Recent Developments in Bone Physiology

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According to the quantum concept of bone remodeling proposed by Frost, bone formation in the adult human normally occurs only at sites where bone resorption has recently been completed. As a result, whole body rates of bone resorption and formation (and their biochemical and kinetic markers) depend mainly on the frequency with which new cycles of erosion and repair are initiated by the fusion of precursors into new osteoclasts (referred to as activation); however, they are largely independent of the function of differentiated cells. By contrast, whole body bone balance is critically dependent on the focal matching of microscopic volumes of bone resorbed and formed by individual teams of osteoclasts and osteoblasts, and, therefore, on the number and lifetime work capacity of these cells.

When first proposed, this concept aroused a great deal of opposition, and even hostility. Its proponents have been so busy defending it and expounding its clinical implications that they have given little attention to the mechanisms involved. Yet the foregoing, deceptively simple description conceals a host of unsolved problems in cell biology:

- What determines the occurrence of activation at a particular location at a particular time?
- Do the newly formed osteoclasts arise only from distant precursors, or are local precursors also involved?
- Do macrophages and other mononuclear cells participate in normal as well as pathologic bone resorption?
- How do osteoclasts gain access to bone beneath its cellular membrane?
- Why do osteoclasts normally avoid unmineralized bone matrix?
- What regulates the size, shape, and depth of individual resorption cavities?
- What is the three-dimensional path of individual osteoclasts?
- Does termination of resorption depend on cessation of osteoclast recruitment or on cessation of activity of osteoclasts in response to some unknown signal?
- What is the fate of the osteoclasts after they have completed their work?

Most crucial is the mechanism of spatial and temporal coupling of formation to resorption. The term "coupling" is often used imprecisely, but logically it encompasses all the mechanisms that ensure that osteoblasts assemble in the right place, at the right time, and in the

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right number to ensure adequate replacement of the resorbed bone.

- What role, if any, is played by the various types of mononuclear cells observed during the reversal phase between the disappearance of osteoclasts and the arrival of osteoblasts?
- Which of these cells is responsible for synthesizing the cement substance that joins the new bone to the old?
- What is the signal to osteoblast precursors to proliferate? Does the need for osteoblast recruitment continue until the new bone structural unit is completed, or are all the osteoblasts in place at the outset?
- Does some constituent of the resorbed bone or of cement substance exert chemotaxis for osteoblasts?
- To what extent does adequate bone formation depend on the availability of precursor cells, on the genesis and effectiveness of mitogenic stimuli, or on the capacity of individual osteoblasts to form bone matrix?
- What is the relationship between the functional and structural changes that occur in osteoblasts during their life span?
- What determines which osteoblasts will become osteocytes, which will become lining cells, and which will disintegrate?
- Is apoptosis involved in osteoblast disappearance?
- Why is the normal net effect of all these processes to add bone at the periosteum and subtract bone at the endosteum?

Many advances have been made in the study of isolated bone cells. Some investigators believe that this approach will answer all the questions just posed. However, it is clear that messages to and between cells are modulated by the local micro-environment, which may encompass different types of contact with other cells, different methods of attachment to connective tissue matrices, and different concentration profiles of ions and macromolecules in the local extracellular fluid. Furthermore, cell activity can be altered by mechanical stimuli and by bioelectric signals that can arise only at higher levels of organization. Fortunately, increasing numbers of investigators are accepting the quantum concept as a framework for their experimental approach and for integrating in vitro and in vivo observations. In this spirit, Peck, et al (pp. 179 ff.) described the many new constituents of bone matrix and new factors that are synthesized by bone cells, and the possible roles of these substances in the local regulation of the remodeling cycle and, eventually, in the treatment of metabolic bone disease. Baylink, et al (pp. 173 ff.) concentrated on the discovery, purification, and characterization of just one of these substances — human skeletal growth factor, a mitogen for bone cells present in bone matrix that may be released during bone resorption and thus function as a coupling signal that could be disturbed in osteoporosis. Finally, Lanyon and Rubin (pp. 183 ff.) demonstrated the crucial importance of strain induced in bone by functional load bearing, as a regulator of bone remodeling. Functional strain could play a major part in orchestrating bone remodeling units and determining the balance within each unit. These effects have obvious relevance to the control of bone mass and the susceptibility to fracture.