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Preface to the 3rd Edition

The 3rd edition of *Vitamin D* was written at a time of great interest, exuberant hype, and even commotion in the public and lay press about vitamin D as a potential drug to treat and/or prevent multiple important and common diseases. Recent noteworthy events impacting the vitamin D field were the launching of the VITAL trial to discover whether vitamin D supplementation can reduce the risk of severe and life-threatening disease and the Institute of Medicine (IOM) report setting new dietary reference intakes (DRIs) for calcium and vitamin D. The IOM report expressed doubt on how well current data supported the beneficial actions of vitamin D on nonskeletal sites and called for more research to prove the hypothesis. This volume marshals the currently available data on basic mechanisms, normal physiology, and effects on disease and lays out for the reader up-to-date and expert information on the role of vitamin D in health and many disorders. These and other current trends in vitamin D research are extensively covered in this new edition.

The editors have continued our basic plan to constantly renew and remodel this book with each successive edition. To this end, we have added a new editor, Dr. John Adams, who has broad skill and knowledge in many areas of vitamin D research at both the basic science and clinical levels. John replaces Francis Glorieux who has undertaken to edit a separate book on pediatric bone disease. We thank Francis for his years of exemplary service to this book and wish him well in his new endeavors. John adds new energy and expertise to the editorial team.

The 3rd edition has 105 chapters, making the book approximately the same size as the 2nd edition. However, the editors have worked very hard to revise and update this edition with new material and the presentation of fresh and different perspectives from respected authors. Some chapters covered in the 2nd edition have not been continued in this edition because relatively little new research was added in those areas. We thank the authors who are no longer contributing to this edition for their previous efforts. They may well be asked to write in the next edition as we continue our strategy of rotating authors. All chapters have been revised and updated and new references added. In our revitalization of the material in the book we have added 32 new chapters to cover previously uncovered areas of research. In addition, we have changed the authorship of 20 additional chapters that are now written by different authors who have been charged with revising and updating previous chapters. These extensive modifications, with major updates and expansion of the content and the addition of totally new material in half of the chapters, has resulted in a substantially reorganized, modified, and modernized book compared to the 2nd edition.

Finally, the expanded internet availability of the text and the figures will make access to the material easier and more flexible.

Among the areas given new emphasis are nutrition, additional diseases that may be affected by vitamin D, and newly recognized biological pathways that regulate or are regulated by vitamin D. As we appreciate the full scope of vitamin D action, it has become clearer that the vitamin D endocrine system affects most if not all tissues in the body. We have tried to keep up with these advances in the state of knowledge about vitamin D by increasing our coverage of these newly
recognized areas. We have enlisted the leading investigators in each area to provide truly expert opinion about each field.

We would like to thank the excellent team at Elsevier/Academic Press for their outstanding support of our efforts to produce this new edition. We especially thank Mara Conner and Megan Wickline for their indispensable contributions to make this edition possible. We also want to extend our thanks and appreciation to the many authors who contributed to this volume. Without their hard work there of course would be no new edition. We therefore wish to express our gratitude for their willingness to offer their time and knowledge to make this book a success. Finally, we hope that this book will provide for our readers the authoritative information that they seek about the significance and importance of vitamin D in health and disease and serve as the means to keep their knowledge current about the continuing growth of the field of vitamin D biology.

David Feldman
J. Wesley Pike
John S. Adams
**Introduction**

On November 30, 2010, after nearly two years of deliberation, an Institute of Medicine (IOM)-appointed committee released their findings, “2011 Report on dietary reference intakes (DRIs) for calcium and vitamin D.” Among their many recommendations the important conclusions regarding vitamin D were: (1) most of the population was not currently vitamin-D-deficient; (2) that 600IU/day for ages 1–70 and 800IU/day if over age 70 was adequate to protect bones; and (3) that all of the other potential benefits of vitamin D, besides bone health, did not yet have compelling evidence to support advising higher doses. They concluded that higher doses of vitamin D should not be advised on a public health basis until further research was done. It should be noted that the European counterpart to this report concluded that 800IU was the suggested daily intake. Although the IOM report was meant to provide the populations of Canada and the United States with Recommended Dietary Allowances (RDAs) and Tolerable Upper Intake Levels (ULs) for calcium and vitamin D, the committee also identified a large number of uncertainties surrounding the DRI values that they recommended. For instance, the committee expressed a need for more research into both the skeletal and nonskeletal actions of vitamin D. Despite the thousands of publications on vitamin D, the committee was clearly disappointed by the lack of rigorous randomized trials and convincing clinically applicable knowledge on the subject of vitamin D benefits beyond the skeleton.

With this in mind, how does the IOM report impact what is written by the contributors to the third edition of “Vitamin D”? It is important for the readers of this book to know that the authors of each of the 105 chapters were asked to consider revising their chapters on the basis of the IOM report. For those authors contributing chapters in the book’s Sections III (Mineral and Bone Homeostasis), V (Human Physiology), VI (Diagnosis and Management), VII (Nutrition, Sunlight, Genetics and Vitamin D Deficiency), and VIII (Disorders) this task was of particular importance, because, as mentioned above, the IOM determined there was insufficient cause-and-effect evidence to support a role for vitamin D beyond its effects on bone health. That is not to say that vitamin D does not impact other human health conditions; the IOM committee simply stated that conclusive causal evidence was lacking in these areas and existing data were insufficient to support a public health statement for nonskeletal outcomes. As the authors in Sections IV (Targets), IX (Analogs), X (Cancer), XI (Immunity, Inflammation, and Disease) and XII (Therapeutic Applications and New Advances) remind us over and over again, definitive, randomized, clinical trial data supporting a role for vitamin D in the pathophysiology and/or treatment of nonskeletal human diseases are still wanting. However, as covered in essentially every chapter in the book, data highly suggestive of benefit in a multitude of diseases are so strong that many vitamin D researchers are persuaded that vitamin D will eventually be convincingly demonstrated to be efficacious in many disease states. Furthermore, many authors express the viewpoint that avoidance of vitamin D deficiency will be shown to prevent, delay, or reduce the development of numerous diseases.

What is the reason convincing clinical studies are missing from the published literature? Most of the previous NIH-sponsored trials of vitamin D have focused on bone or musculoskeletal health. Moreover, there is a lack of pharmaceutical
company interest in a nonpatentable small molecule like vitamin D as a therapeutic. Pharmaceutical companies are at work developing vitamin D analogs, but most of this work has not progressed beyond preclinical studies. Hopefully, much of the lack of interest in the use of vitamin D itself as a preventive or therapeutic agent for extraskeletal chronic diseases, including cardiovascular disease, cancer, diabetes, hypertension, cognitive decline, depression, lung disorders, infections, and autoimmune diseases, will be allayed by the recently initiated, NIH-funded, randomized, placebo-controlled VITamin D-OmegA-3 TriaL (VITAL); VITAL is reviewed by its principal investigator, Dr. JoAnn Manson, in Chapter 105 of this text. The central aim of VITAL is to determine whether the administration of 2000IU daily with or without 1g of marine omega-3 fatty acids (in a 2×2 factorial design) reduces the risk of developing heart disease, stroke, or cancer in those without a prior history of these illnesses. It is of note that all study participants will be allowed to take up to 800IU of personal vitamin D supplements (a dose, when added to dietary sources, exceeds the IOM recommended daily intake). If shown to be efficacious alone or in combination with omega-3 fatty acids in preventing the leading causes of death of American men and women, then vitamin D supplementation at a daily dose higher than the IOM guidelines will be justified. However, even if a 2000IU dose of vitamin D3 daily reduces the risk of one or more of these nonskeletal diseases, other controversies raised by the IOM report will no doubt persist or surface. For example, the IOM report claimed that most of the US population is not vitamin-D-deficient. This obviously raises the discussion of where the cut-points for deficiency should be placed. The IOM has chosen 20ng/ml (50nmol/L) as the cut-off, a concentration they felt was sufficient to maintain bone health. Some would argue this is not high enough even for bone health, let alone the other potential diseases that vitamin D may benefit. There will be much continued discussion of this report in the literature and no doubt there will be spirited debate about some of its findings. It is not our intent to carry out a pro and con discussion of the report but to emphasize several points. Importantly, public health policy must be conservative and risk averse and the IOM concluded that it should await more convincing data before recommending higher vitamin D intakes. The IOM was also concerned that, on a public health level, advising millions of people to take higher doses of vitamin D for extended periods of time could raise safety issues not observed in much smaller and shorter studies. These are real concerns. Finally, the IOM called for continued research efforts to develop compelling data to demonstrate the benefits of vitamin D claimed by many researchers. Although there is disagreement about the potential risks of not instituting vigorous vitamin D supplementation now, the editors and authors agree that more and better research would be welcome. It is our hope that the compilation of evidence about vitamin D action in normal and disease states contained in this volume will help to clarify the state of the science and be of use in elucidating the role of vitamin D in health and disease.