

AUTOIMMUNE DISEASES IN ENDOCRINOLOGY

CONTEMPORARY ENDOCRINOLOGY

P. Michael Conn, *SERIES EDITOR*

- Autoimmune Diseases in Endocrinology*, edited by ANTHONY P. WEETMAN, 2008
- Energy Metabolism and Obesity: Research and Clinical Applications*, edited by PATRICIA A. DONOHOU, 2008
- Polycystic Ovary Syndrome: Current Controversies, from the Ovary to the Pancreas*, edited by ANDREA DUNAIF, JEFFREY R. CHANG, STEPHEN FRANKS, AND RICHARD S. LEGRO, 2008
- The Metabolic Syndrome: Epidemiology, Clinical Treatment, and Underlying Mechanisms*, edited by BARBARA C. HANSEN AND GEORGE A. BRAY, 2008
- Genomics in Endocrinology: DNA Microarray Analysis in Endocrine Health and Disease*, edited by STUART HANDWERGER AND BRUCE ARONOW, 2007
- Controversies in Treating Diabetes: Clinical and Research Aspects*, edited by DEREK LEROITH AND AARON I. VINIK, 2007
- When Puberty is Precocious: Scientific and Clinical Aspects*, edited by ORA H. PESCOVITZ AND EMILY C. WALVOORD, 2007
- Insulin Resistance and Polycystic Ovarian Syndrome: Pathogenesis, Evaluation and Treatment*, edited by JOHN E. NESTLER, EVANTHIA DIAMANTI-KANDARAKIS, RENATO PASQUALI AND D. PANDIS, 2007
- Hypertension and Hormone Mechanisms*, edited by ROBERT M. CAREY, 2007
- The Leydig Cell in Health and Disease*, edited by ANITA H. PAYNE AND MATTHEW PHILLIP HARDY, 2007
- Treatment of the Obese Patient*, edited by ROBERT F. KUSHNER AND DANIEL H. BESSESEN, 2007
- Androgen Excess Disorders in Women: Polycystic Ovary Syndrome and Other Disorders, Second Edition*, edited by RICARDO AZZIS, JOHN E. NESTLER, AND DIDIER DEWAILLY, 2006
- Evidence-Based Endocrinology*, edited by VICTOR M. MONTORI, 2006
- Stem Cells in Endocrinology*, edited by LINDA B. LESTER, 2005
- Office Andrology*, edited by PHILLIP E. PATTON AND DAVID E. BATTAGLIA, 2005
- Male Hypogonadism: Basic, Clinical, and Therapeutic Principles*, edited by STEPHEN J. WINTERS, 2004
- Androgens in Health and Disease*, edited by CARRIE J. BAGATELL AND WILLIAM J. BREMNER, 2003
- Endocrine Replacement Therapy in Clinical Practice*, edited by A. WAYNE MEIKLE, 2003
- Early Diagnosis of Endocrine Diseases*, edited by ROBERT S. BAR, 2003
- Type I Diabetes: Etiology and Treatment*, edited by MARK A. SPERLING, 2003
- Handbook of Diagnostic Endocrinology*, edited by JANET E. HALL AND LYNNETTE K. NIEMAN, 2003
- Pediatric Endocrinology: A Practical Clinical Guide*, edited by SALLY RADOVICK AND MARGARET H. MACGILLIVRAY, 2003
- Diseases of the Thyroid, 2nd ed.*, edited by LEWIS E. BRAVERMAN, 2003
- Developmental Endocrinology: From Research to Clinical Practice*, edited by ERICA A. EUGSTER AND ORA HIRSCH PESCOVITZ, 2002
- Osteoporosis: Pathophysiology and Clinical Management*, edited by ERIC S. ORWOLL AND MICHAEL BLIZIOTES, 2002
- Challenging Cases in Endocrinology*, edited by MARK E. MOLITCH, 2002
- Selective Estrogen Receptor Modulators: Research and Clinical Applications*, edited by ANDREA MANNI AND MICHAEL F. VERDERAME, 2002
- Transgenics in Endocrinology*, edited by MARTIN MATZUK, CHESTER W. BROWN AND T. RAJENDRA KUMAR, 2001
- Assisted Fertilization and Nuclear Transfer in Mammals*, edited by DON P. WOLF AND MARY ZELINSKI-WOOTEN, 2001
- Adrenal Disorders*, edited by ANDREW N. MARGIORIS AND GEORGE P. CHROUSOS, 2001
- Endocrine Oncology*, edited by STEPHEN P. ETHIER, 2000
- Endocrinology of the Lung: Development and Surfactant Synthesis*, edited by CAROLE R. MENDELSON, 2000
- Sports Endocrinology*, edited by MICHELLE P. WARREN AND NAAMA W. CONSTANTINI, 2000
- Gene Engineering in Endocrinology*, edited by MARGARET A. SHUPNIK, 2000
- Endocrinology of Aging*, edited by JOHN E. MORLEY AND LUCRETIA VAN DEN BERG, 2000
- Human Growth Hormone: Research and Clinical Practice*, edited by ROY G. SMITH AND MICHAEL O. THORNER, 2000
- Hormones and the Heart in Health and Disease*, edited by LEONARD SHARE, 1999

AUTOIMMUNE DISEASES IN ENDOCRINOLOGY

Edited by

ANTHONY P. WEETMAN, MD, DSc

*School of Medicine and Biomedical Sciences
University of Sheffield,
Sheffield, United Kingdom*

HUMANA PRESS  TOTOWA, NEW JERSEY

© 2008 Humana Press
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512
www.humanapress.com

All rights reserved. No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.

The content and opinions expressed in this book are the sole work of the authors and editors, who have warranted due diligence in the creation and issuance of their work. The publisher, editors, and authors are not responsible for errors or omissions or for any consequences arising from the information or opinions presented in this book and make no warranty, express or implied, with respect to its contents.

Due diligence has been taken by the publishers, editors, and authors of this book to assure the accuracy of the information published and to describe generally accepted practices. The contributors herein have carefully checked to ensure that the drug selections and dosages set forth in this text are accurate and in accord with the standards accepted at the time of publication. Notwithstanding, since new research, changes in government regulations, and knowledge from clinical experience relating to drug therapy and drug reactions constantly occur, the reader is advised to check the product information provided by the manufacturer of each drug for any change in dosages or for additional warnings and contraindications. This is of utmost importance when the recommended drug herein is a new or infrequently used drug. It is the responsibility of the treating physician to determine dosages and treatment strategies for individual patients. Further, it is the responsibility of the health care provider to ascertain the Food and Drug Administration status of each drug or device used in their clinical practice. The publishers, editors, and authors are not responsible for errors or omissions or for any consequences from the application of the information presented in this book and make no warranty, express or implied, with respect to the contents in this publication.

This publication is printed on acid-free paper. ∞

ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Cover design by Nancy K. Fallatt

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel: 973-256-1699; Fax: 973-256-8341; E-mail: humana@humanapr.com or visit our website at <http://humanapress.com>

Photocopy Authorization Policy:

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Humana Press, provided that the base fee of US \$30 per copy is paid directly to the Copyright Clearance Center at 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license from the CCC, a separate system of payment has been arranged and is acceptable to Humana Press. The fee code for users of the Transactional Reporting Service is: [978-1-58829-733-4/08 \$30].

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN: 978-1-59745-517-6

Library of Congress Control Number: 2007928339

PREFACE

It was a real pleasure to be asked to edit *Autoimmune Diseases in Endocrinology* by the Series Editor, P. Michael Conn. As a contributor to the last volume in this series that addressed the subject, *Autoimmune Endocrinopathies*, edited by Bob Volpé and published in 1999, I was proud to be asked to write a chapter in an outstanding volume of essays on the important topic of autoimmunity and endocrine disease. The present volume will, I hope, be a useful update on what has happened in the intervening eight years. Sadly Bob Volpé died two years ago and I would like to join the many others who have mourned his passing. I remember as a medical student in Newcastle-upon-Tyne this renowned figure in the field visiting us and giving the most impressive lecture I had then heard. Bob's ability to enthuse people and to challenge dogma have been as important as his scientific contributions, and we all owe him a great deal in the development in this field.

Another reason I was delighted to undertake this task was the fact that last year saw the 50th anniversary of the discovery of autoimmunity, with the initial description by Rose & Witebsky of thyroglobulin antibodies and thyroiditis in rabbits immunized with thyroid extract (1), followed in the same year by the description of thyroglobulin antibodies in Hashimoto's thyroiditis (2). This was indeed an *annus mirabilis* because at the same time Adams and Purves described a substance in the serum of Graves' disease patients, which turned out to stimulate the thyroid in a fashion totally different to TSH (3). This long acting thyroid stimulator was later shown independently by Kriss and McKenzie to be an IgG and of course this was a thyroid-stimulating antibody, directed against the TSH receptor, which is the cause of Graves' disease. The initial description of this stimulator appeared in the local medical school journal, something I think that would be unlikely in these days of impact factors and citation indices, but reminds us that highly significant developments can start from simple and apparently modest origins. So I hope that this volume is a celebration of the first half century of discoveries in the field of autoimmunity, and I am particularly pleased that Noel Rose, who has done so much in the discovery and elucidation of autoimmune phenomena, is a contributor to the present volume.

I have grouped the chapters in a somewhat different way to *Autoimmune Endocrinopathies*, and I have also asked an (almost) entirely different group of colleagues to contribute. This is not merely to provide a different perspective but also to give an introduction to what is an increasingly complex field. It is impossible in a book of this size to cover the complexities of modern immunology, but I felt that a set of introductory chapters would provide sufficient information to understand the developments in the field for those without a background in recent immunology, together with suitable references for further reading. The authors of these three introductory chapters are ideally placed to bridge the gap that can exist between theoretical immunology and its application to clinical disease, and have produced an excellent start to the book.

The next section concerns autoimmune thyroid disease and this is unashamedly the largest section. Not only are there diverse mechanisms that lie at the heart of these different autoimmune diseases, but also as a group they constitute the exemplar still of autoimmunity. I have asked the authors of each of the clinical chapters to follow a similar structure, taking the reader through the basic epidemiology, genetic and environmental risk factors, immunopathogenesis and then detailing the diagnostic and management aspects of the disease. Hopefully this will give the reader easy access to the information he or she needs, and this layout will allow comparisons between the different autoimmune disorders under each of these broad headings.

The third section of the book consists of three chapters on type 1 diabetes mellitus. Despite the frequency of thyroid disease and the often neglected fact that many of these patients are less than happy with current treatment, nonetheless type 1 diabetes must be the most severe of the autoimmune endocrinopathies. The autoimmune origin of type 1 diabetes was only suspected in the early 1970s when Bottazzo and colleagues found islet cell autoantibodies at the onset of disease (4). Since then the field has made major progress, particularly with the identification of key islet cell autoantigens and the development of increasingly innovative and complex animal models. If any disease deserves an immunological solution, it is this, given both its frequency and the young population that is affected.

The last section concerns the other autoimmune endocrinopathies, which range in frequency from common to rare, but the immunological changes in each have important clinical and therapeutic implications. Our understanding of these is even more recent than that of type 1 diabetes, and it is salutary to compare the chapters in this volume and *Autoimmune Endocrinopathies* to see really how far we have come. The cloning of the *AIRE* gene has been a major triumph and allowed new insights into type 1 autoimmune polyglandular syndrome, key autoantigens have been identified in Addison's disease and we have a much greater understanding of the tempo of disease evolution, and many more clinical studies have been done in autoimmune hypophysitis. Questions still remain over the role of autoimmunity in many cases of premature ovarian failure, but slowly this condition is becoming disaggregated and better understood, and we also have fresh insights into the mechanisms in autoimmune polyglandular syndrome type 2.

Finally, and most importantly, I want to thank all of the chapter editors who have contributed so diligently and enthusiastically to this project. Their scholarship is evident in each of the chapters and I am deeply grateful to them for all of their hard work. I am also indebted to the Series Editor, Dr. P. Michael Conn, for the invitation to contribute to this series and to Richard Lansing and Sandra Bunton for seeing the project through to completion. Last but certainly not least I need to thank Mrs. Kathryn Watson for her excellent secretarial assistance and help in ensuring the deadlines have been met.

REFERENCES

1. Rose NR, Witebsky E. Studies in organ specificity. V. Changes in the thyroid glands of rabbits following active immunisation with rabbit thyroid extracts. *J Immunol* 1956;**76**:417-427.
2. Roit IM, Doniach D, Campbell PN, Vaughan Hudson R. Autoantibodies in Hashimoto's disease (lymphadenoid goitre). *Lancet* 1956;ii 820-821.

3. Adams DD & Purves HD. Abnormal responses in the assay of thyrotrophin. Proceedings of the University of Otago Medical School. 1956;**34**:11-12.
4. Bottazzo GF, Florin-Christensen A, Doniach D. Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. Lancet 1974;**2**:1279-1283.

Tony Weetman, MD, DSc.

CONTENTS

Preface	v
Contributors	xi

PART I: INTRODUCTORY CHAPTERS

1 Basic Mechanisms in Autoimmunity <i>Sonia Quarantino</i>	3
2 Immunogenetic Factors in Autoimmunity <i>Joanne Heward and Stephen Gough</i>	17
3 Environmental Factors in Autoimmune Endocrinopathies <i>Rajni B. Sharma, C. Lynne Burek, Daniela Cibáková, Dolores B. Njoku, and Noel R. Rose</i>	35

PART II: AUTOIMMUNE THYROID DISEASE

4 Animal Models of Autoimmune Thyroid Disease <i>Marian Ludgate</i>	79
5 Thyroid Autoantigens <i>Philip F. Watson and Nagat Saeed</i>	95
6 Graves' Disease <i>Simon H. S. Pearce</i>	117
7 Autoimmune Hypothyroidism <i>Francesco Latrofa and Aldo Pinchera</i>	137
8 Postpartum Thyroiditis <i>John H. Lazarus and L. D. K. E. Premawardhana</i>	177
9 Thyroid-Associated Ophthalmopathy and Dermopathy <i>Wilmar M. Wiersinga</i>	193

PART III: TYPE 1 DIABETES MELLITUS

10 Animal Models of Type 1 Diabetes Mellitus <i>Lucienne Chatenoud</i>	217
---	-----

- 11 Islet Cell Autoantigens
*Anastasia Katsarou, Barbro Holm, Kristian Lynch,
 and Åke Lernmark* 243
- 12 Type 1 Diabetes Mellitus
Huriya Beyan and R. David G. Leslie..... 275

PART IV: OTHER AUTOIMMUNE ENDOCRINOPATHIES

- 13 Addison's Disease
Corrado Betterle, Renato Zanchetta, and Fabio Presotto..... 303
- 14 Premature Ovarian Failure
*Victoria Sundblad, Violeta A. Chiauzzi,
 and Eduardo H. Charreau*..... 331
- 15 Autoimmune Hypophysitis
*Patrician Anne Crock, Sophie Bensing, Casey Jo Anne
 Smith, Christine Burns, and Phillip J. Robinson*..... 357
- 16 Autoimmune Polyglandular Syndrome Type 1
Pärt Peterson..... 393
- 17 Autoimmune Polyglandular Syndrome Type 2
George J. Kahaly and Manuela Dittmar..... 411
- Index 427

CONTRIBUTORS

SOPHIE BENSING, MD, PHD, *Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden*

CORRADO BETTERLE, MD, *Department of Medical and Surgical Sciences, Unit of Endocrinology, University of Padua, Padua, Italy*

HURIYA BEYAN, PHD, *Institute of Cell and Molecular Science, Queen Mary College, University of London, London, UK*

C. LYNNE BUREK, PHD, *Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD*

CHRISTINE BURNS, BSC, GRAD. DIP. MED. LAB. SCI., *Department of Immunology, Hunter Area Pathology Service, John Hunter Hospital, Newcastle, Australia*

EDUARDO H. CHARREAU, PHD, *Instituto de Biología y Medicina Experimental-CONICET, Buenos Aires, Argentina*

LUCIENNE CHATENAUD, MD, PHD, *Université René Descartes Paris 5, Institut National de la Santé et de la Recherche Médicale U580, Hôpital Necker-Enfants Malades, Paris, France*

VIOLETA A. CHIAUZZI, PHD, *Instituto de Biología y Medicina Experimental-CONICET, Buenos Aires, Argentina*

DANIELA CIHÁKOVA, MD, PHD, *Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD*

PATRICIAN ANNE CROCK, MBBS, FRACP, *Department of Paediatric Endocrinology, John Hunter Children's Hospital, Newcastle, Australia*

MANUELA DITTMAR, PROF, *Department of Biology, Gutenberg University, Mainz, Germany*

STEPHEN GOUGH, MD, *Department of Medicine, Division of Medical Science, Institute of Biomedical Research, University of Birmingham, Birmingham, UK*

JOANNE HEWARD, PHD, *Department of Medicine, Institute of Biomedical Research, University of Birmingham, Birmingham, UK*

BARBRO HOLM, MD, *Department of Clinical Sciences, Diabetes and Celiac Disease Unit, Lund University/CRC, University Hospital MAS, Malmo, Sweden*

GEORGE J. KAHALY, PROF, *Department of Medicine, Gutenberg University, Mainz, Germany*

ANASTASIA KATSAROU, MD, *Department of Clinical Sciences, Diabetes and Celiac Disease Unit, Lund University/CRS, University Hospital MAS, Malmo, Sweden*

FRANCESCO LATROFA, MD, *Department of Endocrinology and Metabolism, University Hospital of Pisa, Pisa, Italy*

JOHN H. LAZARUS, MA, MD, FRCP, FACE, FRCOG, *Centre for Endocrine and Diabetes Sciences, Cardiff University, University Hospital of Wales, Cardiff, UK*

ÅKE LERNMARK, PHD, *Department of Medicine, University of Washington, R.H. Williams Laboratory, Seattle, WA*

- R. DAVID G. LESLIE, FRCP, *Department of Diabetes, St. Bartholomew's Hospital, London, UK*
- MARIAN LUDGATE, BSc, PhD, *Centre for Endocrine and Diabetes Sciences, School of Medicine, Cardiff University, Cardiff, UK*
- KRISTIAN LYNCH, MSc, *Department of Clinical Sciences, Diabetes and Celiac Disease Unit, Lund University/CRC, University Hospital MAS, Malmo, Sweden*
- DOLORES B. NJOKU, MD, *Departments of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Baltimore, MD*
- SIMON H. S. PEARCE, MD, FRCP, *Department of Endocrinology, University of Newcastle and Royal Victoria Infirmary, Newcastle upon Tyne, UK*
- PÄRT PETERSON, PhD, *Molecular Pathology, University of Tartu, Tartu, Estonia*
- ALDO PINCHERA, MD, *Department of Endocrinology and Metabolism, University Hospital of Pisa, Pisa, Italy*
- L. D. K. E. PREMAWARDHANA, MBBS, FRCP, *Centre for Endocrine and Diabetes Sciences, Cardiff University, University Hospital of Wales, Cardiff, UK*
- FABIO PRESOTTO, MD, PhD, *Department of Medical and Surgical Sciences, Third Unit of Internal Medicine, University of Padua, Padua, Italy*
- SONIA QUARATINO, MD, PhD, *Cancer Research UK Clinical Centre, Cancer Sciences Division, University of Southampton, Southampton, UK*
- PHILLIP J. ROBINSON, BSc, PhD, *Cell Signalling Unit, Children's Medical Research Institute, Sydney, Australia*
- NOEL R. ROSE, MD, PhD, *Departments of Pathology, School of Medicine and Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins Medical Institutions, Baltimore, MD*
- NAGAT SAEED, PhD, *Section of Human Metabolism and Endocrinology, School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK*
- RAJNI B. SHARMA, PhD, *Department of Pathology, Johns Hopkins Medical Institutions, Baltimore, MD*
- CASEY JO ANNE SMITH, BBIOMEDSc (HONS), *Department of Paediatric Endocrinology, John Hunter Children's Hospital, Newcastle, Australia*
- VICTORIA SUNDBLAD, PhD, *Instituto de Biología y Medicina Experimental-CONICET, Buenos Aires, Argentina*
- PHILIP F. WATSON, PhD, *Section of Human Metabolism and Endocrinology, School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK*
- ANTHONY P. WEETMAN, MD, DSc, *School of Medicine and Biomedical Sciences, University of Sheffield, Sheffield, UK*
- WILMAR M. WIERSINGA, MD, PhD, *Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*
- RENATO ZANCHETTA, MD, *Department of Medical and Surgical Sciences, Unit of Endocrinology, University of Padua, Padua, Italy*