

The Causes of Epilepsy

Common and Uncommon Causes in Adults and
Children

SECOND EDITION

The Causes of Epilepsy

Common and Uncommon Causes in Adults and
Children

Second Edition

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Preface to the Second Edition

One of the major strides forward in the field of epilepsy in recent years has been a renewed emphasis on its causes. An epileptic seizure, like a headache, is a symptom. It is a symptom furthermore which is known to have numerous different potential causes, but in many cases, these are hidden or obscure (κρυπτός *kryptós*, hidden). Our ability to uncover the underlying causes of epilepsy has been greatly enhanced in the last few decades by the advent of medical technologies, notably in neuro-imaging, molecular genetics and molecular chemistry. These have allowed many new etiologies and causal factors to be recognized. In the preface of the first edition, we cited the famous statement of Kinnier Wilson that to attempt to list all causes of epilepsy would be an act of supererogation. However, with modern developments, we believe that this view is over-pessimistic, and notwithstanding the conceptual issues that complicate the idea of causation, many of which were first enumerated by Hughlings Jackson (as described in Chapter 1), a listing of causes is now feasible to an extent previously not imagined. The identification of the cause of epilepsy is a key element in patient-centered clinical management, and is now increasingly successfully achieved. Long gone is the time when epilepsy was simply described by the characteristics of the seizure (the seizure type) and hopefully, too, less focus can now be placed on the intellectually sterile activity of rejigging terminologies or classification schemes and more on the pathophysiology of underlying causes. What is attempted in this book is a description of all (or almost all) the known causes of epilepsy in a way which is useful for clinical purposes and which can stimulate efforts to produce cause-specific therapies. We have tried to approach the relationships between epilepsy phenomenology and its specific causes in a manner that is informative for both the epilepsy experts, who need to understand more about the underlying pathophysiology, and for those clinicians who may be familiar with the causative disorders but not with the peculiarities that epilepsy adds to a given medical condition.

As far as we are aware, this is the first, and indeed only, textbook to focus specifically on the causes of epilepsy. It is nine years since the publication of the first edition, and during this time, we have learned a great deal from our experience with the first edition and also from the explosion of new information, especially about the genetic and molecular causes of epilepsy. As a result, this edition is expanded and extensively rewritten. In Section I of this second edition, we have included new chapters on the concept of cause in epilepsy and on the basic

principles of causation in epilepsy. Section II is an entirely new section comprising a series of chapters dealing with the clinical approaches to establishing cause in different situations in clinical practice. Sections III and IV cover the genetic causes, and have been greatly expanded with new chapters reflecting the rapid advances in this field. The sections are divided into the genetic causes of the idiopathic (or ‘pure’) epilepsies and into those of the genetically based symptomatic epilepsies. Section V comprises chapters on the non-genetic causes of epilepsy (the symptomatic epilepsies) and many of these too have been extensively rewritten, with an emphasis placed on the clinical features and prognosis. In Section VI, we cover the precipitating factors of epileptic seizures, which we consider to be as much a ‘cause’ of epilepsy as are the underlying conditions, and which emphasise the multifactorial nature of causation in epilepsy. In Section VII, the causes of status epilepticus are described, as these differ in many ways from the causes of other forms of epilepsy.

As with the first edition, the purpose of the book is to be a comprehensive reference work, a catalogue of the known causes of epilepsy, and above all a clinical tool for clinicians caring for patients with epilepsy. The intended audience is both specialists and generalists, and we have asked our contributing authors to follow a predetermined template to provide a concise summary of knowledge about the clinical aspects of the epilepsy in a form that is helpful in both the hospital and outpatient settings.

We are also enormously grateful to Nick Dunton and to Anna Whiting, his successor, the Senior Commissioning Editors at Cambridge University Press. Both have guided the project since its inception with extraordinary skill and expertise, and we are equally grateful to Charlotte Brisley who came to the project in its later stages as content manager and who has worked tirelessly to make it a success. The quality of the book depends on the skill and clarity of the authors of the individual chapters and we have been very fortunate in the high level of expertise and commitment all have brought to the book. We are also very obliged to our colleagues, around the world, who have engaged in stimulating discussions with us, who have shared their ideas and knowledge about the causes of epilepsy and who have guided us in our quest to make this textbook a useful contribution to clinical and experimental work in epilepsy.

**Simon Shorvon, Renzo Guerrini, Steve Schachter
and Eugen Trinkla (editors)**

Preface to the First Edition – 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 catalog 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

Preface to the First Edition

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

Abbreviations

ACh	Acetylcholine	IQ	Intelligence quotient
ACTH	Adrenocorticotrophic hormone	MCD	Malformation of cortical development
AD	Autosomal dominant	MEG	Magnetoencephalography
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid	MRA	Magnetic resonance angiography
AR	Autosomal recessive	MRI	Magnetic resonance imaging
ATN1	Atrophen1	MRS	Magnetic resonance spectroscopy
CDG	Congenital disorder of glycosylation	mtDNA	mitochondrial DNA
CGH	Comparative genomic hybridisation	mTOR	Mammalian target of rapamycin
CI	Confidence interval	NAD ⁺	Nicotinamide adenine dinucleotide
CK	Creatine kinase	NCSE	Nonconvulsive status epilepticus
CMV	Cytomegalovirus	NFLE	Nocturnal frontal lobe epilepsy
CNV	Copy number variation	NGS	Next generation sequencing
CPK	Creatine phosphokinase	NMDA	N-methyl-D-aspartate
CSF	Cerebrospinal fluid	NPY	Neuropeptide Y
CT	Computed tomography	NREM	Non-rapid eye movement
DNA	Deoxyribonucleic acid	OR	Odds ratio
ECG/EKG	Electrocardiography/Electrocardiogram	PCR	Polymerase chain reaction
EE	Epileptic encephalopathy	PET	Positron emission tomography
EEG	Electroencephalography/ Electroencephalogram	PTZ	Pentylentetrazol
EMG	Electromyography	REM	Rapid eye movement
EMG	Electromyography	RNA	Ribonucleic acid
EOEE	Early onset epileptic encephalopathy	SD	Standard deviation
FCD	Focal cortical dysplasia	SDH	Succinate dehydrogenase
FDA	Federal Drugs Administration	SE	Status epilepticus
FDG PET	Fluorodeoxyglucose positron emission tomography	SLE	Systemic lupus erythematoses
FLAIR	Fluid-attenuated inversion recovery	SNP	Single nucleotide polymorphism
fMRI	Functional magnetic resonance imaging	SPECT	Single photon emission computed tomography
GABA	Gamma aminobutyric acid	SSEP	Somatosensory evoked potential
GLU	Glutamate	SUDEP	Sudden unexpected death in epilepsy
GSW	Generalised spike and wave	SW	Spike-wave
GTCS	Generalised tonic-clonic seizure	TCS	Tonic-clonic seizure
ICU/ITU	Intensive care unit	TCSE	Tonic-clonic status epilepticus
IED	Inter-ictal epileptiform discharge	TLE	Temporal lobe epilepsy
IGE	Idiopathic generalised epilepsy	TMS	Transcranial magnetic stimulation
ILAE	International league against epilepsy	WES	Whole exome sequencing
		WGS	Whole genome sequencing
		WT	Wild type
		XL	X-linked