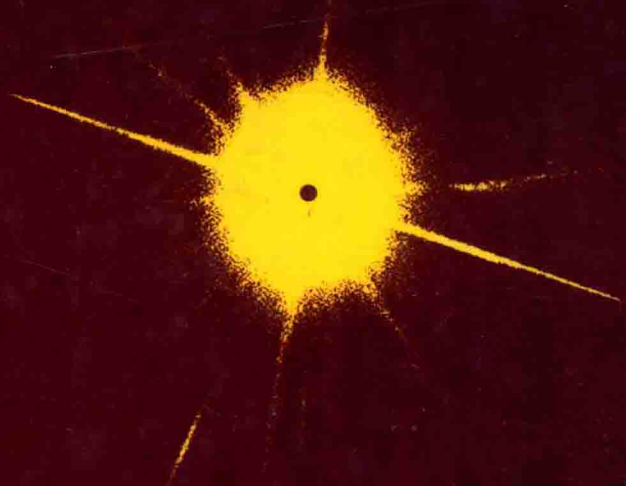


HARRISON'S 15<sup>TH</sup>  
EDITION

PRINCIPLES OF  
**INTERNAL  
MEDICINE**

BRAUNWALD  
FAUCI  
KASPER  
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VOLUME 2



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INTERNATIONAL EDITION

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# HARRISON'S 15<sup>TH</sup> EDITION

## PRINCIPLES OF INTERNAL MEDICINE

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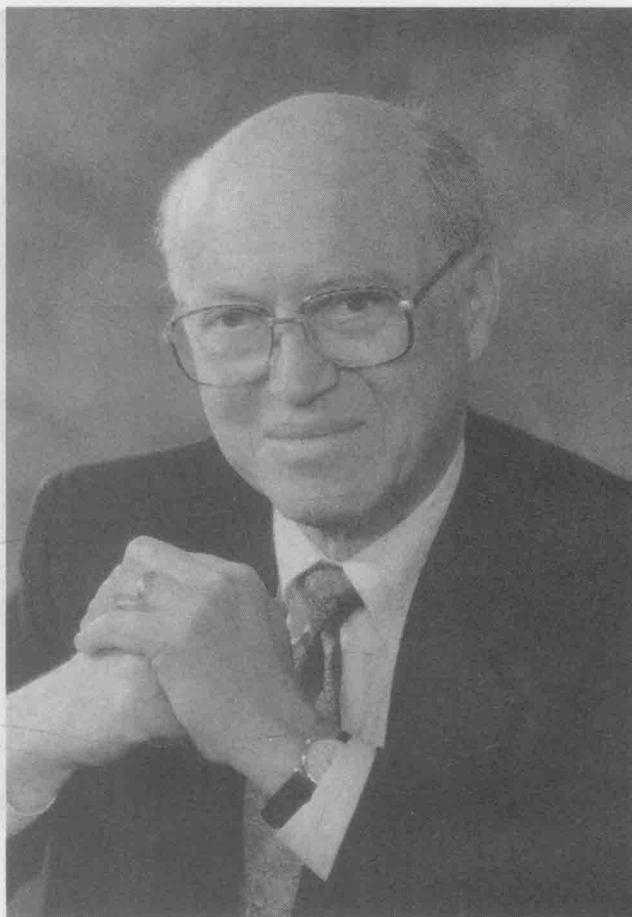
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KURT J. ISSELBACHER

With this edition, the editors acknowledge the many contributions of our colleague Kurt J. Isselbacher, who served as an editor of *Harrison's* for nine editions, the sixth through the fourteenth, including Editor-in-Chief of the ninth and thirteenth editions. For more than three decades Dr. Isselbacher played a decisive role in ensuring that *Harrison's* epitomized the state of the art and science of internal medicine and the essence of accuracy and clarity. His indelible contributions to *Harrison's* are felt in the fifteenth edition and will endure into the future.

Dr. Isselbacher is a graduate of Harvard College and of the Harvard Medical School. His further training included a residency in medicine at the Massachusetts General Hospital and a research fellowship at the National Institutes of Health. Chosen to lead the Gastrointestinal Unit of the MGH at the remarkable age of 31, over the ensuing 30 years as Chief of that Unit, he was a leader in advancing both the clinical specialty of gastroenterology and the basic understanding of gastrointestinal disease. Under his leadership, the MGH Gastrointestinal Unit became renowned for its training program in academic gastroenterology as well as for being one of the world's leading centers for clinical and research activities in gastroenterology. In 1987, Dr. Isselbacher undertook new challenges as the first Director of the Cancer Center at the MGH, bringing his characteristic insight and leadership to this new task. In a relatively short time, the MGH Cancer Center has emerged as a premier cancer research institute. Dr. Isselbacher holds the Mallinckrodt Distinguished Professorship of Medicine at Harvard Medical School, and he has been a powerful force for excellence in scholarship at this institution since his graduation. For almost 30 years he served as Chairman of the

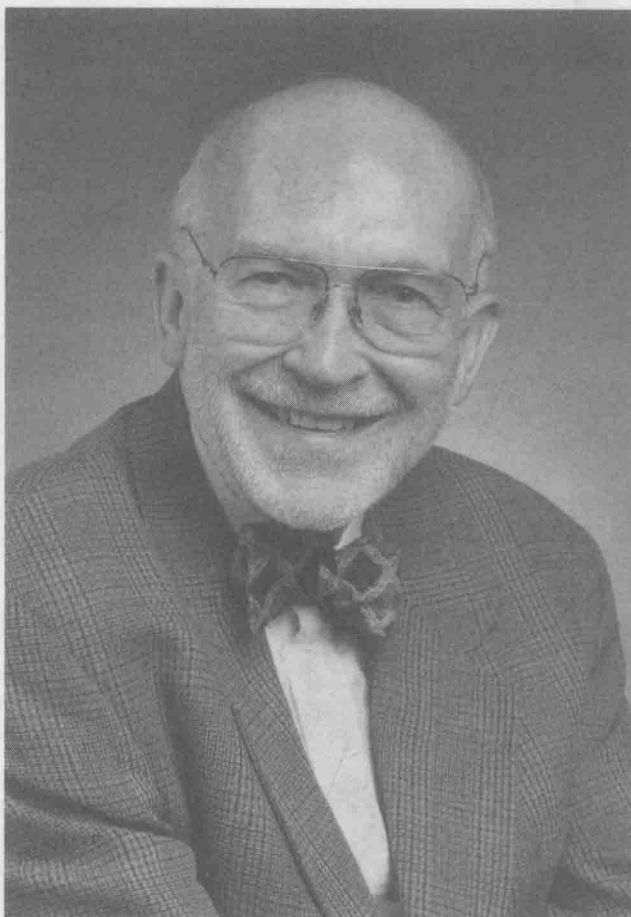
Executive Committee of Harvard's Departments of Medicine and played a pivotal role in the departments' growth and quest for excellence.

Dr. Isselbacher combines the attributes of an excellent scientist with those of a superb clinician and teacher. He has trained generations of physicians and investigators, including many who are now leaders in academic medicine. As the author of more than 400 scientific articles in leading journals, his research contributions include definition of enzymatic defects in absorptive disorders, and delineation of biochemical mechanisms of absorption, malabsorption, protein synthesis, derangements of metabolism, and immunologic aspects of hepatic gastrointestinal disease. Kurt Isselbacher has been a recipient of many well-earned honors, including the Distinguished Achievement Award and the Friedenwald Medal of the American Gastroenterological Association, the John Phillips Memorial Award for distinguished contributions to clinical medicine from the American College of Physicians, as well as the Kober Medal of the Association of American Physicians. He is a member of the National Academy of Sciences and of its Institute of Medicine and has served as President of the American Gastroenterological Association, the American Association for the Study of Liver Disease, and the Association of American Physicians.

Kurt Isselbacher exemplifies the highest values of medicine. A caring, empathic physician, he consistently combines compassion with incisive analysis in the care of patients. With contributions as a clinician, teacher, scientist, and editor, he has advanced the care of patients with gastrointestinal disorders and cancer while educating generations of physicians.



## DEDICATION



JEAN DONALD WILSON

Jean Wilson served as editor of the ninth through the fourteenth editions of *Harrison's Principles of Internal Medicine* from 1978 to 1998; he was Editor-in-Chief of the twelfth edition. A native of Texas, Jean Wilson attended the University of Texas at Austin and the University of Texas Southwestern Medical School in Dallas. He trained as a resident in internal medicine and as a fellow in endocrinology and metabolism at Parkland Hospital. With the exception of 2 years of research in biochemistry in the intramural program of the National Institutes of Health, Dr. Wilson spent his entire career at the University of Texas Southwestern Medical School, where he now holds the Charles Cameron Sprague Distinguished Chair in Biomedical Science.

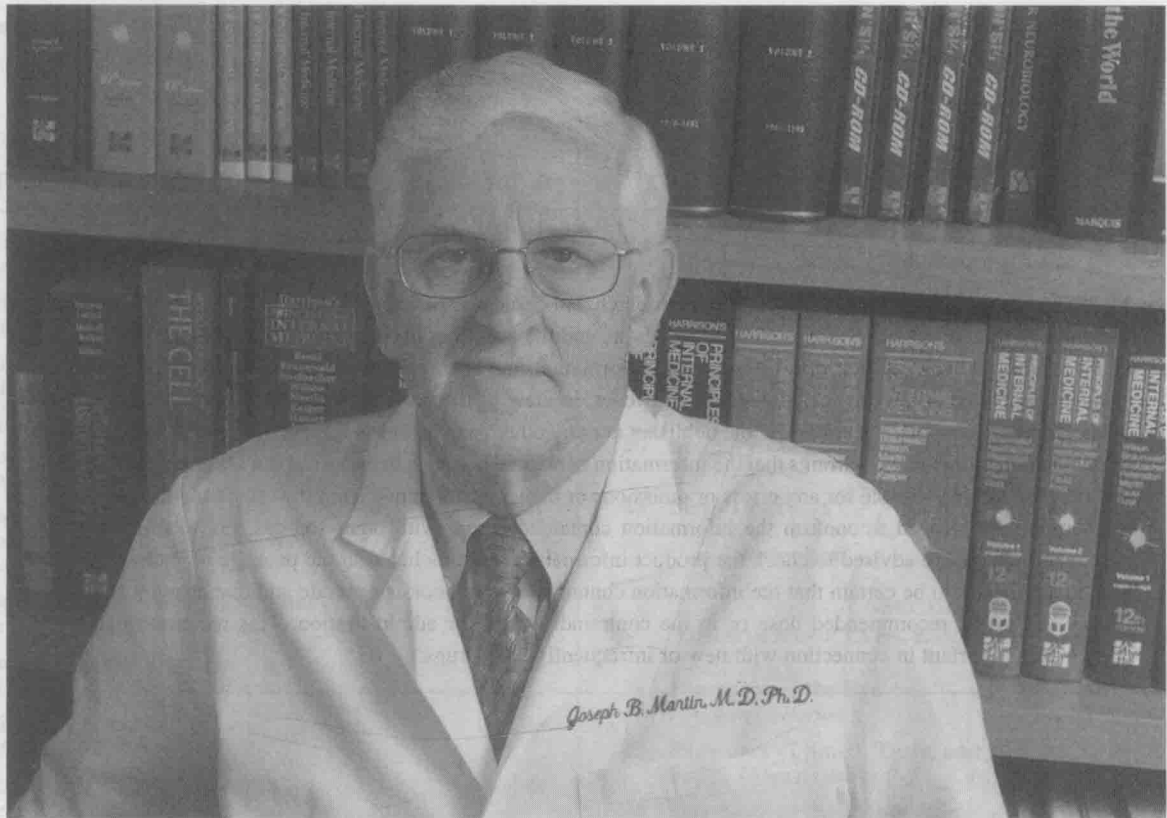
Dr. Wilson is one of America's most distinguished biomedical scientists and is largely responsible for working out the mechanism of action and physiology of the male sex hormones from the embryo to the normal and diseased adult. Among his many important discoveries has been the  $5\alpha$ -reductase reaction, whereby male target tissues convert testosterone to the more active androgen, dihydrotestosterone. He has been honored many times for his research, having received the Ernst Oppenheimer Memorial Award of the Endocrine Society, the Amory Prize of the American Academy of Arts and Sciences, the Lita Annenberg Hazen Award for Excellence in Clinical Research, the Henry Dale Medal of the Society for Endocrinology, the Gregory Pincus Award of the Worcester Foundation for Experimental Biology, the Fred Conrad Koch Award of the Endocrine Society, and the Kober Medal of the Association of American Physicians.

Amongst his memberships are the National Academy of Sciences, the Institute of Medicine of the National Academy of Sciences, and the American Academy of Arts and Sciences. He is a Fellow of the Royal College of Physicians. He has served as President of the American Society for Clinical Investigation, the Association of American Physicians, and the Endocrine Society. For two decades, Dr. Wilson directed the enormously successful MD/PhD program and for 8 years, the highly esteemed Endocrine-Metabolism Division at Southwestern.

Perhaps the finest thing that can be said of Jean Wilson is that he is a professor of internal medicine in the complete sense. He is, and always has been, a superb teacher and exemplary clinician while constantly maintaining a sterling career in research. Perhaps nothing describes him better than the enduring image of this renowned academic physician trimming callouses and ulcers in the Diabetic Foot Care Clinic at Parkland Memorial Hospital, his teaching hospital, where the patients are the medically indigent of Dallas.

Dr. Wilson is a man of diverse interests, a true intellectual. One of his great gifts and loves is scientific and medical editing. He served as Editor-in-Chief of the *Journal of Clinical Investigation* and of *Williams Textbook of Endocrinology*. As an editor of *Harrison's* for two decades, Dr. Wilson made ample use of his conspicuous strengths as clinician, teacher, and scientist. His meticulous scholarship and high standards have had an enormous impact, not only on the Endocrinology, Metabolism, and Genetics sections, for which he had primary responsibility, but on the entire book.

## DEDICATION



JOSEPH B. MARTIN

The editors wish to acknowledge the enormous contributions made by Joseph B. Martin, who edited the Neurology section of *Harrison's* from the tenth to the fourteenth editions. Dr. Martin followed Dr. Raymond D. Adams as editor of the Neurology section. In retrospect, the choice of Joseph Martin to replace Adams was prescient. It foresaw the transformation of neurology in the 1980s and 1990s from a largely descriptive discipline to one of the most dynamic and rapidly evolving areas of internal medicine. With his appointment as editor, the textbook had secured the foremost leader in the new field of molecular neurology to its ranks. Beginning with the tenth edition, Martin built upon the powerful didactic structure of the "syndromic approach" to neurology created by Adams and emphasized advances in molecular genetics and cell biology that reclassify neurologic diseases, clarify disease mechanisms, and offer new insights into clinical diagnosis and therapy. During his tenure, the neurology section of *Harrison's* became the best resource of its kind for the exposition of new discoveries in neurology and contributed substantially to the growing overall success of the textbook.

Born in Bassano, Alberta, Canada, Dr. Martin received his pre-medical and medical education at the University of Alberta, Edmonton, trained in neurology at Case Western University, and received the PhD from the University of Rochester. His career in academic medicine began in 1971 at McGill University in Montreal, where he established an independent laboratory focused on hypothalamic regulation of pituitary hormone secretion, and where he quickly rose to become Chair of the Department of Neurology and Neurosurgery. In 1978, he joined the faculty at Harvard Medical School as Bullard (later Julianne Dorn) Professor of Neurology and Chief of the Neurology Service at Massachusetts General Hospital. While at Harvard,

he established the Huntington's Disease Center Without Walls, which in 1983 reported the spectacular finding of a genetic marker linked to Huntington's disease, thereby inaugurating the modern era of molecular neurogenetics. In 1989 Dr. Martin joined the University of California, San Francisco, initially serving as Dean of the School of Medicine and subsequently as Chancellor. Among his many achievements at UCSF was the conception of a major new research campus in San Francisco, which is fast becoming a reality. In July 1997, he returned to Harvard as the Caroline Shields Walker Professor of Neurobiology and Clinical Neuroscience and Dean of the Faculty of Medicine. A wonderful teacher and physician, Joe Martin has inspired a generation of housestaff, students, and colleagues at Harvard and UCSF.

Dr. Martin has received many honors, including honorary degrees from five distinguished universities and the Abraham Flexner Award of the Association of American Medical Colleges. He serves or has served on the editorial boards of nineteen medical and neurology journals. He is a member of the Institute of Medicine of the National Academy of Sciences and has served as President of the American Neurological Association.

Dr. Martin's many contributions to this textbook were enhanced by his extraordinary organizational skills and by a clear and direct style of writing and editing that permitted him to distill complex concepts into easily readable prose accessible to a general medical readership. As an example, his chapter on neurogenetics has become an instant classic and a highlight of each new edition of the book. The editors greatly value their friendship with this remarkable man whose integrity and intellectual strengths have served *Harrison's* so well during the past two decades.

## NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The editors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the editor nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or the results obtained from the use of such information. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this book is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is particularly important in connection with new or infrequently used drugs.



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