The Causes of Epilepsy

Common and Uncommon Causes in Adults and Children

Second Edition

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Edited by

Simon Shorvon
UCL Queen Square Institute of Neurology

Renzo Guerrini
University of Florence

Steven Schachter
Harvard Medical School, Boston

Eugen Trinka
Paracelsus Medical University, Salzburg

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Contents

Contributors

Patrick Adjei
Department of Medicine and Therapeutics, School of Medicine and Dentistry, College of Health Sciences, University of Ghana, Legon, Accra, Ghana

Nicholas Ah Mew
Rare Disease Institute, Children's National Medical Center, Washington, DC, USA

Cigdem I. Akman
Department of Neurology, Division of Pediatric Neurology Columbia University College of Physicians and Surgeons, New York, NY, USA

Abdulrahman Y. Alturki
Endovascular and Operative Neurovascular Surgery, BIDMC Neurosurgery & Brain Aneurysm Institute, Harvard Medical School, Boston, MA, USA

Anuranjan Anand
Molecular Biology and Genetics Unit, JNCASR, Bangalore, India

Frederick Andermann
Departments of Neurology and Neurosurgery and Pediatrics, McGill University, Montreal, Canada

Alexis Arzimanoglou
Department of Epilepsy, Sleep and Pediatric Neurophysiology, University Hospitals of Lyon (HCL) and Hôpital, Femme Mère Enfant, Lyon, France

Sarah Aylett
Neurosciences, Great Ormond Street Hospital NHS Foundation Trust and Clinical Neurosciences UCL, Great Ormond Street Institute of Child Health, London, UK

Nadia Bahi-Buisson
Pediatric Neurology, Necker Enfants Malades University Hospital, APHP, Paris, France

Carmen Barba
Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Rita Barone
Child Neurology and Psychiatry Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Agatino Battaglia
Stella Maris Clinical Research Institute for Child and Adolescent Neurology and Psychiatry, Pisa, Italy

Gerhard Bauer
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Ronny Beer
Department of Neurology, Neurocritical Care Unit, Medical University of Innsbruck, Innsbruck, Austria

Geneviève Bernard
Associate Professor, Departments of Neurology and Neurosurgery, Pediatrics and Human Genetics, McGill University, Montreal, Canada

Nadir E. Bharucha
Departments of Neurology and Neuroepidemiology, Bombay Hospital Institute of Medical Science, Mumbai, India

Frederico Bianchi
Pediatric Neurosurgery, Institute of Neurosurgery, Catholic University Medical School, Rome, Italy

Christian G. Bien
Epilepsy Centre Bethel, Krankenhaus Mara, Bielefeld, Germany

Laurence A. Bindoff
Department of Clinical Medicine (K1), University of Bergen, and Department of Neurology, Haukeland University Hospital, Bergen, Norway

Francesca Bisulli
Department of Neurological Sciences, University of Bologna, Bologna, Italy

Ingmar Blümcke
Department of Neuropathology, University Hospital Erlangen, Erlangen, Germany

Thomas Boes
NYU School of Medicine Comprehensive Epilepsy Center, New York, NY, USA

Francesco Brigo
Department of Neurology, Franz Tappeiner Hospital, Merano, Italy

Andreas Brunklaus
Fraser of Allander Neurosciences Unit, Royal Hospital for Children, Glasgow, UK

Jaume Campistol
Pediatric Neurology Department, Sant Joan de Déu Hospital, Barcelona University, Barcelona, Spain

Laura Canafoglia
Neurophysiopathology, IRCCS Foundation C. Besta Neurological Institute, Milan, Italy

Maria Paola Canevini
Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

Laura Cantonetti
Bambino Gesù Children's Hospital, Palidoro, Rome, Italy

Roberto H. Caraballo
Department of Neurology, Hospital Nacional de Pediatria, 'Prof. Dr. Juan P. Garrhan,' Buenos Aires, Argentina

Fernando Cendes
Department of Neurology, University of Campinas – UNICAMP, Campinas, SP, Brazil

Richard F. M. Chin
Royal Hospital for Sick Children, Edinburgh, UK

Heng T. Chong
Department of Neurology, Western Health, Melbourne, Australia

Fahmida Amin Chowdhury
The National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London, UK

Catherine J. Chu
Department of Neurology, Programs in Pediatric Epilepsy and Neurophysiology, Massachusetts General Hospital, MA, USA

Rolando Cimaz
Rheumatology Unit, Anna Meyer Children's Hospital, Department of Pediatrics, University of Florence, Firenze, Italy

Antonietta Coppola
Epilepsy Centre, Neurology Department of Neurology, Reproductive and Odontostomalogy, Federico II University, Naples, Italy

Peter Crino
Department of Neurology, University of Maryland School of Medicine, MD, USA

J. Helen Cross
UCL Great Ormond Street Institute of Child Health, London, UK

Bernard Dan
Université Libre de Bruxelles (ULB), Brussels, Belgium
Inkendaal Rehabilitation Hospital, Vlezenbeek, Belgium

Alessio De Ciantis
Department of Neuroscience, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Rolando F. Del Maestro
Neurosurgical Simulation Research and Training Centre, Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada

Chantal Depondt
Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

Darryl C. De Vivo
Department of Neurology, Division of Pediatric Neurology Columbia University College of Physicians and Surgeons, New York, NY, USA

Alissa M. D'Gama
Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Carlo Di Bonaventure
Epilepsy Unit, Department of Neurological Sciences, 'La Sapienza' University of Rome, Rome, Italy

Nataliya Di Donato
Institute for Clinical Genetics, TU Dresden, Dresden, Germany

William Dobyns
Departments of Neurology and Pediatrics, Center for Integrative Brain Research, Seattle Children's Research Institute, Seattle, WA, USA

Alice Donati
Pediatric Neurology and Metabolic Units Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Michael Duchowny
Neuroscience Program and the Comprehensive Epilepsy Center, Miami Children's Hospital, FL, USA

Kiyoshi Egawa
Pediatric Department, Hokkaido University Graduate School of Medicine, Hokkaido, Japan

List of Contributors

Monika Eisermann
Department of Clinical Neurophysiology, Necker Enfants Malades University Hospital, Paris, France

Christian E. Elger
Department of Epileptology, University of Bonn Medical Center, Bonn, Germany

Bernt A. Engelsen
Department of Clinical Medicine (K1), University of Bergen, and Department of Neurology, Haukeland University Hospital, Bergen, Norway

Joshua Ewen
Kennedy Krieger Institute, Baltimore, MD, USA

Natalio Fejerman
Department of Neurology, Hospital Nacional de Pediatria, 'Prof. Dr. Juan P. Garrhan,' Buenos Aires, Argentina

Pawel Fidzinski
Epilepsy-Center Berlin-Brandenburg, Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Mirella Filocamo
Laboratorio di Genetica Molecolare e Biobanche, Istituto G. Gaslini, Genova, Italy

Agata Fiumara
Regional Referral Center for Metabolic Diseases, Pediatric Clinic, Department of Clinical and Experimental Medicine – University of Catania, Catania, Italy

Carmen Fons
Pediatric Neurology Department, Sant Joan de Déu Hospital, Barcelona University, Barcelona, Spain

Silvana Franceschetti
Neurophysiopathology, IRCCS Foundation C. Besta Neurological Institute, Milan, Italy

Richard E. Frye
Barrow Neurological Institute, Phoenix Children's Hospital, Phoenix, AZ, USA

Antonio Gambardella
Institute of Neurology, Department of Medical and Surgical Sciences, University Magna Graecia Catanzaro, Catanzaro, Italy

Hector H. Garcia
Cysticercosis Unit, Instituto Nacional de Ciencias Neurologicas, Lima, Peru

Jutta Gärtner
Department of Pediatrics and Adolescent Medicine, Division of Pediatric Neurology, University Medical Center Göttingen, Göttingen, Germany

Laurence Gauquelin
Department of Neurology and Neurosurgery, McGillUniversity, Montreal, Canada

K. Michael Gibson
Division of Experimental and Systems Pharmacology, College of Pharmacy, Washington State University, Spokane, WA, USA

Ryan E. Gill
Department of Neurology and Developmental Medicine, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Leif Gjerstad
Department of Neurology, Oslo University Hospital - Rikshospitalet, and Faculty of Medicine, University of Oslo, Oslo, Norway.

Sidney M. Gospe Jr.
Division of Pediatric Neurology, University of Washington and Seattle Children's Hospital, Seattle, WA, USA

Isabelle Gourfinkel-An
AP-HP, Epilepsy Unit, Pitié-Salpêtrière Hospital and Sorbonne University, UPMC University Paris, Paris, France

Tiziana Granata
Department of Pediatric Neuroscience, IRCCS-Fondazione Istituto Neurologico 'C.Besta', Milano, Italy

Bartosz T. Grobelny
Department of Neurosurgery, NYU Langone Medical Center, New York, NY, USA

Andrea L. Gropman
Division of Neurogenetics and Neurodevelopmental Disabilities, Children's National Health System
The George Washington University of the Health Sciences, Washington, DC, USA

Renzo Guerrini
Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Marie-Christine Guiot
Department of Neuropathology, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada

Saba Harrach
Psychiatry Department, Kaiser Franz Josef Spital Wien, Vienna, Austria

Raimund Helbok
Department of Neurology, Neurocritical Care Unit, Medical University of Innsbruck, Innsbruck, Austria

Andrew G. Herzog
Harvard Neuroendocrine Unit, Beth Israel Deaconess Medical Center, Boston, MA, USA

Helle Hjalgrim
Danish Epilepsy Centre Filadelfia, University of Southern Denmark, Dianalund, Denmark

Julia Höfler
Department of Neurology, Paracelsus Medical University, Salzburg, Austria

Martin Holtkamp
Epilepsy-Center Berlin-Brandenburg, Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany

Markus Hutterer
Neurooncology Working Group, Department of Neurology 1 – Neuromed Campus, Kepler University Hospital Linz, Linz, Austria

Yushi Inoue
NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Aoi-ku, Shizuoka, Japan

Anna C. Jansen
Pediatric Neurology Unit, Department of Pediatrics, UZ Brussel, Brussels, Belgium

Michael R. Johnson
Division of Brain Sciences, Imperial College London, London, UK

Charuta Joshi
Children's Hospital Colorado, Epilepsy Team, Aurora, CO, USA

Stephen G. Kahler
Arkansas Children's Research Institute, Little Rock, AR, USA

Reetta Kälviäinen
Epilepsy Center/Neurocenter, Kuopio University Hospital and Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

Dorothée Kasteleijn-Nolst Trenité
University of Utrecht, Utrecht, The Netherlands

Mitsuhiro Kato
Department of Pediatrics, Showa University School of Medicine, Tokyo, Japan

Gerhard Kluger
Schön Klinik Vogtareuth, Department of Neuropaediatrics and Neurological Rehabilitation, Epilepsy Centre for Children and Adolescents, Day Clinic for Neuropaediatrics, Vogtareuth, Germany

Matthias J. Koepp
Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK

Giorgi Kuchukhidze
Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria

Gerhard Kurlemann
Department of Neuropediatrics, University Children's Hospital Münster, Albert, Münster, Germany

Anna M. Larson
Department of Neurology, Programs in Pediatric Epilepsy and Neurophysiology, Massachusetts General Hospital, MA, USA

Ahmed Lary
Neurosciences Department, International Medical Center, Jeddah, Makkah Region, Saudi Arabia

Anna-Elina Lehesjoki
Folkhälsan Research Center and Medicum, University of Helsinki, Helsinki, Finland

Anette Leibetseder
Neurooncology Working Group, Department of Neurology 1 – Neuromed Campus, Kepler University Hospital Linz, Linz, Austria

Holger Lerche
Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

Vincenzo Leuzzi
Department of Human Neurosciences, Child Neurology and Psychiatry Unit, Sapienza-University of Rome, Rome, Italy

Snezana Maljevic
The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Mark Manford
University of Cambridge, Cambridge University NHS Foundation Trust, Cambridge, UK

Massimo Mantegazza
Institute of Molecular and Cellular Pharmacology (IPMC), University Côte d'Azur and CNRS UMR7275, Valbonne Sophia Antiplis, France

Carla Marini
Pediatric Neurology Unit and Laboratories, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Mario Mastrangelo
Department of Human Neurosciences, Child Neurology and Psychiatry Unit, Sapienza-University of Rome, Rome, Italy

Takashi Matsudaira
NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Aoi-ku, Shizuoka, Japan

Chiara Mazzocchetti
Department of Pediatrics, University of L'Aquila, L'Aquila, Italy

Davide Mei
Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Bindu Menon
Department of Neurology, Narayana Medical College and Superspeciality Hospital, Nellore, Andhra Pradesh, India

Uma Menon
International Center for Epilepsy, Ochsner Medical Center, New Orleans, LA, USA

Roberto Michelucci
IRCCS-Institute of Neurological Sciences of Bologna, Unit of Neurology, Bellaria Hospital, Bologna, Italy

Berge A. Minassian
Program in Genetics and Genome Biology and Division of Neurology, Department of Paediatrics, The Hospital for Sick Children and the University of Toronto, Toronto, Canada

Manish Modi
Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Márcia Elisabete Morita
Department of Neurology, University of Campinas – UNICAMP, Campinas, SP, Brazil

Amelia Morrone
Pediatric Neurology Unit and Laboratories, Meyer Children's Hospital, University of Florence, Florence, Italy

Marco Mula
Institute of Medical and Biomedical Education, St George's University of London and the Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, UK

Rima Nabbout
Department of Pediatric Neurology, Necker Enfants Malades Hospital, Paris Descartes University, Paris, France

Raffaele Nardone
Department of Neurology, Franz Tappeiner Hospital, Merano, Italy

Lina Nashef
King's College Hospital, London, UK

Vincent Navarro
AP-HP, Epilepsy unit, Pitié-Salpêtrière Hospital and Sorbonne University, UPMC University of Paris, Paris, France

Aidan Neligan
UCL Queen Square Institute of Neurology, University College London, London, UK

Charles R. J. C. Newton
University of Oxford, Oxford, UK

Andreea Nissenkorn
Sackler School Of Medicine, Tel Aviv University, Service for Rare Disorders, Edmond and Lilly Safra Children's Hospital, Chaim Sheba Medical Center, Tel Ha Shomer, Israel

Carlo Nobile
Department of Biomedical Sciences, University of Padua, Padova, Italy

Christopher S. Ogilvy
Harvard Medical School, BIDMC Brain Aneurysm Institute, Endovascular and Operative Neurovascular Surgery, Boston, MA, USA

Mary O'Neal
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Thom O'Neill
Royal Hospital for Sick Children, Edinburgh, UK

Steven V. Pacia
NYU School of Medicine, NYU Comprehensive Epilepsy Center, New York, NY, USA

Eliseu Paglioli
Neurology Service and School of Medicine, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

Andre Palmini
Neurology Service and School of Medicine, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

Pasquale Parisi
NESMOS Department, Faculty of Medicine & Psychology, 'Sapienza' University of Rome, Rome, Italy

Phillip L. Pearl
Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

Elena Parrini
Pediatric Neurology, Neurogenetics and Neurobiology Unit and Laboratories, Neuroscience Department, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Karine Pelc
Université Libre de Bruxelles (ULB), Brussels, Belgium
Inkendaal Rehabilitation Hospital, Vlezenbeek, Belgium

Page Pennell
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Nicola Pietrafusa
Department of Neuroscience, Bambino Gesù Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Taiane Pigozzo
Neurology Service and School of Medicine, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

Tiziana Pisano
Pediatric Neurology Unit and Laboratories, Children's Hospital A. Meyer – University of Florence, Firenze, Italy

Annapurna Poduri
Epilepsy Genetics Program, F.M. Kirby Neurobiology Center, Department of Neurology, Harvard Medical School, Boston, MA, USA

Charles E. Polkey
Department of Clinical Neurosciences, Institute of Psychiatry, King's College, London, UK

Ronit M. Pressler
Clincial Neuroscience, UCL-Great Ormond Street Institute of Child Health, London, UK

Elena Procopio
Metabolic and Muscular Unit, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Attila Rácz
Department of Epileptology, University of Bonn Medical Center, Bonn, Germany

Jelena Radic
Department of Paediatrics, Clinical Hospital Center Rijeka, Croatia

Shamima Rahman
Mitochondrial Research Group, UCL-Great Ormond Street Institute of Child Health, London, UK

R. Eugene Ramsay
International Center for Epilepsy, University of Miami School of Medicine, Miami, FL, USA

Roberta H. Raven
Department of Neuroepidemiology, Bombay Hospital Institute of Medical Science, Mumbai, India

Debra S. Regier
Rare Disease Institute, Children's National Medical Center, Washington, DC, USA

Anna Rosati
Pediatric Neurology Unit, Neuroscience Excellence Center, Children's Hospital A. Meyer-University of Florence, Firenze, Italy

Felix Rosenow
Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, J.W. Goethe-University Frankfurt, Frankfurt am Main, Germany

Hendrik Rosewich
Department of Pediatrics and Adolescent Medicine, Division of Pediatric Neurology, University Medical Center Göttingen, Göttingen, Germany

M. Elizabeth Ross
Laboratory of Neurogenetics and Development, Weill Medical College of Cornell University, New York, NY, USA

Abdulrahman Sabbagh
Division of Neurosurgery, Department of Surgery, Faculty of Medicine and Clinical Skill and Simulation Center, King Abdulaziz University, Jeddah, Saudi Arabia

Parthasarathy Satishchandra
Department of Neurology, NIMHANS, Bangalore, India

Alois J. Schiefecker
Department of Neurology, Neurocritical Care Unit, Medical University of Innsbruck, Innsbruck, Austria

Andreas Schulze-Bonhage
Epilepsy Department, University Hospital Freiburg, Freiburg, Germany

Johann Sellner
Department of Neurology, Christian Doppler Medical Center, Paracelsus Medical University, Slazberg, Austria

Arjune Sen
Oxford Epilepsy Research Group, University of Oxford, Oxford, UK

Simon Shorvon
UCL Queen Square Institute of Neurology, London, UK

Gagandeep Singh
Department of Neurology, Dayanand Medical College, Ludhiana, India

Sanjib Sinha
Department of Neurology, NIMHANS, Bangalore, India

Nicola Specchio
Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Michael R. Sperling
Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA

Sybil Stacpoole
Peterborough and Stamford NHS Foundation Trust and University of Cambridge, Cambridge University NHS Foundation Trust, Cambridge, UK

Carl E. Stafstrom
Division of Pediatric Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Erik K. St. Louis
Mayo Center for Sleep Medicine, Departments of Neurology and Medicine, Mayo Clinic, Rochester, MN, USA

Pasquale Striano
Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, 'G. Gaslini' Institute, Genova, Italy

Adam Strzelczyk
Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, J.W. Goethe-University Frankfurt, Frankfurt am Main, Germany

Marshall L. Summar
Rare Disease Institute, Children's National Medical Center, Washington, DC, USA

Andrea Taddio
Institute for Maternal and Child Health IRCCS 'Burlo Garofolo' and University of Trieste, Trieste, Italy

Yukitoshi Takahashi
National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder, Shizuoka, Japan

Gianpiero Tamburrini
Pediatric Neurosurgery, Institute of Neurosurgery, Catholic University Medical School, Rome, Italy

Chong T. Tan
Division of Neurology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Erik Taubøll
Department of Neurology, Oslo University Hospital – Rikshospitalet, and Faculty of Medicine, University of Oslo, Oslo, Norway

Federica Teutonico
Department of Child Neurology and Psychiatry, 'C. Mondino' Foundation, University of Pavia, Pavia, Italy

Elizabeth A. Thiele
Herscot Center for Tuberous Sclerosis Complex, Boston, MA, USA

Ajith Thomas
BIDMC Neurosurgery & Brain Aneurysm Institute, Harvard Medical School, Boston, MA, USA

Paolo Tinuper
Department of Neurological Sciences, University of Bologna, Bologna, Italy

Eugen Trinka
Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzberg, Austria

Marina Trivisano
Research Fellow Neurology Unit – Bambino Gesù Children's Hospital, Rome, Italy

Iris Unterberger
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Fernando L. Vale
Department of Neurological Surgery and Brain Repair, University of South Florida, Tampa, FL, USA

Patrick Van Bogaert
Department of Pediatric Neurology, CHU d'Angers, and Laboratoire Angevin de Recherche en Ingénierie des Systèmes (LARIS), Université d'Angers, Angers, France

Pierangelo Veggiotti
Department of Child Neurology and Psychiatry, 'C. Mondino' Foundation, University of Pavia, Pavia, Italy

Alberto Verrotti
Department of Pediatrics, University of L'Aquila, L'Aquila, Italy

Annamaria Vezzani
Department of Neuroscience, IRCCS-Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy

Federico Vigevano
Director of Neuroscience Department, Bambino Gesù Children's Hospital, Rome, Italy

Aglaia Vignoli
Department of Health Sciences, Università degli Studi di Milano, Milan, Italy

Andrew C. Vivas
Department of Neurological Surgery and Brain Repair, University of South Florida, Tampa, FL, Italy

Celina von Stülpnagel
Institute for Rehabilitation, Transition and Palliation of Neurologically Ill Children at the Paracelsus Medical University, Salzburg, Austria

Ruth H. Walker
Department of Neurology, James J. Peters Veterans Affairs Medical Center, Bronx, NY, USA

Howard L. Weiner
Division of Pediatric Neurosurgery, Department of Surgery, Texas Children's Hospital, Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA

Angus Wilfong
BARROW Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ, USA

Ruth E. Williams
Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK

Peter Wolf
Danish Epilepsy Centre, Dianalund, Denmark

Elissa Yozawitz
Isabelle Rapin Division of Child Neurology of the Saul R Korey Department of Neurology, Department of Pediatrics, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

Bruria Ben Zeev
Pediatric Neurology Unit and Israeli Rett Centre, Edmond and Lilly Safra Children's Hospital, Chaim Sheba Medical Center, Tel Ha Shomer, Israel

Sameer M. Zuberi
Fraser of Allander Neurosciences Unit, Royal Hospital for Children, Glasgow, UK

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 neuroimaging, 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 overpessimistic, 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 Trinka (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

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
ACTH	Adrenocorticotropic hormone
AD	Autosomal dominant
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AR	Autosomal recessive
ATN1	Atrophin1
CDG	Congenital disorder of glycosylation
CGH	Comparative genomic hybridisation
CI	Confidence interval
CK	Creatine kinase
CMV	Cytomegalovirus
CNV	Copy number variation
CPK	Creatine phosphokinase
CSF	Cerebrospinal fluid
CT	Computed tomography
DNA	Deoxyribonucleic acid
ECG/EKG	Electrocardiography/Electrocardiogram
EE	Epileptic encephalopathy
EEG	Electroencephalography/Electroencephalogram
EMG	Electromyography
EMG	Electromyography
EOEE	Early onset epileptic encephalopathy
FCD	Focal cortical dysplasia
FDA	Federal Drugs Administration
FDG PET	Fluorodeoxyglucose positron emission tomography
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GABA	Gamma aminobutyric acid
GLU	Glutamate
GSW	Generalised spike and wave
GTCS	Generalised tonic-clonic seizure
ICU/ITU	Intensive care unit
IED	Inter-ictal epileptiform discharge
IGE	Idiopathic generalised epilepsy
ILAE	International league against epilepsy
IQ	Intelligence quotient
MCD	Malformation of cortical development
MEG	Magnetoencephalography
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
mtDNA	mitochondrial DNA
mTOR	Mammalian target of rapamycin
NAD+	Nicotinamide adenine dinucleotide
NCSE	Nonconvulsive status epilepticus
NFLE	Nocturnal frontal lobe epilepsy
NGS	Next generation sequencing
NMDA	N-methyl-D-aspartate
NPY	Neuropeptide Y
NREM	Non-rapid eye movement
OR	Odds ratio
PCR	Polymerase chain reaction
PET	Positron emission tomography
PTZ	Pentylenetetrazol
REM	Rapid eye movement
RNA	Ribonucleic acid
SD	Standard deviation
SDH	Succinate dehydrogenase
SE	Status epilepticus
SLE	Systemic lupus erythematodes
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
SSEP	Somatosensory evoked potential
SUDEP	Sudden unexpected death in epilepsy
SW	Spike-wave
TCS	Tonic-clonic seizure
TCSE	Tonic-clonic status epilepticus
TLE	Temporal lobe epilepsy
TMS	Transcranial magnetic stimulation
WES	Whole exome sequencing
WGS	Whole genome sequencing
WT	Wild type
XL	X-linked