The Physiological and Cellular Basis of Metabolic Bone Disease

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The Williams & Wilkins Company
Baltimore

Made in the United States of America
Reprinted 1975

Library of Congress Catalog Card Number 73-4555
SBN 683-07184-X

Composed and printed at the
WAVERLY PRESS, INC.
Mt. Royal and Guilford Aves.
Baltimore, Md. 21202, U.S.A.

Preface

The concept of this book emerged several years ago from a visit of Dr. Bordier to the Laboratories of his co-author in Philadelphia. In this, their second meeting, they discussed bone. During this discussion, each revealed to the other a model of events in bone which he had developed, one primarily from morphological considerations, the other from physiological and biochemical ones. From the similarity in these models, the notion of a monograph, correlating the various kinds of data, naturally followed. However, as it turned out, the matter was not quite so simple. Detailed discussion of what was and wasn't known revealed basic inconsistencies in one or both models, and basic misunderstandings of the meaning of one type of data or another. Nonetheless, having joined in common purpose, the authors persisted. The process became highly enjoyable and educational for both. Mutual respect, and commonness of purpose combined to create something quite different than that originally conceived. It is for others to judge of this creation. The authors can only say that during its creation, this book has been one of the most exciting educational experiences of their lives. They each learned a great deal about bone and bone cells. They each thought new thoughts, and each overcame prejudices of the past. They each feel that out of this has come important new concepts which should inspire thought and experimentation by others. If so the enjoyment will not have been completely selfish.

Like any creative effort, this has not been accomplished alone. We owe a debt of intellectual inheritance to all those who have enquired into the physiology of calcium and bone, and a more immediate debt to Fuller Albright and André Lichtwitz, our teachers. We have been helped by colleagues not only in our own countries but in numerous others. In particular, we are indebted to Doctors H. C. Anderson, C. Arnaud, G. Aurbach, L. Avioli, A. Borle, H. F. DeLuca, S. Doty, M. Holtrop, L. Matthews, M. Pechet, F. Doyle, G. V. Foster, P. Fourman, G. Joplin, H. Matrajt-Denis, P. Meunier, L. Miravet, R. Schenks, H. A. Sissons, S. W. Stanbury, G. Thompson, S. Tun-Chot, and J. Witmer. We are also most grateful to the clinicians who permitted us to study the metabolic bone diseases in their clinics and to perform the bone biopsies on their patient. They are Doctors C. Booth, J. Eastwood, A. Fournier, J. M. Idatte, M. F. Kahn, D. Kuntz, R. Modigliani, G. Neale, J. C. Rambaud, A. Ryckwaert, S. de Sèze, H. E. de Wardener, and N. Woodhouse.

Others have helped in other ways. Miss Gail Rasmussen worked tirelessly to set the bibliographic material in order; Mrs. Mary Jo Larsen was responsible for most of the illustrations; and Mrs. Molly Houseman and Miss Ariel Kahn carried the burden of typing and retyping the manuscript. Misses M. Peron, M. L. Rouquier and Mrs. S. Magne were responsible for most of the clinical chemical analyses; and Mrs. M. L. Queillé, J. Martin

and P. Marie were responsible for embedding, cutting, and staining the more than 1,700 bone biopsies which were prepared and analysed during the course of this work.

A particular note of thanks is due Professor Theo Chalmers of Cambridge University who undertook the task of critically reading the entire manuscript. His suggestions were most valuable in achieving clarification of a number of points. For this we are most grateful.

All gave of themselves unselfishly and with humor. They made our task easier and more enjoyable. To each our deepfelt thanks.

The work of the past fifteen years in Dr. Rasmussen's laboratory, which forms an integral part of this effort, has been supported largely by funds from the National Institute for Arthritis and Metabolic Diseases of the National Institutes of Health of the United States. The bone morphological studies carried out by Dr. Bordier and his colleague was performed in the Research Unit–André Lichtwitz and was supported entirely by the Institut National de la Santé et de la Recherche Médicale. A particular debt of gratitude is owed to Professeur Burg, Directeur General of this organization who stimulated and encouraged the development of the cooperative research efforts between British, American, and French investigators which form a crucial part of the present work.

Finally, no words are adequate to describe the contributions of our wives Jane and Michelle to the success of our efforts. They have given of patience and love at critical times, of generosity throughout.

Contents

Throughout the book, *microfiche* is a reference to the microfiche card in the pocket on the inside back cover.

one

Bone Cells and Skeletal Function

In spite of the overwhelming evidence that change is a prime condition of life, man has always searched for permanence in his quest for understanding. Signs of permanence have been difficult to discover, particularly in biological phenomena. Nevertheless, the one biological artifact which has always been considered permanent is the endoskeleton of higher animals. When all else has subsided into dust, this structure persists as the final testament to a life lived long ago. With this very objective and impressive evidence, it was only natural to assume that these structures exhibited the same permanence when existing as a component of a living organism as when buried in some lonely sand. This underlying assumption determined, in large part, the early scientific views of the nature of bone and its constituent cells. These views held that, in confirmation of the fossil evidence, bones once laid down were largely inert. However, these views changed slowly as it became increasingly evident that certain diseases, including those acquired in adult life after the skeleton was fully formed, could lead to a very marked alteration in the microscopic structure of bone viewed in histological section, or in its radiographic appearance in living organisms. This evidence suggested that bone, even in the adult, was a dynamic tissue. This point of view has become widely accepted as a result of the application of tracer techniques to the study of bone turnover.

One of the earliest applications of radioisotopes to biology involved the study of phosphate turnover in bone. This study showed that, contrary to the prevailing views, the uptake and turnover of phosphate in the bones of an adult mammal were considerable. These initial studies were followed by the much more extensive examination of radiocalcium turnover in the skeleton of experimental animals and man, and more recently by studies of the turnover of the organic components or matrix of bone using ^{14}C-labeled amino acids, particularly proline and glycine. The results of these studies, along with the first intensive period of investigation of human metabolic bone diseases, led to the conclusion that bones in living animals do in fact undergo continuous change and remodeling. This conclusion led to new models of bone structure and function and to a consideration of the role of bone cells in bone metabolism. The most widely accepted model was one in which two types of bone cells were considered of major importance in bone metabolism: active osteoblasts and osteoclasts.

Fuller Albright was responsible for one of the most appealing and clearest presentations of this viewpoint (Albright and Reifenstein, 1948). His concept of the metabolic functions of bone cells is reproduced in Figure I-1. In his view, the major changes in bone metabolism were controlled by two small groups of cells: the active osteoblasts at bone forming surfaces and the osteoclasts at bone resorbing surfaces. The large group of bone cells, representing over 95% of the total, consisting of resting osteoblasts and osteocytes, were considered of minor or no importance to the metabolic events within bone; i.e., they were truly resting cells and were only mobilized to activity in response to physiological stimuli by being converted into either active osteoblasts or osteoclasts.

The important positive feature of this model

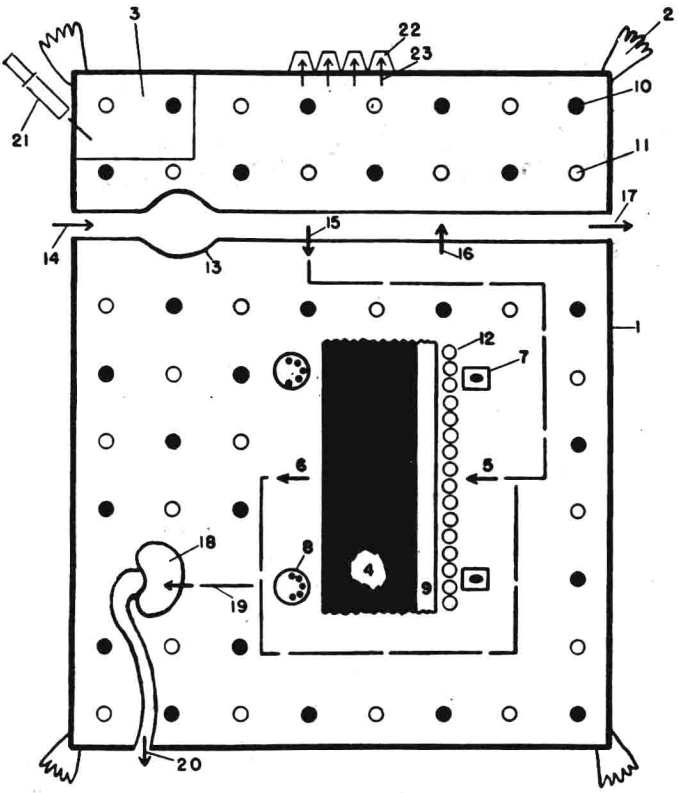

Fig. I-1. A model of events in calcium metabolism in the human *a la* Albright (from figure in Albright and Reifenstein, 1948) in which the major events in bone are the uptake of mineral (5) along the osteoblastic surface (7) and the release (6) of mineral along the osteoclastic (8) surface with the bulk of the bone (4) being metabolically inert.

was that it did, for the first time, focus attention onto the role of bone cells in the regulation of bodily calcium metabolism and thus served as the starting point for intensive investigation of the relationship of cell to organ function in this tissue. On the other hand, its major shortcomings were, in retrospect, the facts that it assigned no role to the majority of bone cells and that it made no distinction between two aspects of skeletal function: that related to *skeletal remodeling* and that to *mineral homeostasis*. For it is now clear that the adult skeleton has two major functions (or three if one includes the marrow cavities): that of providing mechanical support and protection for the organism and that of regulating the concentrations of key blood electrolytes including Ca^{2+}, H^+, Mg^{2+}, and $HPO_4^=$, and to a lesser extend Na^+.

In the case of the first function our knowledge is still grossly inadequate. It is clear that the remodeling of the skeleton is controlled in a very complex fashion, that growth and remodeling take place in response to mechanical stress and strain, and that various hormones alter these processes. This control of structure is *skeletal homeostasis*. The remarkable feature of skeletal homeostasis is that for most humans for most of their lives the strength and unity of the skeleton are maintained in a remarkable balance and the skeleton carries out its supporting and locomotory functions simply and elegantly. The development of the endoskeleton is, in fact, one of the truly remarkable events in biological evolution. In spite of this, our intimate knowledge of skeletal homeostasis is grossly inadequate, primarily, one suspects, because skeletal homeo-

stasis is normally so well maintained. However, with the very significant increase in the average life span of Western man, disorders of skeletal homeostasis have become an important medical problem. Osteoporosis or osteopenia—a marked decrease in total skeletal mass sufficient to lead to skeletal fragility, deformity, and dysfunction—is a common phenomenon in those persons, particularly female, who live well beyond 50.

In the case of the second skeletal function considerably more is known. The skeleton is an important component of the homeostatic mechanisms for maintaining the Mg^{2+}, Ca^{2+}, H^+, Na^+, and HPO_4^{2-} concentrations of the blood plasma within carefully defined limits. These controls of electrolyte metabolism are the basis of *mineral homeostasis.* However, in the context of the skeleton this term is usually used in a more restricted sense to denote those mechanisms that operate to control calcium and phosphate metabolism. On the other hand, it has become increasingly clear that the homeostatic control of blood Na^+ and H^+ is achieved by regulating the same bone cells that control calcium and phosphate metabolism; i.e., the control of blood pH and of blood calcium concentration are intimately related.

Having defined these two skeletal functions, we must add that the two control systems overlap in many ways, although, as will become evident, there are also distinct differences. Of particular importance is the fact that whenever skeletal turnover increases in response to changes in mechanical stresses, there is an increase in mineral turnover. However, the net result of this turnover may be either no net change in extracellular mineral balance (the increase in bone destruction is balanced by an increase in bone formation) or a change to a net deficit or excess of plasma mineral depending upon the balance between formation and resorption. In the latter two cases, the systems controlling mineral homeostasis are perturbed and respond in a fashion aimed at minimizing this perturbation. Conversely, whenever a mineral deficit develops, e.g., lack of calcium intake, bone formation decreases and bone resorption increases in response to this stress, and as a consequence skeletal homeostasis is disturbed.

Within the past 15 years, the application of new morphological, physiological, and biochemical techniques and knowledge has led to a marked increase in our understanding of both skeletal and mineral homeostasis. In large part the morphological knowledge has developed independently of the biochemical and physiological, but within the past 5 years an increasing integration of these different approaches has developed. From this has followed a reconsideration of bone cells and their function.

Perhaps the most important result of this reconsideration is the establishment of the osteocytes and resting osteoblasts, or more correctly the *surface osteocytes or mesenchymal cells,* as cells of great functional importance to bone. Thus, from a major preoccupation with events at the surface of bone, attention has become focused upon events within the interior of bone—to bone as an integrated tissue. This change of focus has led to an entirely new set of questions and problems, few of which have been answered, many of which have not yet been well formulated. The remainder of this book is an attempt to bring a new point of view into focus, to integrate the new knowledge of the morphology, physiology, and biochemistry of bone into a new model of skeletal and mineral homeostasis. This model is based upon experimental results, largely published, but not previously interpreted in this fashion.

This new model of skeletal and mineral homeostasis will be outlined briefly in order to serve as a guide to what follows. The morphological and physiological evidence leads to the conclusion that *osteocytes and resting osteoblasts,* or more appropriately, *surface osteocytes,* form a syncytium of cells which cover, because of their extensions, the entire exterior and interior surface of bone canaliculi and lacunae (Fig. I-2). This cell syncytium is organized as distinct functional units in the bone, bone metabolic units, which serve *a primary role in mineral homeostasis.* On the other hand, the *active osteoblasts and osteoclasts,* long considered the cells of primary importance in regulating mineral homeostasis, are organized in distinct bone remodeling units which are of *primary importance to skeletal remodeling* and normally play a secondary role in mineral homeostasis.

The contrasting functions of osteocytic oste-

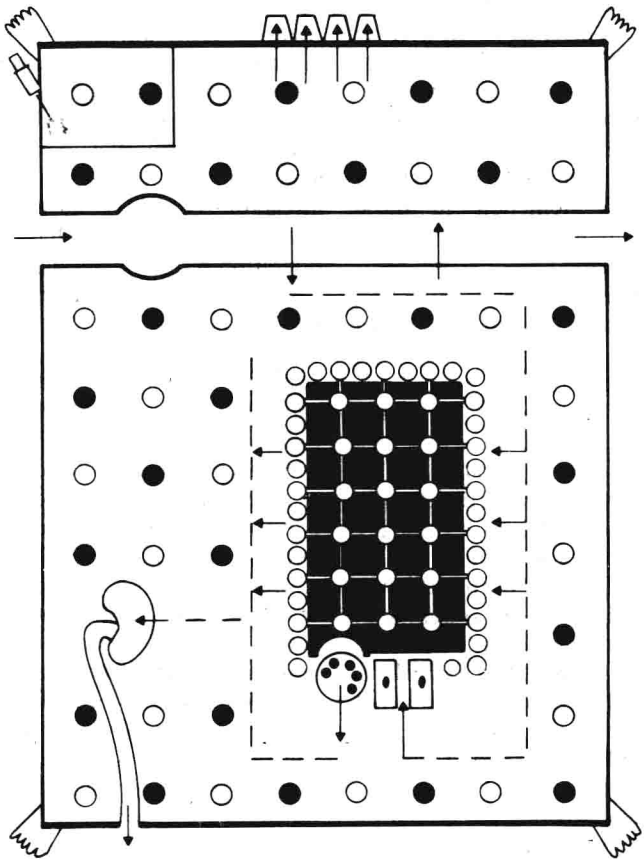

Fig. I-2. An updated Albrightian view of mammalian calcium metabolism in which a network of surface osteocytes and deep osteocytes form a syncytium of cells which regulates the uptake and release of mineral ions from bone in addition to the osteoblastic and osteoclastic surfaces which are minor in surface area compared to that covered by the osteocytic syncytium.

olysis and osteoclastic osteolysis can be best understood by comparing their roles in calcium homeostasis with those which glycogenolysis and gluconeogenesis play in glucose homeostasis. Even though different hormones and different organs are involved in glucose as compared to calcium homeostasis, the general features of the control systems underlying the control of their respective plasma concentrations are quite similar. Osteocytic osteolysis and glycogenolysis are both sensitive to minor changes in respective hormonal concentrations, capable of responding rapidly to these changes, but of having a response of limited magnitude. Osteoclastic osteolysis and gluconeogenesis are less rapidly altered, less sensitive to minor fluctuations in respective hormone concentrations, but capable of a prolonged response of considerable magnitude. In both instances the proper functioning of both aspects of the overall control system is necessary for proper homeostatic control. Thus, even though the amount of potential calcium mobilized by osteocytic osteolysis is considerably less than the potential which can be mobilized by osteoclastic osteolysis, the mobilization and redeposition of bone mineral by osteocytes are critically important components of normal mineral homeostasis.

From the foregoing it should be clear that the single most important change in viewpoint concerns the role of the osteocyte in bone and mineral metabolism. In the skeleton of a normal adult the interior and surface osteocytes

represent well over 95% of the total cells in bone. There is now clear evidence that these cells are directly involved in maintaining mineral homeostasis. In particular it has been shown that they respond to the major hormones controlling calcium homeostasis. In addition, within sites of new bone formation the newly incorporated osteocytes control the initiation of calcification of the newly formed matrix and at sites of bone resorption underlying osteocytic osteolysis serves as an important local signal for controlling osteoclastic osteolysis upon the overlying bone surface. This means that cellular events within bone and those upon its surfaces are integrated so that separate local regions of bone function as units, *bone metabolic units.*

Thus, in a real sense osteocytes participate in skeletal as well as mineral homeostasis. During prolonged calcium deprivation, the primary system in bone for maintaining mineral homeostasis, i.e., the osteocytic syncytium, is unable to maintain extracellular calcium homeostasis. Under these circumstances the osteoclast, a cell engaged in resorption of bone surfaces, becomes of paramount importance to mineral homeostasis. As a consequence of this change the control of mineral homeostasis is achieved by controlling osteoclastic osteolysis. Long continued calcium deprivation leads to a disordered skeletal homeostasis. On the other hand, many disorders of skeletal homeostasis, e.g., Paget's disease, and osteopetrosis can lead to marked changes in the rates of both bone formation and resorption without mineral homeostasis being perturbed. This does not mean that mineral and hormonal metabolism are not altered in cases of disorders of skeletal homeostasis, but that these changes, by influencing the activity of organs other than bone, particularly gut and kidney, can maintain mineral homeostasis in spite of disordered skeletal homeostasis. Finally, it is clear that some disorders, e.g., vitamin D deficiency, lead to alterations in both mineral and skeletal homeostasis. Thus, in some cases primary changes in mineral homeostasis take place without greatly altering skeletal homeostasis; in others mineral homeostasis is maintained in spite of disordered skeletal homeostasis; and in still others both are affected.

Central to an understanding of all of these different states is an understanding of bone cell function and the response of these cells to ionic and hormonal stimuli. This understanding includes an appreciation of how this cell syncytium in bone is supplied with nutrients and made aware of events in the plasma and extracellular fluids of the body. It has become clear that these cells lying within the lacunar-canalicular system of bone are surrounded by a unique bone extracellular fluid which circulates within this canalicular system, perfusing thereby the inlying cells and communicating in turn with the general extracellular fluids. This *minicirculation* in bone, aside from its role of maintaining the bone cells in contact with events in the organism, also plays a critical role in determining the local events within bone and in integrating these with events upon the bone surfaces.

As we shall see, bone cells of whatever type have many properties which are similar to those of many other cell types, but also each type is unique in certain key aspects. The general similarity of bone cell properties to those of other cells is of great importance because much of what we presently consider to be the function of bone cells has been arrived at by inference. From the point of view of the biochemist, bone cells are difficult to study. On the other hand, simpler systems, e.g., isolated thymocytes or isolated kidney cells grown in tissue culture, are easier to handle and have been used extensively to analyze the actions of ions and hormones upon cell function. Studies of this type will be discussed in considerable detail throughout this volume as an indirect but valid way of illustrating how bone cells respond to these stimuli.

The first major concept, which will be illustrated again and again, is that *the concentrations of calcium and phosphate ions within certain cellular compartments are critically important in the regulation of cell function,* including bone cells, parathyroid cells, ultimobranchial cells, renal tubular cells, and mucosal cells of the gastrointestinal tract, all of which are involved in the complex system which operates to maintain extracellular mineral homeostasis. The second major concept to be emphasized is that the *three major hormones operating as part of this system*– 1,25-dihydroxycholecalciferol, parathyroid hor-

mone, and calcitonin—*all exert some of their major effects by regulating the intracellular concentration of calcium and phosphate.*

The other aspect of bone cells which will be dealt with at some length concerns their origins and paths of maturation. Traditionally, two separate pathways of cell differentiation or modulation have been thought to exist: one leading from mesenchymal or progenitor cells to osteoblasts; the other leading from mesenchymal cells to osteoclasts. However, recent evidence has compelled us to reconsider this concept and to propose that, at least upon endosteal bone surfaces, the normal sequence is from mesenchymal cell to preosteoclast → osteoclast → preosteoblast → osteoblast → osteocyte. This proposed sequence of events explains a number of previously unexplained phenomena. However, its greatest importance, if true, lies in our thinking about, and therapeutic approaches to metabolic bone diseases, e.g., osteoporosis.

It is also clear that underlying osteocytes undergo cyclic changes in their function and can participate first in bone resorption and then to its reformation, and that these events are coordinated with cellular events upon endosteal surfaces. This coordination explains why resorption and formation occur in discrete regions or *remodeling units* within the skeleton. It also follows that, at endosteal surfaces in adult bone, the events of formation and resorption are not random, but coupled. Formation follows resorption and takes place at sites of previous resorption. *This coupling and the sequential nature of these surface events are the most important principles to be understood in any discussion of skeletal remodeling* and in the evaluation of the methods employed to estimate the magnitude of resorption and formation within the skeleton. They become of crucial importance when such methods are applied to the study of bone from patients with skeletal disorders because disturbances in the normal coupling between resorption and subsequent formation can lead to situations in which bone surfaces indicative of previous bone resorption increase in extent as a consequence of a decrease in the reformation of new bone rather than as a result of an absolute increase in the rate of resorption of old bone. Thus, our views of the cellular events within bone have immediate practical as well as theoretical consequences. They can determine our approach to rational therapy as well as to further experiment. They form the thread which weaves its way through the remaining pages of this book.

Before following this thread, it is necessary to define certain important terms to be used throughout this discussion, particularly because these terms have been used differently by different investigators. The term bone formation has been used to describe the rate of new bone (both matrix and mineral) formation, the rate of its mineralization, or simply the rate of matrix formation. The last is the sense in which it will be used in the present discussion. The formation of bone is a sequential process which involves: 1) intracellular collagen synthesis; 2) the extrusion of this collagen into the extracellular space and its proper orientation there; 3) the maturation of this collagen so that it becomes a suitable site for mineral crystal nucleation; 4) mineral crystal nucleation; and 5) mineral crystal growth converting matrix successively from uncalcified, to partially, and then fully calcified bone. The rate and extent of collagen synthesis and the proper orientation of this collagen determine the eventual size and shape of bone (along with, of course, the counter activity of bone resorption). Normally, matrix formation is followed in an orderly sequence by nucleation and mineral crystal growth so that matrix synthesis and the formation of fully calcified bone normally proceed in a coupled fashion. However, under a variety of conditions, this coupling between matrix formation and its mineralization is disturbed; hence, to understand the pathogenesis of various skeletal disorders, it is important to make a clear distinction between matrix formation and its subsequent mineralization.

It is equally important to emphasize that the term bone mineralization and the rate of bone mineralization, accretion, or formation, defined by the rate of radiocalcium accumulation *in vivo*, are not the same. When radiocalcium is added to the skeleton, it may be added to sites of net new bone mineral deposition, or it may be exchanged with calcium in fully formed bone crystals (exchange without net accretion). Furthermore, this type of exchange can be of

two types: short term exchange which is rapid and easily differentiated from net mineral deposition; and long term exchange which goes on constantly at a rate similar to that of net mineral accretion. It is generally assumed that there is a constant relationship or proportionality between net accretion and long term exchange, and thus that estimates of accretion by isotopic means (which, of course, include both types of skeletal mineral acquisition) are a valid reflection of net bone mineral accretion. This assumption is clearly invalid in some situations so that bone mineral accretion estimated by the use of radiocalcium, and net bone mineral deposition are not synonymous.

On the other hand, the term bone resorption has classically meant the rate of bone surface resorption brought about by osteoclasts. Several microscopic and microradiographic methods have been developed in an attempt to measure this activity. It has become increasingly clear that cells other than osteoclasts do participate in the resorption of bone. This is particularly true of the mature osteocytes in woven bone. As yet no accurate quantitative method has been devised to evaluate their contribution to the rate of bone resorption.

There is another uncertainty about the process of bone resorption. As generally employed, this term has come to mean the simultaneous removal of mineral and matrix of bone. The possibility exists that in some locations in bone, specifically the lacunar-canalicular surface, mineral exchange can take place without a concomitant shift in matrix turnover (*halisteresis*). There are other features of bone as a tissue which are extremely important in coming to an understanding of the nature of the processes controlling mineral and skeletal homeostasis. The skeleton is changing in two ways with age. The first bone to be deposited is, at the microscopic level, a loosely organized, highly cellular, highly mineralized tissue called *woven bone.* This form predominates in the embryo. With time it is resorbed and replaced by a dense, highly organized *lamellar bone.* As the age of the organism increases, the ratio of woven to lamellar bone decreases. Because the rates of both mineralization and resorption of woven bone are greater than those of lamellar bone, the reactivity of the skeleton, as measured by its ability to take up and release bone mineral, decreases with age. There is an additional factor which helps determine the decreasing reactivity of bone with age. This operates at another level of organization, a macroscopic level. It is the ratio of cancellous to cortical bone. Normally in the long bones at their growing ends, and between the cortical plates of the flat or membranous bone, there is found a less densely arranged trabecular or cancellous bone. In comparison to dense cortical bone, such as that found in the shaft of a long bone, the surface to volume ratio of this cancellous bone is large. This means, all other factors being equal, that it is more reactive metabolically. As the organism grows, the ratio of cancellous to cortical bone declines, and thus the reactivity of the skeleton as a whole declines. As will be discussed repeatedly, the different kinds of bones differ in their responsiveness to both local and humoral factors, and this difference helps to explain the role that various bone cells play in skeletal and mineral homeostasis.

Finally, one of the major problems in coming to grips with events in bone and bone cells is the heterogeneity of the microenvironment of bone cells. They do not all exist in the same environment. In addition, there is a real and important influence of bone upon bone cell function. When a deforming mechanical stress is placed upon bone an electric potential difference and a local electrical current are generated which influence the activity of bone cells. Thus, not only do bone cells determine the organization and mineralization of bone, but the nature of the particular type of bone and its response to stress influence the activity of bone cells. There is a definite feedback relationship between the two. Recognizing the presence of this relationship has not yet led to a true definition of its importance. However, in the long run this relationship will probably prove to be of paramount importance in the control of bone cell function.

two

Bone Cells—Morphology and Physiology

Bone is a connective tissue which is unique in the fact that the extracellular collagenous matrix (the major organic component of all connective tissue) becomes impregnated with a mineral phase. Neither component, the collagenous matrix nor the extracellular mineral crystals, alone determines the tissue behavior. The unique combination of the organic and inorganic phases confers upon bone its mechanical properties. These, in turn, are the determinants of its supportive function.

In order to fulfil this supportive function, however, bone structure must be in a dynamic rather than static state. It is as if each bone contains a resident architect who is continually reinstructing his workers to optimize the structural properties of his residence to meet the changing environmental stresses placed upon it. Pursuing this analogy, it is the various bone cells which are these workers. By their activity they control the turnover or remodeling of bone tissue. When their activities are properly coordinated, they result in the maintenance of *skeletal homeostasis*, a term which we shall employ to describe the factors responsible for maintaining skeletal mass and for optimizing the structural properties of bone as a tissue. These factors are both local and systemic.

There is a recognized autoregulatory type of control of bone turnover which is a property of bone tissue. Perhaps the most important feature of this autoregulatory system in the bones of adult organisms is the relationship between resorptive and formative aspects of bone turnover. It is generally true that bone resorption precedes formation; i.e., when bone is remodeled there is initially a resorption of a portion of the old which is subsequently followed by the formation of new bone which may assume a different shape and volume than the old bone it has replaced.

Hormones are of major importance in influencing the process of bone turnover. The most important are parathyroid hormone, calcitonin, thyroxine, adrenal glucocorticoids, estrogens, growth hormone, 1,25-dihydroxycholecalciferol, and possibly other metabolites of cholecalciferol. Many aspects of their effects will be discussed in subsequent sections of this book. The only important point to be made at this juncture is that *disorders of skeletal homeostasis may result either from a primary dysfunction of the local regulatory system*, e.g., Paget's disease, osteogenesis imperfecta, or from an *over- or underproduction of one or more of the above hormones.*

The skeleton also serves an important role in mineral homeostasis. Again, structural features of bone, particularly the relationship between collagen and mineral, are an important determinant of mineral availability for mineral homeostasis. Equally important in determining the role of bone in mineral homeostasis are the nature and distribution of bone cells. They control the exchange of mineral ions between the bulk extracellular fluid (ECF) phase, i.e., plasma and general ECF, and available bone mineral crystals.

In order to understand much of the ensuing discussion regarding bone cell function, it is necessary to have a working knowledge of bone