CRC REVIVALS

Phosphate in Paediatric Health and Disease

Edited by

Uri Alon, James C. M. Chan

CRC Press
Taylor & Francis Group

Phosphate in Pediatric Health and Disease

Edited by

Uri Alon, M.D.
Professor of Pediatrics
Division of Pediatric Nephrology
The Children's Mercy Hospital
University of Missouri at Kansas City School of Medicine
Kansas City, Missouri

James C. M. Chan, M.D.
Professor and Vice-Chairman, Department of Pediatrics
and
Chief, Division of Pediatric Nephrology
Children's Medical Center
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

First published 1993 by CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Reissued 2018 by CRC Press

Library of Congress Cataloging-in-Publication Data

Phosphate in pediatric health and disease / edited by Uri Alon,
James C. M. Chan.
p. cm.
Includes bibliographical references and index.
ISBN 0-8493-6785-9
1. Phosphorus metabolism disorders in children. 2. Calcium metabolism disorders in children. 3. Phosphates--Metabolism. 4. Calcium--Metabolism. I. Alon, Uri. II. Chan, James C. M.
[DNLM: 1. Calcium--Metabolism. 2. Hypophosphatemia, Familial--in infancy & childhood. 3. Phosphates--metabolism. QV 285 P574 1993]
RJ399.P52P48 1993
618.92'399--dc20
DNLM/DLC
for Library of Congress 92-48459

A Library of Congress record exists under LC control number: 92048459

Publisher's Note
The publisher has gone to great lengths to ensure the quality of this reprint but points out that some imperfections in the original copies may be apparent.

Disclaimer
The publisher has made every effort to trace copyright holders and welcomes correspondence from those they have been unable to contact.

ISBN 13: 978-1-315-89640-3 (hbk)
ISBN 13: 978-1-351-07550-3 (ebk)

Visit the Taylor & Francis Web site at http://www.taylorandfrancis.com and the
CRC Press Web site at http://www.crcpress.com

PREFACE

Phosphorus is the second member of the nitrogen family of elements. Its atomic number is 15 and its atomic weight is 30.9738. Phosphorus was discovered in 1669 by the German alchemist Hennig Brandt from a residue of evaporated urine during his search for the elusive philosophers' stone. The name phosphorus comes from the Greek "phosphoros" which means "light-bringing" and was given to the element because of its spontaneous ignition in air. Phosphorus forms the basis of a very large number of compounds, the most important class of which are the phosphates. For every form of living plant or animal cell, phosphates play an essential role. The importance of phosphorus in the metabolism of human osseous and nonosseous tissues has been well established long ago.

Since its publication in 1979, Helen and her late husband Harold Harrison's book *Disorders of Calcium and Phosphate Metabolism in Childhood and Adolescence* has served as the reference book for mineral disorders in the pediatric age group. With the explosion of information regarding mineral metabolism during the past quarter century, we felt that the time had come for a new book on these issues. In order to provide state-of-the-art, up-to-date coverage within the frame of a concise format, we elected to concentrate, in this book, mainly on phosphate metabolism. Nonetheless, because of the close interaction between calcium and phosphate, the book also covers extensive aspects of calcium metabolism and disorders related to calcium homeostasis. We hope that this book will serve as a guide and a standard reference in the years to come to all those interested in the intriguing fields of physiology, pathophysiology, and clinical aspects of mineral metabolism in childhood.

Our task could not have been accomplished without the help of our colleagues and friends who combined forces with us in writing this book. We are very much obliged to all of them for their much appreciated contributions.

Uri Alon, M.D.
Kansas City, Missouri
James C. M. Chan, M.D.
Richmond, Virginia

THE EDITORS

Uri Alon, M.D., is a Professor of Pediatrics in the School of Medicine at the University of Missouri-Kansas City and a Pediatric Nephrologist at the Children's Mercy Hospital in Kansas City, Missouri.

Dr. Alon received his M.D. degree from the Hebrew University, Hadassah Medical School, Jerusalem, Israel in 1975. After he finished his fellowship training in Pediatric Nephrology at the Medical College of Virginia, Virginia Commonwealth University, Richmond, in 1983, he was appointed an Assistant Professor of Pediatrics at that institution. In 1985 Dr. Alon became a Senior Lecturer in the Faculty of Medicine at the Technion Institute of Technology, Haifa, Israel. In 1988 he was appointed as an Associate Professor at the University of Missouri-Kansas City and became a Professor in 1992.

Dr. Alon is a member of the American Academy of Pediatrics, the American Society of Bone and Mineral Research, the American Society of Nephrology, the American Society of Pediatric Nephrology, the American Federation for Clinical Research, the International Society of Nephrology, the International Society of Pediatric Nephrology, the Midwest Society for Pediatric Research, and the Society for Pediatric Research. He is a member of several regional and national scientific organizations committees and serves on the editorial board and as a reviewer for several scientific journals.

Dr. Alon is the author of more than 100 papers and 15 chapters in books and has presented over 50 lectures in national and international meetings. His current major research interests relate to water, electrolyte and mineral metabolism, and the pathophysiology of kidney diseases.

James C. M. Chan, M.D., is Professor and Chairman, Nephrology Division, Children's Medical Center, as well as Vice-Chairman of the Department of Pediatrics, Virginia Commonwealth University's Medical College of Virginia, Richmond, Virginia. Dr. Chan earned his medical degree in 1964 from McGill University, Montreal, Canada, and received his pediatric and nephrology training at the Mayo Clinic in Minnesota, Oregon Health Sciences University in Portland, and Babies Hospital/Columbia-Presbyterian Hospital in New York.

After holding research and clinical appointments at the University of Southern California's Children's Hospital of Los Angeles, George Washington University's Children's Hospital National Medical Center in Washington, D.C., and the National Institutes of Health in Bethesda, Maryland, he joined the faculty of the Medical College of Virginia in 1977.

Dr. Chan is a diplomat of the American Board of Pediatrics and the Sub-Board of Pediatric Nephrology and a member of the Editorial Board of *Kidney International, Nephron, Kidney,* and *Child Nephrology and Urology,* as well as the Medical Director of the National Kidney Foundation of Virginia.

Dr. Chan's recent research interests have focused on growth hormone and insulin-like growth factor expression in the growth failure in children with renal insufficiency, renal tubular acidosis, and X-linked hypophosphatemic rickets.

Since 1983, Dr. Chan has been the recipient of three research grants from the National Institutes of Health, including a clinical trial involving 27 universities in the U.S. and Canada. He is also currently the Program Director of a Pediatric Nephrology Institutional Training Grant from the National Institute of Diabetes, Digestive and Kidney Diseases. He has published more than 250 research and review papers.

CONTRIBUTORS

Uri Alon, M.D.
Professor of Pediatrics
Division of Pediatric Nephrology
The Children's Mercy Hospital
University of Missouri at Kansas City School of Medicine
Kansas City, Missouri

Frank G. Boineau, M.D.
Professor of Pediatrics
Department of Pediatrics
Tulane University Medical Center
New Orleans, Louisiana

Ben H. Brouhard, M.D.
Director of Research Programs
Departments of Pediatrics, Hypertension/Nephrology, and Heart & Hypertension
The Research Institute
The Cleveland Clinic Foundation
Cleveland, Ohio

James C. M. Chan, M.D.
Professor and Chairman
Nephrology Division
Children's Medical Center
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

Russell W. Chesney, M.D.
Le Bonheur Professor and Chair
Department of Pediatrics
The University of Tennessee, Memphis College of Medicine
Le Bonheur Children's Medical Center
Memphis, Tennessee

Geoffrey D. Clarke, Ph.D.
Assistant Professor
Department of Radiology
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Ronald J. T. Corbett, Ph.D.
Assistant Professor
Department of Radiology
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Jean-Michel Garel, Ph.D.
Professor
Endocrinologie Moléculaire et Métabolique
Université Pierre et Marie Curie
Paris, France

James D. Hanna, M.D.
Assistant Professor of Pediatrics
Department of Pediatrics
Medical College of Georgia
Augusta, Georgia

Aviad Haramati, Ph.D.
Professor
Departments of Physiology & Biophysics and Medicine
Georgetown University School of Medicine
Washington, D.C.

Zeev Hochberg, M.D., D.Sc.
Department of Pediatrics
Rambam Medical Center
Haifa, Israel

Paul S. Kurtin, M.D.
Associate Professor
Children's Hospital of Los Angeles and Department of Pediatrics
University of Southern California School of Medicine
Los Angeles, California

Craig B. Langman, M.D.
Associate Professor of Pediatrics
Division of Nephrology
Children's Memorial Hospital and Department of Pediatrics
Northwestern University Medical School
Chicago, Illinois

John E. Lewy, M.D.
Professor and Chairman
Department of Pediatrics
Tulane University Medical Center
New Orleans, Louisiana

Robert H. K. Mak, M.D., Ph.D.
Assistant Professor
Division of Pediatric Nephrology
Department of Pediatrics
Stanford University School of Medicine
Stanford, California

Morri E. Markowitz, M.D.
Associate Professor
Department of Pediatrics
Montefiore Medical Center and Albert Einstein College of Medicine
Bronx, New York

Dushan J. Martinasek, M.D.
Neonatology Fellow
Division of Neonatology
Department of Pediatrics
University of Cincinnati College of Medicine and Department of Pediatrics
The Children's Hospital Research Foundation
Cincinnati, Ohio

Ralph A. Meyer, Jr., Ph.D.
Director
Biology Division
Orthopaedic Research Laboratory
Department of Orthopaedic Surgery
Carolinas Medical Center
and Adjunct Professor of Biology
University of North Carolina at Charlotte
Charlotte, North Carolina

Charles E. Mize, M.D., Ph.D.
Associate Professor
Department of Pediatrics
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Susan E. Mulroney, Ph.D.
Research Assistant Professor
Department of Physiology & Biophysics
Georgetown University School of Medicine
Washington, D.C.

Reginald C. Tsang, M.B.B.S.
Professor of Pediatrics and
Obstetrics & Gynecology
Division of Neonatology
Departments of Pediatrics and
Obstetrics & Gynecology
and Director
Division of Neonatology
University of Cincinnati College of
Medicine and
The Children's Hospital Medical
Center
Cincinnati, Ohio

Marian Wang, Ph.D.
Professor
Department of Foods and Nutrition
University of Georgia
Athens, Georgia

Yoseph Weisman, M.D.
Associate Professor
Vitamin Laboratory
Ichilov Medical Center and
Tel Aviv University
Tel Aviv, Israel

Darrell M. Wilson, M.D.
Assistant Professor
Division of Endocrinology and
Metabolism
Department of Pediatrics
Stanford University
Stanford, California

We would like
to dedicate this book
to our wives,
Michal and Winnie,
and to our children,
Guy, Saggie, and Ellen.

TABLE OF CONTENTS

Chapter 1

PHOSPHATE NUTRITION

Marian Wang, James D. Hanna, and James C. M. Chan

TABLE OF CONTENTS

I. INTRODUCTION

Phosphorus is one of the most important inorganic elements, second only to calcium in abundance in the human body. In humans, approximately 85% of the total body phosphorus is in bones, 14% in cells and soft tissues, and 1% in extracellular fluids. The phosphorus contained in bone is in the mineral phase as inorganic orthophosphate and small amounts of inorganic phosphate. In soft tissue and cell membranes, phosphorus exists mainly as phosphate esters and to a lesser extent as phosphoproteins and free phosphate ions. In extracellular fluid, about one tenth of the phosphorus content is bound to proteins, one third is complexed to sodium, calcium, and magnesium, and the remainder is present as inorganic phosphate. In biological systems, phosphorus is present as phosphate, and these two terms are used interchangeably in this chapter.

Plasma phosphate and intracellular phosphate have diverse functions. They take part in the formation of hydroxyapatite, the basic crystalline structure present in bone. Additionally, they are essential for the process of bone mineralization. Phosphate serves a vital role in the intermediary metabolism of carbohydrates, lipids, and proteins. It functions as a cofactor in enzyme systems and is of paramount importance in the formation of high energy phosphate compounds. As a component of genetic materials, phosphate is an essential part of the nucleic acid in chromosomes and ribosomes. Phospholipids are major structural constituents of cell membranes and intracellular organelles. Phosphate plays a critical role in secondary messenger systems such as cAMP and phosphatidylinositol, which act as important secondary messengers that mediate the intracellular effects of various hormones, neurotransmitters, and growth factors. Another important phosphate-containing compound, diphosphoglycerate, plays a crucial role in oxygen availability/delivery to the tissue. Phosphate aids in regulating body fluid pH and in modifying the effects of the B vitamins.

The normal plasma inorganic phosphate concentration ranges between 2.5 and 4.5 mg/dl in adults and between 4.0 and 6.5 mg/dl in children (Chapter 6). The concentration of plasma phosphate varies with dietary phosphate intake, age and stage of growth, time of day, hormonal effects, and renal function. Of the total plasma phosphate 88% is ultrafilterable. At pH 7.4, 85% of the ultrafilterable phosphate is in the form of monohydrogen phosphate, and the remainder exists mainly as dihydrogen phosphate. Circulating phosphate is in equilibrium with skeletal and cellular inorganic phosphate as well as with the organic phosphate formed through the processes of cellular metabolism. The concentration of inorganic phosphate in the extracellular fluid is an important factor influencing the mineralization of the skeleton and cell growth. Inorganic phosphate is a partial determinant of the concentration of cellular phosphoric esters such as 2,3-diphosphoglycerate in the blood cells and adenosine triphosphate (ATP) in other cells.

II. PHOSPHATE HOMEOSTASIS

Phosphate homeostasis denotes a balance between intestinal absorption, bone resorption, and renal reabsorption of filtered phosphate. Phosphate homeostasis is achieved by hormonal regulation of the factors that affect phosphate metabolism in the small intestine, kidney, and bone. The small intestine determines the rate of absorption of dietary phosphate. The kidney is the site of phosphate conservation through controlled reabsorption and excretion (Chapter 2). The bones serve as the major reservoir of phosphate.

III. INTESTINAL PHOSPHATE ABSORPTION

Absorption of phosphate in humans occurs throughout the small intestine. The jejunum is the most active absorptive site, although phosphate is also readily absorbed in the duodenum. The ileum is the least efficient in the absorption of phosphate.[1] Most phosphate is absorbed in its inorganic form. Organically bound phosphate is promptly hydrolyzed enzymatically in the intestinal lumen and released as inorganic phosphate. Intestinal absorption of phosphate occurs by two mechanisms: (1) passively by a linear concentration-dependent process, and (2) actively by a sodium gradient-driven phosphate transfer. It has been well established that the sodium electrochemical gradient across the brush-border membrane provides the driving force for active accumulation of phosphate into the cell.[2,3] A sodium-dependent transport system energized by ATP was detected in basolateral membrane vesicles from the human small intestine.[4] This active transport system can be enhanced by calcitriol ($1,25(OH)_2D_3$) and shows a linear relationship to the luminal sodium concentration.[5]

Many factors influence the intestinal absorption of phosphate. Hormones, dietary phosphate intake, age, and other substances in the intestinal lumen all regulate absorption of intestinal phosphate.

The major hormonal control of intestinal phosphate is through vitamin D, especially its metabolite, $1,25(OH)_2D_3$. Calcitriol directly stimulates intestinal absorption of phosphate.[6-9] The mode by which vitamin D exerts this effect has been shown to be activation of sodium (Na^+)-dependent phosphate transport through enhancement of the acceleration to maximum velocity (Vm) of the carrier system.[3,10-12] Data obtained from experiments with cultured embryonic chick jejunum showed that the effect of $1,25(OH)_2D_3$ on Na^+-dependent phosphate absorption was through its influence on the rate of Na^+ gradient-driven phosphate accumulation in brush-border membrane vesicles.[13,14] This $1,25(OH)_2D_3$ induction of Na^+-dependent phosphate transport can be potentiated by thyroid hormones.[15] Triiodothyronine enhances the Na^+ gradient-driven phosphate translocation across the luminal plasma membrane of enterocytes.[15] Glucocorticoids are capable of stimulating vitamin D-independent phosphate uptake by embyronic chick duodenum, and similar to

thyroid hormones they synergistically enhance $1,25(OH)_2D_3$-dependent phosphate uptake.[16,17] Insulin can also modulate the action of vitamin D on Na^+-dependent phosphate transport in enterocytes. This occurs through enhancement of vitamin D-dependent phosphate uptake. Conversely, insulin alone has no effect.[18] Parathyroid hormone (PTH) stimulates the synthesis of $1,25(OH)_2D_3$ in the kidney; thus, it exerts an indirect effect enhancing intestinal phosphate absorption. There is no evidence for direct action of PTH on intestinal Na^+-dependent phosphate transport.[11,19]

Phosphate availability and the stress of growth are known to affect phosphate absorption independent of vitamin D regulation.[20] Balance studies in the rat have demonstrated that net phosphate absorption is linearly related to dietary phosphorus.[21] A similar linear relationship has also been observed in normal humans.[22] Active phosphate absorption has been demonstrated in the intestine of young vitamin D_3-deficient rats.

In addition to phosphate availability, age is also known to influence phosphate absorption, both dependent upon and independent of vitamin D_3 regulation. Increasing phosphate concentration in the intestinal lumen enhances jejunal phosphate absorptive flux in vitamin D-deficient rats.[20] In vitamin D_3- or $1,25(OH)_2D_3$-repleted rats, phosphate depletion has a profound stimulatory effect on active phosphate absorption.[21] A low phosphorus diet also increases Na^+-dependent phosphate uptake by the brush-border membrane vesicles.[22-24]

Phosphate uptake declines significantly in the duodenum and jejunum with increasing age in the rat.[25] This age-related decline in phosphate uptake is restricted to the Na^+-dependent component but not in the Na^+-independent component. This decline in the gut absorption of phosphate parallels the decrease in serum $1,25(OH)_2D_3$ with age.[26] Intestinal vitamin D receptors decrease with age as well and this may be related to the decrease in phosphate absorption.[27]

Other dietary factors such as sodium, potassium, and calcium may also impact on the absorption of phosphate. Increased sodium and potassium concentrations in the intestinal lumen promote the transport of phosphate.[3,28,29] Calcium may affect intestinal absorption of phosphate both directly and indirectly. Excess calcium in the gastrointestinal tract may elevate the calcium-phosphate ratio to greater than 3, and may directly interact with phosphate to form nonabsorbable complexes, thus reducing the bioavailability of phosphate.[23] Calcium exerts an indirect effect mediated through its influence on vitamin D metabolism.[30] Consumption of a low calcium diet increases jejunal phosphate absorption in both young and adult rats.[25] The mechanism responsible for such an adaptation is not clear, but appears to be independent of the circulating concentration of $1,25(OH)_2D_3$ in the adult rats.[26]

IV. PHOSPHATE AND BONE

Bone is the reservoir of phosphate that may replenish blood phosphate by resorption.[31] Bone resorption is mediated by $1,25(OH)_2D_3$ and PTH that stimulate mobilization of bone calcium and phosphate to normalize the blood concentrations of these two minerals. Serum and dietary inorganic phosphorus play a highly significant role in the regulation of 25-OH-D_3-1α-hydroxylase activity in the renal tissue. This enzyme in turn regulates the conversion of vitamin D to its metabolically active form. Phosphate depletion stimulates the activity of 25-hydroxyvitamin D_3-1α-hydroxylase (Chapter 3). When serum inorganic phosphorus level is normal, the predominant enzyme form is $25(OH)D_3$-24-hydroxylase as has been shown in thyroparathyroidectomized rats fed an adequate phosphate and calcium diet.[32] The metabolite $24,25(OH)_2D_3$ is thought to be essential for bone formation and thus removal of phosphate from the plasma into the bone.[33]

Biological mineralization of the cartilage and bone is an extracellular event occurring in the extracellular matrices of these tissues. Cartilage and bone contain varying amounts of type 1 and type 5 collagen within their matrices that serve as a support structure for the process of mineralization that occurs both within the collagen fibrils and external to them in the ground substance.[33,34] It seems that a number of factors operate synergistically or interchangeably to initiate the process of mineralization. In immature bone and cartilage where the initial stages of mineralization take place, matrix vesicles are present and are situated at varying distances from the direct site of mineralization. These vesicles originate by pinching off from the plasma membrane of cells producing the mineralized tissue, such as the osteoblast. Once formed, the loaded vesicles containing calcium, phosphorus, alkaline phosphatase, and varying enzymes migrate to the predestined site of mineral deposition and expel their contents, increasing the local concentration of mineral, possibly increasing the calcium $\times$ phosphorus product sufficiently to initiate the first-formed solid phase of bone formation. Although the exact characteristics of this first-formed solid phase, whether amorphous or crystalline, are not known, it is widely accepted that amorphous calcium-phosphate ($Ca_9[PO_4]_6$) present in early mineralization undergoes progressive transformation into a crystalline structure resulting in hydroxyapatite, the final mineral deposite in bone. This process of crystallization is dependent upon the local calcium-phosphorus product, also known as $[Ca^{2+}] \times [Pi]$ ion product (Pi denotes total free inorganic orthophosphate, HPO_4^{2-}, $H_2PO_4^-$, and PO_4^{3-}).[34] The initiator that operates to raise this ion product, whether local or systemic,[35] remains elusive. The increase in the ion product causes calcium and phosphate to separate out of the solid phase and then to undergo solid phase transition

and interconversion to a host of alternate crystalline structures resulting ultimately in hydroxyapatite deposition.

Intermediate stages in the association between calcium and phosphorus in the process of mineral deposition exist, as shown by the recently developed technique of electron spectroscopic imaging.[36] This analytical technique allows the chemical nature of the elements seen in standard transmission electron microscopy (TEM) to be analyzed and superimposed onto the TEM image. Analysis of calcifying cartilage and bone has shown that calcium in calcifying cartilage is first associated with sulfur, probably in the sulfated glycosaminoglycans of the cartilage matrix.[34] As the mineralization process proceeds, phosphate superimposes with both calcium and sulfur, presumably increasing the ($Ca^{2+} \times Pi$) ion product, and the chain of events leading to crystalline calcium phosphate precipitation, solid phase transition, crystalline interconversion, and eventual hydroxyapatite deposition ensues.[34]

Clinical evidence of the importance of phosphate in the process of laying down newly formed bone (calcification) was underscored in the late 1950s by Fraser and colleagues[37] in their experiments involving rachitic costochondral junctions. Three children with vitamin D-resistant rickets had a rachitic costochondral junction removed which was sectioned, and the slices were subsequently incubated in the sera from the three patients, sera from normal children, or sera from the three patients supplemented with physiologic amounts of calcium and phosphorus. A demonstrable increase in the deposition of bone salts occurred at the zone of provisional calcification in the normal sera and the supplemented patients' sera, but no change in calcification was seen in the sections incubated in the nonenriched patients' sera. The *in vivo* response of rachitic bone to phosphate supplementation was subsequently assessed in two children with untreated vitamin D-resistant rickets who received a continuous intravenous infusion of isotonic sodium phosphate infused at a rate such that the serum inorganic phosphorus concentration was maintained at or above 5 mg/dl. In both patients, the establishment of a normal serum phosphorus concentration induced an immediate fall in the serum calcium followed by radiographic evidence of healing of the rickets in the metaphyseal region of the wrists and knees within 5 d. Concurrent with this healing, the serum alkaline phosphatase concentration showed a gradual decline to the normal range. When the intravenous phosphate therapy was discontinued, biochemical evidence of rickets rapidly reappeared, but the radiographic reappearance of fraying in the wrists and knees was delayed for 2 months.[37] This method of treatment was subsequently extended to other untreated severely rachitic infants with vitamin D deficiency.[38] Continuous intravenous administration of inorganic phosphorus in two patients and phosphate and calcium administered in an alternating regimen to the other children resulted in a rapid calcification of the rachitic lesions such that new bone mineralization was evident radiographically as early as 2 d postinitiation of therapy. Alkaline phosphatase decreased gradually over the 6 to 12 d of treatment. Further evidence, although indirect, of the importance of phosphate in bone cell metabolism is reflected by the growth pattern seen in hereditary hypophos-

phatemia.[39] At birth, these children fall within normal growth percentiles for height and weight and maintain normal growth measurements until such time as the serum phosphorus drops below the normal range. By 6 months of life, this has usually occurred, and anthropometric measurements for length and weight decline to less than or equal to the third percentile. Additionally, radiographic evidence of rickets and bone disease is not evident until the onset of hypophosphatemia.[39] The effect of an elevation of serum phosphorus on growth was interestingly demonstrated in a patient with hereditary hypophosphatemia treated with a high dose of vitamin D who experienced renal damage from vitamin D toxicity; this resulted in a decline of his glomerular filtration rate to 50 to 60% of normal and an elevation of his serum phosphorus from 2.0 to 3.0 mg/dl to 4.0 to 4.5 mg/dl. His growth, which had ceased with the hypervitaminosis, increased with elevation of his serum phosphorus and accelerated to cross several percentile lines, reaching the 50th percentile.[39]

The use of long-term oral phosphate supplementation as a sole therapy in hypophosphatemic vitamin D-resistant rickets, a disease associated with hypophosphatemia and growth failure, induces a transient increase in the serum phosphorus concentration, a sustained rise in the serum PTH concentration (iPTH), and stimulation of both endosteal osteoblastic and osteoclastic activities.[40] Despite the induction of the increased bone cell turnover, growth rates with this form of therapy in most cases are markedly increased.[40,41] The addition of 1,25-dihydroxyvitamin-D has been found to decrease the osteoclastic resorption and allow better control of the iPTH, but does not always promote further increases in growth velocity over phosphate alone.[40] The addition of vitamin D, however, does improve cortical bone mineralization and enhance osteoblastic recruitment.[42] In summary, it appears that phosphate is critical in the process of bone mineralization in conjunction with calcium and sulfur, presumably mediated by matrix vesicles enhancing the local $Ca^{2+} \times$ Pi ion product. Its importance in mediating growth is reflected in patients with hypophosphatemic vitamin D-resistant rickets where supplementation greatly increases growth velocity, but induces secondary hyperparathyroidism (Chapter 9). The addition of 1,25-dihydroxyvitamin-D helps to alleviate this problem, although it is unclear if the improvement in bone mineralization mediated by enhancement of the osteoblast population is a direct effect of 1,25-dihydroxyvitamin-D on the osteoblast or an indirect effect through enhancement of phosphate availability. The oral intake of phosphorus has been shown to determine the production rate of 1,25-dihydroxyvitamin-D as well as regulate its serum concentration. In turn, vitamin D and its metabolites suppress PTH secretion and more recently have been shown to modulate PTH gene transcription (Chapter 3).

V. CELLULAR PHOSPHATE STASIS

Intracellular concentration of phosphate has been implicated in the regulation of glycolysis, oxidative phosphorylation, basal metabolic rate, and

modulation of calcium-activated cellular processes.[43-47] Careful regulation of intracellular phosphate is necessary for normal cell functioning.[48]

Phosphate that enters cells either is incorporated into organic phosphate or remains as an inorganic anion. The concentration of intracellular phosphate is not directly proportional to the plasma concentration. When the extracellular concentration is disturbed, the cells are able to maintain cytosolic phosphate concentration. This intracellular buffering capacity has been demonstrated by nuclear magnetic resonance (NMR) determination of intramuscular phosphate concentrations in patients who exhibit a wide range of plasma phosphate concentrations due to diseases.[49]

Intracellular phosphate concentration is maintained to some extent at the expense of organic phosphates.[50] Phosphate is liberated from the organic pool during ATPase and phosphatase reactions. Mitochondria act as the reservoir to replenish cytosolic phosphate when the metabolic demand for phosphate is greater than the cellular uptake.[50] Further refinement of the cytosolic phosphate concentration is made through the activity of the mitochondrial phosphate transporters. Future studies using NMR techniques may further elucidate the mechanisms responsible for the net transfer and steady-state fluxes of phosphate compounds between the intracellular compartments and plasma membrane.

VI. PHOSPHATE NUTRITION

Phosphate is abundantly available and is present in all natural foods. All foods composed of animal or plant cells are rich in phosphate; the major sources are protein-rich foods and cereal grains. Milk and milk products contain the phosphoprotein casein, making them the richest source of phosphate in the diet.[51] Other good sources of phosphate are meat, fish, poultry, eggs, and peanuts.[52]

Diets providing sufficient protein and calories also contain adequate amounts of phosphate.[30] The mean daily intake of phosphate is approximately 1500 mg for adult males and 1000 mg for adult females.[53]

Phosphate interacts with several dietary minerals such as calcium, sodium, and magnesium.[52] For example, an increase in dietary magnesium results in a decrease in phosphate absorption, and, conversely, a deficiency of luminal magnesium enhances the absorption of phosphate. An adequate luminal concentration of sodium is essential to ensure phosphate absorption.

It has been demonstrated in animal studies that diets low in the calcium/phosphorus (Ca/P) ratio lead to progressive bone loss due to excessive PTH stimulation.[54-57] A similar stimulatory effect may also occur in humans consuming high phosphate diets for prolonged periods.[58] The recommended Ca/P ratio in the diet is between 1.0 and 1.5, but not <0.5.[54] The average ratio in the U.S. diet is 1.0 to 1.8 for adults between 35 to 50 years of age.[53] This ratio is higher in the diets of infants and children due to their greater consumption of milk.

Phosphate deficiency is characterized by weakness, anorexia, malaise, and pain (Chapter 8).[52] Bone loss is the major effect of phosphate deficiency.[52] Mild hypophosphatemia (1.5 to 3.5 mg/dl) seldom produces symptoms, and severe hypophosphatemia (<1.5 mg/dl) often causes symptoms requiring immediate treatment.[31] The phosphate deficiency syndrome[52] is encountered when hypophosphatemia occurs in conjunction with intracellular phosphate depletion. This is usually a chronic syndrome with gradual onset of symptoms seen in chronic negative phosphate balance.[30] The clinical and metabolic manifestations of the syndrome are due mainly to the fall in intracellular levels of ATP and decreased availability of oxygen to the tissues, secondary to 2,3-diphosphoglycerate depletion.[30] Phosphate deficiency may occur secondary to inadequate intake or absorption of phosphate, or alternatively from defects in renal tubular reabsorption of phosphate.

Nutritional deficiencies of phosphate are rare because virtually all foods contain phosphorus.[51] However, in premature infants exclusively fed human milk without additional phosphate, hypophosphatemic rickets may develop (Chapter 7).[59] These premature infants have a high rate of active bone mineralization, and thus they require more phosphate than is contained in human milk.[60] Furthermore, patients receiving phosphate binders such as aluminum hydroxide, an antacid, for prolonged periods may also develop serious phosphate deficiency.[61,62] Patients receiving total parenteral nutrition (TPN) with insufficient amounts of phosphate have been reported to develop manifestations of the phosphate deficiency syndrome.[63] Supplemental phosphate may be required to achieve and maintain normal serum phosphate concentration in patients with severe phosphate depletion who receive commercial enteral feeding solutions.[63,64] Breakdown of intracellular phosphate-containing compounds occurs in starvation, uncontrolled diabetes mellitus, and in chronic alcoholism.[30] This results in tissue phosphate release into the plasma and subsequent loss in the urine. Under conditions of severe malnutrition, i.e., starvation, normal plasma concentrations of phosphate may not reflect total body phosphate depletion. In uncontrolled diabetes mellitus, hyperglycemia, polyuria, acidosis and enhanced osmotic phosphate diuresis cause excessive phosphaturia. In the chronic alcoholic, causes for phosphate depletion include decreased dietary intake, malabsorption, hypomagnesemia, hypokalemia, secondary hyperparathyroidism, ketoacidosis, lactic acidosis, and increased urinary loss. Phosphate repletion should be given serious consideration in the treatment of these metabolic derangements. The major cause of hypophosphatemia in this state is an abnormality in tubular handling of phosphate.

An inborn as well as acquired defect of the disruption of phosphate balance by the proximal tubule is the Fanconi syndrome which causes dysfunction of the proximal renal tubule with attendant defective tubular reabsorption of glucose, amino acids, and phosphate (Chapter 9). This results in renal glycosuria, amino-aciduria, and hyper- and hypophosphatemia.[51] Another inborn error of renal phosphate handling is X-linked hypophosphatemia (Chapter 9). Perturbation of renal phosphate balance also occurs in renal tubular acidosis.

This is a defect in the kidney for the reabsorption of bicarbonate and exchange of hydrogen ion for Na^+ in the renal tubular contents.[51] Defective tubular reabsorption of phosphate resulting from bicarbonate deficiency is corrected by bicarbonate replacement. Further causes of a reduction in the tubular reabsorption of phosphate include genetic and acquired primary hypophosphatemia, cystinosis, tyrosinosis, multiple myeloma, and connective tissue tumors.[31]

Phosphate supplementation is essential in severely hypophosphatemic patients as well as in those who are symptomatic. Phosphate can be administered orally, parenterally, or through dialysis fluids. It should be noted that phosphate treatment must be monitored carefully as it can result in complications such as diarrhea, hyperphosphatemia, hypocalcemia, hypomagnesemia, hyperkalemia, volume excess, and mild acidosis.[30,31] Phosphate supplementation is contraindicated in renal failure.

Hyperphosphatemia occurs primarily from inadequate renal excretion and is an important complication of renal insufficiency. Hyperphosphatemia (>5.0 mg/dl) can develop from the following mechanisms: (1) decreased glomerular filtration rate, (2) increased tubular reabsorption of phosphate, and (3) increased phosphate loading.[31] In disorders such as renal failure, hemolysis, rhabdomyolysis, and tumor lysis syndrome, hyperphosphatemia is a frequent complication. Hyperphosphatemia has effects on multiple systems. Various soft tissues may develop ectopic calcification with prolonged hyperphosphatemia. Precipitation with calcium occurs when the Ca/P ion product exceeds 70.[31] Volume expansion, phosphate binders, or a diet that is low in protein and thus in phosphorus has often been used in the treatment of hyperphosphatemia. The use of phosphate binders is limited by their potential side effects.[30]

The precise dietary requirement of phosphate is not known. If normal caloric requirements are met, an intake of 0.2 mg of phosphorus per calorie consumed is sufficient to meet the needs of the growing child, the adolescent, and the adult.[51] The Recommended Dietary Allowance (RDA 1989) for phosphorus is 800 mg for children 1 to 10 years, 1200 mg for ages 11 to 24 years, and 800 mg beyond age 24.[53] During pregnancy and lactation, the daily allowance is increased to 1200 mg.[53] The RDA of phosphorus for formula-fed infants from birth to 6 months of age is 300 mg/d; for infants 6 to 12 months of age, 500 mg/d.[53]

REFERENCES

1. **Walton, J. and Gray, T. K.,** Absorption of inorganic phosphate in the human small intestine, *Clin. Sci. Mol. Med.*, 56, 407, 1979.
2. **Hoffman, N., Thees, M., and Kinne, R.,** Phosphate transport by isolated brush-border vesicles, *Pflugers' Arch.*, 362, 147, 1976.

3. **Hildman, B., Storelli, C., Danisi, G., and Murer, H.,** Regulation of Na^+-Pi cotransport by 1,25-dihydroxyvitamin D_3 in rabbit duodenum brush-border membrane, *Am. J. Physiol.*, 242, G533, 1982.
4. **Kikuchi, K. and Ghishan, F. K.,** Phosphate transport by basolateral plasma membranes of human small intestines, *Gastroenterology*, 93, 106, 1987.
5. **Danisi, G. and Straub, R. W.,** Unidirectional influx of phosphate across the mucosal membrane of rabbit small intestine, *Pflugers' Arch.*, 385, 117, 1980.
6. **Kowarski, S. and Schacter, D.,** Effects of vitamin D on phosphate transport and incorporation into mucosal constituents of rat intestinal mucosa, *J. Biol. Chem.*, 244, 211, 1969.
7. **Chen, T. C., Castilla, L., Korycka-Dahl, M., and DeLuca, H. F.,** Role of vitamin D metabolites in phosphate transport of rat intestine, *J. Nutr.*, 104, 1056, 1974.
8. **Kabakoff, B., Kendrick, N. C., and DeLuca, H. F.,** 1,25-Dihydroxyvitamin D_3 stimulated active uptake of phosphate by rat jejunum, *Am. J. Physiol.*, 243, E470, 1982.
9. **Lee, D. B. N., Walling, M. W., and Corry, D. B.,** Phosphate transport across rat jejunum: influence of sodium pH and 1,25-dihydroxyvitamin D_3, *Am. J. Physiol.*, 251, G90, 1986.
10. **Peterlik, M.,** Phosphate transport by embryonic chick duodenum: stimulation by vitamin D_3, *Biochim. Biophys. Acta*, 514, 164, 1978.
11. **Walling, M. W.,** Intestinal inorganic phosphate transport, in *Homeostasis of Phosphate and Other Minerals*, Massry, S. G., Ritz, E., and Rapada, A., Eds., Plenum Press, New York, 1978, 81.
12. **Danisi, G., Bonjour, J. P., and Straub, R. W.,** Regulation of Na-dependent phosphate influx across the mucosal border of duodenum by 1,25-dihydroxycholecalciferol, *Pflugers' Arch.*, 388, 227, 1980.
13. **Fuchs, R. and Peterlik, M.,** Vitamin D-induced phosphate transport in intestinal brush-border membrane vesicles, *Biochim. Biophys. Res. Commun.*, 93, 87, 1980.
14. **Matsumoto, T., Fontaine, O., and Rasmussen, H.,** Effect of 1,25-dihydroxyvitamin D_3 on phosphate uptake into duck brush-border membrane vesicles, *Biochim. Biophys. Acta*, 599, 8, 1980.
15. **Cross, H. S., Dubiec, H., and Peterlik, M.,** Mechanism and regulation of intestinal phosphate absorption, *Min. Electrolyte Metab.*, 16, 115, 1990.
16. **Yeb, J. K., Aloia, J. F., and Semla, H. M.,** Interrelation of cortisone and 1,25-dihydroxycholecalciferol on intestinal calcium and phosphate absorption, *Calc. Tissue Int.*, 36, 608, 1984.
17. **Corradino, R. A.,** Hydrocortisone and vitamin D_3 stimulation of ^{32}Pi-phosphate accumulation by organ-culture chick embryo duodenum, *Horm. Metab. Res.*, 11, 519, 1979.
18. **Peterlik, M., Cross, H. S., and Fuchs, R.,** Intestinal phosphate transport: mechanistic and regulatory aspects, in *Current Advances in Skeletogenesis: Induction, Biomineralization, Bone Seeking Hormones, Congenital and Metabolic Bone Diseases*, Ornoy, A., Harnell, A., and Sela, J., Eds., Heliger Publishing, Jerusalem, 1987, 265.
19. **Lee, D. B. N., Walling, M. W., and Tallos, E.,** Jejunal phosphate transport is not mediated by the PTH-adenylate cyclase system. Further studies on contrasting features between intestinal and renal phosphate transport mechanisms, *Min. Electrolyte Metab.*, 12, 293, 1986.
20. **Lee, D. B. N., Hardwick, L. L., Hu, M. S., and Jamgotehian, N.,** Vitamin D-independent regulation of calcium and phosphate absorption, *Min. Electrolyte Metab.*, 16, 167, 1990.
21. **Lee, D. B. N., Brantbar, N., Walling, V. S., Coburn, J. W., and Kleeman, C. R.,** Effect of phosphorus depletion on intestinal calcium and phosphorus absorption, *Am. J. Physiol.*, 236, E451, 1979.
22. **Danisi, G., Caverzasio, J., Bonjour, J. P., Murer, H., and Straub, R. W.,** Mechanism of phosphate transport adaptation in rat intestinal and renal brush-border membranes, *Adv. Exp. Med. Biol.*, 208, 223, 1986.

23. **Clark, I.,** Importance of dietary Ca:PO_4 ratios on skeletal Ca Mg and PO_4 metabolism, *Am. J. Physiol.*, 217, E871, 1969.
24. **Wilkinson, R.,** Absorption of calcium, phosphorus and magnesium, in *Calcium Phosphate and Magnesium Metabolsim: Clinical Physiology and Diagnostic Procedures*, Nordin, B. E. C., Ed., Churchill Livingstone, New York, 1976, 86.
25. **Ambrecht, H. J.,** Age-related changes in calcium and phosphorus uptake by rat small intestine, *Biochim. Biophys. Acta*, 882, 281, 1986.
26. **Ambrecht, H. J.,** Effect of age on calcium and phosphorus absorption — role of 1,25-dihydroxyvitamin D, *Min. Electrolyte Metab.*, 16, 159, 1990.
27. **Ambrecht, H. J., Boltz, M. A., and Bruns, M. E. H.,** Capacity of 1,25-dihydroxyvitamin D to stimulate expression of intestinal calbindin D changes with age in the rat, *J. Bone Min. Res.*, 4, 5350, 1989.
28. **Mettardy, G. J. R. and Parsons, D. S.,** The absorption of inorganic phosphate from the small intestine of the rat, *Q. J. Exp. Physiol.*, 41, 398, 1956.
29. **Harrison, H. E. and Harrison, H. C.,** Intestinal transport of phosphate: action of vitamin D calcium and potassium, *Physiology*, 201, 1007, 1961.
30. **Berner, Y. N. and Shike, M.,** Consequences of phosphate imbalance, in *Annual Review of Nutrition*, Olson, R. E., Ed., Annual Review Inc., Palo Alto, CA, 1988, 8, 125.
31. **Chan, J. C. M. and Bell, N. H.,** Disorders of phosphate metabolism, in *Kidney Electrolyte Disorders*, Chan, J. C. M. and Gill, J. R., Jr., Eds., Churchill Livingstone, New York, 1990, 223.
32. **Tanaka, Y. and DeLuca, H. F.,** Rat renal 25-hydroxyvitamin D3 1- and 24-hydroxylases; their in vivo regulation, *Am. J. Physiol.*, 246, E168, 1984.
33. **Orny, A.** 24,25-Dihydroxyvitamin D is a metabolite of vitamin D essential for bone formation, *Nature*, 276, 517, 1978.
34. **Cormack, D. H.,** Bone, in *Histology*, 8th ed., Cormack, D. H., Ed., Lippincott, Philadelphia, 1987, 273.
35. **Peck, W. A., Rifas, L., Cheng, S., and Shen, V.,** The local regulation of bone remodeling, in *Advances in Experimental Medicine and Biology: Phosphate and Mineral Homeostasis*, Massry, S. G., Olmer, M., and Ritz, E., Eds., Plenum Press, New York, 1986, 255.
36. **Ottensmeyer, F. P.,** Electron spectroscopic imaging: parallel filtering and microanalysis in the fixed-beam electron microscope, *J. Ultrastruct. Res.*, 88, 121, 1984.
37. **Fraser, D., Jaco, N. T., Yendt, E. R., Munn, J. D., and Liu, E.,** The introduction of in vitro and in vivo calcification in bones of children suffering from vitamin D-resistant rickets without recourse to large doses of vitamin D, *Am. J. Dis. Child.*, 93, 84, 1957.
38. **Fraser, D., Geiger, D. E., Munn, J. D., Slater, P. E., Jahn, R., and Liu, E.,** Calcification studies in clinical vitamin D deficiency and hypophosphatemic vitamin D-refractory rickets: the induction of calcium deposition in rachitic cartilage without the administration of vitamin D, *Am. J. Dis. Child.*, 96, 460, 1958.
39. **Harrison, H. E., Harrison, H. C., Lifshitz, F., and Johnson, A. D.,** Growth disturbance in hereditary hypophosphatemia, *Am. J. Dis. Child.*, 112, 290, 1966.
40. **Glorieux, F. H., Marie, P. J., Pettifor, J. M., and Delvin, E. E.,** Bone response to phosphate salts ergocalciferol and calcitriol in hypophosphatemic vitamin D-resistant rickets, *N. Engl. J. Med.*, 303, 1023, 1980.
41. **Glorieux, F. H., Scriver, C. R., Reade, T. M., Goldman, H., and Rosenborough, A.,** Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia, *N. Engl. J. Med.*, 287, 481, 1972.
42. **Marie, P. J. and Glorieux, F. H.,** Stimulation of cortical bone mineralization and remodeling by phosphate and 1,25-dihydroxyvitamin D, in vitamin D-resistant rickets, *Metab. Bone Dis. Rel. Res.*, 3, 159, 1981.
43. **Hattleman, B. D., Sabina, R. L., and Drezner, M. K.,** Defective adenosine triphosphate synthesis: an explanation for skeletal muscle dysfunction in phosphate-deficient mice, *J. Clin. Invest.*, 72, 582, 1983.

44. **Racker, E.,** Approaches to the metabolism of intact cells and to the rate limiting factors in ascites tumor cells, in *Mechanisms in Bioenergetics,* Racker, E., Ed., Academic Press, New York, 1965, 209.
45. **Ross, B. D., Freeman, D. M., and Chan, L.,** Phosphorus metabolites by NMR, in *Advances in Experimental Medicine and Biology: Phosphate and Mineral Metabolism, Proc. 6th Int. Workshop on Phosphate and Other Minerals,* Massry, S. G., Maschio, G., and Ritz, E., Eds., Plenum Press, New York, 1984, 455.
46. **Sestopt, L.,** Is the relationship between the plasma concentration of inorganic phosphate and the role of oxygen consumption of significance in regulating energy metabolism in mammals?, *Scand. J. Clin. Lab. Invest.,* 39, 191, 1979.
47. **Campillo, J. E., Luyckx, A. S., and Lefebvre, P. J.,** Effect of phosphate on the arginine-induced: insulin release by the isolated perfused rat pancreas, in *Advances in Experimental Medicine and Biology: Phosphate and Minerals in Health and Disease, Proc. 4th Int. Workshop on Phosphate and Other Minerals,* Massry, S. G., Ritz, E., and Jahn, H., Eds., Plenum Press, New York, 1980, 128, 229.
48. **Bevington, A., Kemp, G. J., and Russell, R. G. G.,** Factors controlling the intracellular concentration of orthophosphate (Pi) in mammalian cells in *Advances in Experimental Medicine and Biology: Phosphate and Mineral Homeostasis,* Massry, S. G., Olmer, M., and Ritz, E. P., Eds., Plenum Press, New York, 1985, 469.
49. **Bevington, A., Mundy, K. I., Yates, A. J. P., Kanis, J. A., Russell, R. G. G., Taylor, D. J., Rajagopalan, B., and Radda, G. K.,** A study of intracellular orthophosphate concentration in human muscle and erythrocytes by nuclear magnetic resonance spectroscopy and selective chemical assay, *Clin. Sci.,* 71, 729, 1986.
50. **Butterworth, P. J.,** Phosphate homeostasis, *Mol. Aspects Med.,* 9, 289, 1988.
51. **Olsen, R.,** The Nutrition Foundation Inc., Washington, DC, 1984.
52. **Nordin, B. E. C.,** Nutritional consideration, in *Calcium, Phosphate and Magnesium Metabolism: Clinical, Physiology and Diagnostic Procedures,* Nordin, B. E. C., Ed., Churchil Livingstone, Philadelphia, 1976, 1.
53. Subcommittee on the 10th Edition of Recommended Dietary Allowances, National Research Council National Academy Press, Washington, DC, 1989, 184.
54. **Draper, H. H., Sie, T. L., and Bergan, J. G.,** Osteoporosis in aging rats induced by high phosphorus diets, *J. Nutr.,* 102, 183, 1972.
55. **Krook, K., Lutwak, L., Henrikson, A., Kalifelz, F., Hirrsch, C., Romanus, B., Belanger, L. F., Morrier, J. R., and Shefty, B. E.,** Reversibility of nutritional osteoporosis: physicochemical data on bones from an experimental study in dogs, *J. Nutr.,* 101, 233, 1971.
56. **LaFlamme, G. H. and Jowsey, J.,** Bone and soft tissue changes with oral phosphate supplements, *J. Clin. Invest.,* 51, 2834, 1972.
57. **Argenzio, R. A., Lowe, J. E., Hintz, H. F., and Schryver, H. F.,** Calcium and phosphorus homeostasis in horses, *J. Nutr.,* 104, 18, 1974.
58. **Reiss, E., Canterbury, J. A., Bercovitz, M. A., and Kaplan, E. L.,** The role of phosphate in the secretion of parathyroid hormone in man, *J. Clin. Invest.,* 49, 2146, 1970.
59. **Rowe, J. C., Wood, D. H., Rowe, D. W., and Raisz, L. G.,** Nutritional hypophosphaturic rickets in a premature fed breast milk, *N. Engl. J. Med.,* 300, 293, 1979.
60. **Von Sydow, G.,** A study of the developments of rickets in premature infants, *Acta Pediatr. Scand.,* 33(Suppl. 2), 3, 1946.
61. **Bloom, W. and Flinchum, L.,** Osteomalacia with pseudofractures caused by the indigestion of aluminum hydroxide, *JAMA,* 174, 827, 1960.
62. **Lotz, M., Zisman, E., and Barter, F. C.,** Evidence for a phosphorus-depletion syndrome in man, *N. Engl. J. Med.,* 278, 409, 1968.
63. **Sheldon, G. F. and Grzuyb, S.,** Phosphate depletion and repletion. Relation to parenteral nutrition and oxygen transport, *Ann. Surg.,* 182, 683, 1975.
64. **Coburn, J. W. and Massry, S. G.,** Changes in serum and urinary calcium during phosphate depletion: studies on mechanisms, *J. Clin. Invest.,* 49, 1073, 1970.

Chapter 2

RENAL HANDLING OF PHOSPHATE

Russell W. Chesney

TABLE OF CONTENTS

0-8493-6785-9/93/$0.00+$.50