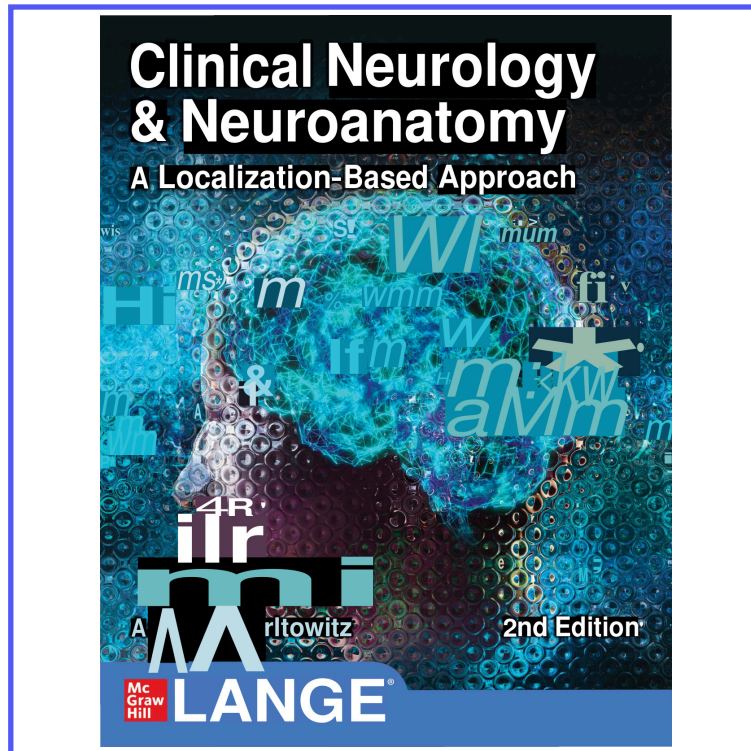




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Foreword

So much of neurology exists only “in use”. This is the neurology that is practiced in the clinics, wards, and offices of seasoned clinicians and cannot be found in large encyclopedic textbooks of neurology or smaller monographs intended for medical students. The accumulated experience of the neurologist can be distilled to a number of action items and thought processes that are challenging to articulate.

Dr. Aaron Berkowitz has written a book that occupies just this position. He has taken the transactional daily work of neurology and produced a wonderfully readable, concise, but by no means superficial book that fits well in the current pedagogic environment. One might ask whether any book on neurology is needed now that disembodied information is so easily available on the web and algorithms for various signs, symptoms, and diseases abound. But between information that is as often misleading as it is useful, and the storehouse of wisdom accumulated over a long career, sits a great body of neurological knowledge. It is this assembled knowledge that allows us to efficiently move through the workday and can be taught to students and residents during their rotations. Berkowitz’s book is more than a compendium or teaching guide and is far superior to

existing books of its size and scope because of the thoughtfulness with which the knowledge about diseases and neurological conditions has been assembled. He gets right down to business, addressing almost every major point that is encountered on the wards and in the clinic.

A book such as this one is more suitable for neurology than for any other branch of medicine. We still depend on the interface between our own refined clinical skills and our decisions regarding diagnosis and treatment. The pearls contained here about the meaning of particulars of the history and examination cannot be found elsewhere. The book makes a seamless transit from these data to practical wisdom about their application. The material is clear and avoids the ambiguity that clutters most other books. In doing so, it also incorporates the latest thinking from clinical trials and together, these features provide one of the best modern outlooks on the pragmatic practice of neurology.

It takes a certain outlook on pedagogy and practice to produce such a book. Dr. Berkowitz has more than succeeded, and I find myself looking at a number of the chapters over and over to reorient myself to solid teaching and practice.

Allan H. Ropper, MD
Professor of Neurology
Harvard Medical School
Boston, Massachusetts

Preface to the First Edition

There are many extraordinary neurology and neuroanatomy textbooks. Innumerable clinical pearls can be gleaned from dedicated time spent with these texts as a student, trainee, and practitioner. Yet when I was a student and then a trainee, I found that there was no single text that provided a comprehensive introduction to clinical neuroanatomy, its application to neurology, and the diagnosis and management of both common and rare neurologic diseases in one concise volume. I had wished that there was a book that could be read cover-to-cover as a student rotating through neurology, or when I was a soon-to-be neurology resident at the end of my medical internship, or as a quick reference to efficiently review topics as a neurology resident—a book in which one or more chapters could be read in a single sitting. As I began to teach neuroanatomy and neurology to students, residents, and non-neurologists, I learned that they too wished for such a book. In *Clinical Neurology & Neuroanatomy: A Localization-Based Approach*, I decided to attempt to write that book.

Some of the many essential textbooks that nearly all neurologists return to throughout training and practice include Brazis' *Localization in Clinical Neurology*, Patten's *Neurologic Differential Diagnosis*, and Blumenfeld's *Neuroanatomy through Clinical Cases* for neurologic localization and clinical neuroanatomy; Adams and Victor's *Principles of Neurology* and Bradley's *Neurology in Clinical Practice* for clinical neurology. *Clinical Neurology & Neuroanatomy: A Localization-Based Approach* is, by design, a fraction of the size of any one of these books, and is meant to provide a concise but comprehensive framework to facilitate engagement with those texts. My goal is to distill clinical neuroanatomy, clinical neurology, and their interrelations to their fundamental principles so as to explain them clearly and simply. In so doing, I hope to convey the core material essential to the practice of neurology in an efficient and easily digestible format with the depth and detail required of neurology residents and neurologists reviewing for

recertification examinations, but also with sufficient clarity and brevity for medical students on neurology rotations and non-neurologists in settings where there are few or no neurologists.

In Part 1 of this book, clinically relevant neuroanatomy is presented in clinical context in order to provide a framework for neurologic localization and differential diagnosis. The diseases mentioned in localization-based discussions of differential diagnoses in Part 1 are then discussed in clinical detail with respect to their diagnosis and management in Part 2. For example, in Chapter 5, the anatomy of the spinal cord and its relation to clinical syndromes involving the spinal cord are discussed. The differential diagnosis of myelopathy is presented, but the evaluation and management of many of the diseases mentioned that can cause myelopathy are discussed in Part 2 (e.g., vascular diseases of the spinal cord are discussed in Ch. 19, infections of the spine in Ch. 20, inflammatory conditions of the spinal cord in Ch. 21). Part 1 of this book can therefore be consulted for a neuroanatomical localization-based approach to symptom evaluation, and Part 2 for the clinical features, diagnosis, and management of neurologic diseases. Certain diseases are more logically discussed directly in the context of their underlying anatomy, and where this is the case, these diseases are discussed in Part 1 (e.g., trigeminal neuralgia and Bell's palsy in Ch. 13 on the trigeminal and facial nerves; benign paroxysmal positional vertigo in Ch. 12 on the vestibular system and the approach to vertigo).

Neurology is learned by taking care of patients: thinking through localization and differential diagnosis, evaluation, and management of individual patients, and discussing these patients' cases with one's clinical teachers and colleagues. This book is of course no replacement for that experience. However, my hope is that this book will serve as a guide to and through that process.

Aaron L. Berkowitz, MD, PhD

Preface to the Second Edition

In the five years since the first edition of this book, there has been an explosion in new knowledge that directly impacts our care of patients with neurologic disease. New treatments have emerged for epilepsy, multiple sclerosis, and migraine. New diseases have been characterized (antibody-mediated syndromes), new criteria for diagnosis of existing diseases have been established (multiple sclerosis), and new categorizations of existing diseases have been created (brain tumors). New clinical trial data has transformed the treatment of acute stroke. New treatments for systemic cancer (immunotherapy and CAR T-cell therapy) have generated a new spectrum of cancer treatment-associated neurologic conditions. All of these exciting updates are included in this second edition, and still this book will likely have aspects that are out-of-date as soon as it goes to press. What other field of medicine has come so far in so short a time, and yet still has so far to go? This constant evolution is one of many aspects that makes neurology such a dynamic, engaging, and meaningful field to study and practice.

When I set out to revise this book to include all of the above developments, some colleagues said, “Well, at least you won’t have to revise the neuroanatomy that doesn’t change.” While neuroanatomy may not change, it is vast and we are constantly learning more through study and practice. I’ve had the great fortune to work with students and residents whose questions have helped me learn more, deepen my understanding, and find new ways to teach. I’ve also been fortunate to receive feedback from readers and colleagues on topics to

add, concepts to clarify, and clinical correlations to emphasize. Thanks to the incredible artistry of Craig Durant and his colleagues at Dragonfly Media. This second edition includes many new drawings of the neuroanatomical pathways as well as narrated animations available on the AccessMedicine website.

In working on this second edition, I have been fortunate to receive feedback from subspecialist experts, who helped to make sure I didn’t miss any developments and that my understanding of the latest updates in their fields were correct, precise, and practical. I extend my utmost gratitude to Dr. Jong Woo Lee (Epilepsy, Brigham and Women’s Hospital), Dr. Tracey Milligan (Epilepsy, New York Medical College), Dr. Justin Sattin (Vascular Neurology, University of Wisconsin), Dr. Eli Zimmerman (Vascular Neurology, Vanderbilt University), Dr. Casey Albin (Neuro-Critical Care, Emory), Dr. Arun Venkatesan (Neuro-Infectious Disease, Johns Hopkins), Dr. Priya Anand (Neuro-Infectious Disease, Boston University), Dr. Shamik Bhattacharyya (Multiple Sclerosis and Auto-immune Neurology, BWH), Dr. Emmanuelle Waubant (Multiple Sclerosis, UCSF), Dr. Andrew Stern (Cognitive/Behavioral Neurology, BWH), Dr. Emily Ferenczi (Movement Disorders, BWH), Dr. Joshua Budhu (Neuro-Oncology, BWH/MGH), Dr. Maya Graham (Neuro-Oncology, Memorial Sloan-Kettering), Dr. Rebecca Burch (Headache, BWH), Dr. Christopher Doughty (Neuromuscular, BWH), Dr. Tabby Kennedy (Neuroradiology, University of Wisconsin).

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I am very fortunate to have trained in neurology under two of the field's great luminaries, Dr. Allan H. Ropper and Dr. Martin A. Samuels. They are not only two virtuosic neurologists, they are extraordinary teachers, inspiring and dedicated mentors, and serve as role models of the Complete Physician toward which to strive.

Dr. Steve Feske has also been an extremely important guru in my development as a neurologist. I have learned so much from discussing cases with him, and admire his balance of clinical wisdom and rigorous analysis of the evidence (or lack thereof) when approaching the most complex cases with extreme clarity. I often find myself "trying to ask my inner Feske" when faced with vexing clinical dilemmas.

I would also like to thank the faculty of the Partners Neurology Residency Program who trained me, with special gratitude to Dr. Tracey Milligan, Dr. Nagagopal Venna, Dr. Steve M. Greenberg, Dr. Albert Hung, Dr. Sashank Prasad, Dr. Anthony Amato, Dr. Tracey Cho, Dr. Joshua Klein, and Dr. Sherry Chou for their clinical teaching and mentorship.

I have learned so much from the residents and students with whom I have been privileged to work in Boston, in Haiti, and in Malawi. Their questions and their pursuit of answers to questions I could not answer have enriched my own knowledge, and in turn, have helped me to develop as a teacher of neurology and neuroanatomy.

In Haiti, where there is one neurologist for 10 million citizens, I have had the honor of teaching neurology to family practitioners and internists for the last several years. Dr. Patrick Jouissance, my long-time colleague in Haiti, once said to me after a week of neurology training for his family medicine residents, "We need a clear and concise neurology textbook- please write one for us!" I hope he and his residents will find that this book fulfills their request.

In writing the first edition of this book, I was fortunate that my expert subspecialty colleagues from Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) took time out of their busy schedules to review individual chapters in their areas of expertise, and this book has benefited greatly from their thoughtful reviews

and insightful suggestions. I extend enormous thanks to Dr. Anthony Amato (Neuromuscular Diseases, BWH), Dr. Shamik Bhattacharyya (Multiple Sclerosis and Autoimmune Neurology, BWH), Dr. Tracey Cho (Neuro-infectious Diseases, MGH), Dr. Thomas Cochrane (Neuromuscular Diseases, BWH), Dr. Barbara Dworetzky (Epilepsy, BWH), Dr. Claudio DeGusmao (Pediatric and Transitional Neurology, BWH), Dr. Steven Feske (Vascular neurology and Neurocritical care, BWH), Dr. Steven M. Greenberg (Vascular neurology, MGH), Dr. Albert Hung (Movement Disorders, BWH/MGH), Dr. Tamara Kaplan (Fellow in Multiple Sclerosis and Demyelinating Diseases, BWH), Dr. Joshua Klein (Neuroradiology and Neurology, BWH), Dr. Jong Woo Lee (Epilepsy, BWH), Dr. Jennifer Lyons (Neuro-infectious Diseases, BWH), Dr. Scott McGinnis (Behavioral and Cognitive Neurology, BWH), Dr. William Mullally (Headache, BWH), Dr. Lakshmi Nayak (Neuro-oncology, BWH), Dr. Page Pennell (Epilepsy, BWH), Dr. Sashank Prasad (Neuro-ophthalmology, BWH), and Dr. James Stankiewicz (Multiple Sclerosis and Demyelinating Diseases, BWH).

I am also grateful to the residents and medical students who took the book for a "test drive" and provided thoughtful feedback: Dr. Emer McGrath, Dr. Pooja Raibagkar, Dr. Francois Roosevelt, Dr. Michael Erkinen, and Cathy Hao.

The first edition of this book would not have been possible without the phenomenal stewardship of Andrew Moyer and the efforts of his team at McGraw Hill. Andrew guided this book from idea to production and he and his team developed creative ways to enhance the pedagogy of the text and figures through their layout and presentation. I am grateful to Tim Hiscock, Peter Boyle, and their team at McGraw Hill for shepherding this book through its second edition. Tasneem Kauser and her team at KnowledgeWorks Global Ltd. effectively and efficiently transformed the countless text and image files with which I provided them into the book you are holding and were a pleasure to work with.

Finally, to the patients who have taught me all of the neurology I know, I hope that this book will honor your courage in facing neurologic disease and your generosity in allowing us to learn from you.

PART I NEUROANATOMY & NEUROANATOMIC LOCALIZATION

Diagnostic Reasoning in Neurology & the Neurologic History & Examination

C H A P T E R

1

CHAPTER CONTENTS

LOCALIZATION IN NEUROLOGIC DIAGNOSIS:
DETERMINING *WHERE* THE PROBLEM IS

TIME COURSE IN NEUROLOGIC DIAGNOSIS:
DETERMINING *WHAT* THE PROBLEM IS

**ASSOCIATED SYMPTOMS & SIGNS IN NEUROLOGIC
DIAGNOSIS**

INTRODUCTION TO THE NEUROLOGIC EXAMINATION
Examination of Mental Status

Examination of the Cranial Nerves

Examination of the Motor System

Examination of the Sensory System

Examination of the Reflexes

Examination of Coordination

Examination of Gait

The General Examination in Neurologic Diagnosis

Differential diagnosis in neurology is based on two main components determined from the clinical history and physical examination:

- The **localization** of the neuroanatomic origin(s) of the patient's symptoms and signs
- The **time course** over which these symptoms and signs have arisen and evolved

These give rise to what I call the “fundamental equation” of differential diagnosis in neurology:

Differential Diagnosis = Localization × Time course

Localization relies on the clinical history and neurologic examination to determine *where* in the nervous system the problem is. To some extent, knowing *where* the problem is already begins to circumscribe *what* the problem is, since each level of the nervous system has a particular differential diagnosis for the types of disease processes that can affect it. The time course over which neurologic symptoms arise and evolve

provides crucial information in determining *what* the problem is, since different disease processes emerge and evolve over different time frames.

LOCALIZATION IN NEUROLOGIC DIAGNOSIS: DETERMINING *WHERE* THE PROBLEM IS

Localization is the process of determining *where* in the nervous system the patient's disease process is occurring: Is the problem in the central nervous system (CNS), the peripheral nervous system (PNS), or both? Within the CNS, is there a lesion in the brain, brainstem, cerebellum, or spinal cord? More precisely, *where* is the lesion within those structures? For example, which *level* of the brainstem or spinal cord? Which hemisphere(s), lobe(s), and gyrus/gyri of the brain? Within the PNS, is the lesion at the level of the spinal roots, dorsal root ganglia, peripheral nerves, neuromuscular junction, or

muscles? If there is a root, nerve, or muscle problem, which root(s), nerve(s), and/or muscle(s) is/are involved?

Nervous system diseases may affect particular **structures** (e.g., the basal ganglia, the cerebellum, the peripheral nerves), a particular **tissue type** (e.g., white matter vs gray matter of the brain; myelin of peripheral nerves vs their axons), or one or more particular **systems** (e.g., the motor system, the limbic system).

Localization requires a detailed understanding of neuroanatomy. Part 1 of this book presents clinical neuroanatomy alongside the clinical approach to symptoms and signs related to the anatomy under discussion. Diseases that are mentioned in Part 1 of this book are discussed in more detail with respect to their clinical features, diagnosis, and treatment in Part 2.

Localization begins with the clinical history, which should elucidate the nature of the patient’s presenting symptom(s) and allow for an initial idea of potential localization(s). For example, is a chief concern of “difficulty walking” due to weakness, impaired coordination, altered sensation, pain, decreased vision, higher-order motor dysfunction, or a non-neurologic (e.g., orthopedic) condition? The neurologic examination provides further clues as to the neuroanatomic

localization of the patient’s symptoms (see “Introduction to the Neurologic Examination”).

TIME COURSE IN NEUROLOGIC DIAGNOSIS: DETERMINING WHAT THE PROBLEM IS (FIG. 1–1)

The time course of symptom onset and evolution may be described as **sudden/hyperacute** (seconds to minutes), **acute** (hours to days), **subacute** (weeks to months), or **chronic** (months to years). The following is a general “first pass” in neurologic differential diagnosis based on the timing of symptom onset and pace of symptom evolution (with a few exceptions noted below):

- **Hyperacute (seconds to minutes):**
 - **Vascular** (e.g., ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage)
 - **Seizure**
 - **Migraine**
 - **Metabolic** (e.g., hyperglycemia or hypoglycemia)
 - **Medications/Toxins**
 - **Trauma**

Hyperacute (Over seconds to minutes)	Acute (Over hours to days)	Subacute (Over weeks to months)	Chronic (Over years)
Vascular Ischemic stroke Intracerebral hemorrhage Subarachnoid hemorrhage	Venous sinus thrombosis	Chronic subdural hematoma Vascular malformation	
Seizure	Infection Bacterial meningitis Cerebral or epidural abscess Viral meningitis Viral encephalitis	Fungal meningitis Tuberculous meningitis Tuberculosis of the spine Progressive multifocal leukoencephalopathy	HTLV-1 HIV/AIDS
Migraine		Syphilis	
Trauma	Inflammatory/Demyelinating Guillain-Barré Syndrome Acute disseminated encephalomyelitis Flare of multiple sclerosis Transverse myelitis Optic neuritis	CIDP Paraneoplastic syndromes	Primary/secondary progressive multiple sclerosis
		Neoplasm Malignant	Benign
			Neurodegenerative Dementia Parkinson's disease
Metabolic Hypoglycemia Hyperglycemia Acute intermittent porphyria	Uremic encephalopathy Hepatic encephalopathy	Vitamin B12 deficiency	
Medications/drugs/toxins Acute intoxication (e.g., alcohol, cocaine) Acute withdrawal (e.g., alcohol, benzodiazepines) Acute dystonic reaction (e.g., metaclopramide)	Antibiotic-induced encephalopathy	Drug-induced neuropathy Tardive dyskinesia Drug-induced parkinsonism	

FIGURE 1–1 Schematic showing differential diagnosis of neurologic disease by time course.

- **Acute (hours to days):**
 - **Infectious** (bacterial and viral infections of the nervous system; e.g., meningitis, encephalitis, abscess)
 - **Immune-mediated** (e.g., Guillain-Barré syndrome, flare of multiple sclerosis)
 - **Metabolic** (e.g., uremia, hepatic encephalopathy, hyponatremia or hypernatremia)
 - **Medications/Toxins**
- **Subacute (weeks to months)**
 - **Neoplastic**
 - **Immune-mediated** (e.g., paraneoplastic/antibody-mediated syndromes)
 - **Infectious** (fungal, tuberculous, and parasitic infections, neurologic complications of HIV)
 - **Metabolic** (e.g., vitamin B12 deficiency)
 - **Medications/Toxins**
- **Chronic (months to years)**
 - **Degenerative diseases** (e.g., Alzheimer's disease, Parkinson's disease)
 - **Genetic** (e.g., Charcot-Marie-Tooth, hereditary spastic paraplegia, Huntington disease)
 - **Metabolic**
 - **Medications/Toxins**

Note that if one keeps in mind that metabolic abnormalities, medications, and toxins can cause neurologic dysfunction over nearly any time course (depending on the metabolic abnormality, medication, or toxin), the rest of this schema distills to:

- **Hyperacute:** vascular, seizure, migraine, trauma
- **Acute to subacute:** infectious, immune-mediated
- **Subacute to chronic:** neoplastic, immune-mediated, infectious
- **Chronic:** degenerative, genetic

There are a few important exceptions to this general schema:

- Nonacute disease processes may present acutely. For example, although focal deficits from tumors usually emerge and evolve subacutely, a brain tumor may be asymptomatic until it causes a seizure. Another example is relapsing-remitting multiple sclerosis, a chronic disease characterized by acute flares.
- Although most vascular problems present hyperacutely, chronic subdural hematoma is an example of a vascular condition that presents subacutely/chronically (see Ch. 19).
- Fungal infections, tuberculosis, and neurologic complications of HIV can present subacutely compared to bacterial and viral infections, which present more acutely (see Ch. 20).

With the exception of seizure and migraine, which are exclusively cerebral phenomena, the other categories apply across most levels of the neuraxis. For example, sudden-onset findings localizing to a particular part of the brain suggest a vascular cause, and this is also true of the spinal cord (e.g.,

spinal infarct, spinal epidural hemorrhage) and even of a sudden-onset peripheral nerve palsy (e.g., nerve infarction as can be seen in vasculitis). Acute inflammatory disease of the brain (e.g., acute flare of multiple sclerosis), spine (e.g., transverse myelitis), or peripheral nerves (e.g., Guillain-Barré syndrome) all emerge and evolve over hours to days.

ASSOCIATED SYMPTOMS & SIGNS IN NEUROLOGIC DIAGNOSIS

In addition to the time course of symptom onset and evolution, the history must elicit associated concurrent or preceding symptoms to contextualize the patient's primary symptom. For example, if the presenting symptom is weakness, is this weakness accompanied by sensory changes and/or pain? Is the presenting symptom restricted to the limb most prominently noted by the patient or is it also present elsewhere? If the symptom is headache, is there associated nausea/vomiting or are there visual changes? Such questions establish the full range of the patient's symptoms beyond the "chief concern" most salient to the patient, aiding in localization of the cause of the patient's symptoms.

Of course, as in all areas of medicine, each symptom must also be fully characterized with respect to its quality, severity, exacerbating and alleviating factors, and any accompanying symptoms. The patient's presenting symptom(s) must also be contextualized with respect to the past medical history, family history, social history, and medications.

The clinical history should allow for an initial hypothesis to be generated about *where* in the nervous system the problem may be as well as *what* it may be, and the neurologic examination provides further information to support or refute this hypothesis.

INTRODUCTION TO THE NEUROLOGIC EXAMINATION

The neurologic examination is a critical tool in localization, confirming or refuting hypotheses generated during the history, or sometimes giving rise to new ones entirely. For example, is the patient's presenting problem of "difficulty moving one hand" due to weakness, slowed movement, numbness, pain, incoordination, or inability to execute a complex movement plan? Each of these possibilities can be tested in the course of the neurologic examination.

With each element of the neurologic examination, it is important to consider which systems and structures within the nervous system are being evaluated and how their dysfunction could manifest. When working toward mastery of the neurologic examination and its interpretation, it is helpful to try to imagine the pathways involved while examining them. For example, when testing the pupillary light reflex, think: "afferent via optic nerve to pretectal nuclei of the midbrain, efferent via Edinger-Westphal nuclei to the oculomotor nerves" (see Ch. 10). When testing a muscle, think about the name of the muscle and its nerve and nerve root supply (see Chs. 16–17).

