
Hypoparathyroidism

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Editors

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 Springer

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Foreword

Hypoparathyroidism, manifesting as tetany, was first encountered in the late nineteenth century as a postoperative complication of total thyroidectomy, but, as described by Mannstadt and Potts in the first chapter of this volume, the connection between parathyroid glands, post-thyroidectomy tetany, and hypocalcemia took years to be elucidated. Isolation and characterization, first from bovine and then from human parathyroid glands, of the biologically relevant agent parathyroid hormone (PTH) took decades more. The pioneering work of the late Gerald Aurbach in this endeavor (as cited by Mannstadt and Potts) and in many other seminal studies that illuminated our understanding of the causes of hypoparathyroidism is especially fitting in this volume, to which so many of Aurbach's collaborators and fellows and even fellows of those fellows have contributed.

The comprehensive scope of this volume reflects the fact that studies of hypoparathyroidism go well beyond a simple delineation of the consequences of hormone deficiency. Part I, "Anatomy and physiology of the parathyroid glands," depicts (a) the complicated embryology and development of the parathyroids, (b) the intricate homeostatic mechanisms involving not only PTH but also vitamin D and FGF23 that maintain normal calcium and phosphate metabolism, (c) the relationship between PTH and PTH-related peptides (PTHrP), and (d) the signal transduction mechanisms that govern Ca^{++} regulation of PTH secretion as well as PTH action on its target organs. Two particularly notable features of signal transduction relevant to PTH are the unique calcium-sensing receptor (CaSR), which in parathyroid cells transduces the signal from extracellular ionized calcium to changes in PTH secretion, and the role of G proteins in coupling both the CaSR and the PTH receptor to downstream intracellular effectors. The Gs protein, which couples not only PTH receptors but many other hormone receptors to stimulation of the second messenger, cyclic AMP, is the subject of its own chapter, given its relevance to a unique form of hypoparathyroidism discussed below.

Part II, "Conditions of hypoparathyroidism," beginning with considerations of epidemiology and clinical presentation, proceeds to detailed descriptions of the genetic and acquired diseases that result in PTH deficiency as either an isolated manifestation or as part of a syndromic constellation of other abnormalities. One of the remarkable features of hypoparathyroidism is that until recently, it represented the sole hormone deficiency disorder for which cognate hormone replacement therapy is not the standard of care. Treatment with vitamin D (in one of its several forms) and calcium supplements, while

effective in restoring normocalcemia, is not, strictly speaking, physiological. Chapters discussing “conventional treatment” (i.e., vitamin D and calcium supplements) and the more physiological replacement approaches with the 1–34 fragment of PTH or the intact 1–84 amino acid hormone provide an important perspective on the potential changes in practice that may ensue.

Mannstadt and Potts, in the first chapter, pay tribute appropriately to one of endocrinology’s greatest figures, Fuller Albright. Without benefit of modern tools such as radioimmunoassay, he astutely recognized that a subset of subjects with hypoparathyroidism suffered from resistance to PTH action rather than true deficiency of the hormone. Hence, he termed the disorder in these subjects *pseudohypoparathyroidism* (PHP), the first description of a hormone resistance syndrome. Analogous disorders were later recognized for most other peptide and also steroid hormones showing how studies of hypoparathyroidism provided a paradigm that influenced our understanding of endocrine disease in general. Perhaps fittingly from a historical perspective, following Albright’s initial description, studies by Aurbach and colleagues localized the site of hormone resistance in PHP as proximal to cyclic AMP generation. Studies by Aurbach’s fellows and others eventually defined the defect in “classic” PHP (characterized by the phenotypic appearance termed *Albright’s hereditary osteodystrophy*) as loss of function mutations in the gene encoding the alpha subunit of the Gs protein. Thus, the first described hormone resistance disorder also became the first human disease recognized to be caused by a G protein mutation. The complex transcriptional regulation of the Gs alpha gene involving multiple transcripts, each with differential parental imprinting, also turned out to have a correlate in human phenotypic expression called pseudoPHP. All of these conditions are well described in Part III of this volume, “Functional Hypoparathyroidism.”

This brief overview should make clear that the editors of this volume, Maria Luisa Brandi and Edward M. Brown, have succeeded in bringing together a broad array of experts from a number of fields, each of whom has contributed to a volume that in aggregate is surely greater than the sum of its parts. From the most basic aspects of biochemistry, molecular biology, and physiology to depiction at the molecular, genetic, and clinical level of a wide variety of disorders, the chapters in this volume define our current understanding of hypoparathyroidism.

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Preface

This volume is the first devoted solely to hypoparathyroidism and is intended for those who must deal with this disorder. The introduction of a book on a field of clinical medicine today requires considerable justification. In the field of hypoparathyroidism, the recent growth of medical knowledge in general has created the need for a new volume fully dedicated to this topic.

That there has been a recent explosion of knowledge on the subject of hypoparathyroidism cannot be doubted, and much of the acceleration in its pace can be attributed to new insights into etiopathogenesis, epidemiology, and substitutive therapy. PubMed offers about 7,100 references to hypoparathyroidism since 1926, with over 1,200 published in the past 5 years. It is now a pleasure to record that the intensified research in hypoparathyroidism has matured to the point that a handbook can be fully dedicated to an area that is enjoying a spectacular increase in interest among basic researchers and clinicians alike.

The information made available in the 38 chapters of this volume has been brought together from widely diverse sources, and, in some instances, is reported here for the first time. Many subjects have been presented both in broad outline and in more comprehensive detail in different chapters to meet the differing requirements of the target audiences. The book is designed for use in the clinic and in the basic science laboratory connected to the clinic. Every effort has been made to make available sufficient basic and clinical knowledge to satisfy the reader's curiosity about each of these aspects.

This book is dedicated to our mentor, Gerald D. Aurbach, MD, whose pioneering studies on parathyroid hormone led to dramatic advances in our understanding of some hereditary diseases of calcium metabolism including pseudohypoparathyroidism. Gerry was not only a fine physician and an elegant scientist but also a lover of classical music and an avid fan of the Washington Redskins football team. Through his wisdom and daring insights, he showed us the way in science and in life. This book honors him as a great scientist but also as a gentle, wise, and supportive person, loved and respected by everyone.

Credits for this book are many. The first of these goes to the authors of the chapters, all leaders in their respective fields, for it is the success of their endeavors that forms the basis of and the reason for this publication. Credit is also due to the Springer team for their formidable effort in attending to the many needs that were part of the making of the handbook on

hypoparathyroidism. The foreword to the book was kindly provided by Dr. Allen M. Spiegel, another of Gerry's students, who has contributed greatly to our understanding of calcium metabolism.

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