel to the longitudinal axis of the bone. On endosteal surfaces (both cortical and trabecular), the bone remodeling centers have a semicircular, shingle-like configuration. In skeletally immature animals this simple morphological picture becomes mixed with quite different forms of bone resorbing and formative activities, ie, forms peculiar to skeletal growth, which effectively overshadowed the remodeling
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patterns from earlier morphologists and physiologists.

In other words, in normal adult bone remodeling one finds that bone resorption and bone formation do not occur as independent cellular activities. This neatly explains why experimental manipulations which after resorption in intact animals also alter formation in the same direction. This occurs after a predictable time lag needed for the typical BMU to progress through its resorption phase into its formation phase (sigma). Naturally this coupling will only be detected if an experiment continues long enough for the "switch-over" to occur, the necessary time varying from about two months in a healthy rabbit to well beyond 10 years in some cases of human osteomalacia. The cellular mechanisms that "couple" resorption to formation in the manner described remain unknown.

The BMU concept as well as the BMU structure, in both the temporal and morphological senses, suggest several possible ways in which the balance between bone resorption and formation within one BMU can change so as to accelerate bone loss. Our own group and others have shown that in the average BMU the balance between the amount of bone removed by the resorptive process and that replaced by the following formation process changes in a characteristic way as one crosses the thickness of the cortex from the periosteal to the endosteal bone surfaces. An excess of formation on the periosteal surface becomes a negligible excess of resorption on haversian surface, which increases as one moves toward the marrow cavity, there to become a relatively large excess. We can summarize these simple but important matters thus:

(i) In normal periosteal remodeling BMU, slightly more bone is replaced than is removed.
(ii) In normal haversian BMU, slightly less bone is replaced than is removed.
(iii) In normal cortical-endosteal BMU, considerably less bone is replaced than is removed.

In 1967 Wu, Jett and the author estimated, on the basis of quantitative histological measurements, that the resorptive excess per endosteal BMU in both normal and osteoporotic patients exceeds by approximately 70 times the resorptive excess found per haversian BMU. (See Figure 1) A

![Figure 1](image-url)

Resorption relative to formation per normal BMU on haversian and cortical-endosteal surfaces, expressed as relative amounts of bone resorbed and made. Any difference in their amount would tend to make bone accumulate (in the case of an excess of formation), or decrease (in the case of a resorptive excess). This probably accounts for expansion of the marrow cavity during adult life in man.
relatively small further increase in the magnitude of that excess could easily account for the actual losses of cortical and trabecular bone observed in patients with osteoporosis. Beginning in early adult life, an increase in the size of each “bite” taken out of the skeleton by the average endosteal BMU and added up over a period of some 20 to 50 years could explain those losses. Observe here the useful facts that, while spongy bone represents only about 20% of the total bone mass, it supplies more than 70% of the total skeletal surface. Partly for that reason any factor which increased the net excess of bone resorption per endosteal BMU would subsequently reduce the amount of trabecular bone faster than it thinned the cortex.

The “independence” assumption, I believe, proves partially false as it applied to adult bone remodeling. Osteoclasts and osteoblasts are somehow tethered to each other in the functional sense and by the BMU structure.

2) The “Singularity” Assumption

In the process of developing quantitative histological techniques for analyzing bone dynamics around 1960, we began to (a) use three anatomically distinguishable types of skeletal bony surfaces (ie, the periosteal, haversian, and cortical-endosteal surfaces), (b) define “envelopes” of bone tissue space, and (c) indicate in those terms the quantity of bone tissue in standard diaphyseal bone cross sections. Thus, the periosteal surfaces of the skeleton periosteal envelope do indeed envelop a definite and easily measured volume of bone and space. Similarly, the haversian canal surfaces (or haversian envelope) envelop a measurable volume of space and, finally, the endosteal envelope encompasses the marrow cavity volume. Note that the volume encompassed by any of these three surfaces in any person represents the arithmetic sum of all previous bone resorption and bone formation on that particular surface. (Figure 2)

![Figure 2](image)

A rib section indicating the anatomical location and meaning of the endosteal surface, periosteal surface, and haversian surface.

This “envelope concept” led quite naturally to studies of changes in envelope cross-sectional sizes in standard biopsy sites during growth, adult life, aging and in a variety of congenital and metabolic bone diseases including the osteoporoses. In human rib sections, transverse expansions of both marrow cavity and outside diameter continue throughout life, although longitudinal growth of bone ceases at skeletal maturity. Initially controversial, that observation has been confirmed by many others. It has been found also in human femur, vertebra, metacarpal, clavicle, skull, and entire skeletons, the only major
exception being the radial diaphysis.

Figure 3 shows that the amount of compacta increases during the growth period because the rate of periosteal expansion exceeds that of the marrow cavity. Once skeletal maturity arrives, the process reverses and the amount of compacta begins gradually to decrease because the marrow cavity expands faster than the periosteal envelope. During all that time, the intracortical porosity or haversian space changes little in relative size. Hence arises the normal age-related thinning of the compacta, termed by some the "physiologic" osteoporosis of aging and, in the clinical sense, not really a disease that requires treatment. Note that trabeculae, surrounded entirely by the marrow cavity, display the same age-related loss. That loss, however, is more pronounced because an expanding marrow cavity erodes only the inner wall of the cortex surrounding it. It is, at the same time, eroding all four sides of a trabeculum.

Thus, the "singularity" assumption did not apply to at least three operationally distinct collections of osteoclasts and the osteoblasts present on the three envelopes of a normal skeleton.

The Envelope Matrix

Since the three skeletal envelopes gain and lose bone independently during growth, adult life, aging, and in a variety of diseases, we can depict skeletal mass problems as morphological entities in terms of the respective sizes of each of these envelopes. Ignoring the haversian envelope for the present, one could construct a matrix of all possible combinations of periosteal and endosteal envelope sizes in simple terms of size-states, such as Increased, Normal, or Decreased. Figure 4 illustrates such a matrix, portrays and lists examples of five possible types of osteoporoses, ie, envelope states which would represent less bony tissue in the skeleton than normal.

Where does postmenopausal osteoporosis (PMO) fit into such a scheme? When examined from the morphological standpoint the bones from afflicted patients reveal only enlargement of the endosteal envelope, and no other envelope size abnormality. (Square 2,
Classification of possible combinations of the cross-sectional sizes of the periosteal and endosteal envelopes, assuming arbitrarily that each can take only one of three states or values-Increased, Normal or Decreased. The combination in square 5 is normal. The combinations in squares 1, 2, 3, 6, and 9 represent various kinds of osteoporoses. Squares 4, 7 and 8 represent situations with too much bone. (Reprinted by permission: H. M. Frost, Bone Dynamics in Osteoporosis and Osteomalacia, Charles C. Thomas, Springfield, U.S.A. 1966).

Figure 4) In other words, patients with PMO and also those with several other varieties of osteoporosis have lost only that bone in physical contact with the bone marrow. This fact implies that accelerated marrow cavity expansion occurred during adult life, and secondly, that whatever changes in systemic "messengers" distributed by the blood might ultimately prove to cause this form of osteoporosis, they do not act directly on osteoclasts and osteoblasts. Rather, they may well act on the soft tissues in the marrow cavity. After all, in the absence of any such anatomically localized intermediary, any blood-borne messengers acting directly on bone cells in such a way as to enhance bone loss should cause such loss on all bony surfaces; yet, in postmenopausal osteoporosis that does not happen. Consequently I have proposed that the bone marrow which is altered by these systemic factors in some way affects the bone cells on the endosteal envelope, causing the marrow cavity expansion.

**Conclusion**
The specific marrow tissue pheno-
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Menopauses which might cause the endosteal bone loss in PMO seems to correlate best with some aspect of bone marrow activity. Several known associations suggest this:

1. Hematopoietic activity in spongy bone exceeds that in cortical bone. So does osteoporosis.
2. During menstrual years women have greater hematopoietic activity than men. They also exhibit more osteoporosis.
3. Some have suggested that heparin might produce osteoporosis. At Henry Ford Hospital, Drs. Boy Frame and Robert Nixon have shown that increased numbers of mast cells, a source of heparin, occur in the marrow of patients with osteoporosis.
4. Osteoporosis in bones with red, hematopoietic marrow usually exceeds that in bones with fatty, yellow marrow. This may explain why it is more severe in the axial skeleton (red marrow) than in the appendicular (yellow marrow).

It is reasonable to conclude that postmenopausal osteoporosis is a marrow tissue disorder which secondarily affects endosteal bone. Therefore, future investigations of the systemic factors which govern its characteristic bone loss should concentrate on the bone marrow and, particularly, on its interactions with endosteal bone.

The following comments may help keep these ideas in perspective:

1. For reasons of space, we have not mentioned here some additional, characteristic, and consistently present abnormal dynamic features which occur in the bony skeleton in postmenopausal and senile osteoporoses.
2. Only a small fraction of all postmenopausal women who display radiographic evidence of subnormal bone density also have the clinical disease of osteoporosis (consisting of clinical disability due to spontaneous structural failure). Our remarks here apply only to osteoporosis, the disease, which may ultimately prove to be no more than an acceleration and augmentation of otherwise perfectly normal age-dependent skeletal trends.
3. The association between the menopause and this disease may prove somewhat incidental, as it fundamentally resembles the “senile” osteoporosis seen in both women and men.
4. At this time, I suspect that neither mast cells nor heparin directly cause the osteoporosis under discussion and that increased mast cells in PMO probably represent a more basic underlying abnormality in the bone marrow which accounts for both phenomena.

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