## Endocrinology and Diabetes

LEONARD J. KRYSTON, M.D. RALPH A. SHAW, M.D. Ph.D. Editors

THE THIRTIETH HALINEMANN SYMPOSIUM

# Endocrinology and Diabetes

**Editors** 

## Leonard J. Kryston, M.D.

Associate Professor of Medicine and Biological Chemistry; Acting Director, Division of Endocrinology and Metabolic Diseases, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

and

## Ralph A. Shaw, M.D., Ph.D.

Professor of Medicine and Biochemistry; Associate Vice President for Medical Affairs, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

### Edith Schwager

Executive Editor



**GRUNE & STRATTON** 

A Subsidiary of Harcourt Brace Jovanovich, Publishers New York San Francisco London

#### Library of Congress Cataloging in Publication Data

Main entry under title:

Endocrinology and diabetes.

Includes index.

- 1. Glands, Ductless-Diseases-Congresses.
- 2. Diabetes-Congresses. I. Kryston, Leonard J., ed.
- II. Shaw, Ralph A., ed. III. Schwager, Edith, ed.
- IV. Hahnemann Medical College and Hospital of Philadelphia. [DNLM: 1. Diabetes mellitus-Congresses.
- 2. Endocrinology—Congresses. WK810 E56] RC648.E46 616.4 74-26871

ISBN 0-8089-0855-3

© 1975 by Grune & Stratton, Inc.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Grune & Stratton, Inc. 111 Fifth Avenue New York, New York 10003

Library of Congress Catalog Card Number 74-26871 International Standard Book Number 0-8089-0855-3 Printed in the United States of America

## **Endocrinology and Diabetes**

#### **Preface**

This volume results from the Thirtieth International Symposium, conducted by the Hahnemann Medical College and Hospital in May 1973. Like the symposium itself, the book covers recent advances in endocrinology and diabetes, and offers rational approaches in the application of these advances to clinical practice.

The content of the book can be divided into two broad categories: endocrinologic disorders and diabetes. The first segment begins with a discussion of hormone action. A systematic review follows of some problems confronting physicians in the care of patients with disease of the endocrine glands.

The segment on diabetes, which is similarly structured, deals with difficulties encountered by clinicians in treating difficult diabetic patients and in handling the complications of diabetes. The differential diagnosis and the treatment of patients with hypoglycemia are considered in great detail.

We were honored to participate in the symposium with such distinguished experts, and would like to thank them for their authoritative and scholarly contributions.

We also wish to thank Robert J. Schaefer, Jane Krumrine and their staff for their part in the organization and conduct of the symposium.

Leonard J. Kryston Ralph A. Shaw Edith Schwager

Philadelphia, Pa.

#### Contributors

- JOHN ANTONIADES, M.D., Associate Professor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- SUCHA O. ASBELL, M.D., Assistant Professor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- GERALD D. AURBACH, M.D., Chief, Metabolic Diseases Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland
- HOWARD BALIN, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- SAMUEL B. BEASER, M.D., Lecturer in Medicine, Tufts College Medical School, Boston, Massachusetts
- ROBERT M. BLIZZARD, M.D., Professor and Chairman, Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, Virginia
- J. M. B. BLOODWORTH, JR., M.D., Professor of Pathology, Department of Pathology, University of Wisconsin Medical School, Madison, Wisconsin
- ALFRED M. BONGIOVANNI, M.D., Professor of Pediatrics, University of Pennsylvania; Director, Department of Endocrinology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
- BURIS R. BOSHELL, M.D., Ruth Lawson Hanson Professor of Medicine and Chief, Division of Endocrinology and Metabolism, University of Alabama in Birmingham, Birmingham, Alabama

xii Contributors

LUTHER W. BRADY, M.D., Professor and Chairman, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

- RAFAEL A. CAMERINI-DAVALOS, M.D., D.Sc., Professor of Medicine, Metabolism Division, Diabetes Center, Department of Medicine, New York Medical College, New York, New York
- JANET M. CANTERBURY, Ph.D., Assistant Professor, Department of Medicine, University of Miami School of Medicine, Miami, Florida
- RONALD E. CHANCE, Ph.D., Research Associate, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana
- THADDEUS S. DANOWSKI, M.D., Clinical Professor of Medicine, University of Pittsburgh School of Medicine; Director of Medicine, Shadyside Hospital, Pittsburgh, Pennsylvania
- JAIME A. DAVIDSON, M.D., Head, Endocrinology-Metabolism Department, Methodist Hospital of Dallas, Dallas, Texas
- THEODORE G. DUNCAN, M.D., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine; and Head, Section on Diabetes and Metabolism, Pennsylvania Hospital, Philadelphia, Pennsylvania
- THEODORE EHRENREICH, M.D., Clinical Professor of Pathology, Department of Pathology, New York Medical College, New York, New York
- STEFAN S. FAJANS, M.D., Professor of Internal Medicine; Head, Division of Endocrinology and Metabolism; and Director, Metabolism Research Unit, University of Michigan, Ann Arbor, Michigan
- GEORGINA FALUDI, M.D., Assistant Professor of Medicine and Director, Obesity and Diabetes Clinics, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- DONALD S. FAUST, M.D., Professor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- JAMES B. FIELD, M.D., Professor of Medicine; Chief of the Division of Endocrinology and Metabolism; and Director, Clinical Research Unit, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
- JOHN C. FLOYD, JR., M.D., Professor of Internal Medicine, Division of Endocrinology and Metabolism, and Metabolism Research Unit, University of Michigan, Ann Arbor, Michigan
- JOHN A. GALLOWAY, M.D., Senior Physician, Lilly Laboratory for Clinical Research, Eli Lilly and Company; Associate Professor of Medicine, Indiana University School of Medicine, Indianapolis, Indiana
- JOHN R. GLASSBURN, M.D., Assistant Professor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- SEYMOUR M. GLICK, M.D., Professor and Chairman, Department of

Contributors

Medicine, Ben Gurion University of the Negev Health Sciences Center, Beer-Sheva, Israel

- RALPH S. GOLDSMITH, M.D., formerly Director, Clinical Study Unit, Mayo Clinical and Mayo Foundation, and Professor of Medicine, Mayo Medical School, Rochester, Minnesota. Now at University of Texas Health Science Center, San Antonio, Texas
- FRANCISCO J. GOMEZ-PEREZ, M.D., Postdoctoral Fellow in Endocrinology and Metabolism, University of Alabama in Birmingham, Birmingham, Alabama
- SANG HO HAN, M.D., Instructor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- DAVID A. HEATH, M.D., M.R.C.P., Visiting Associate, Metabolic Diseases Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland. Now at Department of Medicine, Queen Elizabeth Hospital, Birmingham, England
- JACK W. HINMAN, Ph.D., Head, Natural Products Research, The Upjohn Company, Kalamazoo, Michigan
- RICHARD L. JACKSON, Ph.D., Research Scientist, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana
- MARVIN A. KIRSCHNER, M.D., Director of Medicine, Newark Beth Israel Medical Center; Professor of Medicine, New Jersey Medical School, College of Medicine and Dentistry of New Jersey, Newark, New Jersey
- HARVEY C. KNOWLES, JR., M.D., Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio
- LEONARD J. KRYSTON, M.D., Associate Professor of Medicine and Biological Chemistry; Acting Director, Division of Endocrinology and Metabolic Diseases, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- JOHN H. LARAGH, M.D., Professor of Clinical Medicine; Director, Hypertension Center, Columbia-Presbyterian Medical Center, New York, New York
- ALAN E. LEWIS, M.D., Clinical Assistant Professor of Medicine, Division of Endocrinology and Metabolic Diseases, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- J. MAXWELL McKENZIE, M.D., Professor of Experimental Medicine, McGill University Clinic, Royal Victoria Hospital; Research Associate, Medical Research Council of Canada, Montreal, P.Q., Canada
- ELLIOTT L. MANCALL, M.D., Professor of Medicine and Director, Division of Neurology, Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

xiv Contributors

J. MARTIN MILLER, M.D., Division of Endocrinology, Henry Ford Hospital, Detroit, Michigan

- LEWIS C. MILLS, M.D., Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- AXEL K. OLSEN, M.D., Professor of Neurosurgery, Division of Neurosurgery, Department of Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- WERNER OPPERMANN, M.D., Assistant Professor of Medicine, Metabolism Division, Diabetes Center, Department of Medicine, New York Medical College, New York, New York
- JEWELL L. OSTERHOLM, M.D., Professor of Surgery (Neurosurgery) and Director, Division of Neurosurgery, Department of Surgery, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- HARRY H. POTE, JR., M.D., Nephrology Fellow, Division of Nephrology and Hypertension, Halmemann Medical College and Hospital, Philadelphia, Pennsylvania
- JOHN T. POTTS, JR., M.D., Associate Professor of Medicine, Harvard Medical School; Chief, Endocrine Unit, Massachusetts General Hospital, Boston, Massachusetts
- SRIPRAYOON PRASASVINICHAI, M.D., Assistant Professor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- DON C. PURNELL, M.D., Consultant, Division of Endocrinology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota
- ABRAHAM E. RAKOFF, M.D., Professor of Obstetrics and Gynecology (Endocrinology) and Medicine (Endocrinology), Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania
- HOWARD RASMUSSEN, M.D., Ph.D., Benjamin Rush Professor of Biochemistry and Professor of Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
- ERIC REISS, M.D., Professor and Vice-Chairman, Department of Medicine, University of Miami School of Medicine, Miami, Florida
- MARY A. ROOT, Ph.D., Research Associate, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana
- JOHN A. ROTHSCHILD, M.D., Fellow, Division of Nephrology and Hypertension, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- JOSEPH J. RUPP, M.D., Professor of Medicine and Associate Director of Continuing Education, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania
- NORMAN G. SCHNEEBERG, M.D., Professor of Medicine, Hahnemann Medical College and Hospital; Head, Endocrine Section, Philadelphia General Hospital, Philadelphia, Pennsylvania

Contributors

ALLAN B. SCHWARTZ, M.D., Associate Professor of Medicine, Division of Nephrology and Hypertension, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

- RALPH A. SHAW, M.D., Ph.D., Professor of Medicine and Biochemistry; Associate Vice President for Medical Affairs, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- CHARLES R. SHUMAN, M.D., Professor of Medicine, Temple University School of Medicine; Chief, Department of Metabolism, Temple University Hospital, Philadelphia, Pennsylvania
- ARTHUR R. SOHVAL, M.D., Clinical Professor Emeritus, Department of Medicine, Mount Sinai School of Medicine, City University of New York, New York, New York
- CHARLES SWARTZ, M.D., Professor and Vice-Chairman, Department of Medicine; Director, Division of Nephrology and Hypertension, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- RONALD S. SWERDLOFF, M.D., Associate Professor of Medicine, University of California at Los Angeles School of Medicine, Los Angeles, California; Chief, Division of Endocrinology, Harbor General Hospital, Torrance, California
- RICHARD J. TORPIE, M.D., Assistant Professor, Department of Radiation Therapy and Nuclear Medicine, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania
- MANUEL TZAGOURNIS, M.D., Professor of Medicine, College of Medicine, Ohio State University, Columbus, Ohio
- SATISH K. VIJ, M.D., U.S. Public Health Service Trainee, Division of Endocrinology and Metabolism, and Metabolism Research Unit, University of Michigan, Ann Arbor, Michigan
- JACK L. WARD, M.D., Associate Staff, Mercer Hospital, Trenton, New Jersey
- SAMUEL M. WENTWORTH, M.D., Assistant Professor of Pediatrics, Indiana University School of Medicine; formerly Lilly-Indiana University Fellow in Diabetes, Lilly Laboratory for Clinical Research, Eli Lilly and Company, Indianapolis, Indiana
- SIDNEY C. WERNER, M.D., D.Sc. (Med.), Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons; Attending Physician, The Presbyterian Hospital in the City of New York, New York
- A. CHARLES WINKELMAN, M.D., Associate Professor of Neurology, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania

### Contents

	Preface	ix
	Contributors	xi
<b>PA</b> I	RT I. HORMONAL ACTION AND CONTROL MECHANISMS  Mechanisms of Hormone Action  Howard Rasmussen	3
2.	The Prostaglandins  Jack W. Hinman	
3.	The Role of Hypothalamic Hormones in Controlling Endocrine Function  Leonard J. Kryston	23
4.	Diagnosis and Management of Hypothalamic Disorders Joseph J. Rupp	29
PAI	RT II. PITUITARY DISORDERS	
5.	Anterior Pituitary Failure: Its Recognition and Therapy Norman G. Schneeberg	37
6.	Acromegaly: Newer Methods of Diagnosis and Results of Therapy  Seymour M. Glick	59
7.	Radiation Therapy in Pituitary Adenomas  Luther W. Brady, John Antoniades, Donald S. Faust, Sang Ho Han, Axel K. Olsen, Jewell L. Osterholm, Elliott L. Mancall and Sriprayoon Prasasvinichai	69

٧

vi

PAF	RT III. THYROID DISORDERS			
8.	Current Concepts of the Etiology of Graves' Disease  J. Maxwell McKenzie			
9.	New Laboratory Tests in the Diagnosis of Thyroid Disorders Alan E. Lewis	91		
10.	Some Aspects of the Eye Changes of Graves' Disease Sidney C. Werner	95		
11.	Hashimoto's Disease: A Prototype of Autoimmune Endocrine Disorders  *Robert M. Blizzard*			
12.	An Approach to the Thyroid Nodule  J. Martin Miller	111		
PAF	RT IV. ADRENAL DISEASE			
13.	The Adrenogenital Syndrome: Problems in Biosynthesis of Adrenal Steroids  Alfred M. Bongiovanni	123		
14.	Cushing's Syndrome: Causes, Diagnosis and Management Norman G. Schneeberg	127		
15.	Adrenocortical Failure  Lewis C. Mills	145		
16.	Endocrine Factors in Hypertension and Their Meaning John H. Laragh	153		
PAI	RT V. PROBLEMS OF CALCIUM METABOLISM			
17.	New Aspects of Calcium Regulation John T. Potts, Jr.	165		
18.	Radioimmunoassay and Its Application to the Diagnosis of Hyperparathyroidism  Eric Reiss and Janet M. Canterbury	173		
19.	Indications for Surgery in Hyperparathyroidism  Don C. Purnell	189		
20.	Abnormalities of Calcium, Phosphate and Parathyroid Hormone Metabolism in Chronic Renal Disease Harry H. Pote, Jr. and Allan B. Schwartz	197		
21.	Ectopic Production of Parathyroid Hormone: A Prototype of Nonendocrine Hormone Synthesis  David A. Heath and Gerald D. Aurbach	215		
22.	Medical Therapy of Hypercalcemia	227		

Contents				
PAR	RT VI. GONADAL DISORDERS			
23.	Contraception: Current Status of Hormonal Agents Ronald S. Swerdloff	239		
24.	Side Effects of Oral Contraceptives  Howard Balin			
25.	The Induction of Ovulation  Abraham E. Rakoff			
26.	Genetic Factors in Hypogonadism  Arthur R. Sohval			
27.	Androgen Production and Hirsutism  Marvin A. Kirschner	299		
PAF	RT VII. DIAGNOSIS AND TREATMENT OF DIABETES MELLITUS			
28.	Clinical Clues and Laboratory Criteria in the Diagnosis of Diabetes Mellitus  Leonard J. Kryston	311		
29.	Classification of Diabetes Mellitus  Thaddeus S. Danowski	321		
30.	New Forms of Insulin  John A. Galloway, Mary A. Root, Ronald E. Chance,  Richard L. Jackson, Samuel M. Wentworth  and Jaime A. Davidson	329		
31.	Sulfonylurea Drugs in Diabetes Mellitus Samuel B. Beaser	343		
32.	The Biguanides: Action and Clinical Usefulness  Buris R. Boshell and Francisco J. Gomez-Perez	347		
PAF	RT VIII. MANAGEMENT OF THE DIFFICULT DIABETIC			
33.	The Labile Diabetic Patient  James B. Field	355		
34.	The Diabetic During Surgery  Charles R. Shuman	363		
35.	Diabetes in Pregnancy Georgina Faludi	369		
36.	Diabetic Ketoacidosis  Harvey C. Knowles, Jr.	375		
37.	Hyperosmolar and Other Nonketotic Comas in Diabetes  Thaddeus S. Danowski	385		

viii Contents

PAR	TIX. VASCULAR COMPLICATIONS OF DIABETES	
38.	Atherosclerosis and Diabetes Mellitus  Manuel Tzagournis	391
39.	Diabetes Mellitus and the Hyperlipidemias  Buris R. Boshell and Francisco J. Gomez-Perez	403
40.	Diabetic Nephropathy  John A. Rothschild and Charles Swartz	413
41.	Peripheral Neuropathy A. Charles Winkelman	419
42.	Small-Vessel Disease in Diabetes Mellitus  Werner Oppermann, Theodore Ehrenreich, J.M.B. Bloodworth, Jr. and Raphael A. Camerini-Davalos	427
43.	Small-Vessel Disease and Cyclical Edema in Diabetes Mellitus  Leonard J. Kryston	443
PAI	RT X. HYPOGLYCEMIA	
44.	Differential Diagnosis of Spontaneous Hypoglycemia Stefan S. Fajans, John C. Floyd, Jr. and Satish K. Vij	453
45.	Diabetes and Reactive Hypoglycemia  Leonard J. Kryston	473
46.	Functional Hypoglycemia  James B. Field	479
47.	Emotional Aspects of Hypoglycemia  Jack L. Ward	491
48.	Nutritional Management of Hypoglycemia  Theodore G. Duncan	499
49.	Drug Treatment of Reactive Hypoglycemia Ralph A. Shaw	509
	Index	515

### PART I

# Hormonal Action and Control Mechanisms

1

#### **Mechanisms of Hormone Action**

Great progress has been made in the past decade in elucidating the mechanisms of hormone action. From these studies, two general models have been developed: the one dealing with the mechanism of action of peptide and amine hormones; the other with that of steroid hormones.

#### PEPTIDE AND AMINE HORMONE ACTION

The most widely used model to account for the action of this class of hormones is the second-messenger hypothesis, as developed by Sutherland and coworkers.<sup>1</sup> As depicted in Figure 1-1, this hypothesis proposes that the first messenger, or hormone, interacts with a specific receptor site upon the cell surface, leading thereby to activation of the membrane-bound enzyme adenylate cyclase. The activation of this enzyme leads, in turn, to a rise in the intracellular concentration of 3',5'-cyclic adenosine monophosphate (cAMP), which activates a class of enzymes,<sup>2.3</sup> protein kinases, that have the property of utilizing other proteins (enzymes) as substrates and catalyzing their phosphorylation by adenosine triphosphate (ATP)

$$Pr + ATP \xrightarrow{protein} ADP + Pr - Pi$$

There is an impressive and continually growing list of cells in which activation by one or more extracellular or first messengers leads to an increase in [cAMP] within that particular cell type. This evidence has been taken as support for the universality of the second-messenger hypothesis. However, it is evident that there are certain important exceptions to the universal involvement of cAMP as second messenger. Most notable among these are insulin<sup>4</sup> and acetylcholine.<sup>5</sup>

From the Department of Biochemistry, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Supported by grant No. AM-09650 from the U.S. Public Health Service and contract No. 108-863 from the Office of Naval Research.