Vitamin D

Second Edition
NUTRITION AND HEALTH
Adrianne Bendich, PhD, FACN, Series Editor
I dedicate this book to my best friend, colleague, and business partner for more than 37 years, my loving wife Sally who has always been supportive of my career and has been the absolute joy and love of my life.
Last year I participated in an International Bone and Mineral Society conference for trainees and junior faculty focusing on successful career planning. My message was simple; pick the right mentor. It’s a strategy I know well because any success I’ve enjoyed in my career reflects the wisdom and unselfishness of my mentor, Lou Avioli.

Lou was a self-described public school kid from New Jersey who earned a full scholarship to Princeton from which he graduated magna cum laude. He received his M.D. from Yale and became interested in calcium metabolism during his fellowship at University of North Carolina. In 1966, Lou came to Washington University School of Medicine as assistant professor of medicine and director of endocrinology at the Jewish Hospital of St. Louis. Lou organized the nation’s first Division of Bone and Mineral Diseases
and within just 6 years was appointed the Sidney and Stella Schoenberg Professor of Medicine.

At the time of Lou’s arrival in St. Louis osteoporosis research was pretty much in its infancy. Because techniques of generating authentic bone cells in culture were not in hand, most studies were largely phenomenological. Lou, however, saw the potential of the field and his leadership skills and dynamism enabled him to become its father. His interests were broad but he had a particular passion for vitamin D metabolism and how it relates to the skeleton. When I first met Lou in the early 1970s John Haddad was one of his fellows and together they developed the first assay for serum 25-hydroxyvitamin D. Lou’s had the capacity to consistently visualize his research in the context of patient care and publicize the significance of skeletal disease. He was prolific, publishing in excess of 300 papers and with Steve Krane, “Metabolic Bone Diseases and Related Disorders”. Before Lou Avioli, osteoporosis was a boring entity which did not lend itself to meaningful investigation.

Lou saw the big picture. He realized that progress in skeletal research demanded a first-class research society and so in the mid-1970s he convened a committee of leaders in the field to organize the American Society for Bone and Mineral Research. The ASBMR, which is now a behemoth, began with fewer than 100 members and Lou as its first president. Only one who witnessed the beginning of the society and where it stands today can appreciate the magnitude of Lou’s accomplishment. Principally however, Lou was a mentor who encouraged independence. He pushed each of us to develop our own programs and yet maintain a family and sharing environment within our group. He was devoted to the concept that the welfare of the trainee always supersedes that of the mentor.

We lost Lou in 1999 after a long struggle with prostate cancer. His passing left a void in the lives of many, particularly those with whom he interacted daily. The fun has never been the same.

Steven L. Teitelbaum
Washington University School of Medicine
The Nutrition and Health series of books have, as an overriding mission, to provide health professionals with texts that are considered essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research and (9) balanced, data-driven answers to patient/health professionals questions that are based upon the totality of evidence rather than the findings of any single study.

The goal of the series is to develop volumes that are adopted as the standard text in each area of nutritional sciences that the volume reviews. Evidence of the success of the series is the publication of second, third, and even fourth editions of more than half of the volumes published since the Nutrition and Health Series was initiated in 1997. The series volumes that are considered for second and subsequent editions have clearly demonstrated their value to health professionals. Second editions provide readers with updated information as well as new chapters that contain relevant up-to-date information. Each editor of new and updated volumes has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Vitamin D: Physiology, Molecular Biology and Clinic Aspects, Second Edition," edited by Michael F. Holick, Ph.D., M.D. fully exemplifies the Nutrition and Health Series’ goals for a second edition. This volume is very timely as there have been more scientific papers published about vitamin D than any other essential nutrient over the past several years and the field of vitamin D research has expanded greatly in the decade since the first edition of this volume was published. In fact, Dr. Holick is the recognized leader in the field of vitamin D research and his innovative studies had led literally hundreds of researchers around the globe to join him in the exploration of the role of vitamin D in subcellular interactions, cellular functions, tissue and organ physiology, as well as clinical applications of naturally occurring forms of vitamin D and synthetic variants that have been developed to improve human health. Thus it is not surprising
that the first volume contained 25 important chapters, and the current volume contains more than twice that number of chapters, 59 to be exact, that are either updates of the chapters included in the first edition or brand new chapters that are the result of the recent upsurge in basic as well as clinical research in vitamin D.

This important volume presents a timely review of the latest science concerning vitamin D’s role in optimizing health as well as preventing many chronic diseases. The volume also examines the potential for vitamin D and its synthetic derivatives to act as valuable therapeutic agents in the treatment of serious diseases such as cancer and kidney disease. The overarching goal of the editor is to provide fully referenced information to health professionals so that they may enhance the nutritional welfare and overall health of clients and patients who may not be fully aware of the new findings of vitamin D’s effects in diverse health areas from a to z: in this instance, from asthma to zygote functions. This excellent, up-to-date, and comprehensive volume will add great value to the practicing health professional as well as those professionals and students who have an interest in the latest information on the science behind vitamin D as a component of an individual’s nutritional status and the consequences of low vitamin D levels on organ functions throughout the body. Chapters address the importance of the different requirements of vitamin D throughout the life span as well as the unique needs during pregnancy, lactation, and menopause for women. This timely volume reviews the ability of vitamin D to modulate the effects of the most prevalent chronic diseases and conditions that are widely seen in the majority of patient populations.

Dr. Holick is the internationally recognized leader in the field of vitamin D research with particular expertise in clinical dermatology. Michael F. Holick, Ph.D., M.D., is Professor of medicine, physiology and biophysics; Director of the General Clinical Research Unit and Director of the Bone Health Care Clinic and the Heliotherapy, Light, and Skin Research Center at Boston University Medical Center. Dr. Holick is an excellent communicator to both lay audiences as well as health professionals. He has worked tirelessly to develop the second edition of his *Vitamin D* volume; the first edition was the benchmark in the field when published in 1999. This volume continues to include extensive, in-depth chapters covering the most important aspects of the complex interactions between vitamin D and other dietary components, the ongoing debate concerning the best indicator of optimal vitamin D status and its nutrient requirements, and the impact of less than optimal status on disease risk.

The introductory 11 chapters provide readers with the basics of vitamin D biology including an introduction to the topic of photobiology, the molecular biology of each of the biological forms from pre-vitamin D through the most active form of the vitamin, as well as the molecular biology of the vitamin D receptor and related nuclear receptors. There is a comprehensive chapter on the metabolism of vitamin D, its metabolites, and clinically relevant analogs. There are individual chapters that describe the biological effects of vitamin D on bone, the kidneys, on intestinal absorption of calcium and related minerals as well as vitamin D’s direct effects on the parathyroid glands. The final chapter in this section reviews the diversity of vitamin D target genes and the effects of activation.

The second section contains six chapters that examine the growing area of investigation into the non-skeletal functions of vitamin D. The field of vitamin D research was
greatly enriched with the relatively recent discovery of the extra-renal sites of synthesis of the active form of vitamin D, 1,25-dihydroxyvitamin D. This historic event is chronicled in an excellent chapter written by Dr. Daniel Bilkie who was one of the first investigators to elucidate the extracellular synthesis of active vitamin D. Vitamin D’s role in the immune system and its role in the treatment of tuberculosis, the consequences of D’s effects on immune cells that affect colon cancer risk; direct effects on cancer cells; its functions in the brain and in adipocytes are each examined in detail in separate chapters.

The third section contains the most comprehensive review of the status of vitamin D across the globe that has ever been gathered in one volume. These 14 chapters examine vitamin D status and the effects of deficiency in the United States, Canada, Northern Europe, Mediterranean countries, the Middle East, Africa, India, Asia, and New Zealand. There is a detailed chapter concerning the assays for 25-hydroxyvitamin D and another critically important chapter on vitamin D toxicity. The fourth section describes the health consequences of vitamin D deficiency and resistance on musculoskeletal health and contains eight chapters. The first chapter examines the effects of vitamin D deficiency in pregnancy and lactation. The next two chapters concentrate of the importance of vitamin D in child health and the impact of vitamin D deficiency that results in rickets. A related chapter describes the effects of inherited vitamin D-resistant rickets. Genetic defects in the metabolism of vitamin D as well as receptors are covered in three related chapters. There is also a key chapter on vitamin D’s role in fall and fracture prevention especially in the elderly.

The fifth section looks at the interactions between sunlight, vitamin D, and cancer risks in seven chapters. There are several important chapters, written by the leaders in this field of research, including the Garland brothers that examine the epidemiology that links sunlight exposure and reduced as well as increased risk of specific cancers. We are reminded that aging is associated with both a decreased capacity for skin to synthesize vitamin D and at the same time, an increased risk of most cancers. The data from a recent well-controlled intervention trial that examined the effects of calcium and vitamin D supplementation on fracture risk also collected data of cancer occurrence and found a significantly lower risk of cancer in the supplemented cohort. The authors of the original study, Dr. J. Lappe and Dr. R. Heaney, have contributed this important chapter.

The sixth and seventh sections examine the clinical importance of vitamin D, its naturally occurring active forms, as well as synthetic forms of vitamin D that have been investigated as therapeutics. This section includes a review of the new data linking low vitamin D status during pregnancy and increased risk of type 1 diabetes in the offspring. Survey data have also found associations between vitamin D and certain immune-related chronic diseases including multiple sclerosis and rheumatoid arthritis. Individual, in-depth chapters on type II diabetes, cardiovascular health, blood pressure, and lung disease are included. The molecular development of novel forms and the importance of vitamin D analogues for treatment in chronic kidney disease, for example, are examined in detail. Final chapters look at the importance of vitamin D analogues in the treatment of psoriasis, therapeutic and chemoprevention of prostate cancer, and the use of vitamin D analogues in the treatment of serious autoimmune diseases. From my short descriptions of each section of this volume, it is obvious that Dr. Holick has succeeded
in including the most significant areas of vitamin D research over the past decade in one single volume.

Vitamin D’s role in health and disease resistance is complex, yet the editor and authors have provided chapters that balance the most technical information with practical discussions of their importance for clients and patients as well as graduate and medical students, health professionals, and academicians. Hallmarks of each of the chapters include abstracts at the beginning of each chapter as well as key words. Each chapter has complete definitions of terms with the abbreviation fully defined and there is consistent use of terms between chapters. There are over 260 relevant tables, graphs, and figures as well as more than 5,600 up-to-date references; all of the 59 chapters include a conclusion section that provides the highlights of major findings. The volume contains a highly annotated index and within chapters, readers are referred to relevant information in other chapters.

Dr. Holick has chosen 97 of the most well recognized and respected authors who are internationally distinguished researchers, clinicians, and epidemiologists. The authors provide a broad foundation for understanding the role of nutritional status, dietary intakes, route of vitamin D synthesis, life stages of patients and also disease state and the multiple effects of genetics and molecular biology on the clinical aspects of therapeutic management of chronic conditions that can be affected by vitamin D. The inventory of valuable information on the current vitamin D status of populations around the globe attests to the critical importance of adequate vitamin D especially during pregnancy, lactation, and early childhood. The volume adds further value as recommendations and practice guidelines are included at the end of relevant chapters.

In conclusion, “Vitamin D: Physiology, Molecular Biology and Clinic Aspects, Second Edition,” edited by Michael F. Holick, Ph.D., M.D. provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of vitamin D and its significance in maintaining human health. This volume will again serve the reader as the benchmark in this complex area of interrelationships between vitamin D nutritional status, molecular functions, physiological functioning of organ systems, disease status, age, sex, genetic characteristics, route of administration, duration, vitamin D analogues, and the expanding knowledge of the sites and roles of the extra-renal synthesis of active vitamin D. Moreover, the interactions between genetic and environmental factors and the numerous co-morbidities seen especially in the aging population are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions with regard to vitamin D. Dr. Holick is applauded for his efforts to develop the most authoritative resource in the field to date and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., FACN
Preface

In the past 8 years since this book appeared, it is now being recognized globally that vitamin D deficiency is one of the most if not the most prevalent nutritionally related medical condition in the world. The major reason for this is the lack of appreciation that there is very little vitamin D present either naturally or in fortified foods from dietary sources and that it is exposure to sunlight that has been and continues to be the major source of vitamin D for both children and adults worldwide. Vitamin D deficiency will not only prevent children from attaining their genetically programmed maximum height but will also put them at increased risk for having a lower peak bone density as well as increased risk of fracture later in life. In utero, vitamin D deficiency not only increases the risk of the mother having preeclampsia and a caesarian section for birthing but increases the infant’s risk of wheezing disorders. Vitamin D deficiency during childhood is thought to increase risk of the child developing type I diabetes, multiple sclerosis, rheumatoid arthritis, and Crohn’s disease later in life. Vitamin D deficiency in adults not only will cause osteopenia and osteoporosis but increase risk of many deadly chronic diseases including common cancers, autoimmune diseases, heart disease, stroke, and infectious diseases.

As noted in the first edition of this book, vitamin D is a truly remarkable as it is both an essential nutrient and hormone that has a wide variety of biologic effects on the human body that are important for health. The reason that vitamin D plays such a crucial role in maintaining health is in part due to the fact that vitamin D receptors are present in every tissue and cell in the body. It is also known that once vitamin D is made in the skin or obtained from the diet, it undergoes sequential activation steps in the liver to 25-hydroxyvitamin D and kidney to 1,25-dihydroxyvitamin D before it can act on its vitamin D receptor in target tissues. 1,25-Dihydroxyvitamin D not only regulates calcium metabolism, but interacts with its receptor in various cells to regulate cell growth, insulin production, renin production, modulates immune function, and enhances the destruction of the infectious agents and is important for vascular tone and myocardial function.

The goal of the second edition of this book is to provide the reader with a global appreciation of how common vitamin D deficiency is in the world. It explores how vitamin D is able to maintain not only skeletal health but prevent serious chronic diseases. The book also provides a roadmap for how to evaluate patients with vitamin D deficiency and how to appropriately treat them.

As a result of a mountain of new information about the health benefits of vitamin D, the book has been expanded substantially to include many new topics including several chapters identifying vitamin D deficiency epidemics in Asia, Africa, Europe, and the United States. New chapters on the role of vitamin D in preventing type I diabetes, wheezing disorders in young children, cardiovascular disease, type II diabetes,
infectious diseases, and cancers have been added to this book. As a result, the number of chapters in this book has more than doubled from the original 25 to 59 chapters.

The inspiration for the second edition of the *Vitamin D: Physiology, Molecular Biology and Clinic Aspects* came not only from discussions with medical students, house staff, health-care professionals, internists, dermatologists, basic scientists but also from my interaction with the lay press and from my global travels in response to invitations to provide the latest information concerning the growing vitamin D deficiency epidemic. The second edition brings together leading world experts in various aspects of vitamin D; the same experts who are not only doing cutting edge research in the field of vitamin D, but many are clinicians–scientists who see patients with vitamin D deficiency and all of the serious ramifications. The book is designed and organized not only to be an up-to-date review on the subject, but also to provide medical students, graduate students, health-care professionals, and even the lay public with a reference source for the most up-to-date information about the vitamin D deficiency pandemic and its clinical implications for health and disease. It is hoped that this book will not only stimulate new interest regarding the vitamin D deficiency pandemic, but ignite a grassroots effort to eliminate this insidious deficiency by encouraging worldwide food fortification programs with vitamin D and to educate the public and health-care professionals about the beneficial effect of sensible sun exposure as a major means for satisfying the body’s vitamin D requirement.

**ACKNOWLEDGMENTS**

I am grateful to all of the hard work and efforts that were made by all of the contributing authors. My thanks to Lorrie Butler and the staff at Humana/Springer for all their help in organizing the book. A special thanks to Dr. Adrianne Bendich, Ph.D, for her helpful comments, guidance, and insightfulness in being series editor of the outstanding Nutrition and Health series.
Contents

Dedication .................................................. v
In Memoriam ............................................. vii
Series Editor Introduction ................................. ix
Preface ..................................................... xiii
Contributors ............................................... xxi

PART I:  INTRODUCTION AND BASIC BIOLOGY
1  Vitamin D and Health: Evolution, Biologic Functions,
   and Recommended Dietary Intakes for Vitamin D .......... 3
   Michael F. Holick
2  Photobiology of Vitamin D .............................. 35
   Tai C. Chen, Zhiren Lu, and Michael F. Holick
3  The Functional Metabolism and Molecular Biology of Vitamin D
   Action .................................................. 61
   Lori A. Plum and Hector F. DeLuca
4  Metabolism and Catabolism of Vitamin D, Its Metabolites and Clinically
   Relevant Analogs ........................................ 99
   Glenville Jones
5  The Molecular Biology of the Vitamin D Receptor ........... 135
   Diane R. Dowd and Paul N. MacDonald
6  VDR and RXR Subcellular Trafficking .................... 153
   Julia Barsony
7  Mechanism of Action of 1,25-Dihydroxyvitamin D₃ on Intestinal
   Calcium Absorption and Renal Calcium Transport .......... 175
   Dare Ajibade, Bryan S. Benn, and Sylvia Christakos
8  Biological and Molecular Effects of Vitamin D on Bone ..... 189
   Martin A. Montecino, Jane B. Lian, Janet L. Stein, Gary S. Stein,
   André J. van Wijnen, and Fernando Cruzat
9  Biological and Molecular Effects of Vitamin D on the Kidney .... 211
   Adriana S. Dusso and Masanori Tokumoto
10  Vitamin D and the Parathyroids ........................................ 235
Justin Silver and Tally Naveh-Mani

11  Diversity of Vitamin D Target Genes .......................... 255
Carsten Carlberg

PART II:  NON-SKELETAL/FUNCTIONS OF VITAMIN D
12  Extrarenal Synthesis of 1,25-Dihydroxyvitamin D and Its Health Implications ........ 277
Daniel D. Bikle

13  Vitamin D and the Innate Immunity .......................... 297
Philip T. Liu, Martin Hewison, and John S. Adams

14  Vitamin D and Colon Cancer ................................ 311
Heide S. Cross and Meinrad Peterlik

15  Mechanisms of Resistance to Vitamin D Action in Human Cancer Cells ............ 325
Maria Jesus Larriba and Alberto Munoz

16  Vitamin D and the Brain: A Neuropsychiatric Perspective .................. 335
Louise Harvey, Thomas Burne, Xiaoying Cui, Alan Mackay-Sim,
Darryl Eyles, and John McGrath

17  Vitamin D Modulation of Adipocyte Function ........................ 345
Michael B. Zemel and Xiaocun Sun

PART III: VITAMIN D STATUS – GLOBAL ANALYSIS
18  Determinants of Vitamin D Intake ................................ 361
Mona S. Calvo and Susan J. Whiting

19  25-Hydroxyvitamin D Assays and Their Clinical Utility .................... 383
N. Binkley and G. Lensmeyer

20  Health Disparities and Vitamin D ................................ 401
Douglass Bibuld

21  Vitamin D Deficiency in Canada ................................ 425
David A. Hanley

22  Vitamin D Deficiency and Its Health Consequences in Northern Europe .......... 435
Leif Mosekilde

23  Vitamin D Deficiency and Consequences for the Health of People
in Mediterranean Countries ............................................ 453
Jose Manuel Quesada-Gomez and Manuel Diaz-Curiel

24  Vitamin D Deficiency in the Middle East and Its Health Consequences ........ 469
Ghada El-Hajj Fuleihan

25  Vitamin D Deficiency in the Middle East and Its Health Consequences
for Adults ................................................................. 495
Samer El-Kaissi and Suphia Sherbeeni
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 Vitamin D Deficiency and Its Health Consequences in Africa</td>
<td>505</td>
</tr>
<tr>
<td><em>Ann Prentice, Inez Schoenmakers, Kerry S. Jones, Landing M.A. Jarjou, and Gail R. Goldberg</em></td>
<td></td>
</tr>
<tr>
<td>27 Vitamin D Deficiency and Its Health Consequences in India</td>
<td>529</td>
</tr>
<tr>
<td><em>R.K. Marwaha and R. Goswami</em></td>
<td></td>
</tr>
<tr>
<td>28 Vitamin D Deficiency, Rickets, and Fluorosis in India</td>
<td>543</td>
</tr>
<tr>
<td><em>C. V. Harinarayan and Shashank R. Joshi</em></td>
<td></td>
</tr>
<tr>
<td>29 Vitamin D in Asia</td>
<td>563</td>
</tr>
<tr>
<td><em>Tim Green and Bernard Venn</em></td>
<td></td>
</tr>
<tr>
<td>30 Vitamin D Deficiency and Its Health Consequences in New Zealand</td>
<td>589</td>
</tr>
<tr>
<td><em>Mark J. Bolland and Ian R. Reid</em></td>
<td></td>
</tr>
<tr>
<td>31 Toxicity of Vitamin D</td>
<td>603</td>
</tr>
<tr>
<td><em>Reinhold Vieth</em></td>
<td></td>
</tr>
<tr>
<td><strong>PART IV: HEALTH CONSEQUENCES OF VITAMIN D DEFICIENCY AND RESISTANCE ON MUSCULOSKELETAL HEALTH</strong></td>
<td></td>
</tr>
<tr>
<td>32 Vitamin D Deficiency in Pregnancy and Lactation and Health Consequences</td>
<td>615</td>
</tr>
<tr>
<td><em>Sarah N. Taylor, Carol L. Wagner, and Bruce W. Hollis</em></td>
<td></td>
</tr>
<tr>
<td>33 Vitamin D Deficiency in Children and Its Health Consequences</td>
<td>633</td>
</tr>
<tr>
<td><em>Amy D. DiVasta, Kristen K. van der Veen, and Catherine M. Gordon</em></td>
<td></td>
</tr>
<tr>
<td>34 Dietary Calcium Deficiency and Rickets</td>
<td>651</td>
</tr>
<tr>
<td><em>John M. Pettifor, Philip R. Fischer, and Tom D. Thacher</em></td>
<td></td>
</tr>
<tr>
<td>35 Vitamin D in Fracture Prevention and Muscle Function and Fall Prevention</td>
<td>669</td>
</tr>
<tr>
<td><em>Heike Bischoff-Ferrari</em></td>
<td></td>
</tr>
<tr>
<td>36 Inherited Defects of Vitamin D Metabolism</td>
<td>679</td>
</tr>
<tr>
<td><em>Marie B. Demay</em></td>
<td></td>
</tr>
<tr>
<td>37 Molecular Defects in the Vitamin D Receptor Associated with Hereditary 1,25-Dihydroxyvitamin D-Resistant Rickets (HVDRR)</td>
<td>691</td>
</tr>
<tr>
<td><em>Peter J. Malloy and David Feldman</em></td>
<td></td>
</tr>
<tr>
<td>38 Receptor-Independent Vitamin D Resistance in Subhuman and Human Primates</td>
<td>715</td>
</tr>
<tr>
<td><em>John S. Adams, Hong Chen, Thomas S. Lisse, Rene F. Chun, and Martin Hewison</em></td>
<td></td>
</tr>
<tr>
<td>39 25-Hydroxyvitamin D-1α-Hydroxylase: Studies in Mouse Models and Implications for Human Disease</td>
<td>729</td>
</tr>
<tr>
<td><em>David Golzman</em></td>
<td></td>
</tr>
</tbody>
</table>
PART V:  SUNLIGHT, VITAMIN D AND CANCER

40 The Health Benefits of Solar Irradiance and Vitamin D and the Consequences of Their Deprivation ....................................................... 745
William B. Grant

41 Vitamin D Status, Solar Radiation and Cancer Prognosis ....................................................... 765
Johan Moan, Øyvind Sverre Bruland, Arne Dahlback, Asta Juzeniene, and Alina Carmen Porojnicu

42 The Epidemiology of Vitamin D and Cancer Risk ....................................................... 777
Edward Giovannucci

43 Vitamin D Deficiency and the Epidemiology of Prostate Cancer ....................................................... 797
Gary G. Schwartz

44 Vitamin D for Cancer Prevention and Survival ....................................................... 813
Edward D. Gorham, Sharif B. Mohr, Frank C. Garland, and Cedric F. Garland

45 The Anti-cancer Effect of Vitamin D: What Do the Randomized Trials Show? ....................................................... 841
Joan M. Lappe and Robert P. Heaney

46 Sunlight, Skin Cancer, and Vitamin D ....................................................... 851
Jörg Reichrath

PART VI:  VITAMIN D DEFICIENCY AND CHRONIC DISEASE

47 Vitamin D and the Risk of Type 1 Diabetes ....................................................... 867
Elina Hyppönen

48 Vitamin D and Multiple Sclerosis ....................................................... 881
Alberto Ascherio and Kassandra L. Munger

49 Vitamin D and Type 2 Diabetes ....................................................... 895
Myrto Eliades and Anastassios G. Pittas

50 Role of Vitamin D for Cardiovascular Health ....................................................... 921
Robert Scragg

51 Vitamin D, Renin, and Blood Pressure ....................................................... 937
Yan Chun Li

52 Role of Vitamin D and Vitamin D Analogs for Bone Health and Survival in Chronic Kidney Disease ....................................................... 955
Ishir Bhan, Hector Támez, and Ravi Thadhani

53 Role of Vitamin D and Ultraviolet Radiation in Chronic Kidney Disease ....................................................... 967
Rolfdieter Krause

54 Role of Vitamin D in Rheumatoid Arthritis ....................................................... 985
Linda A. Merlino

55 Vitamin D, Respiratory Infections, and Obstructive Airway Diseases ....................................................... 997
Carlos A. Camargo Jr, Adit A. Ginde, and Jonathan M. Mansbach
### Contents

#### PART VII: CLINICAL USES OF VITAMIN D ANALOGUES

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td>Treatment of Immunomediated Diseases by Vitamin D Analogs</td>
<td>1025</td>
</tr>
<tr>
<td></td>
<td><strong>Luciano Adorini</strong></td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>Clinical Utility of 1,25-Dihydroxyvitamin D₃ and Its Analogues</td>
<td>1043</td>
</tr>
<tr>
<td></td>
<td>for the Treatment of Psoriasis</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Jörg Reichrath and Michael F. Holick</strong></td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>Affinity Alkylation Vitamin D Analogs as Molecular Probes</td>
<td>1061</td>
</tr>
<tr>
<td></td>
<td>and Therapeutic Agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Rahul Ray</strong></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>Anti-inflammatory Activity of Calcitriol That Contributes</td>
<td>1087</td>
</tr>
<tr>
<td></td>
<td>to Its Therapeutic and Chemopreventive Effects in Prostate Cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Aruna V. Krishnan and David Feldman</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subject Index</td>
<td>1105</td>
</tr>
</tbody>
</table>
Contributors

JOHN S. ADAMS, MD • Department of Orthopedic Surgery, University of California at Los Angeles, Los Angeles, CA, USA
LUCIANO ADORINI • Intercept Pharmaceuticals, Corciano (Perugia) 06073, Italy
DARE AJIBADE • Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ 07103, USA
ALBERTO ASCHERIO, MD DrPH • Departments of Nutrition and Epidemiology, Harvard School of Public Health; Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
JULIA BARSONY • Division of Endocrinology and Metabolism, Georgetown University, Washington, DC 20007, USA
BRYAN S. BENN • Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ 07103, USA
ISHIR BHAN, MD, MPH • Renal Unit, Massachusetts General Hospital, Boston, MA 02114, USA
DOUGLASS BIBULD, MD • Mattapan Community Health Center, Mattapan, MA 02126, USA
DANIEL D. BIKLE, MD, PhD • Veterans Affairs Medical Center and University of California, San Francisco, CA, USA
N. BINKLEY • Osteoporosis Clinical Center and Research Program, University of Wisconsin-Madison, Madison, WI 53705, USA
HEIKE BISCHOFF-FERRARI, MD, DrPH • Centre on Aging and Mobility, University of Zurich, Switzerland
MARK J. BOLLAND, MBCHB, PhD • Department of Medicine, University of Auckland, Auckland, New Zealand
ØYVIND SVERRE BRULAND • Department of Oncology, Rikshospitalet-Radiumhospitalet Medical Center, Montebello, 0310 Oslo, Norway
THOMAS BURNE • Queensland Brain Institute, University of Queensland, St Lucia, QLD 4072; Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD 4076, Australia
MONA S. CALVO, PhD • Office of Applied Research and Safety Assessment, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, Laurel, MD, USA
CARLOS A. CAMARGO JR, MD, DrPH • Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA
CARSTEN CARLBERG • Life Sciences Research Unit, University of Luxembourg, L-1511 Luxembourg, Luxembourg; Department of Biochemistry, University of Kuopio, FIN-70211 Kuopio, Finland

TAI C. CHEN • Vitamin D, Skin and Bone Research Laboratory, Section of Endocrinology, Nutrition, and Diabetes, Department of Medicine, Boston University School of Medicine, Boston, MA, USA

HONG CHEN, MD • Department of Orthopedic Surgery and Department of Molecular, Cell and Developmental Biology, Orthopedic Hospital Research Center, UCLA/Orthopedic Hospital UCLA, Los Angeles, CA 90095-7358, USA

SYLVIA CHRISTAKOS • Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ 07103, USA

SUZANNE H. CHUN, PhD • Department of Orthopedic Surgery and Department of Molecular, Cell and Developmental Biology, Orthopedic Hospital Research Center, UCLA/Orthopedic Hospital UCLA, Los Angeles, CA 90095-7358, USA

HEIDE S. CROSS • Department of Pathophysiology, Medical University of Vienna, Austria

FERNANDO CRUZAT • Departamento de Bioquímica y Biología Molecular, Facultad de Ciencias Biológicas, Universidad de Concepción, Concepción, Chile

XIAOYING CUI • Queensland Brain Institute, University of Queensland, St Lucia, QLD 4072; Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD 4076, Australia

ARNE DAHLBACK • Department of Physics, University of Oslo, 0316 Oslo, Norway

HECTOR F. DELUCA • Department of Biochemistry, University of Wisconsin-Madison, Madison, WI 53706, USA

MARIE B. DEMAY • Endocrine Unit, Massachusetts General Hospital, Boston, MA 02114, USA

MANUEL DÍAZ-CURIEL • Department of Internal Medicine/Bone Metabolism Disorders, Fundación Jiménez Díaz, Universidad Autónoma, RETICEF, Madrid, Spain

AMY D. DIVASTA, MD, MMSC • Divisions of Adolescent Medicine and Endocrinology, Children’s Hospital Boston, Boston, MA 02115, USA

DIANE R. DOWD • Department of Pharmacology, Case Western Reserve University, Cleveland, OH 44106, USA

ADRIANA S. DUSSO PHD • Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO 63110. USA

GHADA EL-HAJJ FULEIHAN, MD, MPH • Calcium Metabolism and Osteoporosis Program, American University of Beirut, Beirut, Lebanon

MYRTO ELIADES, MD • Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, MA 02111, USA

SAMER EL-KAISSI, MD, PhD • Specialized Diabetes & Endocrine Center, King Fahad Medical City, Riyadh 11525, Saudi Arabia

DARRYL EYLES • Queensland Brain Institute, University of Queensland, St Lucia, QLD 4072; Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD 4076, Australia
Contributors

DAVID FELDMAN • Division of Endocrinology, Gerontology and Metabolism, Stanford University School of Medicine, Stanford University Medical Center, Stanford, CA 94305-5103, USA

PHILIP R. FISCHER • Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

FRANK C. GARLAND • Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA 92093-0631, USA; Naval Health Research Center, 140 Sylvestor Rd, San Diego, CA 92106-3521, USA

CEDRIC F. GARLAND • Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA 92093-0631, USA; Naval Health Research Center, 140 Sylvestor Rd, San Diego, CA 92106-3521, USA

ADIT A. GINDE, MD, MPH • Department of Emergency Medicine, University of Colorado Denver School of Medicine Aurora, CO

EDWARD GIOVANNUCCI, MD, SCD • Departments of Nutrition, Epidemiology, Harvard School of Public Health; Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115, USA

GAIL R. GOLDBERG • MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge UK; MRC Keneba, The Gambia

DAVID GOLTZMAN, MD • Department of Medicine, McGill University and McGill University Health Centre, Montreal, QC, Canada, H3A 1A1

CATHERINE M. GORDON, MD, MSC • Divisions of Adolescent Medicine and Endocrinology, Children’s Hospital Boston, Boston, MA 02115, USA

EDWARD D. GORHAM • Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA 92093-0631, USA; Naval Health Research Center, 140 Sylvestor Rd, San Diego, CA 92106-3521, USA

RAVINDER GOSWAMI • Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

WILLIAM B. GRANT, PHD • Sunlight, Nutrition, and Health Research Center (SUNARC), San Francisco, CA 94164-1603, USA

TIM GREEN • Food, Nutrition and Health, The University of British Columbia, Vancouver, BC, Canada

DAVID A. HANLEY, MD, FRCPC • Departments of Medicine, Community Health Sciences and Oncology, Faculty of Medicine, University of Calgary, Calgary, Alberta T2N 4N1, Canada

C.V. HARINARAYAN • Department of Endocrinology and Metabolism, Sri Venkateswara Institute of Medical Sciences, Tirupati – 517 507, Andhra Pradesh, India

LOUISE HARVEY • Queensland Brain Institute, University of Queensland, QLD 4072, Australia

ROBERT P. HEANEY, MD • Creighton University, Omaha, NE 68131, USA

MARTIN HEWISON, PhD • Department of Orthopedic Surgery, University of California at Los Angeles, Los Angeles, CA, USA

MICHAEL F. HOLICK, PhD, MD • Vitamin D, Skin and Bone Research Laboratory, Section of Endocrinology, Nutrition, and Diabetes, Department of Medicine, Boston University School of Medicine, Boston, MA, USA
BRUCE W. HOLLIS, PhD ● Darby Children’s Research Institute, Medical University of South Carolina, Charleston, SC 29414, USA
ELINA HYPPERÖNEN, PhD, MSC, MPH ● MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, London WC1N 1EH, UK
LANDING M. A. JARJOU ● MRC Keneba, The Gambia
GLENVILLE JONES ● Department of Biochemistry, Queen’s University, Kingston, Ontario, Canada K7L 3N6
KERRY S. JONES ● MRC Keneba, The Gambia
SHASHANK R. JOSHI ● Lilavati Hospital, Bhatia Hospital and Joshi Clinic; Department of Endocrinology, Seth GS Medical College and KEM Hospital, Mumbai, India
ASTA JUZENIENE ● Department of Radiation Biology, Rikshospitalet-Radiumhospitalet Medical Center, Montebello, 0310 Oslo, Norway
ROLFDIETER KRAUSE, MD ● Chair of Clinical Complementary Medicine1; Nephrological Center Moabit2, Charité – University Medical Center1; KfH Kuratorium for Dialysis and Kidney Transplantation2, Berlin, Germany
ARUNA V. KRISHNAN ● Divisions of Endocrinology, Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305, USA
JOAN M. LAPPLE, PhD, RN, FAAN ● Creighton University, Omaha NE 68131, USA
MARÍA JESÚS LARRIBA ● Instituto de Investigaciones Biomédicas “Alberto Sols”, Consejo Superior de Investigaciones Científicas-Universidad Autónoma de Madrid, Madrid E-28029, Spain.
G. LENSMEYER ● Department of Laboratory Medicine, University of Wisconsin-Madison, Madison, WI 53705, USA
YAN CHUN LI, PhD ● Department of Medicine, The University of Chicago, Chicago, IL 60637, USA
JANE B. LIAN ● Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA 01655, USA
THOMAS S. LISSE, PhD ● Department of Orthopedic Surgery and Department of Molecular, Cell and Developmental Biology, Orthopedic Hospital Research Center, UCLA/Orthopedic Hospital UCLA, Los Angeles, CA 90095-7358, USA
PHILIP LIU, PhD ● Division of Dermatology, Department of Medicine, University of California at Los Angeles, Los Angeles, CA, USA
ZHIREN LU ● Vitamin D, Skin and Bone Research Laboratory, Section of Endocrinology, Nutrition, and Diabetes, Department of Medicine, Boston University School of Medicine, Boston, MA, USA
PAUL N. MACDONALD ● Department of Pharmacology, Case Western Reserve University, Cleveland, OH 44106
ALAN MACKAY-SIM ● Eskitis Institute for Cell and Molecular Therapies, Griffith University, Brisbane, QLD 4111 Australia
PETER J. MALLOY ● Division of Endocrinology, Gerontology and Metabolism, Stanford University School of Medicine, Stanford University Medical Center, Stanford, CA 94305-5103, USA
JONATHAN M. MANSBACH, MD ● Department of Medicine, Children’s Hospital Boston, Harvard Medical School, Boston, MA, USA
RAMAN KUMAR MARWAHA • Department of Endocrinology and Thyroid Research, Institute of Nuclear Medicine & Allied Sciences, Timarpur, Delhi 110054, India
JOHN McGRATH • Queensland Brain Institute, University of Queensland, St Lucia, QLD 4072; Queensland Centre for Mental Health Research, The Park Centre for Mental Health, Wacol, QLD 4076; Department of Psychiatry, University of Queensland, St Lucia, QLD 4072, Australia
LINDA A. MERRINO, MS • The University of Iowa, Iowa City, IA, USA
JOHAN MOAN • Department of Radiation Biology, Rikshospitalet-Radiumhospitalet Medical Center, Montebello, 0310 Oslo; Department of Physics, University of Oslo, Oslo 0316, Norway
SHARIF B. MOHR • Department of Family and Preventive Medicine, University of California San Diego, La Jolla, CA 92093-0631, USA; Naval Health Research Center, 140 Sylvester Rd, San Diego, CA 92106-3521, USA
MARTIN A. MONTECINO • Departamento de Bioquimica y Biologia Molecular, Facultad de Ciencias Biologicas, Universidad de Concepcion, Concepcion, Chile
LEIF MOSEKILDE, MD, DMSc • Department of Endocrinology and Metabolism C, Aarhus University Hospital, DK 8000 Rhus C, Denmark
KASSANDRA L. MUNGER, M.SC. • Department of Nutrition, Harvard School of Public Health, Boston, MA, USA
ALBERTO MUÑOZ • Instituto de Investigaciones Biomédicas “Alberto Sols”, Consejo Superior de Investigaciones Científicas-Universidad Autónoma de Madrid, Madrid E-28029, Spain
TALLY NAVEH-MANY • Hebrew University Hadassah Medical Center, Jerusalem 91120, Israel
MEINRAD PETERLIK • Department of Pathophysiology, Medical University of Vienna, Austria
JOHN M. PETFIFOR • MRC Mineral Metabolism Research Unit, Department of Paediatrics, Chris Hani Baragwanath Hospital and the University of the Witwatersrand, Johannesburg, South Africa
ANASTASSIOS G. PITTAS, MD, MS • Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, MA 02111, USA
LORE A. PLUM • Department of Biochemistry, University of Wisconsin-Madison, Madison, WI 53706, USA
ALINA CARMEN POROJNICU • Department of Radiation Biology, Rikshospitalet-Radiumhospitalet Medical Center, Montebello, 0310 Oslo, Norway
ANN PRENTICE • MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge UK; MRC Keneba, The Gambia
JOSE MANUEL QUESADA-GOMEZ • Unidad de Metabolismo Mineral, Servicio de Endocrinología y Nutrición, Centro CEDOS, Unidad de I+D+i Sanyres, Hospital Universitario Reina Sofia, RETICEF, Córdoba, Spain
RAHUL RAY, PHD • Boston University School of Medicine, Boston, MA 02118, USA
JORG REICHRATH • Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum des Saarlandes, Homburg, Saar 66421, Germany
IAN R. REID, MD • Department of Medicine, University of Auckland, Auckland, New Zealand
INEZ SCHOENMAKERS ● MRC Human Nutrition Research, Elsie Widdowson Laboratory, Cambridge UK
GARY G. SCHWARTZ ● Departments of Cancer Biology and Epidemiology and Prevention, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC 27157, USA
ROBERT SCRAGG, MBBS, PhD ● School of Population Health, University of Auckland Private Bag, Auckland, New Zealand
SUPHIA SHERBEEENI, MD, FRCP ● Specialized Diabetes & Endocrine Center, King Fahad Medical City, Riyadh 11525, Saudi Arabia
JUSTIN SILVER ● Hebrew University Hadassah Medical Center, Jerusalem 91120, Israel
JANET L. STEIN ● Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA 01655, USA
GARY S. STEIN ● Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA 01655, USA
XIAOCUN SUN ● Departments of Nutrition and Medicine, The University of Tennessee, Knoxville, TN 37996-1920, USA
HECTOR TAMEZ, MD, MPH ● Renal Unit, Massachusetts General Hospital, Boston, MA 02114, USA
SARAH N. TAYLOR, MD ● Darby Children’s Research Institute, Medical University of South Carolina, Charleston, SC 29414, USA
STEVEN L. TEITELBAUM ● Washington University School of Medicine, Saint Louis, MO, USA
TOM D. THACHER ● Department of Family Medicine, Mayo Clinic, Rochester, MN, USA
RAVI THADHANI, MD, MPH ● Renal Unit, Massachusetts General Hospital, Boston, MA 02114, USA
MASANORI TOKUMOTO, MD, PhD ● Renal Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO 63110. USA
KRISTEN K. VAN DER VEEEN, BA ● Divisions of Adolescent Medicine and Endocrinology, Children’s Hospital Boston, Boston, MA 02115, USA
ANDRÉ J. VAN WIJNEN ● Department of Cell Biology, University of Massachusetts Medical School, Worcester, MA 01655, USA
BERNARD VENN ● Department of Human Nutrition, University of Otago, Dunedin, New Zealand
REINHOLD VIETH ● Pathology and Laboratory Medicine, Department of Laboratory Medicine and Pathobiology, Mount Sinai Hospital, University of Toronto, Toronto, ON M5G 1X5, Canada
CAROL L. WAGNER, MD ● Darby Children’s Research Institute, Medical University of South Carolina, Charleston, SC 29414, USA
SUSAN J. WHITING, PhD ● College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
MICHAEL B. ZEMEL ● Departments of Nutrition and Medicine, The University of Tennessee, Knoxville, TN 37996-1920, USA