Dedication

To my many teachers and mentors over the years, most especially Lewis Rowland, Robert Fishman, Sidney Carter, Donald Silberberg, Donald Schotland, and Arthur Asbury in neurology, Burton Zweiman in immunology and clinical immunology, Marian Kies in neuroscience, neurochemistry and glial biology, and Elvin Kabat in immunology. To my collaborators, colleagues, students, residents, fellows, and patients over the years. And finally and most importantly to my family, including my late parents Irving and Sylvia Lisak, my sister Nancy Lisak Sager, my wife Deena, my children Ilene and Michael, and my grandchildren Samuel, Isabella, Vivienne, and Sophie.

RPL

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DDT

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WMC

To my beloved grandmother Pranom Chivakiat, my parents Mitr and Nisaratana Bhidayasiri, my family, Nucharee Yoovidhya and Bhiradej Yoovidhya Bhidayasiri, for their continuing support, love, and understanding, all my teachers of neurology, and lastly my patients who have taught me much about neurology.

RB
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I was delighted and honoured a few years ago when Robert Lisak, a neurologist of outstanding ability and merit and former editor of the Journal of Neurological Sciences, invited me to write a foreword to the first edition of this book. I then said that, whereas many notable textbooks on clinical neurology exist, I was not aware that there were any which dealt as comprehensively with international neurology as did that volume, which has proved, as I anticipated, to be outstandingly successful. It is therefore a great pleasure, in my 93rd year, to welcome this second edition, substantially expanded with much new material added, but deploying the same kind of comprehensive and inclusive approach which characterised the first edition. Dr Lisak’s co-editors have recruited an outstanding group of internationally notable colleagues, who have succeeded in bringing this volume and all of its contents well up to date. This new edition represents in my opinion a remarkable achievement, and its contents will be invaluable, not only to neurologists in tropical and developing countries whose interests are fully covered, but also to many of those in the Western world who are interested in international developments in their respective fields of study and practice. All those who will study this work in depth, and also all those who dip into individual chapters in which they have particular expertise or interest, will find it an outstanding teaching tool, a remarkable guide to clinical practice in different countries, and a veritable powerhouse of knowledge which will be widely read and consulted to the profit of its readers. I congratulate Bob Lisak and his co-editors on planning such a remarkable volume and bringing it to fruition.

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The world of neurology has changed. The spectrum and depth of all the conditions affecting the nervous system are now galloping ahead. Clinicians need to keep abreast of the new world. This book is an excellent effort to gather 200 authors from across the globe to distil their knowledge in well-laid-out sections. The true international nature of the authorship is most impressive and gives the reader the ability to see how neurology has changed firstly in its breadth, and secondly in the ability to encompass experts with differing backgrounds yet able to produce a cohesive narrative and message. The shrinking globe in the age of the internet has led to an explosion of knowledge in a manner which is exemplified by the authorship of this book. Moreover, this second edition in six years means that this is a continuous live project both for editors and authors.

The editors are to be congratulated in bringing together all this in one volume and allowing readers access to the most up-to-date information. The World Federation of Neurology is proud to see the wide collaboration, which really represents the ethos of true internationalism.

Raad Shakir MD FRCP
President World Federation of Neurology
June 2015
Preface

The first edition of this text, *International Neurology: A Clinical Approach*, grew out of the involvement of the editors in international meetings held in Vietnam and was published in 2009. The “shrinking of the globe,” with people traveling for pleasure and business, has made it likely that physicians may see individuals as patients who have diseases they have not personally encountered or patients with different manifestations of diseases they have seen. This is true of visitors from developing countries who may become ill in North America, Europe, and other ‘Westernized’ nations as well as the converse. In most texts, some chapters are by authors writing about diseases or groups of diseases they themselves only know from their reading. Other texts deal with disorders seen worldwide, but only emphasize the clinical features encountered in a limited geographic region. We chose authors and section editors who were familiar with and expert in neurological diseases and asked them to cover these diseases as they present in different populations and areas of the world. The section editors and authors were from all regions of the world. They took into account differences in genetic, environmental, and demographic factors as well as therapeutic approaches. In the latter area treatments not based on evidence, or for which clinical evidence was lacking, were not included. Although all of the chapters included sections on etiology and pathogenesis, the emphasis was on clinical neurology, not basic science. To take into account the expense of medical texts, we tried to limit the length of chapters and bibliographies and framed those as suggested further reading. We also limited colored figures.

We were pleased with the acceptance of our efforts and that of the authors and section editors and when approached to consider a second edition, we decided to go forward with the project. We have made some changes in organization, section editors, and authors, and asked authors to update their chapters to capture the exciting changes that are occurring in neurology. We have once again asked them to emphasize, where present, differences in diseases and their manifestations in different populations and locales.

We once again would like to thank the authors and section editors for their efforts and contributions as well as Sally Osborne, Angela Cohen and our Editors at Wiley Blackwell, Devender Gupta of Aptara India and Lisa Bauer for their assistance and support in the project.

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Overview of stroke

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Stroke, encompassing both ischemic and hemorrhagic types, is a major health burden globally, affecting 15 million people each year. It is the second leading cause of death for people above the age of 60 years and the fifth leading cause for those aged 15 to 59 years. Stroke is the most common cause of adult disability and the second most important cause of dementia worldwide. According to World Health Organization (WHO) figures, global stroke deaths were 5.8 million in 2005 and are projected to increase to 6.5 million in 2015 and 7.8 million in 2030. Stroke is the most common disease that practicing neurologists manage. Stroke patients constitute approximately two-thirds of the inpatient neurology ward in virtually every hospital, with comprehensive neurology services in most countries around the world. With advances in evidence-based medicine, consensus on the diagnosis and treatment of selected types of strokes has gradually emerged across national boundaries.

Stroke mortality and incidence declined in developed countries during the 1980s and early 1990s, but this trend appears to have slowed recently. Despite the lack of reliable data on stroke statistics from several developing regions of the world, there are indications that the age-standardized mortality rate of stroke in developing nations may be substantially higher than in developed countries. The burden of stroke is accordingly greater due to relatively larger populations in developing countries. Furthermore, as a result of demographic transition, rapid urbanization, and industrialization, many developing regions show a trend of increased life expectancy, as well as a changing profile of risk factors for developing cardiovascular diseases, including stroke. This may contribute to a looming epidemic of stroke in medium- to low-income nations, as a greater population in these countries is at increased risk of stroke.

Stroke is a preventable disease. Implementation of effective primary and secondary prevention strategies is likely to have an enormous impact in reducing its burden. However, reducing stroke risk factors remains a challenging task, particularly in developing countries. It is appropriate that the WHO has set a priority on stroke prevention with the implementation of practical, accessible, cost-effective, and socially acceptable strategies.

Between the first and second editions of International Neurology, several important therapeutic advances have been made in the treatment of acute stroke and in stroke prevention: (1) endovascular intervention to remove blood clots in the proximal intracranial artery has been found to be safe and efficacious in patients with acute ischemic stroke beyond the approved therapeutic window of tPA (tissue plasminogen activator; 4.5 hours after stroke onset) and in particular in patients who failed intravenous tPA; (2) stroke prevention in patients with atrial fibrillation has been expanded from warfarin and/or heparin to novel oral anticoagulants that can spare patients frequent and inconvenient laboratory monitoring and show a favorable trend in reducing the risk of intracerebral hemorrhage, which is a serious side effect associated with traditional anticoagulants; (3) dual antiplatelets (aspirin plus clopidogrel) have been shown to be more effective than aspirin alone in preventing stroke in a critical period (within three weeks) after minor stroke and TIA.

Therapeutic attempts at applying neuroprotective agents, however, have failed in a series of large clinical trials and have highlighted the obstacles that remain to be overcome in translating promising therapeutic effects in animals in preclinical studies to clinical care for stroke patients based on evidence from clinical trials. Much soul searching has led to recommendations for improvements in the standards for preclinical studies including randomization, blinding, and sample-size calculations for interventional studies in animals, so as to improve the rigor of preclinical data and guide more appropriate selection of novel agents for trials in humans. The use of surrogate efficacy end points in early-phase studies has also been advocated so as to determine a possible efficacy signal before large, costly trials using clinical end points are undertaken. Neuroimaging has also been investigated as a means of selecting patients who would benefit most from treatment while minimizing the risk of serious side effects. Despite the slow rate of progress, it is essential that more clinical studies be undertaken to understand the pathophysiology of stroke, in order to develop appropriate clinical trial protocols to validate promising therapeutic strategies coming out of preclinical investigations.

In developing international standards for stroke prevention and therapy, the differences in stroke etiology and pathology among various ethnic groups cannot be overemphasized. Obvious examples are the higher incidence of intracerebral hemorrhage and higher prevalence of intracranial atherosclerosis in non-white
It is essential that integrated stroke care covers not only treatment of patients in the acute setting, but also post-stroke care, including the prevention of stroke recurrence and complications as well as adequate rehabilitative measures to maximize functional recovery. The guidelines developed by the American Heart Association/American Stroke Association and recommendations from the World Stroke Organization encourage stroke prevention and the implementation of timely and adequate standards of care, especially in the acute setting and post-stroke. These are addressed in the relevant chapters to follow, each of which aims to provide an important source of reference to maintain high-quality stroke prevention and care.

populations, including people of Hispanic, Asian, and African origin. It is encouraging that recent major stroke trials have been expanded to cover non-Western countries. A notable example is the multinational stroke trial to explore the effect of rapid blood pressure lowering in reducing the risk of hematoma expansion following acute intracerebral hemorrhage.

Although modest progress has been made in improving functional recovery after stroke, more research effort is urgently required, including clinical trials to validate innovative rehabilitation measures. Cognitive impairment and consequent dementia after stroke remain a substantial burden in chronic care and there is a great need for developing evidence-based preventive and treatment strategies.
The relevance of timely and appropriate management of a transient ischemic attack (TIA) lies in its frequent role as a forerunner of an impending stroke, which is a leading cause of death, disability, and dementia. We will outline in this chapter the historical context, epidemiology, clinical features, evaluation, and management of TIA patients.

History
Since the seventeenth century, the term “stroke” has represented acute non-traumatic lingering neurological deficits of vascular origin, but it was only in the 1950s that Charles Miller Fisher described the concept of symptomatic yet transient cerebral ischemia received attention. Indeed, it was in 1965 that a consensus term “transient ischemic attack” was introduced to better characterize the occurrence of acute focal, neurological symptoms due to vascular causes that would last “for a shorter period of time.” A key controversy over the ensuing 40 years involved agreeing on the actual length of this period of time. Although an arbitrary 24-hour window was originally chosen, several clinicians observed that most of these transient spells would actually last for just a few minutes, at the most no more than a few hours. Another aspect of contention that has arisen relatively more recently following the advent of multimodal neuroimaging has been whether a tissue-based definition of TIA is more precise and prognostic of stroke risk than a time-based definition. Several studies have revealed that a considerable number of TIA patients actually had initial radiographic evidence of ischemic brain injury, a finding that persisted on follow-up brain imaging in many cases. Thus, in 2009, a committee of experts proposed a new pathological definition of TIA, which emphasized a lack of sustained vascular brain injury: “a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction.” With the introduction of this new tissue-based definition, the old time-based definition for TIA has increasingly fallen into disuse in clinical studies and clinical practice.

Epidemiology
Although the identification of a TIA is considered of major importance to prevent subsequent stroke, estimating its incidence and prevalence can be a challenge. Not infrequently, TIA patients fail to seek medical attention given the transitory nature of symptoms and insufficient knowledge. For other patients, historical details become blurred with time or the symptoms experienced were neurlogically non-specific. Therefore, current statistics likely underestimate the real occurrence of TIA around the world. In spite of these limitations, several studies have examined the incidence and prevalence of classically defined TIAs. Johnston et al. showed that among 10,112 Americans with TIA symptoms, only 64% sought care within 24 hours of the event. In the United Kingdom, a study by Chandratheva and colleagues observed that only about 67% of patients with TIAs contacted a healthcare provider after symptoms. In Switzerland, a survey of 422 habitants of Bern showed that just 64% of the population interviewed had “good knowledge” of stroke warning signs. In all three studies, lower income and fewer years of education were associated with lesser knowledge of stroke risk factors and the need to seek immediate medical attention in the event of stroke-like symptoms.

A study in Rochester, Minnesota, noted a crude age- and sex-adjusted incidence rate of 68 per 100,000 persons per year for the years 1985–89. TIA incidence rose with age, increasing to 584 per 100,000 persons for those aged 75–84 years. There was no clear sex predilection, but rates were slightly higher among men. In this study, 75% of the TIAs were due to carotid circulation insufficiency, and the rest due to problems in the vertebrobasilar circulation. Approximately 18% of the TIAs were transient monocular blindness (amaurosis fugax). Lower age- and sex-adjusted incidence rates for TIA have been reported from other populations, from a low of 18 per 100,000 persons per year from 1987–88 in Novosibirsk, Russia, to a high of 37 per 100,000 persons per year from 1970–73 in Estonia. Data from England, France, Japan, and Sweden showed similar incidence rates. According to Kokubo, the overall incidence rates of TIA in the European population aged 55–64 years were 0.52–2.37 in men and 0.05–1.14 in women. For the age range 65–74 years, men and women had rates of 0.94–3.39 and 0.71–1.47, respectively. Finally, among those aged 75–84 years, women’s TIA incidence ranged from 3.04–7.20, while men’s was 2.18–6.06. Overall, time-based TIA incidence rates appear to have remained stable over time. It has been estimated that adopting a tissue-based definition of TIA in the United States would lower estimates of the annual incidence of TIA by 33%, from approximately 180,000 to about 120,000. Studies on TIA prevalence vary widely, but generally run at between 1% and 6% and not surprisingly increase with age.

Risk factors for TIA are congruent to those for stroke. Conventional yet modifiable risk factors include hypertension, smoking,
diabetes, atrial fibrillation, aortocervicocephalic atherosclerosis, and recent large myocardial infarction.

Comparisons across distinct studies suggest that the 90-day stroke risk is 10–20% after TIA, with the highest risk occurring in the first 48 hours following the TIA, and that when these strokes happen they are disabling or fatal in up to 85% of patients. Some studies suggest that patients with transient monocular blindness have half the risk of stroke compared to patients with a hemispheric TIA, and those with purely sensory symptoms tend to have a lower risk of stroke than patients with motor symptoms or aphasia. Taking into consideration differences between study designs, reviews of prospective emergency department investigations have pointed to the fact that about 1 in 20 patients with a TIA will have a stroke in the next 48 hours, with a 15% chance of the stroke being a fatal event and a 60% risk of sustaining long-term disability. Unfortunately, mounting data indicate that an unacceptably high proportion of TIA patients (vs. stroke patients) are underinvestigated and undertreated during the period of the highest risk of stroke.

**Pathophysiology**

Although there have been several modifications since, the criteria for subdividing stroke events by their underlying mechanism developed in the original TOAST (Trial of ORG 10172 in acute stroke treatment) study are widely used to classify cerebrovascular events into three major types.

**Atherosclerosis of great vessels**

Atherosclerosis of great vessels is defined by obstruction of blood flow due to a localized occlusive disease within large arteries. Atherosclerosis resulting from years of gradual plaque formation is considered to be the main cause of luminal obstruction. These stenotic lesions are most commonly seen in the internal carotid arteries and middle cerebral arteries, as well as in the posterior circulation, affecting the vertebrobasilar system.

**Occlusion of small vessels**

In small artery disease, especially small perforator arterioles, lipohyalinosis is considered to be the main pathological obstructive process, mostly secondarily to poorly controlled hypertension.

**Cardioembolism**

In cardioembolism, a thrombus formed in the heart is dislodged and occludes one of the arteries in the cervicocephalic arterial tree.

The TOAST criteria include two other categories: acute stroke of other determined etiology, which includes patients with rare causes of stroke, such as non-atherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders; and stroke of undetermined etiology, which is estimated to account for approximately 25% of all cerebrovascular events.

The occurrence of non-focal transient cerebral ischemia also deserves mention. TIAs can happen due to reduced blood flow to brain tissue as a result of lower systemic perfusion pressure. Most commonly, this is related to decompensated heart failure, myocardial infarction, cardiac arrhythmias, or hypovolemia. Border zones between major vascular territories, also referred to inaccurately as “watershed territories,” are usually more susceptible to these insults. Therefore, many of these events can occur bilaterally, but it is important to keep in mind that a territory supplied by an already stenosed vessel can be more susceptible to ischemia in the face of systemic hypoperfusion.

**Clinical features**

In most cases, by the time a TIA patient is evaluated by a healthcare provider, his or her neurological deficits have resolved. Therefore, identifying the symptoms as having a vascular origin can be a challenge. A high level of suspicion is fundamental in preventing these “warning signs” from being missed. Some symptoms, such as hemiparesis or dysarthria, are non-specific regarding the location of the vascular injury, since this can be seen in both anterior and posterior circulation ischemia. Other deficits can suggest more specific areas of insult. Aphasia and amaurosis fugax are commonly seen in anterior circulation; that is, carotid territory ischemia. On the other hand, homonymous hemianopia, ataxia, vertigo, diplopia, bilateral weakness, and numbness are mostly ascribed to vertebrobasilar circulation. One should be aware of the so-called stroke and TIA mimics (Table 2.1), especially due to the fact that other neurological processes, such as seizures or demyelinating diseases, also require attention and treatment.

**Investigations**

Major discussions exist throughout the world regarding the extent of investigation that transient focal neurological signs deserve. To assess the risk of short-term stroke after a TIA, risk factor prediction scores have been created. One of the most commonly used is the ABCD2 score (Table 2.2), where a score of 0–3 is considered “low risk,” with a 2-day stroke risk of 1.0%; a score of 4 or 5 is considered “moderate risk,” with a 2-day stroke risk of 4.1%; and a score of 6 or 7 is considered “high risk,” with a 2-day stroke risk of 8.1%.

<table>
<thead>
<tr>
<th>Features to suggest TIA</th>
<th>Features more suggestive of TIA mimics</th>
<th>Can be seen in TIAs or TIA mimics (non-specific)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased strength in one limb or in two ipsilateral limbs</td>
<td>Generalized tonic or clonic motor activity</td>
<td>Unilateral involuntary movements in one limb or two limbs (could be due to seizures or “limb-shaking TIA”)</td>
</tr>
<tr>
<td>Light-headedness, decreased consciousness, confusion, or amnesia in the absence of other symptoms</td>
<td>Positive sensory symptoms, such as tingling</td>
<td></td>
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<tr>
<td>Complete visual loss in one eye or visual field cut in both eyes (quadrantanopia or homonymous hemianopia)</td>
<td>Scintillating scotomas</td>
<td></td>
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<tr>
<td>Bowel or bladder incontinence</td>
<td>Headache during or after the event</td>
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</tbody>
</table>

**Table 2.1.** Comparison of typical features of a transient ischemic attack (TIA) to mimics.