The Aging Skeleton

Edited by

Clifford J. Rosen

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Foreword

This remarkably substantive textbook provides a clear testament to how much new knowledge has been gained over the past 15 years on the causes and treatments of osteoporosis and other bone diseases of the elderly. These advances have all come about by a converging development of expanding activities by several diverse, but complementary, organizational forces that support research: (1) scientific societies; (2) governmental agencies supporting biomedical research; (3) the pharmaceutical and biotechnology industries; and (4) new and vital voluntary health agencies. A generation ago, it was largely held that osteoporosis was, for the most part, the inevitable consequence of aging. Much excellent research on calcium metabolism had pointed to an imbalance. That osteoporosis was largely a disease of elderly women was ascribed to the menopause with its attendant estrogen loss.

It all started in the late 1970s. The "bone doctors" in the Endocrine Society formed their own new scientific association, the American Society for Bone and Mineral Research (ASBMR), recruiting relevant basic and clinical scientists to join them in their work. The growth of the ASBMR has been nothing less than spectacular, with even more abstracts of higher quality competing for presentation at annual scientific meetings, and the creation and success of its *Journal of Bone and Mineral Research.* Even more recently in the 1990s, the International Society for Clinical Densitometry was useful with similarly spectacular growth.

Several initiatives on bone biology and its diseases were launched by the National Institutes of Health (NIH). The NIDDK, NIAMD, and NIDR had been supporting excellent intramural programs of research on bone and bone diseases. In the 1980s other institutes developed new programs targeted to bone research. The new NIAMS (I was its first director) established a new extramural program on bone biology and bone diseases with superb new leadership and became the fastest growing extramural research program in the Institute. The National Institute of Aging (NIA) also formed new programs (e.g., on menopause, frailty, basic biology), as did other Institutes. In 1993, a Federal Working Group on Bone Diseases was formed, with 15 different agencies participating in information exchange and forging collaborative activities. One landmark was the 1984 NIH Consensus Development Conference on Osteoporosis, chaired with great expertise by Dr. William A. Peck; it was a broad-ranging conference that informed both the public and professionals on the importance of hormonal replacement therapy and sufficient calcium intake to combat bone loss and recommended many new directions for research. The NIH investment in research on bone and osteoporosis has grown sharply since that time. Important research advances have been achieved; most are very well documented in this text on the aging skeleton. Moreover, public interest has risen greatly. For example, as a result of the NIH Conference on Optimal Calcium Intake in 1994, so ably chaired by Dr. John Bilezikian, the elderly have responded by increasing their intake of both calcium and vitamin D.

The major contributions of the pharmaceutical industry to the prevention and treatment of osteoporosis deserve emphasis. This excellent textbook documents the research advances that have been made. To mention a few, let us note briefly the development of calcitonin, both by injection and by nasal spray, of bisphosphonates, and of estrogen analogues.

Major contributions have also been made by the biotechnology industry in terms of accurate and precise measures of bone density by dual energy X-ray absorptiometry (DXA) and ultrasound, and new useful bio-

chemical measurements of bone turnover. Appropriately, an entire section of this textbook is devoted to the topic of quantifying the amount and dynamics of bone loss.

In addition, organizations were created to educate the public and professionals about the issues and new developments and to arouse public interest in supporting research on osteoporosis and other bone diseases. These organizations include The National Osteoporosis Foundation, The Paget's Disease Foundation, The Osteoporosis Imperfecta Foundation, and others. Older organizations such as The National Dairy Council renewed its efforts to educate the public in skeletal health. As a result of their dedication and drive, public interest and the number of publications in the various media in this field have soared.

This textbook has been organized in a very effective manner. In the first section, aging is discussed both generally and in terms of the aging skeleton, with separate chapters on cellular, animal, and human models. In the second section, the important concepts of achieving peak bone mass by the end of the third human decade are discussed in detail, with individual chapters on racial, genetic, nutritional, hormonal, and mechanical determinants of peak bone mass. The importance of making every effort to maintain bone mass after 30 years of age is introduced. The many different mechanisms that participate in age-related bone loss are discussed individually in the chapters contained in Section III. In addition to novel perspectives on the "standard topics" of sex steroids, parathyroid hormones, and nutrition, other chapters describe recent interest in cytokines, prostaglandins, growth hormones, and pharmacologic agents. Section IV describes several new methods that have been developed to measure quantitatively, often with great precision, bone mass. Perhaps primary among these has been the development and clinical application of bone densitometry with new technologies such as DXA and ultrasound. Bone densitometry now provides major, essential guideposts to the treatment and prevention of osteoporosis and other bone diseases in our senior citizens. A testament to the importance of these new methods is the creation of a new scientific publication, *The Journal of Clinical Densitometry,* edited by Dr. Clifford J. Rosen.

The final two sections cover the consequences to the patient of bone loss (fractures) and the many methods of treating (and preventing) bone loss and osteoporosis. The discussion of fractures is thorough, including a definition of frailty fractures (more challenging than one might expect); fractures at different anatomic sites; effects of fractures on quality of life; and management issues with respect to orthopedics, pain, and nutrition. Section VI, on therapeutics, is exceptionally comprehensive, reflecting the many scientific advances that have been accomplished in this field in recent years. The rationales for calcium supplementation and vitamin D are discussed individually, as are the important benefits of estrogen replacement. There are excellent chapters on bisphosphonates, calcitonin, and the "paradoxical" efficacy of parathyroid hormone treatment. Promising yet controversial therapeutic approaches—fluorides, androgens, and growth hormones and growth-factors—are also covered individually. Also discussed are the prevention of falls and the impacts of different types of physical activity on bone and bone loss. As a result of the many recent advances in treatment as described in the text, physicians now have at hand a strong armamentarium of agents with which to prevent, and with some agents to reverse, the bone loss of the aging skeleton.

And last, the editors of this textbook deserve to be congratulated on their success in recruiting such a high caliber of contributing authors (authorities) for this volume. They are virtually all national and international leaders, constituting a "Who's Who" in bone and mineral research and related topics.

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Preface

Our understanding of the basic and clinical aspects of bone biology has advanced remarkably in the past decade. In part this advance has been driven by an astonishing increase in the prevalence of osteoporosis due to the "graying" of the world's population, as well as by a heightened awareness of the disease. Equally important, the medical, social, and economic impact of osteoporotic fractures has finally been confirmed. Although it is likely that osteoporosis has existed for centuries, we are now entering a new millennium not only with the hope of effectively managing the consequences of this disease but also with the promise of its potential eradication. This book summarizes and organizes our progress in defining the complex and multifactorial events that contribute to age-related bone disease. In addition, a third of this text is devoted to a comprehensive therapeutic approach for clinicians faced with the unique problems that elderly osteoporotic individuals face on a daily basis.

In retrospect, it is easy to see how this book was born. Yet, a decade ago it would have been inconceivable even to propose a comprehensive treatise about the aging skeleton. Although low bone mass and increased skeletal fragility characterized the aging process, little else was clear. A mere 10 years ago, many clinicians and most scientists viewed osteoporosis as a normal consequence of aging rather than as a disorder with distinct pathophysiological features. There were no therapeutic paradigms for those who had sustained disabling spine and hip fractures. Worse, few older women were ever considered for treatment. Preventive strategies in this age group were not even on the "radar screen." Also, efforts to discern pathogenic pathways on a molecular or cellular level were embryonic. Moreover, little was known about the physiology of skeletal remodeling in the elderly. Clearly, times have changed. In fact, large longitudinal and cross-sectional studies of the elderly, along with newer tools to define bone remodeling, have pointed the way to a clearer understanding of the disease for all individuals. Thus, it is entirely fitting that we commit an entire textbook to delineating the mechanisms and consequences of skeletal aging.

This book is divided into six sections. Together they represent an integration of fundamental biology, epidemiology, and clinical medicine. This alignment matches the perspectives and expertise of the editors, who felt that a comprehensive review of the aging skeleton mandated this approach. In the first section, chapters focus on the general aspects of aging in higher organisms and the application of specific models of senescence to skeletal determinants such as calcium balance and remodeling. Use of *in vitro* and *in vivo* systems, with their strengths and limitations, provides an important backdrop for the next sections and introduces the reader to the rest of the book.

Bone mass is determined by the balance between peak acquisition during adolescence and maintenance throughout adult life. In the second and third sections, nutritional, heritable, environmental, mechanical, and hormonal influences are examined with respect to acquisition, maintenance, and loss of bone mass. Particular attention is given to cellular and tissue responses in the aging skeleton to perturbations of various hormones, growth factors, and cytokines. These sections are followed by an in-depth presentation of quantifiable measures of bone loss, including bone mineral density, histomorphometry, biochemical markers of bone turnover, and biomechanical determinants. In the fifth section, the biomechanical aspects of fractures and their socioeconomic and medical consequences are delineated. In the final section, a wide range of therapeutic interventions from fall prevention, to dietary recommendations,

to pharmacological treatments are considered in depth. For each section, expert clinicians and scientists were selected on the basis of their investigative areas, their contributions to our current understanding of osteoporosis, and their "fit" within the overall perspective of the book. For each chapter individual themes are stressed, but all are written in a manner that is consistent with the principles and practices of both geriatric and skeletal medicine.

This textbook brings together experts in the field of bone biology and medicine to define the "aging" skeleton and to determine its implications for aging individuals. Ultimately, we hope this book will be used by students, basic and clinical scientists, geriatricians, orthopedic and oral surgeons, internists, endocrinologists, rheumatologists, gynecologists, and primary care physicians as they continue their quest for solutions to the enigmas that surround the aging process in bone. We hope that the multidisciplinary themes that emerge will stimulate further attempts to ameliorate and ultimately to prevent osteoporosis.

CLIFFORD J. ROSEN

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PART I

General Aspects and Models of Aging

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Aging through the Ages

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The increasing longevity of modern populations explains much of the alarming increase in the rate of osteoporotic fractures. In many respects, osteoporosis, defined as low bone mass and an increased risk of fracture, can be considered to be a consequence of age-related degenerative effects on the skeleton and other organ systems. It is not clear whether age-related changes are genetically determined (programmed) from birth or whether they result from the lifelong accumulation of structural and functional errors at the cellular level. In either case, the modification of developmental changes over the life span, such that peak bone mass can be maximized or osteoporosis avoided, should be relatively difficult.

Studies of past populations indicate that low bone mass was not a problem in human populations until relatively recently in evolutionary terms. Diseases of aging, including osteoporosis, that we see today are the manifestation of millions of years of genetic and cultural change and adaption. It is difficult to explain the adaptive value of an increased life expectancy when many of the consequences of aging would seem to be maladaptive for the population as well as the individual. This is particularly true because natural selection, the primary force responsible for adaptation, presumably cannot affect biological characteristics that occur after the age of reproduction since it acts through differential reproductive success. Thus, increasing longevity and a rising prevalence of debilitating conditions in the elderly are difficult to explain with traditional evolutionary models of adaptation. It would appear that unless the genetics of bone biology underlying low bone mass with fragility fractures in the elderly can be modified, the prevalence of osteoporosis and its public health costs may unavoidably increase as human life expectancy lengthens.

INTRODUCTION

Members of industrialized societies today look forward to a long life expectancy. However, this is not true of many other human populations, both past and present, where an individual's lifetime may be relatively short. The increase in human longevity is a benefit of relatively recent improvements in health and nutrition, but it does come with costs. Degenerative changes and age-related diseases or conditions, associated with varying levels of morbidity and public health costs, have become more prevalent in modern society. In many respects, osteoporosis can be considered to be a consequence of age-related degenerative effects on the skeleton and other organ systems. There are, of course, well-documented factors other than aging that can contribute to an individual's risk of osteoporosis (e.g., diseases, drug exposures), but the increasing longevity of human populations explains much of the alarming increase in the rate of osteoporotic fractures.

As Stanley Garn reported in his classic study [1], bone loss after middle age is a universal phenomenon in the human species, an observation that has been corroborated by numerous studies since then. This phenomenon appears to extend to nonhuman primates as well [2,3], suggesting that human ancestors might have faced the problem of osteoporosis if they had had longer life spans. However, studies of past populations indicate that low bone mass was not a problem in human populations until the transition from gathering–hunting to agriculture some 10–12,000 years ago [4]. Figure 1 depicts 200 million years of mammalian evolution on a 12-h clock in order to put into perspective how recently hominids (i.e., human ancestors) appeared and food production began in evolutionary time. Some evidence suggests that despite apparent bone loss in some prehistoric groups, bone quality may have been preserved, reducing the likelihood of fragility fractures that are now recognized as osteoporosis (see later) [5]. It is unclear whether the occurrence of low bone mass in such populations was due to longevity in some individuals or groups, to environmental factors, or to both, but osteoporosis per se does not appear to have been a major problem until recently.

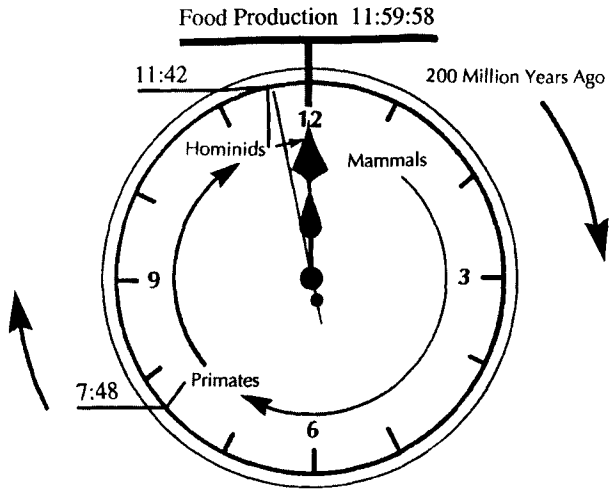

FIGURE 1 Representation of 200 million years of mammalian evolution on a 12-hr clock analog, with emphasis on recent appearance of earliest humans (hominids) and food production. From Nelson [32], copyright by European Foundation for Osteoporosis and the National Osteoporosis Foundation.

This chapter offers an anthropological perspective on aging in relation to bone health and osteoporosis. It explores some of the biocultural correlates of aging and increased longevity and their relationship to osteoporosis in an evolutionary context.

EVOLUTIONARY FORCES AND AGING

Evolution and Genetics

The primary forces of evolution are mutation and natural selection. Mutations are random alterations in the structure of genes and are the ultimate source of new genes. However, it is unlikely that a single mutation or set of mutations has resulted in the universality of age-related bone loss. Natural selection works via the differential reproductive success of the alternative genotypes to which mutation gives rise. As such it is an ordering force that increases the frequency of beneficial mutations while decreasing the frequency of deleterious ones. Benefit and detriment are relative terms and it is important to keep in mind that judging these qualities is dependent on many variables, including the species' genetic background and its ecological situation. The genetic background is determined, in part, by the effects of past evolutionary processes on other genetic traits. Viewed this way we can see that the current genetic structure of a species sets boundaries and channels of change for future possibilities. A species' history delimits a range of possibilities for future change. Adding to the complexity is the need for the coordination of gene actions affecting organisms at different times in their life cycles.

Advanced molecular and statistical techniques have allowed the identification of a number of structural candidate genes that may be involved in the etiology of osteoporosis [6–9]. However, diseases of aging, such as osteoporosis, may be influenced by regulatory loci operating at another level. Over the past several decades, molecular geneticists have elucidated several classes of genes that act as regulators of gene function; determining the timing of gene action, the polarity of the embryo, and other developmental phenomena [10,11]. Although a discussion of developmental pathways is beyond the scope of this chapter, it is important to realize that the genotype guides the development of an organism down a series of channels so as to establish the basic body plan of the individual. The body segmentation, for instance, that is seen in animals from fruit flies to humans, is affected by homeotic genes that have been highly conserved over enormous spans of evolution. The evolutionary conservation of the DNA sequence and number of these homeotic genes is a clear indication of their importance in proper development. The patterning of bone deposition and remodeling throughout the life cycle is also a fundamental developmental process. This developmental path is almost certainly affected by factors other than allelic variation for one or another protein. To the degree that the gain and loss of bone during an individual's lifetime reflects an evolved pattern of developmental rather than variation in the form of a few proteins, modification of this pattern such that peak bone mass can be maximized or osteoporosis avoided should be relatively difficult.

Aging in an Adaptive Framework

Universally encountered biological phenomena, such as age-related bone loss, have traditionally been viewed by physical anthropologists as having adaptive value, if not now, then in past populations living under difficult circumstances. In order to understand this perspective, one must appreciate the time depth over which evolution has occurred in the human species, as well as the complexity of human development over the life cycle of individuals. Both ontogeny and phylogeny are the result of interactions of genetic potential and environmental influences. These complex interrelationships have been acting on human biology over a tremendously long period, beginning with the first humans some 5 million years ago and extending back through the evolu-