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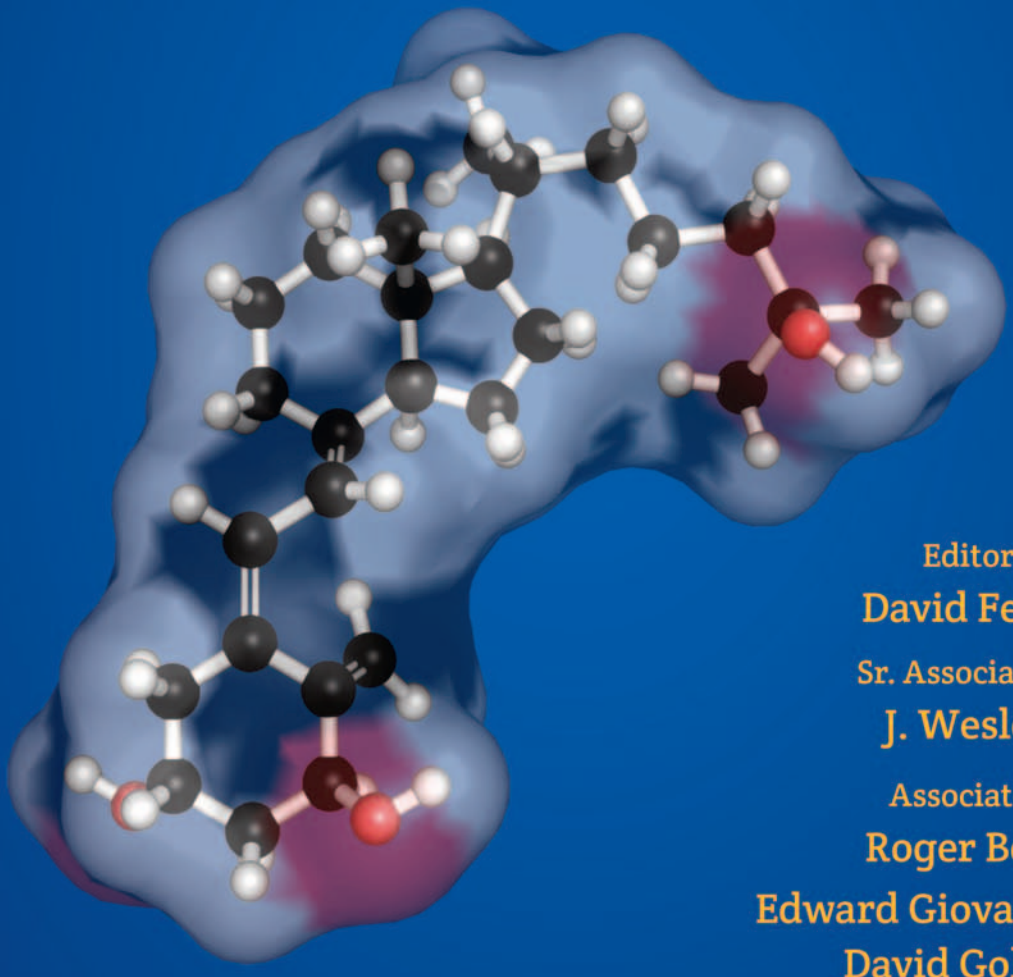

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Volume One | Biochemistry, Physiology and Diagnostics

VITAMIN D
VOLUME 1: BIOCHEMISTRY, PHYSIOLOGY AND DIAGNOSTICS

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VITAMIN D

VOLUME 1: BIOCHEMISTRY, PHYSIOLOGY AND DIAGNOSTICS

FOURTH EDITION

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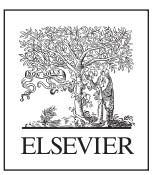

ACADEMIC PRESS

An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-809965-0

Publisher: Mica Haley
Acquisition Editor: Tari Broderick
Editorial Project Manager: Lisa Eppich
Production Project Manager: Mohanambal Natarajan
Designer: Christian Bilbow

Typeset by TNQ Books and Journals

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ROBERT P. HEANEY MD (1928–2016)

The field of bone/vitamin D research lost an iconic figure on August 6, 2016 when Dr. Robert P. Heaney died at age 88. Death was due to a brain tumor, which he had battled for more than a year. However, in true Heaney character, he had been returning to the laboratory several days each week, analyzing data, producing research papers, and providing advice and mentoring.

Dr. Heaney obtained his undergraduate and medical training (1951) at Creighton University in Omaha, NE and completed internship and residency in Internal Medicine at St. Louis University. His postgraduate training included a Public Health Service Postdoctoral Fellowship at the National Cancer Institute. He also was a Clinical Associate at the National Institute of Arthritis and Metabolic Diseases for 2 years. In 1957, he returned to Creighton University, as Assistant Professor, where he had an illustrious career as a scientist, while also serving in various administrative positions, including Vice President for Health Sciences. Since 1984 he was the holder of the John A. Creighton University Professorship. In 2013 Creighton University recognized Dr. Heaney with an award for Lifetime Achievement in Research.

Dr. Heaney's productivity was legend. He authored or coauthored more than 1000 papers, abstracts, review articles, books, book chapters, editorials, letters, and book reviews. His first scientific paper was published in 1956 in the journal, *Cancer*. It described the results of treatment with 6-mercaptopurine in human leukemia. Beginning in 1958, he published radiocalcium studies of bone formation, calcium absorption, calcium balance, bone loss, and calcium physiology in humans. This work formed the basis for recommended dietary calcium intakes for pre- and postmenopausal women. In 2008, the National Osteoporosis Foundation recognized Dr. Heaney with the first "Legends of Osteoporosis" award for his contributions to the field of osteoporosis. He focused widespread attention on the importance of osteoporosis and in recognition of this he was presented a lifetime achievement award from the US House of Representatives on November 10, 2015. In some circles, he is referred to as the "Grandfather of Osteoporosis."

By 1982 Dr. Heaney added vitamin D research to his focus, which he pursued vigorously to the end. He understood the importance of vitamin D for skeletal health but was especially captivated by the discovery of the vitamin D receptor and, subsequently, the nonskeletal effects of vitamin D. He was adamant about the importance of eliminating vitamin D deficiency in human populations and took part in many debates about the levels of serum 25(OH)D needed for optimal health (usually arguing for the higher levels). During the later years of his career, he produced prolific writings on vitamin D physiology, optimal vitamin D intake, and the definition of vitamin D deficiency. In 2012 he was presented a Career Award at the 15th Workshop on Vitamin D.

Dr. Heaney recognized that published clinical vitamin D studies were often flawed, rendering interpretation of findings erroneous or inconclusive. His concern was that the traditional randomized controlled trials of nutritional supplements were inappropriate because it was impossible to have a true placebo group in which no one consumed the nutrient in his/her diet. Thus such trials were probably biased toward a "null" outcome. Dr. Heaney wrote many "persuasive" papers addressing this concern.

He passionately believed that scientific biomedical findings that benefit health needed to be communicated to the public. He often pointed out that "no research project is completed until the findings are disseminated." To this end, he published papers and accepted innumerable speaking engagements throughout the world.

Dr. Heaney's achievements have been widely recognized and his awards include the Frederic C Bartter Award from the American Society for Bone and Mineral Research, the Kappa Delta Award from the American College of Orthopedic Surgeons, the E.V. McConnell Award from American Society for Clinical and Nutrition, and the institute CANDIA Scientific Prize from France.

Dr. Heaney has mentored a large number of people including the authors of this memorial. His mentorship has been inspirational for our students, residents, and fellows at Creighton University as well as similar trainees in other institutions. He has been an enthusiastic, passionate teacher of medicine and bone pathology and physiology.

Dr. Heaney was very active in Creighton University's spiritual community. He was well known for his passion for the scripture and his contributions to "Daily Reflections" on the Creighton website. His spiritual writings have been a source of great inspiration for persons at Creighton University and beyond. He also wrote for a monthly Catholic magazine "America". Shortly before his death, he wrote a poignant piece, "Final Words," for the Creighton Magazine. http://www.creighton.edu/creightonmagazine/2016smranewsheaney/.

Dr. Heaney and his late wife, Barbara, raised 7 children, and at his death his descendants include 14 grandchildren and 3 great grandchildren. They all were a source of great pride and

much enjoyment for him. Dr. Heaney will be remembered as a healer, a thinker, and a man of grace and generosity. We are all greatly saddened by his loss, and we offer our special support to his wife, Janet.

Robert R. Recker, MD
Joan M. Lappe, PhD

MILAN USKOKOVIC PHD (1924–2015)

Dr. Milan Uskokovic, who made major contributions to the vitamin D scientific community, died on May 11, 2015 in Towson, Maryland, just 5 weeks after the death of his beloved wife, Nada. Born in Belgrade, Yugoslavia, on July 14, 1924, he met Nada at the Belgrade Polytechnic University where both studied chemical engineering. They immigrated to the United States after he received a scholarship to study organic chemistry at Clark University. He received his PhD from the Worcester Foundation of Experimental Biology at Clark University in 1960 and joined Hoffmann La Roche in Nutley as a senior scientist. From 1973 to 1995, he led the Roche Natural Products Department and established syntheses of natural products with promising pharmacological activities, including cinchona alkaloids, indole alkaloids, loganin, biotin, statins, and vitamin D.

Dr. Uskokovic authored 219 publications and acquired over 200 US patents. As a result of his ingenuity, he was inducted into the New Jersey Inventors Hall of Fame in 1994. He was a member of the advisory or editorial boards of six professional journals; was a member of the American Chemical Society and the New York Academy of Sciences; and was Adjunct Professor at Rutgers University. A laboratory at the Brown University, School of Medicine, Women and Infants Hospital of Rhode Island, was dedicated in honor of his research mentorship.

Dr. Uskokovic made major contributions to the vitamin D scientific community by establishing and perfecting the syntheses of vitamin D metabolites and multiple analogs. He generously provided and donated research samples of the numerous vitamin D analogs and intermediates that were synthesized in his laboratory. Prior to its commercial availability, Dr. Uskokovic provided 1,25$(OH)_2D_3$, at no cost, to any researcher who asked. In addition, he established strong collaborations with vitamin D scientists at Roche as well as around the world that included, among many others, Anthony W. Norman at University of California Riverside, CA, Phillip Koeffler at University of California, Los Angeles, CA, David Feldman at Stanford University, CA, Michael Sporn at National Cancer Institute, NIH, MD, Sara Peleg at MD Anderson Cancer Center, TX, Michael F. Holick at Boston University, MA, Satyanarayana G. Reddy at Brown University, RI, George Studzinski, Sylvia Christakos, Allan Conney, and Nanjoo Suh at Rutgers University, NJ, John White at McGill University, Canada, Heide Cross at Vienna Medical School, Austria, Carsten Carlberg at the University of Eastern Finland, Finland, T. Okano at Kobe University, Japan, Luciano Adorini at BioXell, Milan, Italy, and Dino Moras and Natacha Rochel, at IGBMC, France.

After his retirement form Roche in 1998, Dr. Uskokovic was instrumental in the support of Bioxell S.p.A., a new pharmaceutical company that emerged from Roche Milano. The medicinal chemistry branch, Bioxell Inc., was installed at Roche Nutley and Dr. Uskokovic headed that division until March 2010. A lead compound, Elocalcitol, a vitamin D analog with reduced calcemic activity, is in clinical trials for treatment of benign prostatic hyperplasia and overactive bladder. BXL746, another vitamin D analog, is in clinical trials for prevention of postsurgical adhesions. Dr. Uskokovic was instrumental in the discovery and development of these analogs.

Recent collaborative publications include the use of Dr. Uskokovich's vitamin D analogs to induce antimicrobial peptides, to inhibit proinflammatory cytokines from the respiratory epithelium in cystic fibrosis, to induce antileukemic activity, and to inhibit mammary carcinogenesis. In some recent studies, various analogs were shown to have activity to reduce tumor-initiating stem cell-like cell populations active in breast cancer development. His modification of structural elements in the vitamin D molecule allowed him to develop analogs that resisted degradation and therefore exhibited increased and prolonged activity. In other approaches to investigate the ligand-vitamin D receptor (VDR) interaction, Dr. Uskokovic designed the Gemini analogs with two side chains. These molecules exhibited high biological activity and reduced calcemic activity and were helpful in exploring the ligand-binding pocket of the VDR as well as many other functional activities.

Dr. Uskokovic had endless curiosity. Research in vitamin D was his passion. He was always enthusiastic about discussing experiments related to the use of vitamin D analogs (particularly if those experiments had possible clinical application) and he was always generous in providing vitamin D metabolites and analogs. He often quoted his fellow New Jersey inventor, Thomas Edison "I never did a day's work in my life. It was all fun". He is survived by his daughters Moira Bogrov, MD and Lila Vidger, PhD, their husbands and five grandchildren. Dr. Milan Uskokovic will be remembered worldwide for his long-lasting contributions to natural product chemistry and especially for his contributions to the vitamin D field that enabled many of the discoveries related to the multiple functions of vitamin D. He will be sorely missed by the entire vitamin D community.

Sylvia Christakos
Hubert Maehr
Nanjoo Suh
Rutgers University, New Jersey

Preface to the Fourth Edition

This new fourth edition of *Vitamin D* was written approximately 5–6 years after the third edition was published in 2011. At that time the exuberant hype about vitamin D as a "cure-all" for many diseases was close to its peak. In the ensuing years the hyperbole has not appeared to continue to escalate but has also not declined substantially. Numerous studies have been published in the intervening years, but many questions remain. The clinical and population studies, many well done, continue to alternate between positive data for benefit to extraskeletal sites and findings that show no value of elevated concentrations of 25(OH)D. Some naysayers have become strident in their conviction that vitamin D benefit is overblown, even for bone. Others remain strongly supportive of the value of vitamin D based on the compelling benefits of vitamin D, which have been demonstrated over and over again in cell cultures, animal models, and other preclinical studies. The population studies are also mixed, some showing positive findings for benefit while others are negative. However, there is a growing consensus that is clearly supportive of the view that vitamin D deficiency should be avoided. Everyone hopes that the randomized controlled trials (RCTs) ongoing in multiple parts of the world will eventually provide clear-cut answers. According to the NIH clinical trial register, there are numerous ongoing RCTs with an end point foreseen in the next 5 years so that we can expect a much broader insight into the clinical implications of vitamin D status. What to advise physicians and the public while we wait for answers that we hope will be coming, however, remains controversial.

In the intervening years between the third and fourth editions, we have seen the Institute of Medicine (IOM) committee report their recommendation for daily requirement of vitamin D to avoid deficiency and their view of the optimal target for circulating concentration of 25(OH)D needed for normal bones. They designate the 25(OH)D concentration of 20 ng/mL (50 nM/L) as the cut point for adequacy and their view that 600 IU per day for most adults and 800 IU for the elderly is sufficient for normal bones. Because extraskeletal benefits have not yet been proven by RCTs, their findings were based on their view of the data showing the vitamin D requirement for normal bones. The Endocrine Society took the issue with some of these findings, and their committee concluded that 30 ng/mL (75 nM/L) of 25(OH)D was required for optimum benefits to bone and suggested that this would require 1500–2000 IU/day to achieve. With the higher cut point for adequacy, the Endocrine Society position, consequently, is that vitamin D deficiency is far more common than that would be concluded from the IOM position, and it therefore would require higher daily intakes to achieve adequate levels of circulating vitamin D for the population. This controversy is highlighted in a new chapter in this edition where well-regarded proponents of each position lay out their arguments and supportive data. We hope the reader will be better informed after reading both the positions.

In the new edition the editors have continued to constantly renew and remodel the book with each successive edition. To this end, David Feldman continues as editor-in-chief and Wes Pike as associate editor, but we have added four new editors with broad expertise to the team. John Adams has stepped down from the editor position, and we thank him for his excellent work on the third edition. As new editors, the undersigned hope to add fresh energy and expertise and expand the skill set of the editorial team to better cover the vast areas of science, health, and disease that is required for a book of this size and breadth.

The fourth edition has 117 chapters making the book somewhat larger than the third edition. The editors have worked very hard to revise and update this edition with new material and presentation of fresh and different perspectives from respected authors. Some chapters covered in the third edition have not been continued 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 many new references added. In our revitalization of the material in the book, we have added 40 new chapters to cover or expand into previously uncovered areas of research or to approach the subject from a different perspective. In addition, we have changed the senior 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 to over half of the chapters in the book, with major updates and expansion of all of the chapters, has resulted in a substantially new, modified, and modernized book compared with the third edition. Finally, the expanded Internet availability of the text and the figures will make access to the material easier and more flexible and the addition of color figures alongside the text should enhance the illustrations and make the displayed data easier to understand.

Some of the areas given new emphasis in this edition include the evolution of vitamin D as a hormone; population studies and their methods of analysis; nutrition, fortification, and worldwide vitamin D deficiency; novel and improved techniques for vitamin D metabolite measurement and dealing with assay problems; new and expanded insights into the mechanism of vitamin D action; updates on vitamin D analogs and their progress in therapeutics; expanded coverage of vitamin D actions in cancer, inflammation and the immune system, diabetes, and other diseases; newly recognized target

tissues; exploration of additional organs and diseases that may be affected by vitamin D; and new biological pathways that regulate or are regulated by vitamin D. As we more fully appreciate the varied scope of vitamin D actions, it has become clearer that the vitamin D endocrine system affects most if not all tissues in the body. In fact, it is now apparent that there are likely two vitamin D systems. First, the well-established, tightly regulated systemic/endocrine system whereby renal synthesis of $1,25(OH)_2D$ adjusts serum calcium concentrations and regulates bone homeostasis. However, data are accumulating for a second parallel, widespread autocrine/paracrine system that can synthesize $1,25(OH)_2D$ locally under separate control mechanisms determined by assorted local factors. The full physiological impact of this paracrine system on extraskeletal sites remains to be fully validated, but the system appears to have disease- and tissue-specificity regulating various functions unrelated to calcium homeostasis. We have attempted to keep up with all of these advances 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.

An innovation in this edition is that we have chosen to commemorate two giants in our field who have recently passed away. We felt that Milan Uskokovich and Robert Heaney are clearly deserving of being honored and remembered in this way for their countless contributions over many years to the field of vitamin D. We cannot attempt to cover the passing of every deserving contributor to the field, and hopefully, this can be accomplished in annual meetings or other venues that occur yearly rather than in our book that is published much less frequently. However, we are very sad to announce that two additional eminent members of the vitamin D community died recently just as our book was going to press, and we are able to add a short paragraph about each of them to recognize their passing and their contributions to the field of vitamin D.

Adele Boskey passed away in May 2017. She was a pioneer in the field of bone mineralization using biophysical and imaging technologies to define the composition, structure, and functional properties of bone of normal subjects or in cases of major bone diseases such as osteoporosis, osteogenesis imperfecta, and rickets. She worked extensively on the nature of fractures and fracture healing, as well as many aspects of bone physiology and pathology. Adele was based in the Hospital for Special Surgery, New York, where she also contributed much to the field of orthopedics and dentistry, as well as endocrinology. A full description of her outstanding career and many contributions can be found in JBMR 32:1597,2017.

Jeffrey O'Riordan who died in October 2017 was a leading figure in vitamin D research during the 1980s and 1990s. Based at the Middlesex Hospital in London, Jeffrey was a multidisciplinary mineral metabolism endocrinologist who played a pivotal role in developing novel areas of vitamin D research, including sarcoidosis and extrarenal 1α-hydroxylase, oncogenic osteomalacia, and hereditary vitamin D–resistant rickets. Jeffery was a prominent member of the international vitamin D community from the early days of its development, and the many successful trainees to come out of the O'Riordan Group in London included other notable vitamin D researchers including Larry Fraher, Tom Clemens, and Martin Hewison. A synopsis of Jeffrey's career achievements and contributions to the field of vitamin D and mineral metabolism research can be found in Journal of Endocrinology 154:S1-2, 1997.

We 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. 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 Tari Broderick, Lisa Eppich, and Jeff Rossetti for their indispensable contributions to make this edition possible. Finally, we hope that this book will provide for our readers the authoritative information they seek about the significance and importance of vitamin D actions and will serve as the means to keep their knowledge current about the continuing growth of the field of vitamin D biology and its potential effects on health and disease.

David Feldman
Wes Pike
Roger Bouillon
Ed Giovannucci
David Goltzman
Martin Hewison

Abbreviations

1α-(OH)D_3 1α-Hydroxyvitamin D_3
1,25(OH)$_2$D$_3$ 1α,25-Dihydroxyvitamin D_3
24,25(OH)$_2$D$_3$ 24,25-Dihydroxyvitamin D_3
25(OH)D_3 25-Hydroxyvitamin D_3
5-ASA 5-Aminosalicylic acid
7-DHC 7-Dehydrocholesterol
9-*cis*-RA 9-*cis*-retinoic acid
AA Arachiadonic acid
AC Adenylyl cyclase
ACE Angiotensin-converting enzyme
ACF Activation frequency
ACTH Adrenocorticotropin
ADH Antidiuretic hormone (vasopressin)
ADHR Autosomal dominant hypophosphatemic rickets
ADP Adenosine diphosphate
AHO Albright's hereditary osteodystrophy
AI Adequate intake
AIDS Acquired immunodeficiency syndrome
Aj.AR Adjusted apposition rate
ALP Alkaline phosphatase
ANG II Angiotensin II
ANP Atrial natriuretic peptide
APC Antigen-presenting cell
APD Aminohydroxypropylidene bisphosphonate
APL Atrichia with papular lesions
AR Androgen receptor
ARC Activator-recruited cofactor
ATP Adenosine triphosphate
ATRA All-*trans*-retinoic acid
AUC Area under the curve
B_{max} Maximum number of binding sites
BARE Bile acid response element
bFGF Basic fibroblast growth factor
BFU Burst-forming unit
BGP Bone Gla protein (osteocalcin)
BLM Basal lateral membrane
BMC Bone mineral content
BMD Bone mineral density
BMI Body mass index
BMP Bone morphogenetic protein
BMU Basic multicellular unit
bp Base pairs
BPH Benign prostatic hyperplasia
BSA Bovine serum albumin
BUA Bone ultrasound attenuation
$[Ca^{2+}]_i$ Internal calcium ion molar concentration
CaBP Calcium-binding protein
CAD Coronary artery disease
CaM Calmodulin
cAMP Cyclic AMP
CaSR or CaR Calcium-sensing receptor
CAT Chloramphenicol acetyltransferase
CBG Corticosteroid-binding globulin
CBP Competitive protein-binding assay
CC Chief complaint
CD Crohn's disease
CDCA Chenodeoxycholic acid
CDK or Cdk Cyclin-dependent kinase
cDNA Complementary DNA
CDP Collagenase-digestible protein
Cdx-2 Caudal-related homeodomain protein
CFU Colony-forming unit
cGMP Cyclic GMP
CGRP Calcitonin gene-related peptide
CHF Congestive heart failure
CK-II Casein kinase-II
CLIA Competitive chemiluminescence immunoassay
cM Centimorgans
Cm. Ln. Cement line
CNS Central nervous system
CPBA Competitive protein-binding assay
cpm Counts per minute
CRE cAMP response element
CREB cAMP response element binding protein
CRF Chronic renal failure
CsA Cyclosporin A
CSF Colony-stimulating factor
CT Calcitonin or computerized tomography
CTR Calcitonin receptor
CTX Cerebrotendinous xanthomatosis
CVC Calcifying vascular cell
CYP Cytochrome P450
CYP24 Cytochrome P450, 24-hydroxylase
DAG Diacylglycerol
DBD DNA-binding domain
DBP Diastolic blood pressure
DBP Vitamin-D-binding protein
DC Dendritic cell
DCA Deoxycholic acid
DCT Distal convoluted tubule
DEXA or DXA Dual energy X-ray absorptiometry
DHEA Dehydroepiandrosterone
DHT Dihydrotachysterol or dihydrotestosterone
DIC Disseminated intravascular coagulation
DMSO Dimethyl sulfoxide
DR Direct repeat
DRIP Vitamin D receptor interacting protein
DSP Dental sialoprotein
DSS Dextran sodium sulfate
E_1 Estrone
E_2 Estradiol
EAE Experimental autoimmune encephalitis
EBT Electron beam computed technology
EBV Epstein–Barr virus
EC Endothelial cells
EC_{50} or ED_{50} Effective concentration (dose) to cause 50% effect
ECaC Epithelium calcium channel
ECF Extracellular fluid
EDTA Ethylenediaminetetraacetic acid
EGF Epidermal growth factor
ELISA Enzyme-linked immunosorbent assay
EMSA Electrophoretic mobility shift assay
EP_1 PG receptor-1
ER Estrogen receptor or endoplasmic reticulum

ERE Estrogen response element
ERK Extracellular signal-regulated kinase
Et Endothelin
FACS Fluorescence-activated cell sorting or sorter
FAD Flavin adenine dinucleotide
FCS Fetal calf serum
FDA US Food and Drug Administration
FFA Free fatty acid
FIT Fracture Intervention Trial
FMTC Familial medullary thyroid carcinoma
FP Formation period
FRAP Fluorescence recovery after photobleaching
FS Fanconi syndrome
FSK Forskolin
FXR Farnesoid X receptor
g Gram
g Acceleration due to gravity
G_0, G_1, G_2 Gap phases of the cell cycle
GAG Glycosaminoglycan
GC-MS Gas chromatography–mass spectrometry
G-CSF Granulocyte colony-stimulating factor
GDNF Glial-cell-derived neurotrophic factor
GFP Green fluorescent protein
GFR Glomerular filtration rate
GH Growth hormone
GHRH Growth-hormone-releasing hormone
GIO Glucocorticoid-induced osteoporosis
GM-CSF Granulocyte-macrophage colony-stimulating factor
GnRH Gonadotropin-releasing hormone
GR Glucocorticoid receptor
GRE Glucocorticoid response element
GRTH Generalized resistance to thyroid hormone
GWAS Genome-wide association study
HAT Histone acetyltransferase
HDAC Histone deacetylase
HEK Human embryonic kidney
HHRH Hereditary hypophosphatemic rickets with hypercalciuria
HIV Human immunodeficiency virus
HNF Hepatocyte nuclear factor
HPI History of present illness
HPLC High-performance liquid chromatography
HPV Human papilloma virus
h Hour
HR *Hairless*
HRE Hormone response element
HSA Human serum albumin
Hsp Heat-shock protein
HSV Herpes simplex virus
HVDRR Hereditary vitamin-D-resistant rickets
HVO Hypovitaminosis D osteopathy
IBD Inflammatory bowel disease
IBMX Isobutylmethylxanthine
IC_{50} Concentration to inhibit 50% effect
ICA Intestinal calcium absorption
ICMA Immunochemiluminometric assay
IDBP Intracellular vitamin-D-binding protein
IDDM Insulin-dependent diabetes mellitus
IDM Infants of diabetic mothers
IEL Intraepithelial cells
IFN Interferon
Ig Immunoglobulin
IGFBP IGF-binding protein
IGF-I, -II Insulin-like growth factor type I, II
IGF-IR IGF-I receptor
IL Interleukin (e.g., IL-1, IL-lβ, etc.)
i.m. Intramuscular
IMCal Intestinal membrane calcium-binding complex
iNKT Invariant NKT
i.p. Intraperitoneal
IP_3 Inositol trisphosphate
IRMA Immunoradiometric assay
IU International units
IUPAC International Union of Pure and Applied Chemists
i.v. Intravenous
JG Juxtaglomerular
JNK c-Jun NH_2-terminal kinase
***K*d** Dissociation constant
***K*m** Michaelis constant
kb Kilobases
kbp Kilobase pairs
kDa Kilodaltons
KO knockout
LBD Ligand-binding domain
LCA Lithocholic acid
LDL Low-density lipoprotein
Li. Ce. Lining cell
LIF Leukemia inhibitory factor
LNH Late neonatal hypocalcemia
LOD Logarithm of the odds
LPS Lipopolysaccharide
LT Leukotriene
LXR Liver X receptor
M Mitosis phase of cell cycle
M molar
MAPK Mitogen-activated protein kinase
Mab Monoclonal antibody
MAR Matrix attachment region
MAR Mineral apposition rate
MARRS Membrane-associated rapid response steroid
MCR Metabolic clearance rate
M-CSF Macrophage colony-stimulating factor
MEN2 Multiple endocrine neoplasia type 2
MGP Matrix Gla protein
MHC Major histocompatibility complex
min Minute
MIU Million international units
MLR Mixed lymphocyte reaction
Mlt Mineralization lag time
MR Mineralocorticoid receptor
MRI Magnetic resonance imaging
mRNA Messenger ribonucleic acid
MS Multiple sclerosis
MT Metric ton
MTC Medullary thyroid carcinoma
NADH Nicotinamide adenine dinucleotide
NADPH Nicotinamide adenine dinucleotide phosphate
NAF Nuclear accessory factor
NBT Nitroblue tetrazolium
NcAMP Nephrogenous cAMP
NCP Noncollagen protein
NFκB Nuclear factor kappa B
NGF Nerve growth factor
NHANES III National Health and Nutrition Examination Survey III
NHL Non-Hodgkin's lymphoma
NIDDM Non-insulin-dependent diabetes mellitus
NIH National Institutes of Health
NK cell Natural killer cell
NLS Nuclear localization signal
NMR Nuclear magnetic resonance
NOD Nod-like
NPT Sodium/phosphate cotransporter
NR Nuclear receptor

Ob Osteoblast
Oc Osteocalcin or osteoclast
OCIF Osteoclastogenesis inhibitory factor (same as OPG)
OCT 22-Oxacalcitriol
ODF Osteoclast differentiation factor (same as RANKL)
OHO Oncogenic hypophosphatemic osteomalacia
Omt Osteoid maturation time
OPG Osteoprotegerin
OPN Osteopontin
OSM Oncostatin M
OVX Ovariectomy
P_i Inorganic phosphate
PA_2 Phospholipase A_2
PAD Peripheral arterial vascular disease
PAM Pulmonary alveolar macrophage
PBL Peripheral blood lymphocyte
PBMC Peripheral blood mononuclear cells
PBS Phosphate-buffered saline
PC Phosphatidylcholine
PCNA Proliferating cell nuclear antigen
PCR Polymerase chain reaction
PCT Proximal convoluted tubule
PDDR Pseudovitamin D deficiency rickets
PDGF Platelet-derived growth factor
PEIT Percutaneous ethanol injection therapy
PHEX Phosphate-regulating gene with homologies to endopeptidases on the X chromosome
PG Prostaglandin
PHA Phytohemagglutinin
PHP Pseudohypoparathyroidism
PIC Preinitiation complex
PKA Protein kinase A
PKC Protein kinase C
PKI Protein kinase inhibitor
PLA_2 Phospholipase A_2
PLC Phospholipase C
PMA Phorbol 12-myristate 13-acetate
PMCA Plasma membrane calcium pump
PMH Past medical history
p.o. Oral
poly(A) Polyadenosine
PPAR Peroxisome proliferator-activated receptor
PR Progesterone receptor
PRA Plasma renin activity
PRL Prolactin
PRR Pattern recognition receptors
PSA Prostate-specific antigen
PSI Psoriasis severity index
PT Parathyroid
PTH Parathyroid hormone
PTHrP Parathyroid hormone–related peptide
PTX Parathyroidectomy
PUVA Psoralen-ultraviolet A
QCT Quantitative computerized tomography
QSAR Quantitative structure–activity relationship
RA Retinoic acid
RA Rheumatoid arthritis
Rag Recombination-activating gene
RANK Receptor activator NF-κB
RANKL Receptor activator NF-κB ligand
RAP Receptor-associated protein
RAR Retinoic acid receptor
RARE Retinoic acid response element
RAS Rennin–angiotensin system
RBP Retinol-binding protein
RCI Relative competitive index
RDA Recommended dietary allowance
RFLP Restriction fragment length polymorphism
RIA Radioimmunoassay
RID Receptor interacting domain
RNase Ribonuclease
ROCs Receptor-operated calcium channels
ROS Reactive oxygen species
RPA Ribonuclease protection assay
RRA Radioreceptor assay
RT-PCR Reverse transcriptase-polymerase chain reaction
RXR Retinoid X receptor
RXRE Retinoid X receptor response element
SBP Systolic blood pressure
SD Standard deviation
SDS Sodium dodecyl sulfate
SE Standard error
SEM Standard error of the mean
SH Social history
SHBG Sex-hormone-binding globulin
SLE Systematic lupus erythematosus
SNP Single nucleotide polymorphism
SOS Speed of sound
Sp1 Selective promoter factor 1
SPF Sun protection factor
SRC-1 Steroid receptor coactivator-1
SSCP Single-strand conformational polymorphism
SV40 Simian virus 40
SXA Single energy X-ray absorptiometry
$t_{1/2}$ Half-time
T_3 Triiodothyronine
T_4 Thyroxine
TBG Thyroid-binding globulin
TBP TATA-binding protein
TC Tumoral calcinosis
TF Tubular fluid
TFIIB General transcription factor IIB
TG Transgenic
TGF Transforming growth factor
TIO Tumor-induced osteomalacia
TK Thymidine kinase
TLR Toll-like receptor
TmP or TmPi Tubular absorptive maximum for phosphorus
TNBS Trinitrobenzene sulfonic acid
TNF Tumor necrosis factor
TPA 12-*O*-tetradecanoylphorbol-13-acetate
TPN Total parenteral nutrition
TPTX Thyroparathyroidectomized
TR Thyroid hormone receptor
TRAP Tartrate-resistant acid phosphatase
TRAP Thyroid hormone receptor–associated proteins
TRP Transient receptor potential
TRE Thyroid hormone response element
TRE TPA response element
TRH Thyrotropin-releasing hormone
Trk Tyrosine kinase
TSH Thyrotropin
TSS Transcription start site
UF Ultrafiltrable fluid
US Ultrasonography
USDA US Department of Agriculture
UTR Untranslated region
UV Ultraviolet
VDDR-I Vitamin-D-dependent rickets type I (*see* PDDR)
VDDR-II Vitamin-D-dependent rickets type II (*see* HVDRR)
VDR Vitamin D receptor
VDRE Vitamin D response element

VDRL Vitamin D receptor ligand
VEGF Vascular endothelial growth factor
VERT Vertebral Efficacy with Risedronate Therapy studies
VICCs Voltage-insensitive calcium channels
VSMC Vascular smooth muscle cell
VSSCs Voltage-sensitive calcium channels
WHI Women's Health Initiative
WRE Wilms' tumor gene, WT1, responsive element
WSTF Williams syndrome transcription factor
WT Wild-type
XLH X-linked hypophosphatemic rickets
XRD X-ray diffraction
ZEB Zinc finger, E box-binding transcription factor

Relevant Lab Values in Adults and Children

CRITERIA FOR VITAMIN D DEFICIENCY: 25(OH)D SERUM LEVELS

Recommendations for Adults

Institute of Medicine recommendations

	Conventional Units (ng/mL)	SI Units (nmol/L)
Deficient	<20	<50
Normal	≥20	≥50
Excessive	>50	>125

Frequently used vitamin D cut points by many laboratories similar to the Endocrine Society guidelines

	Conventional Units (ng/mL)	SI Units (nmol/L)
Deficient	<20	<50
Insufficient	20–29.9	50–74.9
Sufficient	30	>75

Recommendations for pediatrics

nmol/L	ng/mL	Journal of Clinical Endocrinology and Metabolism[a]	Nature Rev Endo[b]
>50	20	Sufficiency	Sufficiency
30–50	12–20	Insufficiency	Deficiency
<30	12	Deficiency	Severe deficiency

[a]Munns CF, et al. Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 2016;101: 394–415.
[b]Bouillon R. Nat Rev Endocrinol August 2017;13(8):466–79.

Approximate normal ranges for serum values in adults[a]

Measure	Conventional Units	SI Units	Conversion Factor[b]
Ionized calcium	4.5–5.3 mg/dL	1.12–1.32 mmol/L	0.2495
Total calcium	8.7–10.1 mg/dL	2.17–2.52 mmol/L	0.2495
Phosphorous, inorganic	2.4–4.6 mg/dL	0.77–1.49 mol/L	0.3229
$1,25(OH)_2D$	25–45 pg/mL	60–108 pmol/L	2.40

[a]Normal ranges differ in various laboratories and these values are provided only as a general guide.
[b]Conversion factor X conventional units = SI units.

Approximate normal ranges for serum values in children[a]

Measure	Conventional Units	SI Units	Conversion Factor[b]
Ionized calcium	4.8–5.2 mg/dL	1.19–1.29 mmol/L	0.2495
Total calcium	9.0–10.5 mg/dL	2.25–2.63 mmol/L	0.2495
Phosphorous, inorganic	3.8–5.0 mg/dL	1.23–1.62 mol/L	0.3229
$1,25(OH)_2D$	27–56 pg/mL	65–134 pmol/L	2.40

[a]Normal ranges differ in various laboratories and these values are provided only as a general guide.
[b]Conversion factor X conventional units = SI units.

Useful equivalencies of different units

Vitamin D	1 µg = 40 IU
Calcium	1 mmol = 40 mg
Phosphorus	1 mmol = 30 mg

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SECTION I

HISTORY, CHEMISTRY METABOLISM, CIRCULATION & REGULATION

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CHAPTER

1

Historical Overview of Vitamin D

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OUTLINE

DISCOVERY OF THE VITAMINS

Early Nutritional Views

The field of nutrition was largely dominated in the 19th century by German chemists, led by Justus von Liebig [1]. They taught that adequacy of the diet could be described by an analysis of protein, carbohydrate, fat, and mineral. Thus, a diet containing 12% protein, 5% mineral, 10%–30% fat, and the remainder as carbohydrate would be expected to support normal growth and reproduction. This view remained largely unchallenged until the very end of the 19th century and the beginning of the 20th century [2–5]. However, evidence opposing this view began to appear. One of the first was the famous study of Eijkman who studied prisoners in the Dutch East Indies maintained on a diet of polished rice [6]. A high incidence of the neurological disorder beriberi was recorded in these inmates. Eijkman found that either feeding whole rice or returning the hulls of the polished rice could eliminate beriberi. Eijkman reasoned that polished rice contained a toxin that was somehow neutralized by the rice hulls. Later, a colleague, Grijns [7], revisited the question and correctly demonstrated that hulls contained an important and required nutrient that prevented beriberi.

Other reports revealed that microorganic nutrients might be present. The development of scurvy in mariners was a common problem. This disease was prevented by the consumption of limes on British ships (hence, the term "Limey" to describe British sailors) and sauerkraut and fruits on other ships. This led Holst and Frohlich to conclude that scurvy could be prevented by a nutrient present in these foods [8]. Experiments by Lunin, Magendie, Hopkins, and Funk showed that a diet of purified carbohydrate, protein, fat, and salt is unable to support growth and life of experimental animals [2–5]. This suggested that some unknown or vital factor present in natural foods was missing from the purified diets. Hopkins developed a growth test in which natural foods were found to support rapid growth of experimental animals, whereas purified

materials could not [3]. Funk had found similar results for the prevention of neuritis and reasoned that there were "vital amines" present in foods from natural sources and actually provided the basis for the term "vitamins" used later to describe essential micronutrients [5].

McCollum and Osborne and Mendel's Discovery of Vitamin A and B Complex

A key experiment demonstrating essential micronutrients was one carried out at the Wisconsin Agricultural Experiment Station, engineered by Stephen Moulton Babcock and carried out by E. B. Hart supported by McCollum and Steenbock [9]. Herds of dairy cows were maintained on a diet composed individually only of corn, oats, or wheat or were fed a mixture of all of these grains, all receiving the same amount of carbohydrate, protein, fat, and salts and all providing equal analysis according to the German chemists [1]. The animals on the corn diet did very well, produced milk in large amounts, and reproduced normally. Those on the wheat diet failed to thrive and soon were unable to reproduce or lactate. The oat group was found to be intermediate between the corn and wheat groups, and the mixture approximated the growth and reproduction found with corn. Yet all these diets had the same proximate analysis.

The conclusion of the Wisconsin Experiment Station study was that there are unknown nutrients present in corn and not found in wheat that are essential for life and reproduction. This led E. B. Hart, Chairman of Agricultural Chemistry (now Biochemistry) at Wisconsin, to conceive that a search for these nutrients must begin. Professor Hart assigned this task to Professor Elmer McCollum. Professor McCollum decided to search for these nutrients using small experimental animals to minimize the cost and labor associated with large animals used in the single-grain experiments. McCollum and Davis demonstrated in rats there was present in butter fat a substance that prevented xerophthalmia and was also required for growth. They termed this "a lipid-soluble growth factor" [10]. McCollum later named this factor "vitamin A" [11]. This substance was absent from lard and other fats but was found in large amounts in cod liver oil. In constructing the diets, McCollum obtained the carbohydrates and salts from milk whey that, unknown to him, supplied the vitamin B complex group of micronutrients that permitted him to observe a vitamin A deficiency. McCollum at Wisconsin [11] and Osborne and Mendel [12] at the Connecticut Experiment Station carried out experiments in which cod liver oil was used as a source of fat in the diet, but the minerals were supplied from pure chemicals mixed to approximate the mineral composition of milk. Starch or sugar was used as the carbohydrate. These animals developed a different group of symptoms, namely, neuritis, which could be cured by the provision of the milk components. McCollum and Osborne and Mendel correctly concluded that this activity was because of a different micronutrient called "vitamin B." These experiments ushered in the concept of the organic micronutrients known as vitamins.

History of Rickets

The disease rickets was very likely known in antiquity but was described in the 15th century as revealed by later writings. Whistler first provided a clear description of rickets in which the skeleton was poorly mineralized and deformed [13]. Rickets undoubtedly in ancient times appeared only on rare occasions and hence was not considered a problem. However, at the end of the 19th century, the Industrial Revolution had taken place: a highly agrarian population had become urbanized, and smoke from the industrial plants polluted the atmosphere. Thus, in low-sunlight countries such as England, rickets appeared in epidemic proportions. In fact, it was known as the English Disease [14]. Some reports of the beneficial action of cod liver oil had appeared. However, they were not given scientific credence.

With the discovery of the vitamins, Sir Edward Mellanby in Great Britain began to reason that rickets might also be a disease caused by a dietary deficiency [15]. Mellanby fed dogs a diet composed primarily of oatmeal, which was the diet consumed where the incidence of rickets was the highest (i.e., Scotland). McCollum inadvertently maintained the dogs indoors and away from ultraviolet light. The dogs developed severe rickets. Learning from the experiments of McCollum, Mellanby provided cod liver oil to cure or prevent the disease. Mellanby could not decide whether the healing of rickets was because of vitamin A known to be present in the cod liver oil or whether it was a new and unknown substance. Therefore, the activity of healing rickets was first attributed to vitamin A.

Discovery of Vitamin D

McCollum, who had moved to Johns Hopkins from Wisconsin, continued his experiments on the fat-soluble materials. McCollum used aeration and heating of cod liver oil to destroy the vitamin A activity or the ability to support growth and prevent xerophthalmia [16]. However, cod liver oil treated in this manner still retained the ability to cure rickets. McCollum correctly reasoned that the activity in healing rickets was due to a new and heretofore unknown vitamin that became known as vitamin D. Vitamin C was assigned to the antiscorbutic substance [17]. On the basis of the experiments of McCollum and Mellanby, vitamin D became known as an essential nutrient.

Discovery That Vitamin D Is Not a Vitamin

At the same time Sir Edward Mellanby was carrying out the experiments in dogs, Huldshinsky [18] and Chick et al. [19] independently found that rickets in children could be prevented or cured by exposing them to sunlight or to artificially induced ultraviolet light. Thus, the curious findings were that sunlight and ultraviolet light somehow equaled cod liver oil. These strange and divergent results required resolution.

Steenbock and Hart had noted in 1916 the importance of sunlight in restoring positive calcium balance in goats [20]. At Wisconsin, with McCollum carrying out experiments in small

experimental animals (i.e., rats), Steenbock was required to work with larger animals. Steenbock then began to study goats because they would consume less material and could serve as better experimental animals than cows. Steenbock began to study the calcium balance of lactating goats and found that those goats maintained outdoors in the sunlight were found to be in positive calcium balance, whereas those maintained indoors lost a great deal of their skeletal calcium to lactation [20]. Steenbock and Hart, therefore, noted the importance of sunlight (or at least, outdoors) on calcium balance. This work then undoubtedly led Steenbock to realize that the ultraviolet healing properties described by Huldschinky might be related to the calcium balance experiments in goats. By irradiating the animals and diets, Steenbock and Black found that vitamin D activity could be induced and rickets could be cured [21]. A similar finding was reported soon thereafter by Hess and Weinstock [22]. Steenbock then traced this to the nonsaponifiable fraction of the lipids in foods [23]. He found that ultraviolet light activated an inactive substance to become a vitamin D-active material. Thus, ultraviolet light could be used to irradiate foods, induce vitamin D activity, and fortify foods to eliminate rickets as a major medical problem. This discovery also made available a source of vitamin D for isolation and identification.

Isolation and Identification of Nutritional Forms of Vitamin D

From irradiation of mixtures of plant sterols, Windaus and colleagues isolated a material that was active in healing rickets [24]. This substance was called "vitamin D_1," but its structure was not determined. Vitamin D_1 proved to be an adduct of tachysterol and vitamin D_2, and thus vitamin D_1 was actually an error in identification. The British group led by Askew was successful in isolating and determining the structure of the first vitamin D, vitamin D_2 or ergocalciferol, from irradiation of plant sterols [25]. A similar identification by the Windaus group confirmed the structure of vitamin D_2 [26]. Windaus and Bock also isolated the precursor of vitamin D_3 from skin, namely, 7-dehydrocholesterol [27]. Furthermore, 7-dehydrocholesterol was synthesized [28] and converted to vitamin D_3 (cholecalciferol) as identified by the Windaus group [29]. Thus, the structures of nutritional forms of vitamin D became known (Fig. 1.1). Windaus and Bock, having isolated 7-dehydrocholesterol from skin, provided the presumptive evidence that vitamin D_3 is the form of vitamin D produced in skin, a discovery that was later confirmed by the chemical identification of vitamin D_3 in skin by Esvelt et al. [30] and of a previtamin D_3 in skin by Holick et al. [31]. Synthetic vitamin D as produced by the irradiation process replaced the irradiation of foods as a means of fortifying foods with vitamin D and was also rapidly applied to rickets and tetany and in the provision to domestic animals such as chickens, cows, and pigs.

Windaus' group provided chemical syntheses of the vitamin D compounds, confirming their structures and thus ending the era of the isolation and identification of nutritional forms of vitamin D and making them available for the treatment of disease. Although Windaus received the 1928 Nobel Prize in chemistry, it was for his general work on steroids.

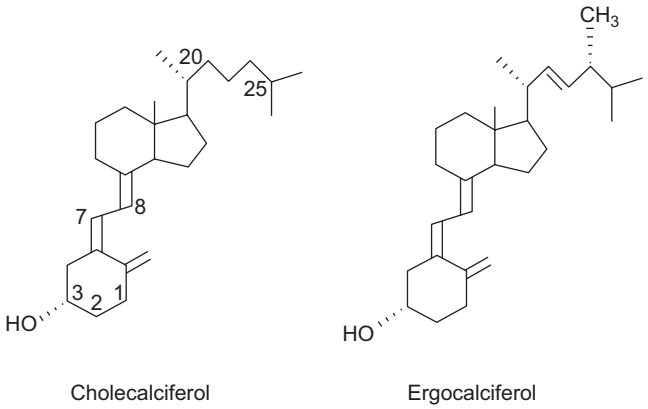

FIGURE 1.1 Nutritional forms of vitamin D.

DISCOVERY OF THE PHYSIOLOGICAL FUNCTIONS OF VITAMIN D

Intestinal Calcium and Phosphorus Absorption

Besides bone mineralization, the earliest discovered function of vitamin D is its important role in the absorption and utilization of calcium. The first report of this finding was in the early 1920s by Orr and colleagues [32]. Kletzien et al. [33] demonstrated that vitamin D plays an important role in the utilization of calcium from the diet, and a number of experiments were carried out on the utilization of calcium and phosphorus from cereal diets. Nicolaysen was responsible, however, for demonstrating unequivocally the role of vitamin D in the absorption of calcium and independently of phosphorus from the diet [34]. Nicolaysen also followed the early work of Kletzien et al. [33] in which animals adapted to a low-calcium diet were better able to utilize calcium than animals on an adequate calcium diet. This work was confirmed by Nicolaysen, who postulated the existence of an "endogenous factor" that would inform the intestine of the skeletal needs for calcium [35]. This endogenous factor later proved to be largely the active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) [36]. Strong support for this concept was provided by the studies of Ribovitch et al. [37], which showed animals maintained on a constant exogenous source of $1,25(OH)_2D_3$ are unable to change intestinal calcium transport in response to changes in dietary calcium levels. Chapter 20 will present a detailed review of the role of vitamin D in the regulation of intestinal calcium absorption.

Mobilization of Calcium From Bone

For many years, investigators have attempted to show that vitamin D plays a role directly on the mineralization process of the skeleton. However, early work by Howland

and Kramer [38], later work by Lamm and Neuman [39], and more recent work by Underwood and DeLuca [40] demonstrated very clearly that vitamin D does not play a significant role in the actual mineralization process of the skeleton but that the failure to mineralize the skeleton in vitamin D deficiency is due to inadequate levels of calcium and phosphorus in the plasma. Thus, the action of vitamin D in mineralizing the skeleton and in preventing hypocalcemic tetany is the elevation of plasma calcium and phosphorus [41]. These discoveries laid to rest the concept of a role of vitamin D in mineralization. However, Carlsson [42] and Bauer et al. [43] were the first to realize that a major function of vitamin D is to induce the mobilization of calcium from bone when required. Thus, in animals on a low-calcium diet, the rise in serum calcium induced by vitamin D is the result of actual mobilization of calcium from bone [44]. This important function is known to be essential for the provision of calcium to meet soft tissue needs, especially those of nerves and muscle, on a minute-to-minute basis when it is in insufficient supply from the diet. It is likely that the function of vitamin D in mobilizing calcium from bone is an osteoclastic-mediated process [45]. It is clear, however, that both vitamin D and parathyroid hormone are required for this function [46]. Furthermore, it is clear that vitamin D plays an important role in osteoclastic-mediated bone resorption [47], which is certainly the first and essential event in bone remodeling [48].

Renal Reabsorption of Calcium and Phosphorus

A significant site of vitamin D action to elevate plasma calcium is in the distal renal tubule. Although experiments were suggestive of a role for vitamin D in increasing renal tubule reabsorption of calcium, a clear demonstration of this did not occur until the late 1980s at the hands of Yamamoto et al. [49]. The renal tubule reabsorbs 99% of the filtered calcium even in the absence of vitamin D. However, reabsorption of the last 1% of the filtered load requires both vitamin D and parathyroid hormone. Thus, these agents work in concert in the renal reabsorption of calcium as well as in the mobilization of calcium from bone. Both agents are required to carry out this function. A review of the renal actions of vitamin D can be found in Chapters 26 and 79.

Discovery of New Functions of Vitamin D

With discovery of the receptor for the vitamin D hormone (described below) came the surprising result that this receptor could be found in a variety of tissues not previously appreciated as targets of vitamin D action. It localizes in the distal renal tubule cells, enterocytes of the small intestine, bone lining cells, osteoblasts, and osteoclasts in keeping with its known role in calcium metabolism [50,51]. However, its appearance in tissues such as parathyroid gland, islet cells of the pancreas, cells in bone marrow (i.e., promyelocytes), lymphocytes, and certain neural cells raised the question of whether the functions of vitamin D might be broader than previously anticipated [50,51]. As a result of those findings, new functions of vitamin D have been found. For example, vitamin D plays a role in causing differentiation of promyelocytes to monocytes and the subsequent coalescing of the monocytes into multinuclear osteoclast precursors and ultimately into active osteoclasts [52,53]. The target of vitamin D in this function is the osteoblast and osteocyte. In response to the hormonal form of vitamin D (see below), RANK ligand is produced, which signals osteoclastogenesis and osteoclastic activation [52,53]. Suppression of parathyroid cell growth and suppression of parathyroid hormone gene expression represent other new vitamin D actions [54,55]. In keratinocytes of skin, vitamin D appears to play a role in suppression of growth and in cellular differentiation [56]. Likely, discoveries of many new functions of $1,25(OH)_2D_3$ will be made and are well on their way, as described in the later chapters of this volume.

DISCOVERY OF THE HORMONAL FORM OF VITAMIN D

Early Work of Kodicek

The true pioneer of vitamin D metabolism was Egan Kodicek working at the Dunn Nutritional Laboratory in Cambridge. Kodicek used a bioassay at first to study the fate of the vitamin D molecule and found that much vitamin D was converted to biologically inactive products [57]. Clearly, however, this approach of assaying vitamin D activity following administration of known doses of vitamin D was of limited value in determining metabolism.

Radiolabeled Vitamin D Experiments

Professor Kodicek then began to synthesize radiolabeled vitamin D_2. Unfortunately, the degree of labeling was not sufficient to permit the administration of truly physiological doses of vitamin D. Nevertheless, Professor Kodicek continued investigations into this important area. At the conclusion of 10 years of work, he concluded that vitamin D was active without metabolic modification and that the metabolites that were found were biologically inactive [58]. This conclusion was reached even as late as 1967, when it was concluded that vitamin D_3 itself was the active form of vitamin D in the intestine [59]. However, chemical synthesis of radiolabeled vitamin D_3 of high specific activity in the laboratory of the author proved to be of key importance in the demonstration of biologically active metabolites [60]. By providing a truly physiological dose of vitamin D, it could be learned that the vitamin D itself disappeared and instead polar metabolites could be found in the target tissues before those tissues responded [61]. The polar metabolites proved to be more biologically active and acted more rapidly than vitamin D itself [62]. Thus, presumptive evidence of conversion of vitamin D to active forms had been obtained as early as 1967.