The Causes of Epilepsy
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Common and Uncommon Causes in Adults and Children

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Foreword

The written history of epilepsy goes back 3000 years with accurate descriptions of epileptic phenomena appearing in the writings of ancient Mesopotamia and the Indian Ayurvedic texts. Although physicians of the Hippocratic school in Greece, about 400 BC, understood that epileptic seizures originated in the brain, as did Galen several hundred years later, epilepsy was generally viewed as a mysterious condition attributed to supernatural causes, at least in the West, until the mid nineteenth century. At that time, the nascent disciplines of basic neuroscience and clinical neurology defined a variety of ictal manifestations, including focal seizures and absences, and recognized them as part of a constellation of disorders referred to as epilepsy. In particular, postmortem clinical pathological correlations not only revealed specific anatomic substrates for different ictal manifestations, but led directly to concepts of localization of function within the human brain, and to surgical treatment for certain types of focal epilepsies. The development of radiology in the twentieth century further improved physicians’ abilities to identify “invisible” lesions as responsible for epileptic seizures in some patients, but it was application of the electroencephalogram (EEG), and the subsequent field of both clinical and basic electrophysiology, that provided a means to begin classifying and characterizing different types of epileptic seizures and epilepsy syndromes, and investigating their underlying fundamental pathophysiological neuronal mechanisms.

The careful delineation of different types of ictal phenomena provided the basis for creating experimental animal models for both in vitro and in vivo electrophysiological and microanatomical investigations of epilepsy. EEG localization of the epileptogenic region greatly increased the application of surgical treatment for focal epilepsies, which also provided novel opportunities for parallel invasive in vitro and in vivo electrophysiological and microanatomical investigations in patients. Towards the end of the twentieth century, explosive advances in three-dimensional neuroimaging, first with structural X-ray computerized tomography (CT), then functional positron emission tomography (PET), and finally both structural and functional high-resolution magnetic resonance imaging (MRI) provided intricate insights into the pathophysiological mechanisms and anatomic substrates of epilepsy disorders in individual patients that could be used to create more informed categorizations and classifications. These efforts were joined by the burgeoning field of neurogenetics, which not only is identifying an increasing number of “epilepsy genes” responsible for specific types of epilepsy, and further characterizing genetic disorders associated with epilepsy, but also advancing the concept of susceptibility genes, which will explain variable individual predispositions to develop certain forms of acquired epilepsies. Now, in the twenty-first century, we are poised to reap the benefits of these dramatic advances in our understanding of the causes of epilepsy.

Methodology for characterizing different types of epileptic seizures and the disorders associated with them, particularly through electroclinical correlations, that is the association of particular behavioral ictal signs and symptoms with their unique EEG correlates, led the International League Against Epilepsy (ILAE) to propose international classifications for epileptic seizures, and for the epilepsies in 1970. These have undergone several revisions, but the most recent version of the International Classification of Epileptic Seizures was proposed in 1981, and the most recent International Classification of the Epilepsies was proposed in 1989. These were purported to be purely phenomenological, because the authors felt there was, at the time, insufficient mechanistic information on which to base a classification on specific causes of epilepsy. Nevertheless, the inclusion of EEG characteristics permitted categorization of ictal phenomena in a way that implied certain pathophysiological differences, as well as anatomic substrates. For instance, generalized seizures were distinguished from focal seizures that appeared to originate in a part of one hemisphere. Epilepsies were classified not only based on their characteristic associated seizure types, but also according to broad etiologic categories: idiopathic, meaning epilepsy and nothing else, presumably primary genetic disorders; and symptomatic, meaning secondary to some other disease process. In addition, diseases associated with epilepsy were well described, and some epilepsy diseases were recognized as conditions with a single known cause, but most of the defined epilepsy conditions were syndromes, characterized by specific seizure types, and other clinical features, such as age of onset, response to antiepileptic drugs, and comorbidity. Using this approach, the vast majority of accepted epilepsy syndromes are pediatric idiopathic conditions, while the majority of epilepsies that affect adults, most of which are symptomatic, still defy a reasonable syndromic classification.

For over a decade, the ILAE has attempted to revise the 1981 and 1989 classifications, with multiple reports that have
updated the list of epileptic seizure types and epilepsy syndromes. They now recognize certain seizure types as diagnostic entities with associated therapeutic, prognostic, and etiologic implications that can be used when a definitive syndrome or disease diagnosis cannot be made. These deliberations provide a basis for a more scientific classification of epilepsy disorders based on underlying genetic and pathophysiologic mechanisms, as well as anatomic substrates. Ironically, however, as the chapters in this book clearly confirm, with the increasing sophistication of our investigative methodology, the elucidation of distinctive epilepsy conditions as diagnostic entities has become more, rather than less, complicated. The old dichotomies of idiopathic versus symptomatic, and generalized versus focal, are artificial and often impossible to apply. Well-defined classical syndromes, such as childhood absence epilepsy, are not as homogeneous as once believed. Some idiopathic childhood epilepsies, such as Dravet syndrome, are not benign, and there appear to be several distinctly different forms of temporal lobe epilepsy with hippocampal sclerosis. However, the causes of epilepsy discussed in this textbook represent a major effort to put flesh on the bones of what hopefully will ultimately become a biologically based international classification of the epilepsies.

With the hundreds of textbooks that have been published on epilepsy in the past decade or so, it is rather amazing that none have focused specifically on the causes of epilepsy. The editors have undertaken this monumental task and succeeded in documenting the current state of knowledge concerning the genetic and pathological substrates of disorders characterized by epileptic seizures, as well as the situations that provoke ictal events. This comprehensive compendium will not only serve as an important resource for rethinking the organization and classification of epileptic phenomena and epilepsy syndromes and diseases, but will also provide a foundation for basic research attempting to identify the diverse pathophysiological mechanisms at the subcellular, cellular, and systems levels, that are responsible for epileptogenesis and seizure generation. Identification of these fundamental neuronal processes in turn will lead to novel and more effective approaches to treatment, cure, and prevention of epilepsy.

Jerome Engel, Jr
Los Angeles, California

Medicine is undergoing a remarkable transition as we move from descriptions of disease and a taxonomy based on clinical characteristics to a more detailed and precise understanding of disease pathogenesis. This revolution has been driven by the adoption of a range of molecular tools and, more particularly, by the application of molecular genetics to medicine. These approaches are providing us with insights, often for the first time, of the pathways and precise events associated with disease pathogenesis and this will change forever the foundations on which we base diagnosis and treatment of disease.

The developments in the molecular understanding of disease are nowhere more evident than in neurological disease, particularly the epilepsies. These clinical syndromes, often dramatic in their clinical characteristics, have been associated with a range of taxonomies that have developed over many centuries. The clinical characteristics of seizures and an understanding of the abnormal electrophysiology provided a framework on which taxonomy could be based, but clearly could not address the fundamental issue of the underpinning events in disease pathogenesis. That has had to wait until the past twenty years when the tools available for characterizing both families and individual patients have gradually become available.

Initial progress in this field focused, as with other diseases, on Mendelian forms of epilepsy using family based studies. Although these studies revealed a range of interesting pathophysiological mechanisms, including a number of ion channels, it has been clear that this describes only a portion of the epilepsy syndromes, many of which involve more complex genetics. These now are increasingly tractable with the new tools for genetic association and these are beginning to reveal non-channel molecules and pathways associated with neural excitation. Together, these techniques are providing a crucial framework for redefining the epilepsies based on pathophysiology and, in turn, this will have a profound impact on our ability to predict, diagnose, and, ultimately, treat disease. Anticonvulsive therapy has been remarkably successful, given how little we know about the pathogenic mechanisms of the disease, so it is likely that future therapeutic interventions based on a clearer understanding of the relevant pathways will be even more effective.

Together, these advances have made epilepsy one of the most significant examples in medicine of the importance of genetic tools in clarifying pathophysiology and these disorders demonstrate clearly how powerful the change from pure phenotypic classification of disease to one based on pathophysiology can be. The authors of this important book have been able to bring together a wide range of scientific insight and data on this topic into a single volume that covers the whole range of clinical syndromes. They demonstrate how powerful these new genetic tools have already been in defining pathways in disease and they also clearly demonstrate that, together, their observations are likely to lead to a fundamental new classification of these diseases. Not only is this volume timely, given the recent exciting developments in this field, but it also demonstrates the enormous influence that these key basic insights will have on the way we categorize and, ultimately, treat individuals with disease. Epilepsy and its associated syndromes give us a clear vision of what the future of medicine is likely to look like.

Professor Sir John Bell,
University of Oxford, UK
Preface – an act of supererogation?

An inquiring mind must return again and again to the problem of origin or cause... physicians have dug away at diverse etiologic theories or facts; physical or psychic; general or individual; genetic or acquired; fundamental or contributory. When a crime is committed, everyone in the vicinity is suspect. William Lennox, Epilepsy and Related Conditions, 1960

Thus Lennox opened his chapter on "The diverse sources of seizures," and indeed he devoted a great many pages of his famous book to the question of etiology. Yet, 50 years later, causation is an aspect of epilepsy now somewhat neglected in the scientific literature on epilepsy, in the classification of epilepsy, and in the conceptualization of epilepsy at a clinical and experimental level. It was to go some way to remedying this deficiency that this book was conceived.

Kinnier Wilson in 1940 wrote that the listing of all causes of epilepsy would be an act of supererogation, but the editors of this book beg to differ. This is the first book ever published, as far as we know, which is devoted to the topic of causation in epilepsy, and we have attempted within its 800 pages to catalog the known causes of epilepsy, and corral these into a single tome.

Such an attempt is only possible because of the great advances made in imaging, molecular biology, and molecular genetics in the last 40 years or so, and we believe that progress has now been sufficient to permit at least a stab at a comprehensive listing of causation. The literature on epilepsy has rapidly increased in recent years. Kinnier Wilson noted that the index catalogue of the US Surgeon-General’s office (1925) contained about 3000 titles and the “Gruhle’s review for the years 1910–1920 deals with some 1000 articles.” In the last 10-year period, a search on PubMed® using the keyword epilepsy produces more than 37,000 references, many of which deal at least tangentially with etiology. It is this literature-base which we have asked our contributors to summarize in the various chapters of this volume.

One striking omission has been the absence of any detailed consideration of etiology in the standard classifications of epilepsy. This is partly because at the time that these schemes were being devised neither modern investigatory imaging methods nor modern molecular biology were available – and the ascertainment of “cause” in life was often simply not possible. Although it was fully recognized that epilepsy was often “a symptom” of neurological disease, the underlying cause of the symptom was completely absent from the current classification schemes, based as they are largely on clinical semiology and electroencephalography, and it is interesting to muse on what form the epilepsy classification might have taken if MRI scanning had preceded EEG as a clinical investigatory tool.

We thus open this book with, in Chapter 2, the presentation of a draft etiological classification which goes some way we hope to filling the nosological void. The main part of the book is organized according to this classificatory scheme. We have divided the etiologies into four categories: idiopathic epilepsies, symptomatic epilepsies, cryptogenic epilepsies, and provoked epilepsies, and these are defined in Chapter 2. In doing so, of course, we recognize, as Lennox, and many before him, frequently reiterated, that epilepsy is in the great majority of cases multifactorial, and frequently has a developmental basis with therefore a temporal dimension. The epilepsy is often the result of both genetic and acquired influences and also influenced by provoking factors, and assignment in such cases to any single etiology is therefore to an extent arbitrary.

The approach to the problem of etiology between 1860 and 1960 forms the subject of the historical introduction (Chapter 1) which ends with Lennox’s work, and this is included as we believe it is important to understand the evolution of concepts of causation within its historical context.

In subsequent chapters, we have asked the authors to consider their topic in a consistent fashion, dealing with the phenomenon of epilepsy in each etiology, including its epidemiology, clinical features, and prognosis, and any specific aspects of investigation or treatment.

The purpose of the book is to be a comprehensive reference work, a catalog of all the important causes of epilepsy, and a clinical tool for all clinicians dealing with patients with epilepsy. It is aimed at specialists and the interested generalist and it is hoped provides a distillation of knowledge in a form that is helpful in the clinical setting. We hope too that it will act as a clinical guide to scientists probing the dark interior of the subject.

We have attempted to take a worldwide perspective, and have included chapters on the causes of epilepsy that are rare in the West but common in other parts of the world. To match the worldwide spread of the conditions considered here, we have a distinguished faculty with a similar global reach, and
the book has 165 contributors from 21 countries and all continents many of whom are the leaders in their fields.

The editors have exercised a heavy editorial blue pen, have tried to minimize overlap or repetition, and have asked the authors to follow where possible a pre-assigned template. Our contributors have responded magnificently in our opinion, and we extend our grateful thanks for their hard work and for their time and effort. We would like to thank also Professor Jerome (Pete) Engel and Professor Sir John Bell for graciously agreeing to write the foreword to the book. Pete Engel is a famous leader in the field of epilepsy and a prolific author, who has made major contributions to many fields of epilepsy. Sir John Bell is President of the Academy of Medical Sciences and Regius Professor of Medicine at the University of Oxford, and a renowned medical geneticist. The book is indeed fortunate to have their contributions. We are also enormously grateful to Nicholas Dunton, the Senior Commissioning Editor at Cambridge University Press, who has guided the project since its inception with extraordinary skill and expertise, and without whose assistance the book would not have made it to the shelves. We also thank Assistant Editor Joanna Chamberlin and Production Editor Caroline Brown for their great efforts on behalf of the book. Finally, we would like to thank all our colleagues around the world for their stimulating ideas and knowledge, which have informed and illuminated all the pages of this book.

Simon Shorvon, Renzo Guerrini, and Fred Andermann