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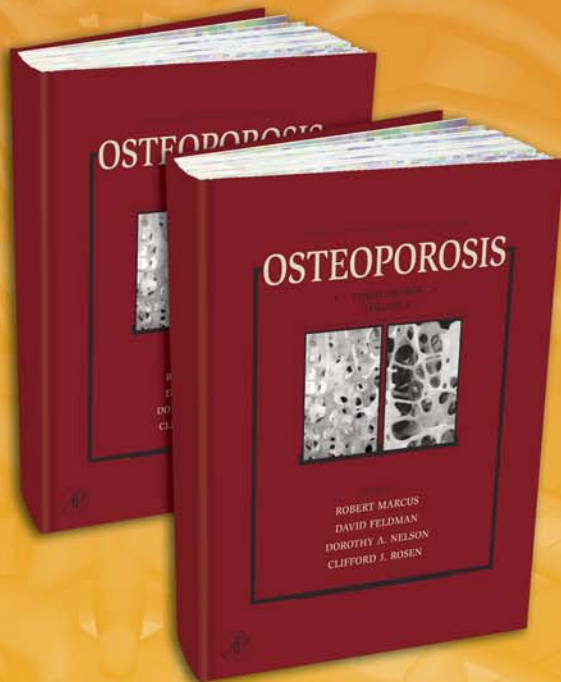
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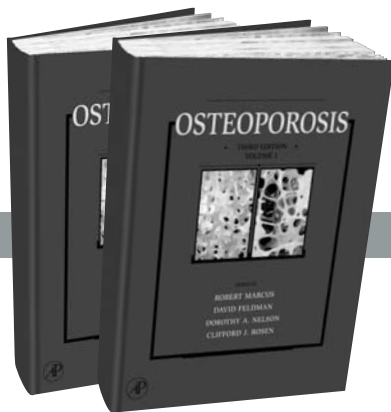
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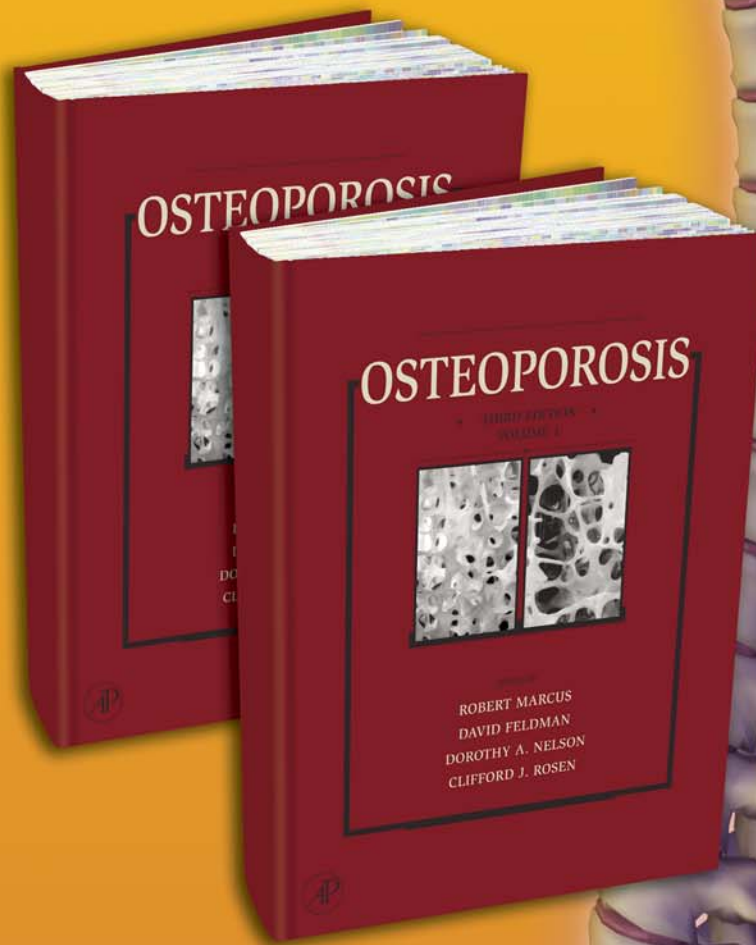
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Skeletal Heterogeneity and the Purposes of Bone Remodeling: Implications for the Understanding of Osteoporosis

A. M. PARFITT

- I. Introduction
- II. Skeletal Heterogeneity

- III. The Purposes of Bone Remodeling
- IV. Implications for Understanding Osteoporosis

I. INTRODUCTION

The cells of bone influence its structure by means of four processes: growth, repair, modeling, and remodeling, the last being the basis of bone tissue turnover in the adult skeleton. The purposes of growth and repair are obvious. Modeling serves to adapt bones to changes in mechanical loading [1], and remodeling serves to thicken trabeculae in the growing skeleton [2], processes that are most effective during adolescence [3]. But why does a tissue that can survive for thousands of years after death need to be maintained by periodic replacement during life? Most of those interested in bone, whether as physicians, as clinical investigators, or as basic scientists, show remarkably little interest in this fundamental question. Many articles and book chapters discuss the regulation of bone remodeling, but regulation, at least in the physiologic sense, implies a target [4]. The target value of any regulatory process in biology has been optimized by natural selection. Mechanisms have evolved which ensure that deviations from the target are detected and that corrective measures to restore the target value are carried out. In this sense, body temperature, extracellular fluid osmolality, tissue oxygen tension, and countless other physiologic quantities are regulated, but the mechanisms of regulation could not be determined until the existence of the target had been recognized and its precise nature defined. Is there a target for bone remodeling or for some characteristic of bone that is influenced by remodeling?

The piecemeal, quantal nature of bone remodeling is well known. The process is carried out by temporary anatomic structures known as basic multicellular units, or BMUs [5-8], which excavate and replace tunnels through cortical bone (osteonal remodeling) or trenches across the surface of cancellous bone

(hemiosteonal remodeling). Each BMU includes two teams of executive cells (osteoclasts and osteoblasts), supported by blood vessels, nerves, and loose connective tissue. The life span of the BMU is measured in months, but the life span of osteoblasts while they are making bone is measured in weeks, and the life span of osteoclast nuclei is measured in days. During progression of the BMU through or across the surface of bone, the spatial and temporal relationships between its components are maintained by the continued growth of the central capillary in cortical bone [9], and extension of the remodeling compartment in cancellous bone [10], together with recruitment of new cells [9-11]. These cells, like the formed elements of the blood, originate from stem cells in the bone marrow [12] except that in the peripheral skeleton osteoblasts are derived from local precursors [13].

Each type of blood cell is normally produced at a basal rate that is sufficient for ordinary purposes but can be increased when needed [13]. For each cell the circumstances under which demand is increased are well known, and are related to the function of the particular cell, although the cell types differ with respect to the time scale of this response, its specificity, and the relative importance of reactive and adaptive mechanisms [14], and the extent to which these relationships between supply and demand, between demand and function, applies to the cells. For osteoblasts in the adult nongrowing bone the demand is created by bone resorption; the function of osteoblasts is to replace the resorbed bone by osteoclasts. However, the circumstances

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a demand for osteoclasts are much less well defined, since these circumstances are dictated by the purposes of bone remodeling. Indeed, the questions "What are the purposes of bone remodeling and how are they achieved?" are essentially equivalent to the questions "Where and when are osteoclasts needed, and how is this need recognized and satisfied?" The answers to these questions are different in different types of bone and in different regions of the skeleton.

II. SKELETAL HETEROGENEITY

A. Structure and Function

The structural differences between cortical bone, in which porosity and surface-to-volume ratio are low, and cancellous bone, in which these geometric quantities are high [15], are now widely recognized. All intermediate values for these quantities can occur, but they tend to be temporary and short-lived [16]. Less often noted are the differences between the axial and appendicular skeleton (Table 5-1); the axial skeleton, which is important because the primary function is load-bearing—to support posture, protection for the soft tissues, and provide a favorable microenvironment for hematopoiesis. For convenience the former functions will be referred to as "mechanical" and the latter as "metabolic" [13].

It is commonly believed that the mechanical functions are carried out mainly by cortical bone and the metabolic functions mainly by cancellous bone, regardless of their central or peripheral locations. In fact, the

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TABLE 5-1 Subdivisions of the Skeleton

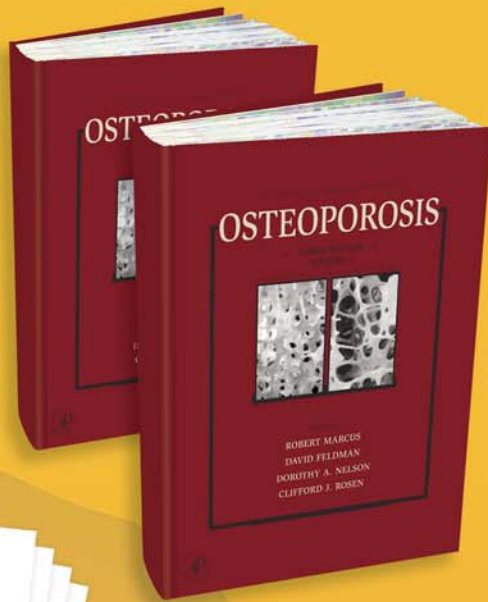
Feature	Central	Peripheral
Main bone tissue	Cancellous	Cortical
Main soft tissue	Viscera	Muscle
Main joint type	Various	Synovial
Cortices	Thin	Thick
Marrow	Hemopoietic	Fatty
Turnover	High	Low

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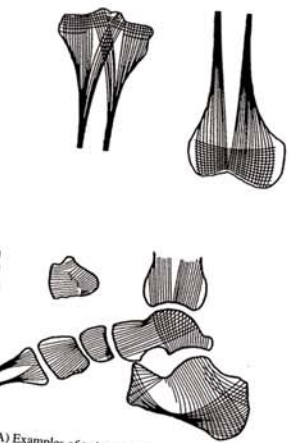


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A. M. PARFITT

functions of the peripheral skeleton, cancellous as well as cortical, are mainly mechanical, whereas the central skeleton, cortical as well as cancellous, in addition to its mechanical function, participates to a much greater extent in the metabolic functions of bone. This revision of the functional attribution is most striking for peripheral cancellous bone, such as in the metaphyses of the long bones [17]. As is evident from the orientation of the trabeculae (Figure 5-1a), metaphyseal cancellous bone transmits loads from the joint surfaces to diaphyseal cortical bone. Indeed, the metaphyses are flared in order to precisely make such load transmission possible. Similar functional and architectural considerations apply to the cancellous bone in the small bones of the hands and feet (Figure 5-1b). As will be discussed in detail, there is no evidence that such peripheral cancellous bone participates to a significant extent in the metabolic functions of the skeleton, other than related to mineral homeostasis or to hematopoiesis.

Cross references lead reader to explore articles of related interest



(A) Examples of trabecular orientation in cancellous bone in the appendicular skeleton. The different trajectories facilitate transmission of loads from the joint surfaces to diaphyseal cortical bone. (B) Examples of load transmission in the small bones of the feet. The alignment of the trabeculae facilitates transmission of loads during weight-bearing. The alignment of the trabeculae at the ankle joint and thence to diaphyseal cortical bone is modified from [17].

value. To date, however, concern to those conducting research because individuals concerned to do so early, incurring in some jurisdictions, such as decision makers considering health policy decisions, pharmaceuticals, an analytical continuation is required. "best-case" theoretical ecological studies showing relatively adherence suggest that such imistic [60]. As additional studies with different adherence important to integrate such economic and quality of determinants of the cost-intervention. Early menopausal hormone therapy and menopause symptoms of treatment may be out-effects if associated with year [61, 62]. Thus, the biological agents to adversely sidered. In this context, a Y impact of side effects following a BMD test is reassuring because it is identified for women date [63].

CONCLUSIONS

Evidence that osteoporosis is a major public health problem in elderly populations has established a high priority. Cost-effective approaches to prevent the economic costs of osteoporosis, it is imperative that cost-effective approaches to osteoporosis prevention and treatment be identified and successfully implemented. To accomplish this, additional data on the longitudinal impact of fractures on both health care expenditures and quality of life are required.

ACKNOWLEDGMENTS

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