DISORDERS OF MINERAL METABOLISM

Volume III

Pathophysiology of Calcium, Phosphorus, and Magnesium

Edited by
Felix Bronner / Jack W. Coburn

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Disorders of Mineral Metabolism

VOLUME III

Pathophysiology of Calcium, Phosphorus, and Magnesium

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Preface

"Disorders of Mineral Metabolism" is intended as a comprehensive, up-to-date treatise on the pathophysiology of calcium, phosphorus, and magnesium and of other clinically relevant minerals and elements, such as iron, copper, zinc, fluoride, and the like.

Recent years have seen major advances in our understanding of how these minerals function in the mammalian body and why they are important in medicine. Thus the failure to provide adequate concentrations of calcium in hemodialysis fluids or to regulate their fluoride or aluminum concentrations may lead to severe bone disease of patients who are being maintained on dialysis. Understanding of the metabolism of vitamin D has underscored the pivotal role played by renal tissue in providing the body with an adequate supply of 1,25-dihydroxyvitamin D_3, the metabolite active in the intestinal cell and modulating one component of calcium absorption. Indeed, what characterizes current understanding is the appreciation of what may at first appear to be remote control loops, as in the role played by the vitamin D-regulated component of bone metabolism in the body handling of cadmium.

It therefore seems entirely fitting that this treatise unites what appear to be disparate subjects whose detailed understanding differs widely. It is the editors' hope that knowledge gained in one area may serve to stimulate research in another. An example is the high intracellular concentration of magnesium whose regulation and relationship to extracellular magnesium are not understood. The total intracellular calcium is low and the intracellular free calcium concentration is carefully regulated at between 10^{-7} and 10^{-6} M. This appears to involve complicated interactions between various cellular organelles, all of which have calcium-binding proteins with an association constant of about 10^6 M^{-1}. Yet

extracellular calcium is also closely regulated at 10^{-3} *M*, and the body expends considerable energy in the regulation of both intra- and extracellular calcium. How are these two related and could intra- and extracellular calcium regulation serve as a model for understanding the regulation of magnesium? Such questions could be multiplied manyfold. We hope this treatise will not only serve as a useful reference, but stimulate readers to reflect on parallels and distinctions between subjects.

Volume I of the treatise deals with minerals and elements whose average daily intake is under 50 mg. They are therefore conveniently termed "trace elements." While many are essential for life, the essentiality of others has not been established. Inclusion was largely a matter of clinical interest and relevance.

Volume II deals with the normal function of calcium, knowledge of which has exploded in recent years, with much emphasis on a host of intracellular functions. These have been summarized in the first chapter. In the remainder of the volume, calcium absorption, excretion, and homeostasis are discussed in detail, along with the hormonal modifiers of its metabolism. The role of connective tissue and bone, the major storehouse of body calcium, is reviewed in terms of collagen metabolism.

Volume III deals with the pathophysiology of calcium in bone and kidney and their disorders, along with detailed consideration of phosphate and magnesium metabolism. Throughout this and the other volumes the viewpoint has been that of disorders and how they arise; therapy has been discussed in terms of principles rather than from the viewpoint of specific management.

This treatise was inspired by a desire to bring up-to-date the earlier one on "Mineral Metabolism," edited by C. L. Comar and Felix Bronner. It became apparent early that comprehensive updating and expansion were no longer possible. An example is the Na^+-K^+ ATPase, mentioned in a footnote in the earlier treatise, which could now easily command its own volume. Similar comments apply to iodine and the thyroid diseases, to the electrolytes Na^+ and K^+ and their diseases, and a host of other subjects. Not only has there been an expansion of knowledge, the approach has changed, with much greater emphasis on an understanding of the molecular basis of many events. Some subjects have not advanced as much as others. This applies in particular to the relationship between events at the cellular, tissue, and organism levels. Just as true understanding of a mechanism requires reconstitution experiments, so appreciation of the disease process ultimately demands integration of events at all levels of organization, from the molecular to the whole organism. While this treatise makes halting steps in that direction, we hope future research will bring us closer to that goal.

Felix Bronner
Jack W. Coburn

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Disorders of Bone Resorption

Gregory R. Mundy and Lawrence G. Raisz

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I. INTRODUCTION

A. Mechanism of Bone Resorption

The resorption of bone involves release of bone mineral and degradation of bone matrix. Most bone resorption is probably cell-mediated, so that mineral release accompanies matrix degradation and probably slightly precedes it. However, mineral may also be exchanged between bone and extracellular fluid without removal or degradation of the bone matrix. This process has been termed calciolysis (Bohatirchuk, 1966). The significance of mineral exchange without matrix degradation *in vivo* is unknown but may play a role in the minute-to-minute regulation of the ionized calcium in the extracellular fluid. As far as is known, calcium regulation is primarily controlled by bone resorption, which is a hormonally regulated process mediated by bone cells.

1. Cell-Mediated Bone Resorption

The large multinucleated osteoclast is responsible for most if not all bone resorption that occurs under physiological circumstances. There is also morphologic evidence that osteocytes may contribute to bone resorption by enlarging the lacunae in which they reside (Bélanger *et al.*, 1963; Bélanger, 1965). Recently it has also been shown that cultured human monocytes (Mundy *et al.*, 1977) and breast cancer cells (G. R. Mundy and G. Eilon, unpublished observations, 1977) resorb cultured devitalized bone, although the physiologic relevance of these *in vitro* phenomena is still not clear.

a. Osteoclasts. Osteoclasts are large cells with foamy vacuolated cytoplasms, particularly when they are actively resorbing bone. Osteoclasts are usually multinucleated, but it is probable that mononucleated osteoclasts also occur. The number of nuclei varies from one or two to several hundred. The number of nuclei is increased in Paget's disease of bone, in hyperparathyroidism (Rasmussen and Bordier, 1974), and in other states where there is a stimulus to bone resorption, such as myeloma (Mundy *et al.*, 1974b). The nuclear number is decreased in elderly patients and in patients with postmenopausal osteoporosis (Rasmussen and Bordier, 1974). There is some species variation both in the size of the cells and in the number of nuclei (Hancox, 1972), with human osteoclasts being intermediate between the rat and the cat. The cytoplasm is acidophilic and most of the nuclei contain one single nucleolus. The nuclear chromatin is usually clumped towards the center of the nucleus.

The ultrastructure of the osteoclast is characterized by a ruffled or brush border (Palade, 1955; Scott and Pease, 1956). This was first observed by Kölliker (1873). This ruffled border is the *sine qua non* of the osteoclast. It is a specialized area of the cell membrane that consists of cytoplasmic processes

which extend into the adjacent bone. Within these cytoplasmic extensions can be found semi-digested bone matrix and free apatite crystals. These fragments are not seen within the cell cytoplasm. The proportion of osteoclast area occupied by ruffled borders and clear zones is increased in those osteoclasts that are actively resorbing bone (Holtrop *et al.*, 1974), and the area of ruffled borders and clear zones per cell may be used as a morphologic parameter of osteoclast activity. Another feature of the osteoclast ultrastructure is abundant mitochondria that occur predominantly on the opposite side of the cell from the bone. These mitochondria probably provide energy for osteoclast motility and for the resorbing process. The osteoclast contains scanty endoplasmic reticulum but has a well developed Golgi system. Many vesicles are present and some are probably lysosomes that may be involved in the resorptive process. Adjacent to the ruffled border is a clear zone devoid of subcellular organelles (Holtrop *et al.*, 1974).

The evidence that osteoclasts resorb bone is based on quantitative morphology from electron microscope sections of bone undergoing resorption (Holtrop *et al.*, 1974) as well as cinephotomicrography (Gaillard, 1955; Goldhaber, 1960). Although osteoclasts are usually closely apposed to bone in Howship's lacunae, they are very highly mobile cells that migrate from the primary resorptive site, leaving a scalloped margin which can be recognized as a bone resorbing surface.

Osteoclast number and activity can be regulated by a number of humoral mediators. The activity of osteoclasts is increased by parathyroid hormone (Raisz, 1965), the active metabolites of vitamin D (Trummel *et al.*, 1969; Raisz *et al.*, 1972a), thyroxine and triiodothyronine (Mundy *et al.*, 1976b), prostaglandins (Klein and Raisz, 1970), and osteoclast-activating factor (Horton *et al.*, 1972). Osteoclast activity is inhibited by cortisol (Raisz *et al.*, 1972b), phosphate (Raisz and Niemann, 1969), calcitonin (Raisz and Niemann, 1967), and colchicine (Raisz *et al.*, 1973). Stimulation of osteoclast activity by PTH has been associated with a number of metabolic events which are associated with the bone resorbing process. However, osteoclast stimulation by PTH is accompanied by inhibition of bone collagen synthesis (Dietrich *et al.*, 1976) and some of these events may be linked to this latter effect. They include adenylate cyclase activation (Chase and Aurbach, 1970), the increased entry of calcium into cells (Parsons and Robinson, 1971), citrate accumulation with decreased oxidation, increased glucose oxidation and increased lactate production (Martin *et al.*, 1965), increased intracellular accumulation of acid phosphatase (Walker, 1972), increased release of lysosomal enzymes (Vaes, 1969; Eilon and Raisz, 1978), increased RNA synthesis (Bingham *et al.*, 1969), and increased hexosamine incorporation and hyaluronate synthesis (Johnston *et al.*, 1972; Luben *et al.*, 1974a). Stimulation of osteoclasts by parathyroid hormone also results in changes in osteoclast membrane potential (Mears, 1971). Normally, osteoclasts occur in two populations with high and low membrane potentials. After activation with parathyroid hormone most of the osteoclasts have a low membrane