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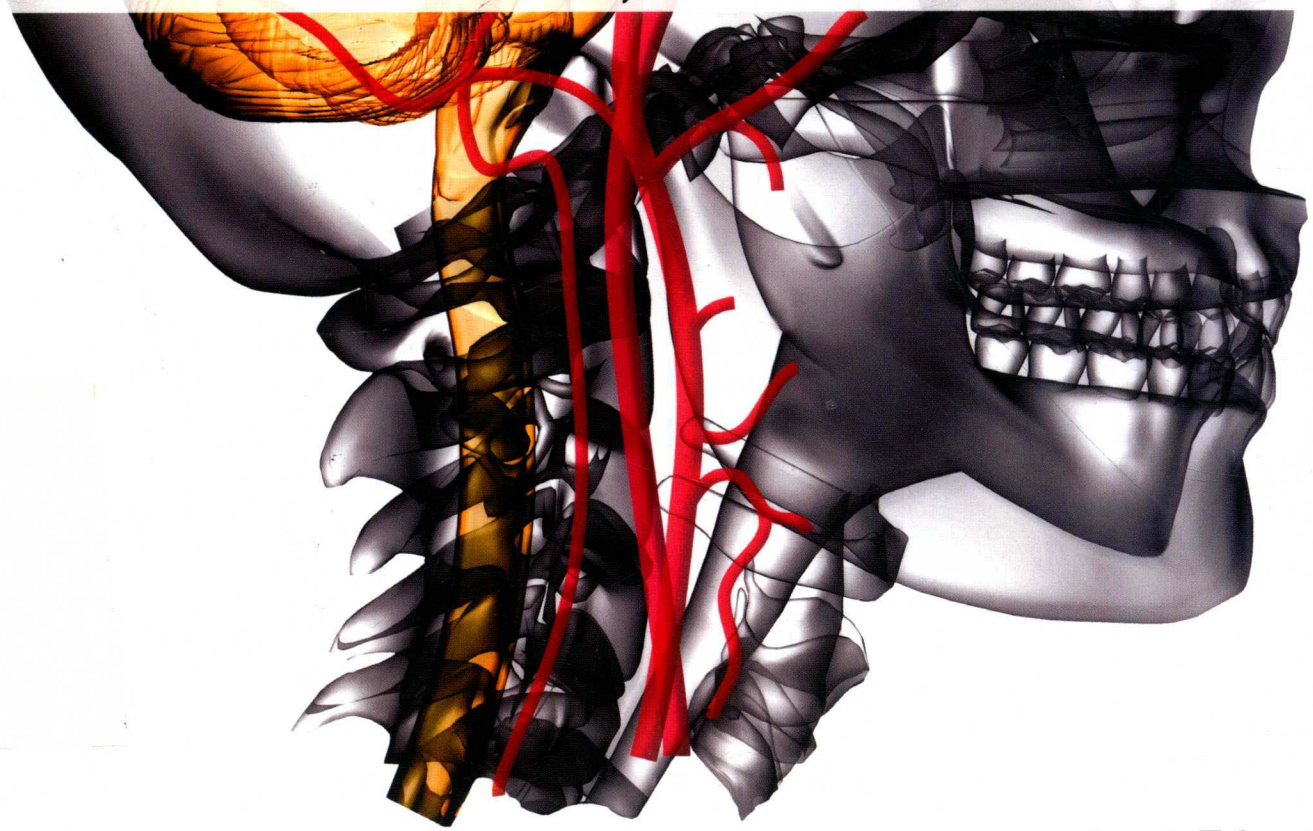
STROKE

Pathophysiology, Diagnosis, and Management

Foreword by J. P. Mohr



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Sixth Edition

Stroke

Pathophysiology, Diagnosis, and Management

SIXTH EDITION

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Foreword to the Sixth Edition

This, the sixth edition of *Stroke*, has passed from the hands of the last of the original four editors to a distinguished and experienced group now numbering eight. The chapter numbers have also increased from the original 61 to 76. The content of these chapters is altered by the very advances the first-edition authors had hoped for.

The few involved in the brief hallway discussion that led to the first edition could not foresee – but certainly hoped for – the expansion in the scope of interest in the field. In 1986 it was still struggling for independence as a justifiable multidisciplinary specialty. Considerable latitude existed for management using experience-based bias, heavy reliance on clinical semiology, and for some an uncertainty of the value of imaging. Few clinicians focused disproportionately on stroke, and most of them were in major centers. Many outside the field still thought of stroke as a bed-occupying distraction lacking therapy, suitable for early discharge. "It's just a stroke" was a common observation.

Contrast that with today, where stroke is the main inpatient service for the clinical neurosciences – for many also including a separate neuro-intensive care unit. Success in very early therapy has changed the attitude of patients toward the disease. Career efforts are made from many disciplines, subspecialty ACGME certification exists, heavy reliance is placed on imaging, emergency management is focused on the very earliest intervention, sophisticated statistical models dictate plans for clinical trials, and we are expected to "Get with the Guidelines".

Along the way semiology has properly given way to pathophysiology as revealed by imaging, biomarkers, and intervention – both physical and medical. While there is an asymptote of treatment effect in sight, a resurgence of interest in semiology is in the offing. Given the current opportunities to understand brain reorganization, ways will eventually be found to ameliorate those syndromes that occur despite the best efforts at their prevention. This emeritus editor sees a bright future ahead.

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Preface

Welcome to the 6th edition of *Stroke: Pathophysiology, Diagnosis, and Management*. Much has changed in the world of cerebrovascular disease since the first edition edited by Barnett, Mohr, Stein, and Yatsu in 1986. One thing that has remained constant, however, is that this textbook continues to be the most authoritative resource in the field of stroke. Nevertheless, a major milestone with this text has occurred with the baton of editorship being passed from JP Mohr, the sole remaining editor from the first edition, to a new generation of editors to carry the text forward into future decades. Dr Mohr has left an indelible mark on the body of knowledge surrounding many aspects of cerebrovascular disease, including his scholarship and leadership as senior author of *Stroke: Pathophysiology, Diagnosis, and Management*. He will be missed, though the reader will recognize many of his teachings and observations preserved throughout; especially in the section on Clinical Manifestations.

While the basic organization of the text is maintained, and the various sections and many of the chapter titles are the same, there have been some important changes and additions. Within most sections, chapters have been re-ordered into a more logical sequence. The titles of many chapters have been updated to reflect the new information contained in each, and the authorships altered to include clinicians/investigators who are current experts on each topic. Several new chapters have been added, and most importantly, there has been an almost complete change in the cadre of editors.

The editors reflect the "new" generation of senior leadership in the field. The section editor of Pathophysiology has been turned over from Mike Moskowitz to Eng Lo. This was an easy transition since the two have worked together at the same institution for many years, and Dr Lo's expertise in cell signaling and cell death mechanisms reflects the current focus in the understanding of the process of cell injury after stroke. The section contains new chapters on the Neurovascular Unit, and on Mechanisms of Cerebral Hemorrhage. The Epidemiology and Risk Factor section has transitioned from Phil Wolf to Ralph Sacco. Dr Sacco has been a leader in the understanding of ethnic stroke trends based on his work with the Northern Manhattan study and has led the American Heart Association and American Stroke Association as they have focused on stroke risk factors and prevention. Dr Mohr's section on Clinical Manifestations is now edited by Lawrence Wong, a world-class clinical neurologist, who not only understands classical clinical neurology, but also has identified how these may differ in various parts of the world, in particular Asia with its huge burden of stroke.

The section on Specific Conditions and Stroke, also previously edited by Dr Mohr, is now edited by Scott Kasner. Dr Kasner's career as a Vascular Neurologist has paralleled the explosive growth in our ability to diagnose and understand the multifaceted causes and manifestations of stroke, in particular dissections and other vasculopathies. Several new chapters have been added to this section; Stroke Related to Surgery and Other Procedures, Cryptogenic Stroke, and Cerebral Venous Thrombosis. Nowhere has technology advanced faster than in diagnosis, and Greg Albers now assumes editorship of the Diagnostic Studies section from Rüdiger von Kummer. Dr Albers has been a pioneer in the application of brain imaging, in particular MRI to identify, prognosticate and guide treatment of acute stroke, and his innovations reflect the growing integration of imaging into all aspects of stroke management.

James Grotta remains the editor of the section on Medical Therapy which still centers on the appropriate use of tPA – a topic on which he has devoted a substantial part of his productive career. The section now includes a new chapter on Interventions to Improve Recovery after Stroke, reflecting emerging and ongoing research in this area. Exciting new data have been generated in several aspects of Interventional Therapy, and the editorship of that section has passed from Rüdiger von Kummer to Joseph Broderick, who has led one of the major clinical trials in that area. As this text goes to press, recent results and perspectives in the field of endovascular thrombectomy are outlined in Dr Broderick's Introduction to that section. Finally, David Mendelow brings his perspective as a clinical trialist in the surgical management of intracranial hemorrhage to the editorship of the Surgical Therapy section, which he assumes from Marc Mayberg. Under his supervision, the previous 14 chapters in the section have been distilled into eight, all of which have been updated with important information.

The text continues to be developed and guided by experienced and able hands at Elsevier, namely Charlotta Kryhl, Senior Content Strategist, and Nani Clansey, Senior Content Development Specialist.

The 6th edition of *Stroke: Pathophysiology, Diagnosis, and Management* includes an interactive online version housed on www.expertconsult.inkling.com, which can also be downloaded for offline use on phones or tablets.

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AHA Evidence-based Classifications

TABLE 1 Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →				
	CLASS I	**CLASS IIa**	**CLASS IIb**	**CLASS III *No Benefit* or CLASS III *Harm***	
	Benefit > > > Risk **Procedure/ Treatment SHOULD be performed/ administered**	***Benefit > > Risk*** ***Additional studies with focused objectives needed*** **IT IS REASONABLE** to perform procedure/ administer treatment	***Benefit ≥ Risk*** ***Additional studies with broad objectives needed; additional registry data would be helpful*** Procedure/Treatment **MAY BE CONSIDERED**	**Procedure/ Test** / **Treatment** **COR III: No benefit** — **Not Helpful** / **No Proves Benefit** **COR III: Harm** — **Excess Cost w/o Benefit or Harmful** / **Harmful to Patients**	
LEVEL A **Multiple populations evaluated*** **Data derived from multiple randomized clinical trials or meta-analyses**	• **Recommendation that procedure or treatment is useful/effective** • **Sufficient evidence from multiple randomized trails or meta-analyses**	• **Recommendation in favor of treatment or procedure being useful/effective** • **Some conflicting evidence from multiple randomized trials or meta-analyses**	• **Recommendation's usefulness/efficacy less well established** • **Greater conflicting evidence from multiple randomized trials or meta-analyses**	• **Recommendation that procedure or treatment is not useful/effective and may be harmful** • **Sufficient evidence from multiple randomized trials or meta-analyses**	
LEVEL B **Limited populations evaluated*** **Data derived from a single randomized trial or nonrandomized studies**	• **Recommendation that procedure or treatment is useful/effective** • **Evidence from single randomized trial or nonrandomized studies**	• **Recommendation in favor of treatment or procedure being useful/effective** • **Some conflicting evidence from single randomized trial or nonrandomized studies**	• **Recommendation's usefulness/efficacy less well established** • **Greater conflicting evidence from single randomized trial or nonrandomized studies**	• **Recommendation that procedure or treatment is not useful/effective and may be harmful** • **Evidence from single randomized trial or nonrandomized studies**	
LEVEL C **Very limited populations evaluated*** **Only consensus opinion of experts, case studies, or standard of care**	• **Recommendation that procedure or treatment is useful/effective** • **Only expert opinion, case studies, or standard of care**	• **Recommendation in favor of treatment or procedure being useful/effective** • **Only diverging expert opinion, case studies, or standard of care**	• **Recommendation's usefulness/efficacy less well established** • **Only diverging expert opinion, case studies, or standard of care**	• **Recommendation that procedure or treatment is not useful/effective and may be harmful** • **Only expert opinion, case studies, or standard of care**	
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/ beneficial	is reasonable can be useful/effective/ beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/ uncertain or not well established	COR III No Benefit: is not recommended is not indicated should not be done is not useful/ beneficial/effective	COR III Harm: potentially harmful causes harm associated with excess morbidity/ mortality should not be done
Comparative effectiveness phrases†	treatment/strategy A is recommended/ indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/ indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

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Box: Evidence Classifications

- Size of treatment effect
  - Class I: Benefit >>> Risk. Procedure/treatment **SHOULD** be performed/administered
  - Class IIa: Benefit >> Risk. **IT IS REASONABLE** to perform procedure/administer treatment
  - Class IIb: Benefit ≥ Risk. Procedure/treatment **MAY BE CONSIDERED**
  - Class III: No Benefit/Harm. Procedure/treatment is not useful/ effective and may be harmful
- Certainty of treatment effect
  - Level A: Data derived from multiple randomized clinical trials or meta-analyses.
  - Level B: Data derived from a single randomized trial or nonrandomized studies
  - Level C: Only consensus opinion of experts, case studies, or standard of care

Adapted from Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. Stroke 2006;37:577–617.

Contents

SECTION I Pathophysiology

Eng H. Lo

Despite impressive advances in the molecular biology of cell death, the development of clinically effective neuroprotectants for the stroke patient remains challenging. An emerging hypothesis now states that a purely intracellular and "neurocentric" focus may not suffice. Stroke is a complex disease and so its pathophysiology comprises multiple signals and mechanisms in multiple cells and systems. The first section in this new edition of *Stroke* surveys the state-of-the-art in the field from this perspective.

At the cellular level, stroke affects mechanisms of hemostasis and perturbs interactions between circulating blood elements, the blood vessel itself, and brain parenchyma. At the functional level, the regulation and dysregulation of hemodynamics and metabolism remains a central event. At the organ level, stroke induces histopathologic reactions in all neural, glial and vascular cells. Hence, this section begins with chapters that define basic principles of vascular biology, cerebral blood flow and metabolism, and the brain tissue response to injury.

Building on this initial survey of key principles, the next few chapters then explore the molecular mechanisms of cell death and survival. Genes and pathways underlying necrosis and programmed cell death are balanced against an expanding family of endogenous neuroprotection and tolerance mediators. Beyond the brain itself, interactions with other organ systems are discussed in terms of crosstalk with neuroinflammatory cascades and immune cells. Stroke recovery is discussed in terms of multi-cellular signals for remodeling in the neurovascular unit, as well as compensatory response in resident and circulating progenitor cells. Because brain compartments are heterogeneous, two chapters are dedicated to assessing the nuances of molecular and cellular phenomena in white matter and hemorrhage. Finally, the section concludes with a chapter that links these molecular, cellular and physiologic principles in stroke to important categories of vascular malformations that contribute to cerebrovascular disease.

Stroke science will continue to advance. Molecular details may be revised and clinical opportunities may evolve. But it is hoped that the basic principles in this section will stand the test of time by providing the mechanistic foundations for stroke pathophysiology and a rational basis for pursuing potential therapeutics and diagnostics.