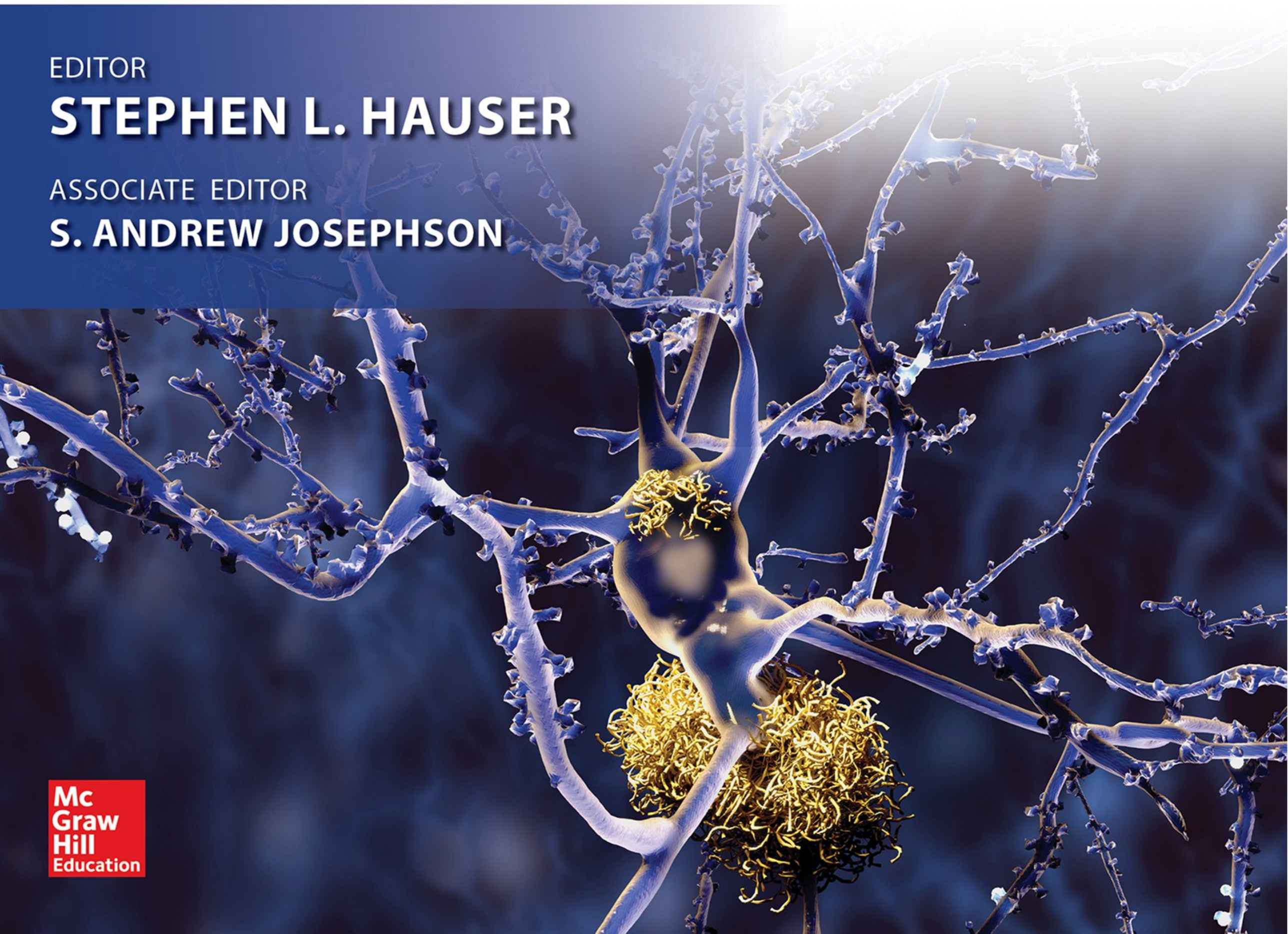
4th Edition

HARRISON'S™

NEUROLOGY IN CLINICAL MEDICINE

EDITOR
STEPHEN L. HAUSER

ASSOCIATE EDITOR
S. ANDREW JOSEPHSON



Mc Graw Hill Education

4th Edition

HARRISON'S™

NEUROLOGY IN CLINICAL MEDICINE

Derived from Harrison's Principles of Internal Medicine, 19th Edition

Editors

DENNIS L. KASPER, md
William Ellery Channing Professor of Medicine,
Professor of Microbiology and Immunobiology,
Department of Microbiology and Immunobiology,
Harvard Medical School; Division of Infectious Diseases,
Brigham and Women's Hospital, Boston, Massachusetts

ANTHONY S. FAUCI, md
Chief, Laboratory of Immunoregulation; Director,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda, Maryland

STEPHEN L. HAUSER, md
Director, UCSF Weill Institute for Neurosciences,
Robert A. Fishman Distinguished Professor and Chairman,
Department of Neurology, University of California,
San Francisco, San Francisco, California

DAN L. LONGO, md
Professor of Medicine, Harvard Medical School; Senior Physician,
Brigham and Women's Hospital; Deputy Editor, New England
Journal *of* Medicine, Boston, Massachusetts

J. LARRY JAMESON, md, phd
Robert G. Dunlop Professor of Medicine; Dean,
Perelman School of Medicine at the University of Pennsylvania;
Executive Vice President, University of Pennsylvania for the Health
System, Philadelphia, Pennsylvania

JOSEPH LOSCALZO, md, phd
Hersey Professor of the T eory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine,
and Physician-in-Chief, Brigham and Women's Hospital,
Boston, Massachusetts

4th Edition

HARRISON'S™

NEUROLOGY IN CLINICAL MEDICINE

EDITOR

Stephen L. Hauser, MD
Director, UCSF Weill Institute for Neurosciences
Robert A. Fishman Distinguished Professor and Chairman
Department of Neurology
University of California, San Francisco, San Francisco, California

ASSOCIATE EDITOR

S. Andrew Josephson, MD
C. Castro-Franceschi and G. Mitchell Endowed Neurohospitalist Professor
Senior Executive Vice-Chairman, Department of Neurology
University of California, San Francisco, San Francisco, California

Mc Graw Hill Education

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

ISBN: 978-1-25-983587-2
MHID: 1-26-001210-7.

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-986096-6,
MHID: 1-25-986096-5.

eBook conversion by codeMantra
Version 1.0

CONTENTS

SECTION III
DISEASES OF THE NERVOUS SYSTEM

SECTION IV
CHRONIC FATIGUE SYNDROME

SECTION V
PSYCHIATRIC DISORDERS

SECTION VI
ALCOHOLISM AND DRUG DEPENDENCY

This page intentionally left blank

CONTRIBUTORS

Numbers in brackets refer to the chapter(s) written or co-written by the contributor.

Anthony A. Amato, MD
Professor of Neurology, Harvard Medical School; Vice-Chairman, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts [53–56]

Michael J. Aminoff, MD, DSc, FRCP
Professor of Neurology, School of Medicine, University of California, San Francisco, San Francisco, California [6, 14, 15]

Richard J. Barohn, MD
Chairman, Department of Neurology; Gertrude and Dewey Ziegler Professor of Neurology, University of Kansas Medical Center, Kansas City, Kansas [53]

Robert C. Basner, MD
Professor of Clinical Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University College of Physicians and Surgeons, New York, New York [Appendix]

M. Flint Beal, MD
University Professor of Neurology and Neuroscience; Neurologist, New York Presbyterian Hospital; Weill Cornell Medical College, New York, New York [30, 42]

Gijs Bleijenberg, PhD
Professor Emeritus, Expert Centre for Chronic Fatigue, Radboud University Medical Centre, Nijmegen, T e Netherlands [59]

Steven M. Bromley, MD
Director, Outpatient Services, Virtua Neuroscience, Voorhees, New Jersey; Director, Bromley Neurology, PC, Audubon, New Jersey [28]

Cynthia D. Brown, MD
Associate Professor of Clinical Medicine, Division of Pulmonary, Critical Care, Sleep and Occupational Medicine, Indiana University, Indianapolis, Indiana [Review and Self-Assessment]

Robert H. Brown, Jr., MD, PhD
Chairman, Department of Neurology, University of Massachusetts Medical School, Worchester, Massachusetts [39, 56]

David M. Burns, MD
Professor Emeritus, Department of Family and Preventive Medicine, University of California, San Diego School of Medicine, San Diego, California [66]

Charles A. Czeisler, MD, PhD
Frank Baldino, Jr., PhD Professor of Sleep Medicine, Professor of Medicine, and Director, Division of Sleep Medicine, Harvard Medical School; Chief, Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, Massachusetts [24]

Marinos C. Dalakas, MD
Professor of Neurology, University of Athens Medical School, Athens, Greece; T omas Jefferson University, Philadelphia, Pennsylvania [57]

Josep Dalmau, MD, PhD
ICREA Professor, Institut d'Investigació Biomèdica August Pi i Sunyer, University of Barcelona, Barcelona, Spain; Adjunct Professor, University of Pennsylvania, Philadelphia, Pennsylvania [50]

Robert B. Daroff, MD
Professor and Chair Emeritus, Department of Neurology, Case Western Reserve University School of Medicine; University Hospitals–Case Medical Center, Cleveland, Ohio [12]

Lisa M. DeAngelis, MD
Professor of Neurology, Weill Cornell Medical College; Chair, Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York [49]

Richard A. Deyo, MD, MPH
Kaiser Permanente Professor of Evidence-Based Family Medicine, Department of Family Medicine, Department of Medicine, Department of Public Health and Preventive Medicine, Oregon Institute of Occupational Health Sciences; Oregon Health and Science University; Clinical Investigator, Kaiser Permanente Center for Health Research, Portland, Oregon [10]

William P. Dillon, MD
Professor and Executive Vice-Chair; Chief, Section of Neuroradiology, Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, California [4, 5]

Richard L. Doty, PhD, MA
Director, T e Smell and Taste Center; Professor, Department of Otorhinolaryngology: Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania [28]

Vanja C. Douglas, MD
Assistant Professor of Clinical Neurology and Sara and Evan Williams Foundation Endowed Neurohospitalist Chair, University of California, San Francisco, San Francisco, California [13]

Daniel B. Drachman, MD
Professor of Neurology and Neuroscience, W. W. Smith Charitable Trust Professor of Neuroimmunology, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland [55]

Andrew J. Einstein, MD, PhD
Victoria and Esther Aboodi Assistant Professor of Medicine; Director, Cardiac CT Research; Co-Director, Cardiac CT and MRI, Department of Medicine, Cardiology Division, Department of Radiology, Columbia University College of Physicians and Surgeons, New York-Presbyterian Hospital, New York, New York [Appendix]

John W. Engstrom, MD
Betty Anker Fife Distinguished Professor and Vice-Chairman; Neurology Residency Program Director, University of California, San Francisco, San Francisco, California [10, 41]

Anthony S. Fauci, MD
Chief, Laboratory of Immunoregulation; Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [48]

Howard L. Fields, MD, PhD
Professor, Department of Neurology, University of California, San Francisco, San Francisco, California [8]

Roy Freeman, MD
Professor of Neurology, Harvard Medical School; Director, Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center, Boston, Massachusetts [11]

Andre D. Furtado, MD
Assistant Professor, Department of Radiology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania [5]

Nicholas B. Galif anakis, MD, MPH
Assistant Clinical Professor, Surgical Movement Disorders Center, Department of Neurology, University of California, San Francisco, San Francisco, California [17]

Jeffrey M. Gelfand, MD, MAS
Assistant Professor of Clinical Neurology, Department of Neurology, University of California, San Francisco, San Francisco, California [13]

Michael D. Geschwind, MD, PhD
Associate Professor of Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [17]

Peter J. Goadsby, MD, PhD, DSc, FRACp, FRCP
Professor, NIHR-Wellcome Trust Clinical Research Facility, King's College, London, United Kingdom; Professor, Department of Neurology, University of California, San Francisco, San Francisco, California [9, 34]

Morton F. Goldberg, MD, FACS, FAOS
Director Emeritus and Joseph Green Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins University School of Medicine and Johns Hopkins Hospital, Baltimore, Maryland [26]

Douglas S. Goodin, MD
Professor, Department of Neurology, School of Medicine, University of California, San Francisco, San Francisco, California [45]

Maria Luisa Gorno-Tempini, MD, PhD
Professor, Department of Neurology; Language Neurobiology Lab, Memory and Aging Center; Dyslexia Center, University of California, San Francisco, San Francisco, California [23]

Daryl R. Gress, MD, FAAN, FCCM, FNCS
Associate Professor of Neurology, University of Virginia, Charlottesville, Virginia [33]

Colin N. Haile, MD, PhD
Assistant Professor, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine; Michael E. DeBakey VA Medical Center, Houston, Texas [64]

Stephen L. Hauser, MD
Director, UCSF Weill Institute for Neurosciences, Robert A. Fishman Distinguished Professor and Chairman, Department of Neurology, University of California, San Francisco, San Francisco, California [1, 7, 30, 42, 43, 45, 54]

J. Claude Hemphill, III, MD, MAS
Professor of Neurology and Neurological Surgery, University of California, San Francisco; Chief of Neurology, San Francisco General Hospital, San Francisco, California [32, 33]

Charles W. Hoge, MD
Senior Scientist, Center for Psychiatry and Neuroscience, Walter Reed Army Institute of Research, Silver Spring, Maryland [62]

Jonathan C. Horton, MD, PhD
William F. Hoyt Professor of Neuro-ophthalmology, Professor of Ophthalmology, Neurology, and Physiology, University of California, San Francisco School of Medicine, San Francisco, California [25]

Brian Houston, MD
Division of Cardiology, Department of Medicine Johns Hopkins Hospital Baltimore, Maryland [Review and Self-Assessment]

J. Larry Jameson, MD, PhD
Robert G. Dunlop Professor of Medicine; Dean, Perelman School of Medicine at the University of Pennsylvania; Executive Vice President, University of Pennsylvania for the Health System, Philadelphia, Pennsylvania [51]

S. Clairborne Johnston, MD, PhD
Dean, Dell Medical School; Frank Denius Distinguished Dean's Chair in Medical Leadership; Vice President for Medical Affairs, University of Texas, Austin, Austin, Texas [32]

S. Andrew Josephson, MD
Carmen Castro Franceschi and Gladyne Mitchell Neurohospitalist Distinguished Professor Senior Executive Vice-Chairman, Department of Neurology, University of California, San Francisco, San Francisco, California [18, 20, 58]

Gail Kang, MD
San Francisco, California [17]

Walter J. Koroshetz, MD
National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland [47]

T omas R. Kosten, MD
J. H. Waggoner Professor of Psychiatry, Pharmacology, Immunology, Neuroscience, Baylor College of Medicine, Houston, Texas [64]

Joel Kramer, PsyD
Professor of Neuropsychology in Neurology; Director of Neuropsychology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [23]

Alexander Kratz, MD, MPH, PhD
Associate Professor of Clinical Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Core Laboratory, Columbia University Medical Center and New York Presbyterian Hospital; Director, Allen Hospital Laboratory, New York, New York [Appendix]

Anil K. Lalwani, MD
Professor and Vice Chair for Research; Director, Division of Otology, Neurotology, and Skull Base Surgery; Director, Columbia Cochlear Implant Center, Columbia University College of Physicians and Surgeons, New York, New York [29]

H. Clifford Lane, MD
Clinical Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland [48]

Phillip A. Low, MD, FRACP, FRCP(Hon)
Robert D. and Patricia E. Kern Professor of Neurology, Mayo Clinic, College of Medicine, Rochester, Minnesota [41]

Daniel H. Lowenstein, MD
Dr. Robert B. and Mrs. Ellinor Aird Professor of Neurology; Director, Epilepsy Center, University of California, San Francisco, San Francisco, California [1, 2, 31]

Joseph B. Martin, MD, PhD
Edward R. and Anne G. Lefler Professor, Department of Neurobiology, Harvard Medical School, Boston, Massachusetts [1]

Nancy K. Mello,[1] PhD
Professor of Psychology (Neuroscience), Harvard Medical School, Boston, Massachusetts; Director, Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, Massachusetts [65]

Shlomo Melmed, MD
Senior Vice President and Dean of the Medical Faculty, Cedars-Sinai Medical Center, Los Angeles, California [51]

Jack H. Mendelson,[1] MD
Professor of Psychiatry (Neuroscience), Harvard Medical School, Belmont, Massachusetts [65]

Robert O. Messing, MD
Professor, Division of Pharmacology and Toxicology, College of Pharmacy; Associate Director, Waggoner Center for Alcohol and Addiction Research, University of Texas at Austin, Austin, Texas [60]

M.-Marsel Mesulam, MD
Professor of Neurology, Psychiatry and Psychology, Cognitive Neurology and Alzheimer's Disease Center, Northwestern University Feinberg School of Medicine, Chicago, Illinois [22]

Bruce L. Miller, MD
A. W. and Mary Margaret Clausen Distinguished Professor of Neurology, University of California, San Francisco School of Medicine, San Francisco, California [18, 21, 23, 35, 40]

Avindra Nath, MD
Chief, Section of Infections of the Nervous System; Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland [47]

Eric J. Nestler, MD, PhD
Nash Family Professor and Chair, Department of Neuroscience; Director, Friedman Brain Institute, Ichan School of Medicine at Mount Sinai, New York, New York [60]

Jose A. Obeso, MD
Professor of Neurology and Director, CIINAC, Hospital de Madrid; Medical School, CEU-San Pablo, Madrid, Spain [36]

Jennifer Ogar, MS CCC-SLP
Speech-Language Pathologist, Memory and Aging Center, University of California, San Francisco, San Francisco, California [23]

C. Warren Olanow, MD, FRCPC, FRCP(hon)
Henry P. and Georgette Goldschmidt Professor and Chairman Emeritus, Department of Neurology; Professor, Department of Neuroscience, Mount Sinai School of Medicine, New York, New York [36]

Michael A. Pesce, PhD
Professor Emeritus of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons; Director, Biochemical Genetics Laboratory, Columbia University Medical Center, New York Presbyterian Hospital, New York, New York [Appendix]

Stanley B. Prusiner, MD
Director, Institute for Neurodegenerative Diseases; Professor, Department of Neurology, University of California, San Francisco, San Francisco, California [30, 40]

Gil Rabinovici, MD
Associate Professor in Neurology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [23]

Neil H. Raskin, MD
Department of Neurology, University of California, San Francisco, San Francisco, California [9, 34]

James P. Rathmell, MD
Henry Knowles Beecher Professor of Anesthesiology, Harvard Medical School; Executive Vice Chair and Chief, Division of Pain Medicine, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts [8]

Victor I. Reus, MD
Department of Psychiatry, University of California, San Francisco School of Medicine; Langley Porter Neuropsychiatric Institute, San Francisco, California [61]

Elizabeth Robbins, MD
Clinical Professor of Pediatrics, University of California, San Francisco, San Francisco, California [7]

Gary L. Robertson, MD
Emeritus Professor of Medicine, Northwestern University School of Medicine, Chicago, Illinois [52]

Karen L. Roos, MD
John and Nancy Nelson Professor of Neurology; Professor of Neurological Surgery, Indiana University School of Medicine, Indianapolis, Indiana [46]

Allan H. Ropper, MD, FRCP, FACP
Professor of Neurology, Harvard Medical School; Raymond D. Adams Master Clinician; Executive Vice Chair, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts [19, 43, 44]

Roger N. Rosenberg, MD
Zale Distinguished Chair and Professor of Neurology, Department of Neurology, University of Texas Southwestern Medical Center, Dallas, Texas [37, 38]

Myrna R. Rosenfeld, MD, PhD
Department of Neurology, Hospital Clínic/IDIBAPS, Barcelona, Spain [50]

Martin A. Samuels, MD
Professor of Neurology, Harvard Medical School; Chair, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts [3, 58]

Clifford B. Saper, MD, PhD
James Jackson Putnam Professor of Neurology and Neuroscience, Harvard Medical School; Chairman, Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts [24]

T omas E. Scammell, MD
Professor, Harvard Medical School; Beth Israel Deaconess Medical Center; Boston Children's Hospital, Boston, Massachusetts [24]

Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci
Chair and Professor of Clinical Neurosciences, UCL Institute of Neurology, London, United Kingdom [36]

Marc A. Schuckit, MD
Distinguished Professor of Psychiatry, University of California, San Diego School of Medicine, La Jolla, California [63]

[1]Deceased

William W. Seeley, MD
Associate Professor of Neurology and Pathology, Memory and Aging Center, University of California, San Francisco, San Francisco, California [21, 35]

Wade S. Smith, MD, PhD
Professor of Neurology, Daryl R. Gress Endowed Chair of Neurocritical Care and Stroke; Director, University of California, San Francisco Neurovascular Service, San Francisco, California [32, 33]

Lewis Sudarsky, MD
Associate Professor of Neurology, Harvard Medical School; Director of Movement Disorders, Brigham and Women's Hospital, Boston, Massachusetts [16]

Homayoun Tabandeh, MD
Retina-Vitreous Associates Medical Group, Los Angeles, California [26]

Maria Carmela Tartaglia, MD
Assistant Professor, Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada [23]

Kenneth L. Tyler, MD
Reuler-Lewin Family Professor and Chair of Neurology; Professor of Medicine, Immunology, and Microbiology, University of Colorado School of Medicine, Aurora, Colorado; Neurologist, Denver Veterans Affairs Medical Center, Denver, Colorado [46]

Jos W. M. van der Meer, MD, PhD
Professor of Medicine; Head, Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, T e Netherlands [59]

Mark F. Walker, MD
Associate Professor, Neurology, Case Western Reserve University; Cleveland VA Medical Center, Cleveland, Ohio [12]

Patrick Y. Wen, MD
Professor of Neurology, Harvard Medical School; Director, Center for Neuro-Oncology, Dana-Farber Cancer Institute; Director, Division of Neuro-Oncology, Department of Neurology, Brigham and Women's Hospital; Dana-Farber Cancer Institute, Boston, Massachusetts [49]

Charles M. Wiener, MD
Vice President of Academic Affairs Johns Hopkins Medicine International Professor of Medicine and Physiology Johns Hopkins School of Medicine Baltimore, Maryland [Review and Self-Assessment]

Shirley H. Wray, MD, PhD, FRCP
Professor of Neurology, Harvard Medical School; Master Clinician, Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts [27]

PREFACE

T e first three editions of Harrison's Neurology in Clinical Medicine were unqualified successes. Readers responded enthusiastically to the convenient, attractive, expanded, and updated stand-alone volume, which was based upon the neurology and psychiatry sections from Harrison's Principles *of* Internal Medicine. Our original goal was to provide, in an easy-to-use format, full coverage of the most authoritative information available anywhere of clinically important topics in neurology and psychiatry, while retaining the focus on pathophysiology and therapy that has always been characteristic of Harrison's.

T is new fourth edition of Harrison's Neurology in Clinical Medicine has been extensively updated to highlight recent advances in the understanding, diagnosis, treatment, and prevention of neurologic and psychiatric diseases. Readers will find expanded coverage of the neurodegenerative diseases, highlighting advances in their classification and management, and delineating the new understanding of mechanisms responsible for the deposition and spread of pathogenic protein aggregates in these disorders. Neuroimmunology is another dynamic and rapidly changing field of neurology, and the new edition of Harrison's provides extensive coverage of progress in this area, including a timely summary of advances in understanding paraneoplastic syndromes, autoimmune encephalitis, and neuromyelitis optica, as well as a practical guide to navigating the large number of treatment options now available for multiple sclerosis. T e chapter on cerebrovascular diseases has also been extensively revised to reflect the exciting new opportunities for acute treatment and prevention of ischemic and hemorrhagic stroke. Sleep disorders and migraine are additional areas in which important advances are highlighted in the new edition. Many illustrative neuroimaging figures appear throughout the section, and an updated and expanded atlas of neuroimaging findings is also included. We have been extremely pleased with the warm reception that greeted the high-definition video presentations introduced in the last edition of Harrison's, and in the fourth edition we have added to the collection new videos illustrating sleep disorders and examination of the comatose patient.

For many physicians, neurologic diseases represent particularly challenging problems. Acquisition of the requisite clinical skills is often viewed as time-consuming, dif cult to master, and requiring a working knowledge of obscure anatomic facts and laundry lists of diagnostic possibilities. T e patients themselves may be dif cult, as neurologic disorders often alter an individual's capacity to recount the history of an illness or to even recognize that something is wrong. An additional obstacle is the development of independent neurology services, departments, and training programs at many medical centers, reducing the exposure of trainees in internal medicine to neurologic problems. All of these forces, acting within the fast paced environment of modern medical practice, can lead to an overreliance on unfocused neuroimaging tests, suboptimal patient care, and unfortunate outcomes. Because neurologists represent less than 1% of all physicians, the vast majority of neurologic care must be delivered by nonspecialists who are often generalists and usually internists.

T e old adage that neurologists "know everything but do nothing" has been rendered obsolete by advances in molecular medicine, imaging, bioengineering, and clinical research. Examples of new therapies include intravenous and endovascular recanalization in acute ischemic stroke, intensive monitoring of brain pressure and cerebral blood flow for brain injury, effective therapies for immune-mediated neurologic disorders, new designer drugs for migraine, the first generation of rational therapies for neurodegenerative diseases, neural stimulators for Parkinson's disease, drugs for narcolepsy and other sleep disorders, and control of epilepsy by surgical resection of small seizure foci precisely localized by functional imaging and electrophysiology. T e pipeline continues to grow, stimulated by a quickening tempo of discoveries generating opportunities for rational design of new diagnostics, interventions, and drugs.

T e founding editors of Harrison's Principles *of* Internal Medicine acknowledged the importance of neurology but were uncertain as to its proper role in a textbook of internal medicine. An initial plan to exclude neurology from the first edition (1950) was reversed at the eleventh hour, and a neurology section was hastily prepared by Houston Merritt. By the second edition, the section was considerably enlarged by Raymond D. Adams, whose influence on the textbook was profound. T e third neurology editor, Joseph B. Martin, brilliantly led the book during the 1980s and 1990s as neurology was transformed from a largely descriptive discipline to one of the most dynamic and rapidly evolving areas of medicine. With these changes, the growth of neurology coverage in Harrison's became so pronounced that Harrison suggested the book be retitled, T e Details *of* Neurology and Some Principles *of* Internal Medicine. His humorous comment, now legendary, underscores the depth of coverage

of neurologic medicine in Harrison's befitting its critical role in the practice of internal medicine.

T e editors are indebted to our authors, a group of internationally recognized authorities who have magnificently distilled a daunting body of information into the essential principles required to understand and manage commonly encountered neurologic problems. T anks also to Dr. Elizabeth Robbins who has served for more than 20 years as managing editor of the neurology section of Harrison's; she has overseen the complex logistics required to produce a multiauthored textbook, and has promoted exceptional standards for clarity, language, and style. Finally, we wish to acknowledge and express our great appreciation to our colleagues at McGraw-Hill. T is new volume was championed by James Shanahan and impeccably managed by Kim Davis.

We live in an electronic, wireless age. Information is downloaded rather than pulled from the shelf. Some have questioned the value of traditional books in this new era. We believe that as the volume of information, and the ways to access this information, continue to grow, the need to grasp the essential concepts of medical practice becomes even more challenging. One of our young colleagues recently remarked that he uses the Internet to find facts, but that he reads Harrison's to learn medicine. Our aim has always been to provide the reader with an integrated, organic summary of the science and the practice of medicine rather than a mere compendium of chapters, and we are delighted and humbled by the continuing and quite remarkable growth in popularity of Harrison's at a time when many "classics" in medicine seem less relevant than in years past. We are of course cognizant of the flexibility in information delivery that today's readers seek, and so we have also made the fourth edition of Harrison's Neurology in Clinical Medicine available in a number of eBook formats for all major devices, including the iPad (available via the iBookstore).

It is our sincere hope that you will enjoy using Harrison's Neurology in Clinical Medicine, Fourth Edition, as an authoritative source for the most up-to-date information in clinical neurology.

T e Editors

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. T e authors 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 authors 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 disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. 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 work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. T is recommendation is of particular importance in connection with new or infrequently used drugs.

Review and self-assessment questions and answers were taken from Wiener CM, Brown CD, Houston B (eds). Harrison's Self-Assessment and Board Review, 19th ed. New York, McGraw-Hill, 2017, ISBN 978-1-259-64288-3.

T e global icons call greater attention to key epidemiologic and clinical differences in the practice of medicine throughout the world.

T e genetic icons identify a clinical issue with an explicit genetic relationship.

This page intentionally left blank

SECTION I

INTRODUCTION TO NEUROLOGY

CHAPTER 1

APPROACH TO THE PATIENT WITH NEUROLOGIC DISEASE

Daniel H. Lowenstein ■ Joseph B. Martin ■ Stephen L. Hauser

Neurologic diseases are common and costly. According to estimates by the World Health Organization, neurologic disorders affect over 1 billion people worldwide, constitute 12% of the global burden of disease, and cause 14% of global deaths **(Table 1-1)**. T ese numbers are only expected to increase as the world's population ages. Most patients with neurologic symptoms seek care from internists and other generalists rather than from neurologists. Because therapies now exist for many neurologic disorders, a skillful approach to diagnosis is essential. Errors commonly result from an overreliance on costly neuroimaging procedures and laboratory tests, which, while useful, do not substitute for an adequate history and examination. T e proper approach to the patient with a neurologic illness begins with the patient and focuses the clinical problem first in anatomic and then in pathophysiologic terms; only then should a specific diagnosis be entertained. T is method ensures that technology is judiciously applied, a correct diagnosis is established in an efficient manner, and treatment is promptly initiated.

TABLE 1-1

GLOBAL DISABILITY-ADJUSTED LIFE-YEARS (DALYS) AND NUMBER OF ANNUAL DEATHS FOR SELECTED NEUROLOGIC DISORDERS IN 2010

DISORDER	DALYS	DEATHS
Low back and neck pain	116,704,000	—
Cerebrovascular diseases	102,232,000	5,874,000
Meningitis and encephalitis	26,540,000	541,000
Migraine	22,362,000	—
Epilepsy	17,429,000	177,000
Dementia	11,349,000	485,000
Parkinson's disease	1,918,000	111,000
% of total DALYs or deaths for all causes that are neurologic	**12.0%**	**13.6%**
% change of DALYs for neurologic disorders between 2000 and 2010	**51.6%**	**114.3%**

Source: R Lozano et al: Lancet 380: 2095, 2012.

THE NEUROLOGIC METHOD

DEFINE THE ANATOMY

T e first priority is to identify the region of the nervous system that is likely to be responsible for the symptoms. Can the disorder be mapped to one specific location, is it multifocal, or is a diffuse process present? Are the symptoms restricted to the nervous system, or do they arise in the context of a systemic illness? Is the problem in the central nervous system (CNS), the peripheral nervous system (PNS), or both? If in the CNS, is the cerebral cortex, basal ganglia, brainstem, cerebellum, or spinal cord responsible? Are the pain-sensitive meninges involved? If in the PNS, could the disorder be located in peripheral nerves and, if so, are motor or sensory nerves primarily affected, or is a lesion in the neuromuscular junction or muscle more likely?

T e first clues to defining the anatomic area of involvement appear in the history, and the examination is then directed to confirm or rule out these impressions and to clarify uncertainties. A more detailed examination of a particular region of the CNS or PNS is often indicated. For example, the examination of a patient who presents with a history of ascending paresthesias and weakness should be directed toward deciding, among other things, if the location of the lesion is in the spinal cord or peripheral nerves. Focal back pain, a spinal cord sensory level, and incontinence

suggest a spinal cord origin, whereas a stocking-glove pattern of sensory loss suggests peripheral nerve disease; areflexia usually indicates peripheral neuropathy but may also be present with spinal shock in acute spinal cord disorders.

Deciding "where the lesion is" accomplishes the task of limiting the possible etiologies to a manageable, finite number. In addition, this strategy safeguards against making serious errors. Symptoms of recurrent vertigo, diplopia, and nystagmus should not trigger "multiple sclerosis" as an answer (etiology) but "brainstem" or "pons" (location); then a diagnosis of brainstem arteriovenous malformation will not be missed for lack of consideration. Similarly, the combination of optic neuritis and spastic ataxic paraparesis suggests optic nerve and spinal cord disease; multiple sclerosis (MS), CNS syphilis, and vitamin B_{12} deficiency are treatable disorders that can produce this syndrome. Once the question, "Where is the lesion?" is answered, then the question, "What is the lesion?" can be addressed.

IDENTIFY THE PATHOPHYSIOLOGY

Clues to the pathophysiology of the disease process may also be present in the history. Primary neuronal (gray matter) disorders may present as early cognitive disturbances, movement disorders, or seizures, whereas white matter involvement produces predominantly "long tract" disorders of motor, sensory, visual, and cerebellar pathways. Progressive and symmetric symptoms often have a metabolic or degenerative origin; in such cases lesions are usually not sharply circumscribed. Thus, a patient with paraparesis and a clear spinal cord sensory level is unlikely to have vitamin B_{12} deficiency as the explanation. A Lhermitte symptom (electric shock–like sensations evoked by neck flexion) is due to ectopic impulse generation in white matter pathways and occurs with demyelination in the cervical spinal cord; among many possible causes, this symptom may indicate MS in a young adult or compressive cervical spondylosis in an older person. Symptoms that worsen after exposure to heat or exercise may indicate conduction block in demyelinated axons, as occurs in MS. A patient with recurrent episodes of diplopia and dysarthria associated with exercise or fatigue may have a disorder of neuromuscular transmission such as myasthenia gravis. Slowly advancing visual scotoma with luminous edges, termed *fortification spectra*, indicates spreading cortical depression, typically with migraine.

THE NEUROLOGIC HISTORY

Attention to the description of the symptoms experienced by the patient and substantiated by family members and others often permits an accurate localization and determination of the probable cause of the complaints, even before the neurologic examination is performed. The history also helps to bring a focus to the neurologic examination that follows. Each complaint should be pursued as far as possible to elucidate the location of the lesion, the likely underlying pathophysiology, and potential etiologies. For example, a patient complains of weakness of the right arm. What are the associated features? Does the patient have difficulty with brushing hair or reaching upward (proximal) or buttoning buttons or opening a twist-top bottle (distal)? Negative associations may also be crucial. A patient with a right hemiparesis without a language deficit likely has a lesion (internal capsule, brainstem, or spinal cord) different from that of a patient with a right hemiparesis and aphasia (left hemisphere). Other pertinent features of the history include the following:

1. *Temporal course of* the illness. It is important to determine the precise time of appearance and rate of progression of the symptoms experienced by the patient. The rapid onset of a neurologic complaint, occurring within seconds or minutes, usually indicates a vascular event, a seizure, or migraine. The onset of sensory symptoms located in one extremity that spread over a few seconds to adjacent portions of that extremity and then to the other regions of the body suggests a seizure. A more gradual onset and less well-localized symptoms point to the possibility of a transient ischemic attack (TIA). A similar but slower temporal march of symptoms accompanied by headache, nausea, or visual disturbance suggests migraine. The presence of "positive" sensory symptoms (e.g., tingling or sensations that are difficult to describe) or involuntary motor movements suggests a seizure; in contrast, transient loss of function (negative symptoms) suggests a TIA. A stuttering onset where symptoms appear, stabilize, and then progress over hours or days also suggests cerebrovascular disease; an additional history of transient remission or regression indicates that the process is more likely due to ischemia rather than hemorrhage. A gradual evolution of symptoms over hours or days suggests a toxic, metabolic, infectious, or inflammatory process. Progressing symptoms associated with the systemic manifestations of fever, stiff neck, and altered level of consciousness imply an infectious process. Relapsing and remitting symptoms involving different levels of the nervous system suggest MS or other inflammatory processes. Slowly progressive symptoms without remissions are characteristic of neurodegenerative disorders, chronic infections, gradual intoxications, and neoplasms.
2. Patients' descriptions *of* the complaint. The same words often mean different things to different patients. "Dizziness" may imply impending syncope,

a sense of disequilibrium, or true spinning vertigo. "Numbness" may mean a complete loss of feeling, a positive sensation such as tingling, or even weakness. "Blurred vision" may be used to describe unilateral visual loss, as in transient monocular blindness, or diplopia. T e interpretation of the true meaning of the words used by patients to describe symptoms obviously becomes even more complex when there are differences in primary languages and cultures.

3. Corroboration *of* the history by others. It is almost always helpful to obtain additional information from family, friends, or other observers to corroborate or expand the patient's description. Memory loss, aphasia, loss of insight, intoxication, and other factors may impair the patient's capacity to communicate normally with the examiner or prevent openness about factors that have contributed to the illness. Episodes of loss of consciousness necessitate that details be sought from observers to ascertain precisely what has happened during the event.
4. Family history. Many neurologic disorders have an underlying genetic component. T e presence of a Mendelian disorder, such as Huntington's disease or Charcot-Marie-Tooth neuropathy, is often obvious if family data are available. More detailed questions about family history are often necessary in polygenic disorders such as MS, migraine, and many types of epilepsy. It is important to elicit family history about all illnesses, in addition to neurologic and psychiatric disorders. A familial propensity to hypertension or heart disease is relevant in a patient who presents with a stroke. T ere are numerous inherited neurologic diseases that are associated with multisystem manifestations that may provide clues to the correct diagnosis (e.g., neurofibromatosis, Wilson's disease, mitochondrial disorders).
5. Medical illnesses. Many neurologic diseases occur in the context of systemic disorders. Diabetes mellitus, hypertension, and abnormalities of blood lipids predispose to cerebrovascular disease. A solitary mass lesion in the brain may be an abscess in a patient with valvular heart disease, a primary hemorrhage in a patient with a coagulopathy, a lymphoma or toxoplasmosis in a patient with AIDS, or a metastasis in a patient with underlying cancer. Patients with malignancy may also present with a neurologic paraneoplastic syndrome **(Chap. 50)** or complications from chemotherapy or radiotherapy. Marfan's syndrome and related collagen disorders predispose to dissection of the cranial arteries and aneurysmal subarachnoid hemorrhage; the latter may also occur with polycystic kidney disease. Various neurologic disorders occur with dysthyroid states or other endocrinopathies. It is especially important to look for the presence of systemic diseases in patients with peripheral neuropathy. Most patients with coma in a hospital setting have a metabolic, toxic, or infectious cause.
6. Drug use and abuse and toxin exposure. It is essential to inquire about the history of drug use, both prescribed and illicit. Sedatives, antidepressants, and other psychoactive medications are frequently associated with acute confusional states, especially in the elderly. Aminoglycoside antibiotics may exacerbate symptoms of weakness in patients with disorders of neuromuscular transmission, such as myasthenia gravis, and may cause dizziness secondary to ototoxicity. Vincristine and other antineoplastic drugs can cause peripheral neuropathy, and immunosuppressive agents such as cyclosporine can produce encephalopathy. Excessive vitamin ingestion can lead to disease; examples include vitamin A and pseudotumor cerebri or pyridoxine and peripheral neuropathy. Many patients are unaware that over-the-counter sleeping pills, cold preparations, and diet pills are actually drugs. Alcohol, the most prevalent neurotoxin, is often not recognized as such by patients, and other drugs of abuse such as cocaine and heroin can cause a wide range of neurologic abnormalities. A history of environmental or industrial exposure to neurotoxins may provide an essential clue; consultation with the patient's coworkers or employer may be required.
7. Formulating an impression *of* the patient. Use the opportunity while taking the history to form an impression of the patient. Is the information forthcoming, or does it take a circuitous course? Is there evidence of anxiety, depression, or hypochondriasis? Are there any clues to problems with language, memory, insight, comportment, or behavior? T e neurologic assessment begins as soon as the patient comes into the room and the first introduction is made.

THE NEUROLOGIC EXAMINATION

T e neurologic examination is challenging and complex; it has many components and includes a number of skills that can be mastered only through repeated use of the same techniques on a large number of individuals with and without neurologic disease. Mastery of the complete neurologic examination is usually important only for physicians in neurology and associated specialties. However, knowledge of the basics of the examination, especially those components that are effective in screening for neurologic dysfunction, is essential for all clinicians, especially generalists.

T ere is no single, universally accepted sequence of the examination that must be followed, but most

clinicians begin with assessment of mental status followed by the cranial nerves, motor system, reflexes, sensory system, coordination, and gait. Whether the examination is basic or comprehensive, it is essential that it be performed in an orderly and systematic fashion to avoid errors and serious omissions. Thus, the best way to learn and gain expertise in the examination is to choose one's own approach and practice it frequently and do it in the same exact sequence each time.

The detailed description that follows describes the more commonly used parts of the neurologic examination, with a particular emphasis on the components that are considered most helpful for the assessment of common neurologic problems. Each section also includes a brief description of the minimal examination necessary to adequately screen for abnormalities in a patient who has no symptoms suggesting neurologic dysfunction. A screening examination done in this way can be completed in 3–5 min.

Several additional points about the examination are worth noting. First, in recording observations, it is important to describe what is found rather than to apply a poorly defined medical term (e.g., "patient groans to sternal rub" rather than "obtunded"). Second, subtle CNS abnormalities are best detected by carefully comparing a patient's performance on tasks that require simultaneous activation of both cerebral hemispheres (e.g., eliciting a pronator drift of an outstretched arm with the eyes closed; extinction on one side of bilaterally applied light touch, also with eyes closed; or decreased arm swing or a slight asymmetry when walking). Third, if the patient's complaint is brought on by some activity, reproduce the activity in the office. If the complaint is of dizziness when the head is turned in one direction, have the patient do this and also look for associated signs on examination (e.g., nystagmus or dysmetria). If pain occurs after walking two blocks, have the patient leave the office and walk this distance and immediately return, and repeat the relevant parts of the examination. Finally, the use of tests that are individually tailored to the patient's problem can be of value in assessing changes over time. Tests of walking a 7.5-m (25-ft) distance (normal, 5–6 s; note assistance, if any), repetitive finger or toe tapping (normal, 20–25 taps in 5 s), or handwriting are examples.

MENTAL STATUS EXAMINATION

- The bare minimum: During the interview, look *for* difficulties with communication and determine whether the patient has recall and insight into recent and past events.

The mental status examination is under way as soon as the physician begins observing and speaking with the patient. If the history raises any concern for abnormalities of higher cortical function or if cognitive problems are observed during the interview, then detailed testing of the mental status is indicated. The patient's ability to understand the language used for the examination, cultural background, educational experience, sensory or motor problems, or comorbid conditions need to be factored into the applicability of the tests and interpretation of results.

The Folstein mini-mental status examination (MMSE) is a standardized screening examination of cognitive function that is extremely easy to administer and takes <10 min to complete. Using age-adjusted values for defining normal performance, the test is ~85% sensitive and 85% specific for making the diagnosis of dementia that is moderate or severe, especially in educated patients. When there is sufficient time available, the MMSE is one of the best methods for documenting the current mental status of the patient, and this is especially useful as a baseline assessment to which future scores of the MMSE can be compared.

Individual elements of the mental status examination can be subdivided into level of consciousness, orientation, speech and language, memory, fund of information, insight and judgment, abstract thought, and calculations.

Level *of* consciousness is the patient's relative state of awareness of the self and the environment, and ranges from fully awake to comatose. When the patient is not fully awake, the examiner should describe the responses to the minimum stimulus necessary to elicit a reaction, ranging from verbal commands to a brief, painful stimulus such as a squeeze of the trapezius muscle. Responses that are directed toward the stimulus and signify some degree of intact cerebral function (e.g., opening the eyes and looking at the examiner or reaching to push away a painful stimulus) must be distinguished from reflex responses of a spinal origin (e.g., triple flexion response—flexion at the ankle, knee, and hip in response to a painful stimulus to the foot).

Orientation is tested by asking the person to state his or her name, location, and time (day of the week and date); time is usually the first to be affected in a variety of conditions.

Speech is assessed by observing articulation, rate, rhythm, and prosody (i.e., the changes in pitch and accentuation of syllables and words).

Language is assessed by observing the content of the patient's verbal and written output, response to spoken commands, and ability to read. A typical testing sequence is to ask the patient to name successively more detailed components of clothing, a watch, or a pen; repeat the phrase "No ifs, ands, or buts"; follow a three-step, verbal command; write a sentence; and read and respond to a written command.

Memory should be analyzed according to three main time scales: (1) immediate memory is assessed by saying a list of three items and having the patient repeat the list immediately; (2) short-term memory is tested by asking the patient to recall the same three items 5 and 15 min later; and (3) long-term memory is evaluated by determining how well the patient is able to provide a coherent chronologic history of his or her illness or personal events.

Fund *of* in*f*ormation is assessed by asking questions about major historic or current events, with special attention to educational level and life experiences.

Abnormalities of insight and judgment are usually detected during the patient interview; a more detailed assessment can be elicited by asking the patient to describe how he or she would respond to situations having a variety of potential outcomes (e.g., "What would you do if you found a wallet on the sidewalk?").

Abstract thought can be tested by asking the patient to describe similarities between various objects or concepts (e.g., apple and orange, desk and chair, poetry and sculpture) or to list items having the same attributes (e.g., a list of four-legged animals).

Calculation ability is assessed by having the patient carry out a computation that is appropriate to the patient's age and education (e.g., serial subtraction of 7 from 100 or 3 from 20; or word problems involving simple arithmetic).

CRANIAL NERVE EXAMINATION

- T e bare minimum: Check the *f*undi, visual *f*ields, pupil size and reactivity, extraocular movements, and *f*acial movements.

T e cranial nerves (CN) are best examined in numerical order, except for grouping together CN III, IV, and VI because of their similar function.

CN I (ol*f*actory)

Testing is often omitted unless there is suspicion for inferior frontal lobe disease (e.g., meningioma). With eyes closed, ask the patient to sniff a mild stimulus such as toothpaste or coffee and identify the odorant.

CN II (optic)

Check visual acuity (with eyeglasses or contact lens correction) using a Snellen chart or similar tool. Test the visual fields by confrontation, i.e., by comparing the patient's visual fields to your own. As a screening test, it is usually sufficient to examine the visual fields of both eyes simultaneously; individual eye fields should be tested if there is any reason to suspect a problem of vision by the history or other elements of the examination, or if the screening test reveals an abnormality. Face the patient at a distance of approximately 0.6–1.0 m (2–3 ft) and place your hands at the periphery of your visual fields in the plane that is equidistant between you and the patient. Instruct the patient to look directly at the center of your face and to indicate when and where he or she sees one of your fingers moving. Beginning with the two inferior quadrants and then the two superior quadrants, move your index finger of the right hand, left hand, or both hands simultaneously and observe whether the patient detects the movements. A single small-amplitude movement of the finger is sufficient for a normal response. Focal perimetry and tangent screen examinations should be used to map out visual field defects fully or to search for subtle abnormalities. Optic fundi should be examined with an ophthalmoscope, and the color, size, and degree of swelling or elevation of the optic disc noted, as well as the color and texture of the retina. T e retinal vessels should be checked for size, regularity, arteriovenous nicking at crossing points, hemorrhage, exudates, etc.

CN III, IV, VI (oculomotor, trochlear, abducens)

Describe the size and shape of pupils and reaction to light and accommodation (i.e., as the eyes converge while following your finger as it moves toward the bridge of the nose). To check extraocular movements, ask the patient to keep his or her head still while tracking the movement of the tip of your finger. Move the target slowly in the horizontal and vertical planes; observe any paresis, nystagmus, or abnormalities of smooth pursuit (saccades, oculomotor ataxia, etc.). If necessary, the relative position of the two eyes, both in primary and multidirectional gaze, can be assessed by comparing the ref ections of a bright light off both pupils. However, in practice it is typically more useful to determine whether the patient describes diplopia in any direction of gaze; true diplopia should almost always resolve with one eye closed. Horizontal nystagmus is best assessed at 45° and not at extreme lateral gaze (which is uncomfortable for the patient); the target must often be held at the lateral position for at least a few seconds to detect an abnormality.

CN V (trigeminal)

Examine sensation within the three territories of the branches of the trigeminal nerve (ophthalmic, maxillary, and mandibular) on each side of the face. As with other parts of the sensory examination, testing of two sensory modalities derived from different anatomic pathways (e.g., light touch and temperature) is sufficient for a screening examination. Testing of other modalities, the corneal ref ex, and the motor component of

CN V (jaw clench—masseter muscle) is indicated when suggested by the history.

CN VII (facial)

Look for facial asymmetry at rest and with spontaneous movements. Test eyebrow elevation, forehead wrinkling, eye closure, smiling, and cheek puff. Look in particular for differences in the lower versus upper facial muscles; weakness of the lower two-thirds of the face with preservation of the upper third suggests an upper motor neuron lesion, whereas weakness of an entire side suggests a lower motor neuron lesion.

CN VIII (vestibulocochlear)

Check the patient's ability to hear a finger rub or whispered voice with each ear. Further testing for air versus mastoid bone conduction (Rinne) and lateralization of a 512-Hz tuning fork placed at the center of the forehead (Weber) should be done if an abnormality is detected by history or examination. Any suspected problem should be followed up with formal audiometry. **For further discussion of assessing vestibular nerve function in the setting of dizziness, hearing loss, or coma, see Chaps. 12, 29, and 19, respectively.**

CN IX, X (glossopharyngeal, vagus)

Observe the position and symmetry of the palate and uvula at rest and with phonation ("aah"). The pharyngeal ("gag") reflex is evaluated by stimulating the posterior pharyngeal wall on each side with a sterile, blunt object (e.g., tongue blade), but the reflex is often absent in normal individuals.

CN XI (spinal accessory)

Check shoulder shrug (trapezius muscle) and head rotation to each side (sternocleidomastoid) against resistance.

CN XII (hypoglossal)

Inspect the tongue for atrophy or fasciculations, position with protrusion, and strength when extended against the inner surface of the cheeks on each side.

MOTOR EXAMINATION

- The bare minimum: Look for muscle atrophy and check extremity tone. Assess upper extremity strength by checking for pronator drift and strength of wrist or finger extensors. Assess lower extremity strength by checking strength of the toe extensors and having the patient walk normally and on heels and toes.

The motor examination includes observations of muscle appearance, tone, and strength. Although gait is in part a test of motor function, it is usually evaluated separately at the end of the examination.

Appearance

Inspect and palpate muscle groups under good light and with the patient in a comfortable and symmetric position. Check for muscle fasciculations, tenderness, and atrophy or hypertrophy. Involuntary movements may be present at rest (e.g., tics, myoclonus, choreoathetosis), during maintained posture (pill-rolling tremor of Parkinson's disease), or with voluntary movements (intention tremor of cerebellar disease or familial tremor).

Tone

Muscle tone is tested by measuring the resistance to passive movement of a relaxed limb. Patients often have difficulty relaxing during this procedure, so it is useful to distract the patient to minimize active movements. In the upper limbs, tone is assessed by rapid pronation and supination of the forearm and flexion and extension at the wrist. In the lower limbs, while the patient is supine the examiner's hands are placed behind the knees and rapidly raised; with normal tone, the ankles drag along the table surface for a variable distance before rising, whereas increased tone results in an immediate lift of the heel off the surface. Decreased tone is most commonly due to lower motor neuron or peripheral nerve disorders. Increased tone may be evident as spasticity (resistance determined by the angle and velocity of motion; corticospinal tract disease), rigidity (similar resistance in all angles of motion; extrapyramidal disease), or paratonia (fluctuating changes in resistance; frontal lobe pathways or normal difficulty in relaxing). Cogwheel rigidity, in which passive motion elicits jerky interruptions in resistance, is seen in parkinsonism.

Strength

Testing for pronator drift is an extremely useful method for screening upper limb weakness. The patient is asked to hold both arms fully extended and parallel to the ground with eyes closed. This position should be maintained for ~10 s; any flexion at the elbow or fingers or pronation of the forearm, especially if asymmetric, is a sign of potential weakness. Muscle strength is further assessed by having the patient exert maximal effort for the particular muscle or muscle group being tested. It is important to isolate the muscles as much as possible, i.e., hold the limb so that only the muscles of interest are active. It is also helpful to palpate accessible muscles

as they contract. Grading muscle strength and evaluating the patient's effort is an art that takes time and practice. Muscle strength is traditionally graded using the following scale:

0 = no movement
1 = flicker or trace of contraction but no associated movement at a joint
2 = movement with gravity eliminated
3 = movement against gravity but not against resistance
4– = movement against a mild degree of resistance
4 = movement against moderate resistance
4+ = movement against strong resistance
5 = full power

However, in many cases, it is more practical to use the following terms:

Paralysis = no movement
Severe weakness = movement with gravity eliminated
Moderate weakness = movement against gravity but not against mild resistance
Mild weakness = movement against moderate resistance
Full strength

Noting the pattern of weakness is as important as assessing the magnitude of weakness. Unilateral or bilateral weakness of the upper limb extensors and lower limb flexors ("pyramidal weakness") suggests a lesion of the pyramidal tract, bilateral proximal weakness suggests myopathy, and bilateral distal weakness suggests peripheral neuropathy.

REFLEX EXAMINATION

- The bare minimum: Check the biceps, patellar, and Achilles reflexes.

Muscle stretch reflexes

Those that are typically assessed include the biceps (C5, C6), brachioradialis (C5, C6), and triceps (C7, C8) reflexes in the upper limbs and the patellar or quadriceps (L3, L4) and Achilles (S1, S2) reflexes in the lower limbs. The patient should be relaxed and the muscle positioned midway between full contraction and extension. Reflexes may be enhanced by asking the patient to voluntarily contract other, distant muscle groups (Jendrassik maneuver). For example, upper limb reflexes may be reinforced by voluntary teeth-clenching, and the Achilles reflex by hooking the flexed fingers of the two hands together and attempting to pull them apart. For each reflex tested, the two sides should be tested sequentially, and it is important to determine the smallest stimulus required to elicit a reflex rather than the maximum response. Reflexes are graded according to the following scale:

0 = absent
1 = present but diminished
2 = normoactive
3 = exaggerated
4 = clonus

Cutaneous reflexes

The plantar reflex is elicited by stroking, with a noxious stimulus such as a tongue blade, the lateral surface of the sole of the foot beginning near the heel and moving across the ball of the foot to the great toe. The normal reflex consists of plantar flexion of the toes. With upper motor neuron lesions above the S1 level of the spinal cord, a paradoxical extension of the toe is observed, associated with fanning and extension of the other toes (termed an extensor plantar response, or Babinski sign). However, despite its popularity, the reliability and validity of the Babinski sign for identifying upper motor neuron weakness is limited—it is far more useful to rely on tests of tone, strength, stretch reflexes, and coordination. Superficial abdominal reflexes are elicited by gently stroking the abdominal surface near the umbilicus in a diagonal fashion with a sharp object (e.g., the wooden end of a cotton-tipped swab) and observing the movement of the umbilicus. Normally, the umbilicus will pull toward the stimulated quadrant. With upper motor neuron lesions, these reflexes are absent. They are most helpful when there is preservation of the upper (spinal cord level T9) but not lower (T12) abdominal reflexes, indicating a spinal lesion between T9 and T12, or when the response is asymmetric. Other useful cutaneous reflexes include the cremasteric (ipsilateral elevation of the testicle following stroking of the medial thigh; mediated by L1 and L2) and anal (contraction of the anal sphincter when the perianal skin is scratched; mediated by S2, S3, S4) reflexes. It is particularly important to test for these reflexes in any patient with suspected injury to the spinal cord or lumbosacral roots.

Primitive reflexes

With disease of the frontal lobe pathways, several primitive reflexes not normally present in the adult may appear. The suck response is elicited by lightly touching with a tongue blade the center of the lips, and the root response the corner of the lips; the patient will move the lips to suck or root in the direction of the stimulus. The grasp reflex is elicited by touching the palm between the thumb and index finger with the examiner's fingers; a positive response is a forced grasp of the examiner's hand. In many instances, stroking the back of the hand

will lead to its release. The palmomental response is contraction of the mentalis muscle (chin) ipsilateral to a scratch stimulus diagonally applied to the palm.

SENSORY EXAMINATION

- The bare minimum: Ask whether the patient can *f*eel light touch and the temperature *of* a cool object in each distal extremity. Check double simultaneous stimulation using light touch on the hands. Per*f*orm the Romberg maneuver.

Evaluating sensation is usually the most unreliable part of the examination because it is subjective and is difficult to quantify. In the compliant and discerning patient, the sensory examination can be extremely helpful for the precise localization of a lesion. With patients who are uncooperative or lack an understanding of the tests, it may be useless. The examination should be focused on the suspected lesion. For example, in spinal cord, spinal root, or peripheral nerve abnormalities, all major sensory modalities should be tested while looking for a pattern consistent with a spinal level and dermatomal or nerve distribution. In patients with lesions at or above the brainstem, screening the primary sensory modalities in the distal extremities along with tests of "cortical" sensation is usually sufficient.

The five primary sensory modalities—light touch, pain, temperature, vibration, and joint position—are tested in each limb. Light touch is assessed by stimulating the skin with single, very gentle touches of the examiner's finger or a wisp of cotton. Pain is tested using a new pin, and temperature is assessed using a metal object (e.g., tuning fork) that has been immersed in cold and warm water. Vibration is tested using a 128-Hz tuning fork applied to the distal phalanx of the great toe or index finger just below the nail bed. By placing a finger on the opposite side of the joint being tested, the examiner compares the patient's threshold of vibration perception with his or her own. For joint position testing, the examiner grasps the digit or limb laterally and distal to the joint being assessed; small 1- to 2-mm excursions can usually be sensed. The Romberg maneuver is primarily a test of proprioception. The patient is asked to stand with the feet as close together as necessary to maintain balance while the eyes are open, and the eyes are then closed. A loss of balance with the eyes closed is an abnormal response.

"Cortical" sensation is mediated by the parietal lobes and represents an integration of the primary sensory modalities; testing cortical sensation is only meaningful when primary sensation is intact. Double simultaneous stimulation is especially useful as a screening test for cortical function; with the patient's eyes closed, the examiner lightly touches one or both hands and asks the patient to identify the stimuli. With a parietal lobe lesion, the patient may be unable to identify the stimulus on the contralateral side when both hands are touched. Other modalities relying on the parietal cortex include the discrimination of two closely placed stimuli as separate (two-point discrimination), identification of an object by touch and manipulation alone (stereognosis), and the identification of numbers or letters written on the skin surface (graphesthesia).

COORDINATION EXAMINATION

- The bare minimum: Observe the patient at rest and during spontaneous movements. *T*est rapid alternating movements *of* the hands and *f*eet and *f*inger to nose.

Coordination refers to the orchestration and fluidity of movements. Even simple acts require cooperation of agonist and antagonist muscles, maintenance of posture, and complex servomechanisms to control the rate and range of movements. Part of this integration relies on normal function of the cerebellar and basal ganglia systems. However, coordination also requires intact muscle strength and kinesthetic and proprioceptive information. Thus, if the examination has disclosed abnormalities of the motor or sensory systems, the patient's coordination should be assessed with these limitations in mind.

Rapid alternating movements in the upper limbs are tested separately on each side by having the patient make a fist, partially extend the index finger, and then tap the index finger on the distal thumb as quickly as possible. In the lower limb, the patient rapidly taps the foot against the floor or the examiner's hand. Finger-to-nose testing is primarily a test of cerebellar function; the patient is asked to touch his or her index finger repetitively to the nose and then to the examiner's outstretched finger, which moves with each repetition. A similar test in the lower extremity is to have the patient raise the leg and touch the examiner's finger with the great toe. Another cerebellar test in the lower limbs is the heel-knee-shin maneuver; in the supine position the patient is asked to slide the heel of each foot from the knee down the shin of the other leg. For all these movements, the accuracy, speed, and rhythm are noted.

GAIT EXAMINATION

- The bare minimum: Observe the patient while walking normally, on the heels and toes, and along a straight line.

Watching the patient walk is the most important part of the neurologic examination. Normal gait requires that multiple systems—including strength, sensation, and coordination—function in a highly integrated fashion. Unexpected abnormalities may be detected that prompt

the examiner to return in more detail to other aspects of the examination. The patient should be observed while walking and turning normally, walking on the heels, walking on the toes, and walking heel-to-toe along a straight line. The examination may reveal decreased arm swing on one side (corticospinal tract disease), a stooped posture and short-stepped gait (parkinsonism), a broad-based unstable gait (ataxia), scissoring (spasticity), or a high-stepped, slapping gait (posterior column or peripheral nerve disease), or the patient may appear to be stuck in place (apraxia with frontal lobe disease).

NEUROLOGIC DIAGNOSIS

The clinical data obtained from the history and examination are interpreted to arrive at an anatomic localization that best explains the clinical findings **(Table 1-2)**, to narrow the list of diagnostic possibilities, and to select the laboratory tests most likely to be informative. The laboratory assessment may include (1) serum electrolytes; complete blood count; and renal, hepatic, endocrine, and immune studies; (2) cerebrospinal fluid examination; (3) focused neuroimaging studies **(Chap. 4)**; or (4) electrophysiologic studies **(Chap. 6)**. The anatomic localization, mode of onset and course of illness, other medical data, and laboratory findings are then integrated to establish an etiologic diagnosis.

The neurologic examination may be normal even in patients with a serious neurologic disease, such as seizures, chronic meningitis, or a TIA. A comatose patient may arrive with no available history, and in such cases, the approach is as described in **Chap. 19**. In other patients, an inadequate history may be overcome by a succession of examinations from which the course of the illness can be inferred. In perplexing cases it is useful to remember that uncommon presentations of common diseases are more likely than rare etiologies. Thus, even in tertiary care settings, multiple strokes are usually due to emboli and not vasculitis, and dementia with myoclonus is usually Alzheimer's disease and not a prion disorder or a paraneoplastic illness. Finally, the most important task of a primary care physician faced with a patient who has a new neurologic complaint is to assess the urgency of referral to a specialist. Here, the imperative is to rapidly identify patients likely to have nervous system infections, acute strokes, and spinal cord compression or other treatable mass lesions and arrange for immediate care.

TABLE 1-2

FINDINGS HELPFUL FOR LOCALIZATIONS WITHIN THE NERVOUS SYSTEM

	SIGNS
Cerebrum	Abnormal mental status or cognitive impairment Seizures Unilateral weakness[a] and sensory abnormalities including head and limbs Visual field abnormalities Movement abnormalities (e.g., diffuse incoordination, tremor, chorea)
Brainstem	Isolated cranial nerve abnormalities (single or multiple) "Crossed" weakness[a] and sensory abnormalities of head and limbs, e.g., weakness of right face and left arm and leg
Spinal cord	Back pain or tenderness Weakness[a] and sensory abnormalities sparing the head Mixed upper and lower motor neuron findings Sensory level Sphincter dysfunction
Spinal roots	Radiating limb pain Weakness[b] or sensory abnormalities following root distribution (see Figs. 15-2 and 15-3) Loss of reflexes
Peripheral nerve	Mid or distal limb pain Weakness[b] or sensory abnormalities following nerve distribution (see Figs. 15-2 and 15-3) "Stocking or glove" distribution of sensory loss Loss of reflexes
Neuromuscular junction	Bilateral weakness including face (ptosis, diplopia, dysphagia) and proximal limbs Increasing weakness with exertion Sparing of sensation
Muscle	Bilateral proximal or distal weakness Sparing of sensation

[a]Weakness along with other abnormalities having an "upper motor neuron" pattern, i.e., spasticity, weakness of extensors > flexors in the upper extremity and flexors > extensors in the lower extremity, and hyperreflexia.
[b]Weakness along with other abnormalities having a "lower motor neuron" pattern, i.e., flaccidity and hyporeflexia.

CHAPTER 2

THE NEUROLOGIC SCREENING EXAM

Daniel H. Lowenstein

Knowledge of the basic neurologic examination is an essential clinical skill. A simple neurologic screening examination—assessment of mental status, cranial nerves, motor system, sensory system, coordination, and gait—can be reliably performed in 3–5 min. Although the components of the examination may appear daunting at first, skills usually improve rapidly with repetition and practice. In this video, the technique of performing a simple and ef cient screening examination is presented.

Video for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 2–1. The Neurologic Screening Exam

CHAPTER 3

VIDEO ATLAS OF THE DETAILED NEUROLOGIC EXAMINATION

Martin A. Samuels

T e comprehensive neurologic examination is an irreplaceable tool for the ef cient diagnosis of neurologic disorders. Mastery of its details requires knowledge of normal nervous system anatomy and physiology combined with personal experience performing orderly and systematic examinations on large numbers of patients and healthy individuals. In the hands of a great clinician, the neurologic examination also becomes a thing of beauty—the pinnacle of the art of medicine. In these videos, the most commonly used components of the examination are presented in detail, with a particular emphasis on those elements that are most helpful for assessment of common neurologic problems.

Videos for this chapter can be accessed at the following link: https://www.mhprofessional.com/mediacenter/

Video 3–1. Introduction and the General Physical Examination Relevant to Neurology

Video 3–2. Mental Status

Video 3–3. Cranial Nerves

Video 3–4. Motor

Video 3–5. Sensory

Video 3–6. Ref exes

Video 3–7. Coordination and Gait

CHAPTER 4

NEUROIMAGING IN NEUROLOGIC DISORDERS

William P. Dillon

The clinician caring for patients with neurologic symptoms is faced with myriad imaging options, including computed tomography (CT), CT angiography (CTA), perfusion CT (pCT), magnetic resonance (MR) imaging (MRI), MR angiography (MRA), functional MRI (fMRI), MR spectroscopy (MRS), MR neurography (MRN), diffusion and diffusion tensor imaging, susceptibility-weighted MR imaging (SWI), arterial spin label MRI (ASL) and perfusion MRI (pMRI). In addition, an increasing number of interventional neuroradiologic techniques are available, including angiography catheter embolization, coiling, and stenting of vascular structures, and spine diagnostic and interventional techniques, such as diskography, transforaminal and translaminar epidural and nerve root injections, and blood patches. Multidetector CTA (MDCTA) and gadolinium-enhanced MRA have narrowed the indications for conventional angiography, which is now reserved for patients in whom small-vessel detail is essential for diagnosis or for whom concurrent interventional therapy is planned **(Table 4-1)**.

In general, MRI is more sensitive than CT for the detection of lesions affecting the central nervous system (CNS), particularly those of the spinal cord, cranial nerves, and posterior fossa structures. Diffusion MR, a sequence sensitive to the microscopic motion of water, is the most sensitive technique for detecting acute ischemic stroke of the brain or spinal cord, and it is also useful in the detection of encephalitis, abscesses, and prion diseases. CT, however, is quickly acquired and is widely available, making it a pragmatic choice for the initial evaluation of patients with acute changes in mental status, suspected acute stroke, hemorrhage, and intracranial or spinal trauma. CT is also more sensitive than MRI for visualizing fine osseous detail and is indicated in the initial imaging evaluation of conductive hearing loss as well as lesions affecting the skull base and calvarium. MR may, however, add important diagnostic information regarding bone marrow infiltrative processes that are difficult to detect on CT.

COMPUTED TOMOGRAPHY

TECHNIQUE

The CT image is a cross-sectional representation of anatomy created by a computer-generated analysis of the attenuation of x-ray beams passed through a section of the body. As the x-ray beam, collimated to the desired slice width, rotates around the patient, it passes through selected regions in the body. X-rays that are not attenuated by body structures are detected by sensitive x-ray detectors aligned 180° from the x-ray tube. A computer calculates a "back projection" image from the 360° x-ray attenuation profile. Greater x-ray attenuation (e.g., as caused by bone), results in areas of high "density" (whiter) on the scan, whereas soft tissue structures that have poor attenuation of x-rays, such as organs and air-filled cavities, are lower (blacker) in density. The resolution of an image depends on the radiation dose, the detector size, collimation (slice thickness), the field of view, and the matrix size of the display. A modern CT scanner is capable of obtaining sections as thin as 0.5–1 mm with 0.4-mm in-plane resolution at a speed of 0.3 s per rotation; complete studies of the brain can be completed in 1–10 s.

Multidetector CT (MDCT) is now standard in most radiology departments. Single or multiple (from 4 to 320) solid-state detectors positioned opposite to the x-ray source result in multiple slices per revolution of the beam around the patient. The table moves continuously through the rotating x-ray beam, generating a continuous "helix" of information that can be reformatted into various slice thicknesses and planes. Advantages of MDCT include shorter scan times, reduced