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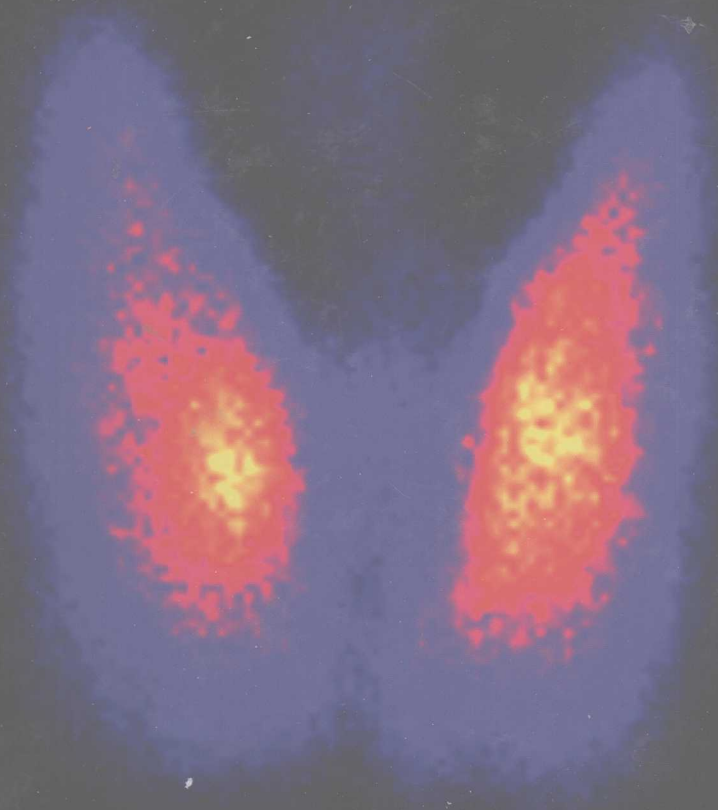
THE

THYROID

A Fundamental and Clinical Text

Lewis E. Braverman

David S. Cooper



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TENTH EDITION



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WERNER & INGBAR'S THE THYROID A FUNDAMENTAL AND CLINICAL TEXT TENTH EDITION

Editors

LEWIS E. BRAVERMAN, MD

Professor of Medicine
Section of Endocrinology, Diabetes, and Nutrition
Boston University School of Medicine
Boston, Massachusetts

DAVID S. COOPER, MD

Professor of Medicine and Radiology
Division of Endocrinology
The Johns Hopkins University School of Medicine
Professor of International Health
The Bloomberg Johns Hopkins School of Public Health
Baltimore, Maryland



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Senior Acquisitions Editor: Sonya Seigafuse
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Vendor Manager: Bridgett Dougherty
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Werner and Ingbar's the thyroid

Thyroid

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Summary: "The most comprehensive textbook on the thyroid appears in an extensively revised 10th edition. This classic text provides comprehensive coverage of every aspect of thyroid anatomy, development, biochemistry, physiology, pathophysiology, and treatment of all thyroid disorders. This edition has a more international group of contributors and new chapters on surgical management of thyroid cancer, thyroid disrupters and thyroid hormone analogs. Chapters address clinical controversies regarding subclinical hypothyroidism and hyperthyroidism"—Provided by publisher.

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CONTRIBUTORS

Stephen D. Ayers, PhD

Instructor
Genomic Medicine
Methodist Hospital Research Institute
Houston, Texas

Zubair Wahid Baloch, MD, PhD

Professor of Pathology and Laboratory Medicine
University of Pennsylvania Medical Center
Perelman School of Medicine
Philadelphia, Pennsylvania

Michael Bauer, MD, PhD

Director
Department of Psychiatry and Psychotherapy
University Hospital Carl Gustav Carus
Technische Universität Dresden
Dresden, Germany

***John D. Baxter, MD**

Senior Member
The Methodist Hospital Research Institute
Director
Genomic Medicine Program
Co-Director
Methodist Diabetes and Metabolism Institute
Chief
Division of Endocrinology
The Methodist Hospital
Houston, Texas

Paolo Beck-Peccoz, MD

Professor of Medical Sciences
University of Milan
Milan, Italy

Finn Noe Bencedbaek, MD, PhD

Associate Professor
Department of Endocrinology
University of Copenhagen
Herlev, Denmark

Salvatore Benvenga, MD

Chief
Programma di Endocrinologia
Molecolare Clinica, Policlinico Universitario
Messina, Italy

Antonio C. Bianco, MD, PhD

Professor of Medicine
Chief, Division of Endocrinology, Diabetes and
Metabolism
University of Miami Miller School of Medicine
Miami, Florida

Laura Boucai, MD, MS

Attending Physician
Department of Medicine
Montefiore Medical Center
Bronx, New York

Lewis E. Braverman, MD

Professor of Medicine
Section of Endocrinology, Diabetes, and
Nutrition
Boston University School of Medicine
Boston, Massachusetts

Alina V. Brenner, MD, PhD, MPH

Staff Scientist
Radiation Epidemiology Branch
DCEG, NCI, NIH, DHHS
Bethesda, Maryland

Gregory A. Brent, MD

Professor
Departments of Medicine and Physiology
David Geffen School of Medicine at UCLA
Chair
Department of Medicine
VA Greater Los Angeles Healthcare System
Los Angeles, California

Rosalind S. Brown, MD, CM

Associate Professor
Department of Pediatrics
Harvard Medical School
Boston, Massachusetts
Director
Clinical Trials Research
Division of Endocrinology
Children's Hospital Boston
Boston, Massachusetts

*Deceased

Henry B. Burch, MD

Chair, Endocrinology Division
Uniformed Services University of the Health Sciences
Endocrinology Service
Walter Reed National Military Medical Center
Bethesda, Maryland

Nancy Carrasco, MD

Professor
Department of Cellular and Molecular Physiology
Yale University School of Medicine
New Haven, Connecticut

Ronald N. Cohen, MD

Associate Professor, Medicine
University of Chicago
Chicago, Illinois

David S. Cooper, MD

Professor of Medicine and Radiology
Division of Endocrinology
The Johns Hopkins University School of Medicine
Professor of International Health
The Bloomberg Johns Hopkins School of
Public Health
Baltimore, Maryland

Gilbert J. Cote, PhD

Professor
Department of Endocrine Neoplasia and
Hormonal Disorders
MD Anderson Cancer Center
Houston, Texas

Sara Danzi, PhD

Assistant Professor
Department of Biological Sciences and
Geology
Queensborough Community College
Bayside, New York

Terry F. Davies, MD

Professor of Endocrinology
Diabetes and Bone Disease
Professor of Obstetrics
Gynecology and Reproductive Science
Mount Sinai School of Medicine
New York, New York

Jan J.M. de Vijlder, PhD

Professor
Division of Pediatric Endocrinology
Emma Children's Hospital
University of Amsterdam
Amsterdam, The Netherlands

Johnny Deladoëy, MD, PhD

Assistant Professor, Pediatrics
University of Montreal
Staff
Endocrinology Service
St. Justine Hospital
Montreal, Quebec

A. Jane Dickinson, MB, ChB

Associate Clinical Researcher of
Ophthalmology
Consultant Ophthalmologist
Newcastle University
Newcastle upon Tyne
Tyne and Wear, UK

Gerard M. Doherty, MD

NW Thompson Professor of Surgery
Department of Surgery
University of Michigan Medical School
Vice Chair
Department of Surgery
University of Michigan Hospital
Ann Arbor, Michigan

Alexandra M. Dumitrescu, MD, PhD

Department of Medicine
The University of Chicago
Chicago, Illinois

James A. Fagin, MD

Department of Medicine and Human Oncology and
Pathogenesis Program
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Joan and Sanford I. Weill Medical College, Cornell
University
New York, New York

Alan P. Farwell, MD

Director, Endocrine Clinics
Associate Professor of Medicine
Section of Endocrinology, Diabetes and Nutrition
Boston Medical Center
Boston University School of Medicine
Boston, Massachusetts

Vahab Fatourechi, MD

Consultant
Division of Endocrinology, Diabetes, Metabolism, and
Nutrition
Professor of Medicine
College of Medicine, Mayo Clinic
Rochester, Minnesota

Sebastiano Filetti, MD

Full Professor
Department of Internal Medicine
Sapienza University di Roma
Roma, Italy

Delbert A. Fisher, MD

Professor of Pediatrics and Medicine Emeritus
Department of Pediatrics
David Geffen School of Medicine at UCLA
Los Angeles, California

Robert F. Gagel, MD

Professor and Head
Division of Internal Medicine
MD Anderson Cancer Center
Houston, Texas

Hans Graf, MD, PhD

Associate Professor
Department of Internal Medicine
Federal University of Parana
Chief
Thyroid Unit – SEMPR
Clinical Hospital of the UFPR
Curitiba, Brazil

Cheryl E. Hanna, MD

Clinical Professor
Department of Pediatrics
Oregon Health & Sciences University
Portland, Oregon

Bryan R. Haugen, MD

Professor of Medicine and Pathology
Head
Division of Endocrinology, Metabolism and
Diabetes
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Laszlo Hegedüs, MD, DMSc

Professor
Department of Endocrinology & Metabolism
Consultant Physician
University of Southern Denmark
Odense, Denmark

James V. Hennessey, MD

Director
Clinical Endocrinology
Division of Endocrinology
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Jerome M. Hershman, MD, MS, MACP

Distinguished Professor of Medicine
David Geffen School of Medicine at UCLA
Associate Chief
Endocrinology and Diabetes
West Los Angeles VA Medical Center
Los Angeles, California

Anthony N. Hollenberg, MD

Professor of Medicine
Harvard Medical School
Chief
Division of Endocrinology, Diabetes and
Metabolism Medicine
Beth Israel Deaconess Medical School
Boston, Massachusetts

Eva Horvath, PhD

Professor of Pathology
St. Michael's Hospital
Department of Laboratory Medicine
Toronto, Ontario

Mimi I. Hu, MD

Assistant Professor
Endocrine Neoplasia and Hormonal Disorders
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Camilo Jimenez, MD

Assistant Professor
Endocrine Neoplasia and Hormonal Disorders
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Jacqueline Jonklaas, MD, PhD

Associate Professor
Division of Endocrinology
Georgetown University
Washington, DC

Madeleine A. Kane, MD

Professor of Medicine
University of Colorado, Anschutz Medical Campus
Physician, Active Medical Staff
University of Colorado Hospital
Aurora, Colorado

Michael M. Kaplan, MD

Physician
Associated Endocrinologists
West Bloomfield, Michigan
Physician
Departments of Internal Medicine and Nuclear Medicine
William Beaumont Hospital
Royal Oak, Michigan

Brian W. Kim, MD

Assistant Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
University of Miami, Miller School of Medicine
Miami, Florida

Irwin L. Klein, MD

Professor of Medicine
North Shore University Hospital
Manhasset, New York

Richard T. Kloos MD

Professor
The Ohio State University
Divisions of Endocrinology and Nuclear Medicine
Co-Director
The Ohio State University
Columbus, Ohio

Joshua P. Klover, MD

Assistant Professor of Medicine and Radiology
Division of Endocrinology, Metabolism and Diabetes,
Subspecialty Associate Program
Director
Department of Internal Medicine Residency
Training Program
University of Colorado
School of Medicine
Aurora, Colorado

Peter Kopp, MD

Associate Professor
Division of Endocrinology, Metabolism and Molecular
Medicine
Northwestern University
Chicago, Illinois

Kalman Kovacs, MD, PhD

Department of Laboratory Medicine
Division of Pathology
St. Michael's Hospital
Toronto, Ontario

Gerasimos E. Krassas, MD, PhD

Unsalaries Professor
Medical School
University of Athens
Athens, Greece
Chief Endocrinologist
Endocrinology, Diabetes and Metabolism
Interbalkan European Center
Thessaloniki, Greece

Paul W. Ladenson, MD

Professor and Director
Division of Endocrinology & Metabolism
Department of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Stephen H. LaFranchi, MD

Professor
Department of Pediatrics
Oregon Health & Science University
Staff Physician
Department of Pediatrics
Doernbecher Children's Hospital
Portland, Oregon

Jill E. Langer, MD

Associate Professor of Radiology
Clinical Practices of the University of
Pennsylvania
Hospital of the University of Pennsylvania
Perelman Center for Advanced Medicine
Philadelphia, Pennsylvania

**John H. Lazarus, MD, FRCP (Lon. Ed. Glas.),
FRCOG, FACE**

Professor of Clinical Endocrinology
Center for Endocrine and Diabetes Sciences
Cardiff University School of Medicine
Professor Emeritus
Center for Endocrine and Diabetes Sciences
University Hospital of Wales
Cardiff, Wales, UK

Angela M. Leung, MD, MSc

Assistant Professor of Medicine
Department of Medicine
Boston University School of Medicine
Boston, Massachusetts

Virginia A. LiVolsi, MD

Professor of Pathology and Laboratory Medicine
Department of Pathology and Laboratory
Medicine
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

Susan J. Mandel, MD, MPH

Professor of Medicine and Radiology
Division of Endocrinology, Diabetes, and
Metabolism
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Michael T. McDermott, MD

Professor of Medicine and Clinical Pharmacy,
Medicine
Division of Endocrinology
University of Colorado
Denver School of Medicine
Aurora, Colorado

Christoph A. Meier, MD

Professor of Medicine
University of Geneva Medical School
Geneva, Switzerland
Chief of Department of Internal Medicine and
Specialities
Triemli Hospital
Zürich, Switzerland

Jorge H. Mestman, MD

Professor of Medicine and Obstetrics and
Gynecology
Keck School of Medicine
University of Southern California
Los Angeles, California

Yuri Efimovich Nikiforov, MD, PhD

Professor of Pathology
Department of Pathology
University of Pittsburgh
Director
Division of Molecular Anatomic Pathology
Department of Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Ralf Paschke, MD

Professor
Klinik für Endokrinologie und Nephrologie
Universität Leipzig
Leipzig, Germany

Elizabeth N. Pearce, MD, MSc

Associate Professor of Medicine
Section of Endocrinology, Diabetics and
Nutrition
Boston University School of Medicine
Boston, Massachusetts

Petros Perros, MD

Institute of Human Genetics
Newcastle University
International Centre for Life
Royal Victoria Infirmary
Newcastle upon Tyne, UK

Luca Persani, MD, PhD

Associate Professor
 Dipartimento di Scienze Mediche
 Università degli Studi di Milano
 Chief
 Division of Endocrinology and Metabolism
 San Luca Hospital, Istituto Auxologico
 Italiano
 Milano, Italy

Nikolaos E. Pontikides, MD

Consultant Endocrinologist
 Department of Endocrinology
 Diabetes and Metabolism
 Panagia General Hospital
 Thessaloniki, Greece

Gregory W. Randolph, MD

Director
 General and Thyroid Surgical Services
 Associate Professor
 Otolaryngology Head and Neck Surgery
 Harvard Medical School
 Director
 General Otolaryngology Division
 Director
 Division of Thyroid and Parathyroid Surgery
 Mass General Hospital, Mass Eye and Ear
 Infirmery
 Boston, Massachusetts

Samuel Refetoff, MD

Professor Emeritus of Medicine and
 Pediatrics
 The University of Chicago Medical Center
 Chicago, Illinois

Thomas Reinehr, MD

Head, Associate Professor
 Pediatric Endocrinology
 University of Witten/Herdecke
 Head
 Pediatric Endocrinology
 Diabetes and Nutrition Medicine
 Vestische Children's Hospital
 Datteln, Germany

Douglas S. Ross, MD

Professor of Medicine
 Harvard Medical School
 Co-Director, Thyroid Associates
 Massachusetts General Hospital
 Boston, Massachusetts

Elio Roti, MD

Director
 Internal Medicine Unit
 Ospedale di Suzzara SpA
 Suzzara, Italy

Fabio Rotondo, BSc

Research Associate
 Department of Laboratory Medicine
 Division of Pathology
 St. Michael's Hospital
 Toronto, Ontario

Joshua D. Safer, MD

Associate Professor of Medicine and Molecular Medicine
 Director
 Endocrinology Fellowship Training
 Section of Endocrinology, Department of Medicine
 Boston University Medical Center
 Boston, Massachusetts

Mary H. Samuels, MD

Professor
 Department of Medicine
 Oregon Health and Science University
 Portland, Oregon

Pilar Santisteban, PhD

Research Professor
 Instituto de Investigaciones Biomédicas (IIBM)
 Consejo Superior de Investigaciones Científicas (CSIC)
 Universidad Autónoma de Madrid (UAM)
 Madrid, Spain

***Clark T. Sawin, MD**

Department of Veterans Affairs
 Office of the Medical Inspector, Veterans Administration
 Washington, DC

Arthur B. Schneider, MD, PhD

Professor of Medicine Emeritus
 Section of Endocrinology, Diabetes and Metabolism
 University of Illinois
 Chicago, Illinois

Kathryn G. Schuff, MD, MRC

Associate Professor
 Division of Endocrinology
 Diabetes, and Clinical Nutrition
 Oregon Health & Science University
 Portland, Oregon

Steven I. Sherman, MD

Chair, Naguib Samaan Distinguished Professor in
 Endocrinology
 Endocrine Neoplasia and Hormonal Disorders
 Medical Director
 Endocrine Multidisciplinary Center
 University of Texas, MD Anderson Cancer Center
 Houston, Texas

Peter A. Singer, MD

Professor of Clinical Medicine
 Chief, Clinical Endocrinology
 Keck School of Medicine of USC
 University of Southern California
 Los Angeles, California

Offie P. Soldin, PhD

Director
PregnaTox, Lombardi Comprehensive Cancer Center
Departments of Medicine, Oncology, Obstetrics &
Gynecology, Pharmacology & Physiology
Georgetown University Medical Center
Washington, DC

Carole Ann Spencer, MT, PhD, FACB

Professor of Medicine
University of Southern California
Technical Director
USC Endocrine Laboratories
Pasadena, California

Martin I. Surks, MD

Program Director
Division of Endocrinology and Metabolism
Professor of Medicine and Pathology
Montefiore Medical Center and the Albert Einstein
College of Medicine
Bronx, New York

Héctor M. Targovnik, MD, PhD

Associate Professor
Cátedra de Genética y Biología Molecular
Facultad de Farmacia y Bioquímica
Buenos Aires University
Buenos Aires, Argentina

Sébastien Thalmann, MD, PhD

Attending Physician
Department of Medicine and Specialties
Triemli Hospital
Zurich, Switzerland

R. Michael Tuttle, MD

Professor of Medicine
Endocrinology Service
Memorial Sloan-Kettering Cancer Center
Weill Cornell Medical School, Cornell University
New York, New York

Apostolos G. Vagenakis, MD

Emeritus Professor of Medicine
Department of Medicine
University of Patras Medical School
Patras, Greece

Greet Van den Berghe, MD, PhD

Professor of Medicine
Intensive Care Medicine
Katholieke Universiteit Leuven
Head
Division of Intensive Care Medicine
Chair
Department of Acute Medical Sciences
Intensive Care Medicine
University Hospitals Leuven – Campus Gasthuisberg
Leuven, Belgium

Guy Van Vliet, MD

Professor of Pediatrics
University of Montreal
Chief
Endocrinology Service
St. Justine Hospital
Montreal, Quebec

Gilbert Vassart, MD, PhD

Emeritus professor
IRIBHM
Faculty of Medicine
Free University of Brussels
Brussels, Belgium

Thomas Vulmsa, MD, PhD, MSc

Emma Children's Hospital
University of Amsterdam
Pediatric Endocrinologist
Academic Medical Center
Amsterdam, The Netherlands

Richard L. Wahl, MD

Director
Division of Nuclear Medicine/PET
Vice Chair
Technology and New Business Development
Department of Radiology
Henry N. Wagner, Jr. Professor of Nuclear
Medicine
Professor of Radiology and Oncology
Johns Hopkins University School of
Medicine
Baltimore, Maryland

Leonard Wartofsky, MD, MBH, NACP

Professor of Medicine Anatomy, Physiology
and Genetic Department of Medicine
Uniformed Services University of the Health Sciences,
Bethesda, Maryland
Chairman
Department of Medicine
Washington Hospital Center
Washington, DC

Paul Webb, PhD

Co-Director of Genomic Medicine
Associate Member
The Methodist Hospital Research
Institute
Houston, Texas

Anthony P. Weetman, MD, DSc

Professor of Medicine
Department of Human Metabolism
University of Sheffield
Consultant Endocrinologist
Sheffield Teaching Hospitals
Sheffield, UK

Peter C. Whybrow, MD

Director
Semel Institute for Neuroscience and Human Behavior
Judson Braun Distinguished Professor and Executive Chair
Department of Psychiatry and Biobehavioral Sciences
David Geffen School of Medicine, UCLA
Physician-In-Chief & CEO
Resnick Neuropsychiatric Hospital
UCLA Health System
Los Angeles, California

Wilmar M. Wiersinga, MD, PhD, FRCP (Lond)

Emeritus Professor
University of Amsterdam
The Netherlands
Endocrinology and Metabolism
Academic Medical Center
Amsterdam, The Netherlands

Graham R. Williams, MB, BS, PhD

Professor of Endocrinology
Molecular Endocrinology Group
Department of Medicine
Imperial College London
London, UK

Fredric E. Wondisford, MD

Professor of Medicine
Pediatrics & Physiology Director
Metabolism Division Director
JHU-UMD Diabetes Research & Training
Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

Paul M. Yen, MD

Cardiovascular and Metabolic Disorders
Program
Duke-NUS Graduate Medical School
Singapore

Michael B. Zimmermann, MSc, MD

Professor
Department of Health Sciences and
Technology
ETH Zurich
Zurich, Switzerland

■ PREFACE TO THE TENTH EDITION

The first edition of *The Thyroid*, conceived by Dr. Sidney Werner who believed, and we agree, that a comprehensive clinical and basic textbook devoted to the thyroid was needed, was first published in 1955 and again in 1962. Dr. Werner recruited Dr. Sidney Ingbar to co-edit the third and fourth editions in 1971 and 1978. Following Dr. Werner's retirement, Dr. Ingbar asked his former endocrine fellow, colleague, and close friend, Dr. Lewis Braverman to co-edit the fifth edition, published in 1986. Unfortunately, Dr. Ingbar's untimely death in 1988 left a tremendous void in the scientific community and in the publication of this book. Dr. Robert Utiger, a renowned investigator, clinician, and deputy editor of *The New England Journal of Medicine*, joined Dr. Braverman to co-edit the next four editions, the ninth published in 2005. Unfortunately, Dr. Utiger died in 2008 after a brief illness and it was unclear whether another edition of *The Thyroid* would be published. Fortunately, Lippincott Williams and Wilkins believed that a tenth edition was needed in view of the popularity of the previous editions and the ability to publish textbooks both in print and online. A new co-editor was desperately needed. Dr. David Cooper, an outstanding teacher, co-editor of scientific journals including the *Journal of Clinical Endocrinology and Metabolism* and the *Journal of American Medical Association*, author of numerous research and review articles, and past president of the American Thyroid Association, agreed to co-edit this tenth edition.

The creation of this book was just one of Dr. Werner's many contributions to thyroidology. Long interested in Graves' disease, he carried out many of the early studies of the therapeutic efficacy and side effects of radioiodine therapy for Graves' thyrotoxicosis, and was one of the first to question whether it was a pituitary disease, as many had thought. He was responsible for the first system for classifying the ocular manifestations of Graves' disease, and he carried out many studies of the pathogenesis and therapy of Graves' ophthalmopathy. He was a long-time member of the American Thyroid Association, a member of its board of directors from 1968 to 1974, and its president in 1973. In short, he was a leader in the field of thyroidology for many years. Dr. Werner died in 1994 in Arizona where he lived in retirement with his wife.

Dr. Ingbar was a giant in the field. He was at the forefront of thyroid research for over 40 years, and his studies spanned all of thyroidology. He made seminal contributions to our understanding of the mechanisms of action of thyroid hormone, the effects of iodine on thyroid function, the physiology of thyroid hormone secretion, the transport and metabolism of thyroid hormones, the mechanisms of action of antithyroid drugs, and the diagnosis and treatment of virtually every thyroid

disease. He was also a long-time member of the American Thyroid Association, a member of its Board of Directors from 1971 to 1975, and president in 1976. Dr. Ingbar was also the president of the Endocrine Society, a member and leader of the NIH Endocrine Study Section for many years, and was a mentor for many national and international fellows who rose to leadership positions.

In his preface to the first edition, which is reprinted on the following pages, Dr. Werner commented that the book "is intended for those who must deal with the problems of thyroid function and thyroid disease in man." That has been our intention as well. We want this book to be useful to anyone who is interested in any aspect of the thyroid in both health and disease. This includes not only clinicians and investigators, but also research and clinical fellows just entering the field, and perhaps even younger students at the time of their first exposure to thyroidology.

This tenth edition of *The Thyroid* owes much to its predecessors, but it has been changed, too. Authorship has become more international. There are new chapters, and some old ones are missing, their contents incorporated into related chapters, especially those related to the effects of thyroid dysfunction on other organ systems. As in the past, we have tried to minimize overlap among different chapters, but some overlap is inevitable and probably essential. For example, the topics of iodine metabolism and the effects of iodine deficiency and excess on thyroid function are so central to any understanding of the thyroid gland and its diseases, and yet so diverse, that they must be considered in many chapters. The same is true for the actions of the thyroid hormone, to the many different yet related aspects of thyroid autoimmunity, and to nodular goiter and thyroid cancer.

Research into the thyroid gland and its disorders has flourished in recent years, as a result of application of a wide array of new research methods, from those of molecular biology to those of clinical trials and meta-analysis. We know much more about the mechanisms of action of thyroid hormone and the metabolism of thyroid hormones than just a few years ago. The genes for the transporters and enzymes involved in thyroid iodine metabolism and thyroid hormone production have been cloned. Studies of these and other previously cloned thyroid-related genes (e.g., those of the thyrotropin receptor and thyroglobulin) have provided much new knowledge about both normal and abnormal physiology. With respect to the common thyroid diseases, iodine deficiency is still the most common, and much progress has been made to eradicate iodine deficiency but more is needed. The success of programs for screening newborn infants for hypothyroidism is surely a major triumph, and

the continued expansion of these programs worldwide has the potential to eliminate the most common treatable cause of mental retardation. We still know little about the pathogenesis of the thyroid autoimmune diseases or thyroid nodular disease, but even in these areas progress is being made. Over the past few years, many advances have been made in the therapy of both metastatic -differentiated thyroid cancer and medullary thyroid cancer, and this topic is covered in greater detail in this edition. Finally, we are learning more about the transport of thyroid hormone into the cell, and the newly described transporters are described in detail.

We wish to thank all the contributors to the book. Their charge was to ensure that their chapters are current and comprehensive, and to provide interpretation and guidance in areas of controversy. We have tried to guide but not dictate to them.

We also wish to thank Ms. Kerry Barrett of Lippincott Williams and Wilkins for her tremendous encouragement and assistance in the production of the book.

In this era of ready access to many small packets of information, we still believe that there is a need for comprehensive review and evaluation of what is known and what is not known—in other words, a book, and it has been our goal to provide this review and evaluation. We hope this new edition of *The Thyroid* will match up with the preceding ones, and that it will provide guidance and even inspiration to those who seek to increase their understanding of the thyroid gland and to treat or prevent its diseases.

Lewis E. Braverman
David S. Cooper

■ PREFACE TO THE FIRST EDITION

This book is intended for those who must deal with the problems of thyroid function and thyroid disease in man. It is designed for use in the clinic and in the basic science laboratory connected with the clinic. The information made available 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 to meet differing requirements. It has been planned to provide sufficient documentation to satisfy most needs and, for more exhaustive requirements, to provide a bibliography adequate enough to initiate a search of the literature.

The introduction of a book into a field of clinical medicine today requires considerable justification. In the thyroid field particularly, there already is a profusion of books including the almost classic works of Means in this country and of Joll in England, recently and capably revised by Rundle. Nevertheless, the recent growth of medical knowledge in general, and about the thyroid in particular, appears to have created need for a new volume constructed on a somewhat different basis from those of previous works.

Barry Wood has compared the growth of medical information to that of bacteria. Bacteria show a lag at the beginning of growth and then multiply at a logarithmic rate. Wood considers the growth of current-day medicine to have reached the logarithmic phase. The accumulation of data about the thyroid provides a good example of this acceleration. One author of a recent review claims to have unearthed 3,000 new references pertaining to the gland and published during the single year before he wrote his article. *The Quarterly Cumulative Index Medicus* offers about 7,800 references to the thyroid in the past decade. More than this, the thyroid field is permeated by contributions from the cardiologist, neurologist, muscle physiologist, and many others, bringing the highly unique techniques of their particular specialties to bear on the subject.

It is evident that the ability of any one individual to follow progress in all directions at once has all but vanished. As a consequence, marked subspecialization of interest has developed and advances have come to depend upon the interchange of information among many specialists, each providing his own orientation. This trend has suggested that the information in a book about the healthy and diseased thyroid should also be subjected to the process of sifting and appraising through many eyes. The various specialists present material with which they have had direct experience, and the editor functions as the overseer to provide orientation and preserve the inherent orderliness of the entire subject. The total clinical and research experience made available in this way exceeds that of one person alone.

Each topic can be subjected to the critique of a man who has worked intensively with the problem. Finally, a book of this sort can be readily kept current, because of the authors' continued contact with investigation and the fact that there are no large sections to be rewritten by any one individual.

Every effort has been made to make available sufficient basic and clinical knowledge to satisfy curiosity about either of these aspects. For example, sections on the fundamental properties of radioiodine that permit the use of the isotope and on the instrumentation that facilitates such use are presented as well as a discussion of the clinical application. Most basic sections are separated from the clinical material, but are incorporated with it where this has seemed reasonable.

The fundamental aspects of thyroid function in man and the mechanisms which control the activity of the gland; the biochemistry of the hormone; and histology and comparative anatomy make up Part I. The mechanisms of action of the antithyroid drugs are included because of the intimate relationship of their effects to the problems of basic physiology.

Part II presents the laboratory methods which supplement the clinical appraisal of thyroid secretory activity. The presentations of the basic principles involved in radioiodine usage and the instrumentation which is employed are included within the laboratory section and are available here for later reference when the therapeutic as well as diagnostic use of the isotope are considered.

The diseases of the thyroid are considered in Part III. The disorders first described are those in which the level of thyroid hormone in the circulation and tissues is within normal limits—euthyroidism. After this come the derangements in which hormone levels are increased—toxic goiter or hyperthyroidism—or decreased—hypothyroidism or myxedema. The effects of hyperthyroidism and of hypothyroidism upon the individual body systems have been subjected to fairly detailed analysis.

The plan to arrange disease by functional categories breaks down in relation to inflammation of the thyroid including the peculiar composite entity, chronic thyroiditis. Inflammations of the thyroid tend to inactivate the gland but chronic thyroiditis is almost as often associated with evidence of hyperthyroidism as with hypothyroidism. The inflammations have been placed under a separate heading on this account.

Before the disease states are presented, several important preliminary subjects are considered in Part III. The normal and abnormal developments of the gland are described, together with the surgical anatomy and a method of physical examination that is an essential procedure because of the accessibility of the thyroid to this approach. The pathology is presented in its

entirety in the introductory sections and is not dispersed among the various diseases. A concept of change in thyroid disease emerges in this way which could not otherwise become evident.

A major goal throughout the volume has been to assess the validity of the facts on which current information or procedure is based. Corroborative information is often documented beyond reasonable doubt, but too often is based only on speculation or custom or is wanting altogether. The fact that a critical appraisal has been accomplished is a tribute to the contributors. The world today, as in the past, is threatened by prejudice, of which racial, social, and economic prejudices are but a few. Equally influential, but less well recognized, is the prejudice of "experience," derived from uncritical or uncontrolled observation, from the word of an "authority," or from emotional bias.* Fortunately there are those who are willing to give time and effort to seek out and correct such distortions of the truth.

Considerable aid has come to the editor from several sources. Dr. John Stanbury has been particularly helpful. The members of the Thyroid Clinic at the Presbyterian Hospital need recognition for their influence upon the formulation of many of the views presented herein. Credit must be given to the patience and forbearance of the many contributors who tolerated changes in style and length of manuscript in the interest of creating an integrated volume out of a series of individual essays. The editor's wife has acted as guardian of clarity, upon the thesis that even the layman should be able to read and understand a well-written article. Miss Anne Powell, of the librarian staff at P. & S., was extremely generous with her time. Finally, Mrs. R. Levine and Mrs. K. Sorenson were more than patient with the secretarial details.

Sidney C. Werner
New York City

*"Conviction is by no means devoid of emotion but is a disciplined and differentiated emotion, pointed to the removal of a realistic obstacle.

By contrast, the emotion behind prejudice is diffused and overgeneralized, saturating unrelated objects."—Gordon W. Allport: *The Nature of Prejudice*.

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