Endocrine, *vol. 17, no. 1, 1–2, February 2002* 0969–711X/02/17:1–2/$10.50

Overview

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To develop an interesting and innovative overview of osteoporosis in light of the numerous reviews and textbook updates in the past 2 yr is quite a challenge. The goals of this issue are to review aspects of osteoporosis that have been neglected and to include some views on future directions in basic research that may lead to new strategies for the treatment of osteoporosis.

In 1993, a consensus conference defined osteoporosis as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. The sophisticated diagnostic tools of today allow us to look at many different aspects of bone structure and function. It is difficult to imagine the challenges faced by early physicians in assessing bone disease in the absence of detailed knowledge of normal bone structure. Santiago Gomez recently uncovered a beautiful folio showing the exquisite drawings of a Spanish scientist/artist, Crisóstomo Martinez, who was commissioned by his authorities in the late 1800s to develop an atlas of osteology. As happens only too frequently, he did not meet his deadlines, despite working around the clock for 2 yr in Paris under extremely difficult conditions; the atlas was never published. Only a few meticulous drawings are available to us; we include some of these in the note by Santiago Gomez.

Showing that pictures may effectively substitute for text, the photo-article by Alan Boyde illustrates views of bone using the most recent innovative three-dimensional, high-resolution microscopy technologies that he has developed. The high magnification of these photographs beautifully chronicles changes with aging and disease in the microarchitecture of human bone from the iliac crest, providing an additional dimension to the views of osteoporosis determined by more conventional bone imaging techniques and histomorphometry.

The microarchitectural changes in bone of osteoporotic patients likely contribute to the impaired biomechanical properties and likelihood of fracture in the event of a fall. Programs to develop drugs for osteoporosis have paid great attention to the increased risk of the disease following menopause in women and the presence of low bone density, but they have not always addressed other risk factors that may be as critical when considering risk of fracture at the hip. Changes in bone mass and microarchitecture only partially explain the dynamics that may lead to hip fracture. Mark Grabiner addresses the biomechanical issues involved in patients at risk for osteoporosis when they cannot recover their balance in a fall. He shows that certain aspects of walking style significantly increase the risk of falling. His data suggest that relatively simple measures could be introduced in a public health strategy to reduce the probability of a fall in a subject at risk for bone fractures.

After considering how the structure and biomechanics of the skeleton may impact the risk of osteoporotic fracture, we transition into how drugs may reduce the risk of fracture through their effects on bone mass. Juliet Compston critically reviews drugs currently used to treat osteoporosis, using bone histomorphometry as a tool to understanding their mechanisms. In addition to her evaluation of the many effective antiresorptive drugs, such as bisphosphonates, calcitonin, and hormone replacement regimens already on the market, she includes an overview of parathyroid hormone (PTH) [1-34, rhPTH 1-34. This recombinant peptide, which represents the amino terminal of PTH, a calcium-regulating hormone that has been studied since the late 1890s, is in the final stages of regulatory approval as a new class of anabolic therapy. Data from its Phase 3 trial showed an impressive 65% reduction in spine fractures and 54% reduction in nonvertebral fractures. The ability of PTH to prevent moderate to severe fractures by 78–90% and multiple new fractures by 77–86% in the spine is striking.

Despite these steadily improving treatments for vertebral osteoporosis, our ability to predict hip fracture or make a diagnosis and predict the response to treatment of individual patients remains less than optimal. The next two reviews examine basic research that may lead to new insights in how drugs can regulate bone turnover and production. The paradoxical ability of once daily PTH to induce an anabolic response in bone, while continuous exposure to PTH induces a catabolic effect, is not well understood. Using microarray technologies, Russell Turner and his group have identified differences in genes regulated by PTH when the hormone was given to rats in two different regimens. These differences led to the discovery of a novel pathway by which the fibrosis of hyperparathyroidism can be explained, and

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an improved understanding of how varying the exposure to PTH alters the fate of bone marrow stromal cell differentiation. In another example of paradoxical hormone effects on bone mass, Barbara Kream and John Harrison examine the discrepancy between the observations that glucocorticoids induce low bone mass and osteoporosis in vivo, yet in vitro stimulate osteoblast differentiation, indicative of a putative anabolic effect. Their imaginative application of technology to genetically modify mice has enabled the development of new strategies to understand how glucocorticoids may regulate bone turnover.

Because low bone mineral density (BMD) is not associated with signs and symptoms obvious to a patient, awareness and diagnosis of disease depends on when a physician sees the patient. In females, the opportunity for a physician to intervene may come during adolescence, when lifestyle behaviors may put a young girl at risk; in premenopausal women who are pregnant or lactating; and during and following menopause. Most of our attention in the past decade has centered on the risk to postmenopausal women, in whom fractures become a more foreseeable occurrence. Because failure to gain peak bone mass on completion of skeletal growth and development may put a person at risk for osteoporotic fracture later in life, it is equally important to be aware of potential skeletal problems in children and young women. Connie Weaver reviews the factors controlling BMD during adolescence, the dangers to skeletal development of lifestyles popular among teens, and the current dietary recommendations to optimize bone mass during skeletal growth. In adult premenopausal women, controversy persists on the risk of bone loss during pregnancy and lactation. Bonnie Specker and Heidi Kalkorf review the published studies and find little support for permanent bone reduction following completion of lactation. They show that care needs to be taken in the clinical assessment and diagnosis of the fluctuations in BMD, which may be detected for the first time in a woman's life during pregnancy and lactation.

Finally, the reviews consider how the application of genetics may cause a paradigm shift in our future thinking about osteoporosis, its etiology, and new possibilities for more effective treatments. Robert Recker and Hong-Wen Zhang describe how genetics studies of osteoporosis have been used to try to isolate and discriminate between those factors that contribute to fracture and those that contribute to bone mass. Their most recent contribution within this field has been their exciting discovery of the genetic link between lipoprotein receptor 5 (lpr5) and high bone density within a related family. In one step closer to the future, Alex Lichtler and David Rowe's current innovative work with bone marrow stromal stem cells and the genetic modifications that allow them to be tracked within bone allows one to speculate how bone marrow stromal stem cells could be used in cell and gene therapy approaches to healing diseases of bone fragility.

We hope that these reviews draw attention to bone architecture and the biomechanics of the failing skeleton in osteoporosis; to the opportunities for medical assessment and intervention in populations other than postmenopausal women at risk for the disease later in life; to how leveraging our knowledge of drug actions in bone may provide new targets for therapy; and, finally, to how genetics studies may completely change our concepts of etiology and pathogenesis of osteoporosis as a metabolic bone disease to facilitate more effective and targeted therapies.

Acknowledgment: The interest and support of Eli Lilly & Co. is gratefully acknowledged.