The Treatment of Epilepsy
Fourth edition

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Preface to the Fourth Edition

The first edition of this book was published in 1996, the second in 2004, the third in 2009, and this edition, the fourth, in 2016. In the 20 years that have passed since the appearance of the first edition, therapy in epilepsy has evolved perhaps not in quantum leaps but certainly incrementally. The additive effect of these incremental changes has been very considerable and this is reflected in these volumes. Furthermore, over the course of the four editions, the editors have tightened their grip on the quality of chapters and of writing, and tried progressively to ensure that the text provides accurate and well-grounded information. Throughout all four editions, the basic format of the book has not changed. The same section structure has been maintained, and all aspects of clinical medical therapy are covered. The number of chapters has grown from 63 in the first edition to 81 in this. An historical introduction has been added to provide a synoptical overview of the evolution of the treatment of epilepsy between 1860 and the present day. The focus of the entire book is on treatment, and we have endeavoured to produce a thoroughly up-to-date and detailed, independent and authoritative account of all aspects of modern clinical therapy. The authorship has been changed in crucial ways, and each of our authors, new and old, have been urged to sift information carefully and to take a considered and definitive view of their topic. Tabulated information has been included where possible, and summary tables have been drawn up at the head of each chapter on individual drugs. One major change to the format has been the introduction of full colour to the text, which we feel improves the readability and clarity as well as the aesthetic aspects of the book. There is also an enhanced online presence.

The passage of 20 years is a good time to reflect on the changes of treatment that have occurred during this time. Over this period, perhaps the most important advances have been in the understanding of the molecular and neurophysiological bases of epilepsy, and discoveries in these areas are beginning to feed through into clinical therapeutics. The impact of clinical genetics on treatment remains relatively marginal, but neuroimmunology is changing clinical practice and carries the promise of quite fundamental changes in approach to therapeutics in epilepsy. Over this period, too, 11 new drugs have been introduced into global clinical practice for epilepsy and also a variety of new approaches to the treatment of acute seizures and status epilepticus. On the surgical side, most of the advances have been technical rather than theoretical, and perhaps the biggest change has been the various forms of brain stimulation now entering clinical practice. All of these developments are included in this volume. We have also tried to keep the book at the cutting edge, by including details of what we predict will be the next changes in clinical practice. We have taken a global view, hoping to cover the variations in practice in the many different settings around the world, and have chosen our authorship,

from 17 countries, to reflect this global reach. The regulatory and administrative frameworks governing pharmaceutical and clinical activity continue to change and one thing complained about by all is the enormous growth in administrative oversight. Too much bureaucracy is the enemy of innovation, and one wonders whether the balance is currently correctly struck. In the book, these aspects too are covered.

The purpose of the book has not changed over the four editions and, as in the preface of the third edition, I here quote what was written in the second edition:

> The primary objective is unaltered [from the first edition] – namely to provide a systematic review of the whole field of contemporary therapy in epilepsy. The emphasis is, as before, on a text that provides practical information, useful for the clinician but which is comprehensive, accurate and concisely given. We [the editors] have asked the contributors to examine the evidential basis of both conventional and experimental therapies and have attempted to cover all therapeutic options… It remains the basic purpose of the book to guide clinical practice and rational therapy, and to be a source of reference for clinicians at every level.

I here wish also to record my gratitude to my two co-editors. All three of us edited the last edition, and my co-editors have undertaken the task of producing a new edition with undiminished enthusiasm and expertise. They possess unparalleled skill in both book editing and in epileptology, and the mixture of the two is unbeatable. Extensive editing has been carried out in parts of the book to ensure a consistency of approach and style and to ensure clarity and accuracy, and this job has been superbly done. Of course, also, enormous thanks from all three of us go to all the chapter authors. Many are new to the book, some have contributed before, and some indeed have been called upon for all four editions. All have produced superb chapters, and dealt with our tiresome editing queries and suggestions with universal good humour. The timetable imposed on the book was very tight, with chapters written within 8 months of commissioning and production within 9 months of receipt of the completed draft manuscript. Despite this, the book kept to schedule. The standard of the writing is high and a tribute to the commitment and work of all the authors; the world of epileptology is lucky to have such a talented group of writers. I also would like to thank Wiley Blackwell for suggesting the new edition, and for producing it to such a high standard. It has been a particular pleasure to work with Claire Bonnett who is a delightful person and who became our publisher half way through the project. She has provided excellent advice, ideas and guidance throughout on the intricacies of book publication. The production aspects were outsourced to PM-Bookpublishing, with the project led by Kathy Syplywczak, who has been an extraordinarily efficient colleague, extremely responsive to all the detailed requests for

amendments by the editors and authors, and a joy to work with; the book has been greatly improved by her expertise, and that of her colleagues, and it would not be possible to have had a better team running the production aspects. The book is embedded in our clinical practices, and our final thanks must go to our patients. A thorough understanding of epilepsy is gained best by listening to, and discussing with, those whom we see in our clinics, and it is the privilege of medicine to be able to gain experience and knowledge in this way. Our book reflects our clinical experience, and we hope will improve our own and our readers' therapeutic knowledge and practice.

Simon Shorvon, for the editors
London, 2015

Preface to the First Edition

Epilepsy is one of the oldest recorded diseases. Throughout its history strange and varied methods of therapy have been employed. Medicaments, potions, ointments, amulets, enemas, exorcism, magic, spiritualism, magnetism, galvanism, dietary regimens, surgical and physical and moral and behavioural therapies have all been popular; reputations have been made (less often broken) and are still being made by therapeutic manoeuvres, yet none has provided the cure. Within this compass have been some effective therapies but others which are ill-directed, useless, misleading, and at times frankly fraudulent. Epilepsy is, of course, a difficult taskmaster for the inquisitive. Its fluctuating nature, its ready influence by environmental factors, its easy confusion with hysterical disorders, its multi factorial causation and its tendency to spontaneous remission, all render judgements of treatment difficult. Such confounding factors allowed ineffective and fashionable therapies to flourish in the past, and today marketing and commercial pressures add to the difficulties of evaluation.

This book is an attempt to catalogue the contemporary treatment of epilepsy in the late 1990s, both medical and surgical, in a comprehensive, concise, balanced and practical manner. Each chapter has been commissioned from an acknowledged authority, known personally to the editors as knowledgeable, intellectually honest and capable of clear communication. We have covered all matters of importance to those treating patients with epilepsy, and provide clear clinical advice on these issues. We have avoided unsupported speculation and highly biased opinion, but have asked our contributors to be as up-to-date as is compatible with our evidence-based exigencies. These are difficult and challenging requirements, which, I hope, have been largely realized.

What are the boundaries of the volume? When bromide was introduced in 1857, a new era can be said to have been entered, with a treatment that was indubitably effective. Ironically, one can note that similar claims had been made many times before in earlier and less competitive times, and the single most important lesson of history is surely scepticism. In our historical chapter, we have surveyed treatment from the time of the introduction of bromides to the outbreak of World War II, a fascinating period which provides the context for today's therapeutic approaches. From about 1940 onwards, more scientific methods were adopted to devise and assess therapy, and more rigid standards were set for proof of effectiveness. Various new therapies were introduced, but most have not stood the test of time. Even as recently as 1970, the orthodox practitioner in most countries could still offer only phenytoin and phenobarbitone as effective options for most epileptic patients.

There has been, however, in the past decade or so, a sea change, almost a revolution in the field, and a wide range of highly effective new therapeutic possibilities has become available. Not only has a series of new medicaments been introduced, but new approaches to drug therapy have become possible, and also with improvements in the investigation of epilepsy, much more effective and ambitious surgical treatment. This expansion in the options for effective treatment, both medical and surgical, is enormously welcome, but brings its own problems. The physician now has to make much more difficult decisions about treatment because of the greater range of therapeutic choices and also because the evidence on which to base rational therapy is more complex, at times contradictory, and not all readily accessible. In this book we have addressed these issues.

Our principal objective is to provide a systematic review of the whole field of contemporary therapy. We have included individual chapters on all licensed medications, on drugs in an advanced stage of clinical trial, on all specific surgical therapies of value in epilepsy, and also chapters on treatment in specific clinical situations. The contributors were asked to examine the evidential basis of both conventional and experimental therapies, and to provide a clear assessment of this. We have attempted, therefore, to encompass all therapeutic options, and their relative values in the varied clinical circumstances of the person with epilepsy. In this sense, the book should be a useful platform for all doctors treating epilepsy. Although the book is primarily about the treatment of epilepsy, we have also included an initial section of six chapters, the purpose of which is to place therapy in context. In these chapters we have also highlighted those areas in which rapid advances are being made, for herein will the context of treatment also change (the chapters on pathophysiology, the developmental basis of epilepsy, diagnosis and prognosis, and on economic cost, for example).

The information contained within the pages of this book is sufficiently comprehensive to act as a reference for specialists, and concise enough for more general clinical usage. It is very much a hands-on text, and, we hope, a constant companion. The aim of the book is to guide clinical practice and rational therapy and to be a source of reference. It has been designed for doctors in adult and paediatric medicine, both generalists and also specialists in the fields of neurology, neurosurgery, psychiatry, paediatrics, alienist medicine and in learning difficulty. It will also appeal to practitioners of the paramedical specialties who are involved in the management of epilepsy.

One remarkable fact about modern epileptology is its internationalism. In countries all around the world, the same issues about the treatment of epilepsy arise, the same therapeutic questions are debated, and there is a large and surprising measure of agreement on specific points. The international nature of epilepsy is in no small part due to the endeavours of the International League Against Epilepsy (ILAE) which has chapters now in 48 countries and nearly 10 000 members, and whose meetings are a forum for the dissemination of information about epilepsy and its treatment. The influence of the league has left no area of epilepsy untouched. We are therefore greatly honoured, in this book, to Dr E.H. Reynolds, the current president of the ILAE, for contributing a foreword.

A distinguished and accomplished physician, Dr Reynolds is also a mentor and a friend, and a person whose influence on modern British and international epileptology has been benevolent and all-embracing. Our contributors are from four continents and provide a truly international perspective. Almost all are active in the ILAE, and the text reflects to a great extent the current interest and research of ILAE members. Matching this internationalism, nearly half of the chapters are by contributors (from various countries and continents) whose training was partly at the National Hospital for Neurology and Neurosurgery at Queen Square in London. Our preliminary historical chapter looks at the history of epilepsy therapy (from 1857 to 1939) using the National Hospital as an historical mirror, and as epilepsy is still an important area of contemporary neurology at Queen Square, subsequent chapters also reflect current practice at the National Hospital. This is another thread which runs through the book and gives to the volume, at least in part, a specific favour which I hope provides the text with an interesting perspective.

A book of 63 chapters will always pose a challenge for its editors and its publisher. In this volume, we have heavily edited some individual contributions, and worked assiduously in conjunction with the authors to avoid repetition or overlap. Where overlap has been permitted between chapters, this is because individual authors have taken differing (and occasionally conflicting) approaches which are, in the editors' view, sufficiently instructive to allow inclusion. We have also added editorial tables in places to ease comprehension and in particular to make the information contained in the text easy to follow and readily accessible to the reader, often a busy clinician. Also, we have tried to provide a uniform style, and a high quality of writing. To assemble chapters on such a disparate subject from authorities around the world, to edit and to produce a pleasing and useful book has been a major task. In this, the editors have been expertly helped by Dr Stuart Taylor from Blackwell Science, the publishers, whose skill and expertise were the essential ingredients of the successful completion of our work. We are enormously grateful to Dr Taylor, not least for his humour and forbearance in executing (a seemingly, at times, well-chosen word) the task, also to Lorna Dickson, our production editor who has worked absolutely tirelessly on this project, and other members of the design and production team at Blackwells; they have all been pre-eminent in their work. Finally, we would like to thank the chapter authors for their outstanding contributions, their patients for providing the experience on which our current therapeutics is based, and epileptologists around the world, ILAE members and others, who have stimulated our thoughts and actions in the field of epilepsy treatment.

Every effort has been made in the preparation and editing of this book to ensure that the details given (for instance of drug dosages and pharmacokinetic values) are correct, but it is possible that errors have been overlooked. The reader is advised to refer to published information from the pharmaceutical companies and other reference works to check accuracy.

Simon Shorvon, for the editors
London, 1996

Historical Introduction
The Drug Treatment of Epilepsy from 1857 to 2015

Simon Shorvon

In the historical introductions to the three previous editions of this book, therapeutic developments in three periods were covered, each from a different historical viewpoint: 1857–1939, 1938–1955, 1955–1989 [1,2,3]. In this, the fourth edition, I decided not to produce a further update (from 1989), judging this to be too close to garner an appropriate perspective. In its place, I have attempted to provide a timeline of antiepileptic drug therapy, listing pharmaceutical developments in mainstream clinical practice for the treatment of epilepsy since 1857. A second timeline is also provided, in which surgical and other non-drug epilepsy therapies are listed, with events of importance for epileptology. Both are accompanied by a commentary providing a brief contextual narrative. Finally, in the appendix, a snapshot of drug use at different times during this period is given as a series of tables. The purpose of this introductory chapter is to provide a synoptical overview of epilepsy therapeutics since 11 May 1857. This date was chosen as it was then that bromides, the first modern therapy, were introduced into epilepsy practice, and as we pass the sesquicentennial of this momentous therapeutic advance, it seems an appropriate topic to introduce this edition.

Now, in the early twenty-first century, and for most of the past 150 years, the treatment of epilepsy has been dominated by pharmaceuticals. Almost all the most significant advances in therapy have revolved around medicinal treatment. Although much effort has been devoted to surgical treatment, the number of patients receiving surgery is still extremely small when compared with those treated with drugs, and it remains a therapy largely of last resort. Other non-drug, non-surgical therapies are also mainly confined to the margins of clinical therapeutics, at least in contemporary hospital practice. Pharmaceutical developments have dwarfed all others, and in relation to treatment and outcome most other clinical development have been of marginal importance (it is striking how relatively little impact all the work on clinical description, classification and clinical investigation has had on drug therapy). Perhaps only developments in relation to the social aspects of epilepsy (reducing stigma, reforms of marriage and employment law, etc.) have had as much impact as drug therapy on the lives of those with epilepsy.

The evolution of therapy for epilepsy, however, is not a simple linear trajectory of constant progress, but more an erratic journey, full of false starts and dead ends. It is striking to observe how similar have been the claims made for past and current drugs, even though these claims have often turned out to be overblown, and how much therapy is dictated by fashion as much as science. These facts alone emphasize the need for historical perspective, for without a knowledge of history the same mistakes made in the past are inevitably repeated.

Over these 150 or so years, a few general themes have emerged which are worth enumeration. First, it is clear that most of the drugs introduced over this period have not stood the test of time, despite exaggerated claims made at the time. There have been various reasons for this, but usually their failure to make long-term impact has been because of an erroneous theoretical basis, an only modest impact on seizure control — if any impact at all — or the development of sometimes serious side-effects, some of which took years to be recognized. It is not so much that the many adulatory claims made for medicaments, now discarded, were deliberate deception, but more that they reflected the theoretical mores and fashions of the day. However, they do induce a sense of déjà vu — and should encourage a degree of skepticism when presented with assertions about contemporary therapies which are themselves based on an equally transient state of knowledge.

Secondly, the pace of new drug introductions varied considerably over time. There has been a clear 'concertina effect' with bursts of activity followed by fallow periods. These periods of activity have often been due, after the discovery of a new class of drug, to the development of close structural derivatives ('me-too' drugs; this happened for bromides, barbiturates, hydantoins, oxalozolidine diones, iminodibenzyls, pyrrolidones). Sometimes the derivatives have fared better than the parent drug, as has been the case with ethosuximide and levetiracetam, for instance, but sometimes the reverse has been the case (e.g. with phenytoin and phenobarbital).

Thirdly, the introduction of the most effective drugs has depended on new technology, new models or new scientific paradigms, albeit often laced with a large element of serendipity. The introduction of phenytoin thus depended on the new maximal electroshock model, the introduction of pregabalin, gabapentin, vigabatrin, tiagabine on the 'GABA' wave of experimental work, of perampanel on the glutamate wave, and of lamotrigine on the now abandoned 'folate theory' and so on. The underpinning of drug discovery by physiology and biochemistry shows how science leads and commercialism follows, but the influence of chance and of providence can never be underestimated. Epilepsy therapeutics has never been entirely rationally based.

Fourthly, the theoretical underpinning of drug introductions was often also based on concepts of aetiology of epilepsy. Thus, at the beginning of this period, therapy was devised on theories of nutritional balance, vascular congestion, autointoxication, masturbation and hereditary degeneration, and therapies based on restoring balance, reducing congestion, cleansing the bowel, castration and eugenics rose in and out of fashion. In recent times, the concept that epilepsy is caused by a loss of the normal balance between excitation and inhibition, of specific molecular or biochemical defects, of reducing inflammation or influencing specific genetic pathways are not altogether dissimilar. The relativism of our current scientific orthodoxies should not be underestimated, and current theories are likely to fall out of fashion as the restless focus of science shifts.

Finally, the social, commercial and political contexts have an enormous influence, and this influence is realized through such processes as regulation and commercial practice. The rapid development of drugs in the 1940s in the USA and in the 1950s–1960s in Europe were a result of light-touch regulation, and the dearth of

drugs in the 1960s–1970s in the USA was due in part to a regulatory reaction to the thalidomide tragedy. The current lack of new compounds is partly due also to the increasing bureaucracy and regulation of recent years. Another notable development has been the transfer of drug discovery from the hospital or university setting, typical in the first half of the period, to the situation now where drugs emerge mainly from the hidden interstices of the pharmaceutical industry in a heavily commercialized context. The rise in power and profitability of the pharmaceutical industry is one of the striking features of the post-war therapeutic scene and of epilepsy treatment. Epilepsy has interested the pharmaceutical industry also as the most successful drugs have been found to have uses in other indications (e.g. pain, depression) as well as in epilepsy, and these indications are often larger and more profitable than epilepsy itself.

Commentary

1857–1911

At the start of our period, 150 years ago, there were, by general agreement, few if any 'specifics' for the treatment of epilepsy. This was the point made by Dr Edward Henry Sieveking, soon to become physician at the National Hospital for the Paralysed and Epileptic in London, the first hospital providing outpatient treatment of epilepsy, and later physician to Queen Victoria, at a celebrated meeting of the London Royal Medical and Chirurgical Society on 11 May 1857 [4]. In his paper, he dismissed specific remedies and recommended a more rounded approach with the use of counter-irritants, the promotion of healthy action of the secernent organs (secreting organs), and the toning up of the constitution by vegetable and metallic roborants (tonics). Delasiauve, in his book *Traité de l'épilepsie* of 1854, made the same point, dividing therapy into:

1 *Debilitating therapies,* such as bleeding, tepid baths;
2 *Evacuant therapies,* including emetics and purgatives;
3 *Sedative therapies,* including ether;
4 *Specifics,* including valarian and opiates; the latter being not very successful.

This was indeed the orthodoxy of the day. The 1857 meeting was celebrated though, not for Sieveking's paper — excellent though it was – but for the remarks in the discussion that followed. In this, the royal obstetrician Sir Charles Locock, chairman of the meeting, reported his use of potassium bromide in hysterical catamenial epilepsy. Thus, on this rainy evening in London, the first modern medical treatment for epilepsy, and the first really effective 'specific' (or at least near-specific), was launched. There were further reports by Wilks, Radcliffe, Ramskill and Hughlings Jackson over the next few years, and by 1864 bromides had began to be very widely used.

In passing, it is interesting to note that at the meeting Locock also recommended removing over-crowded teeth and the cessation of masturbation. In the same vein, Webster remarked after Sieveking's paper that onanism was a frequent cause of epilepsy especially in southern climates, but Sieveking said he had not referred to the practice as 'it was difficult to arrive at the truth in regard to this', and that 'he did not know how to proceed to determine it in the case of females'.

Sieveking had also in that year published a book *Epilepsy and Epileptiform Seizures: Their Causes, Pathology and Treatment* [5] which was a landmark in epilepsy therapeutics. The second edition was completed in 1861 and in this Sieveking divided treatment into that of the 'acute paroxysm', for which he recommended the prevention of injury, counter-irritation by terebinthenate fomentations or sinapisms or leeches to the temple, removal of all restraint, avoidance of sedatives, cool air, carotid compression, cold applications, Galvanism, avoidance of ammonia and volatile stimulants and chloroform. He then considered the treatment of the premonitory stage and chronic epilepsy and recommended ligatures to the extremities, counter-irritation (e.g. setons, blisters), dry cupping and the abstraction of blood (by various means), trephining, moral treatment, purgatives, mineral tonics ('heroic antiphlogistic treatments should be eschewed'), nitro-muriatic acid, gentian, decoction of bark and sulphuric acid, olcum morrhuae (in other words, cod liver oil!), as well as bromide, which he thought of only moderate benefit, and potassium iodide for epilepsy due to secondary syphilis and lead poisoning. Sieveking remained skeptical about the use of specifics, as he put it:

> I make these remarks not only as an apology for not entering more fully into the consideration of a host of drugs that may be used in the course of the treatment of epilepsy with more or less advantage; but also as a protest against that specialism, fostered by the public as well as the profession, which converts every disease into a separate entity, breaks up the unity of the science of medicine, and, in its extremes, does more harm than any extra-professional quackery.

He listed therapies which in general he had found unhelpful: opiates and narcotics, hyoscine, conium, belladonna, hydrocyanic acid, belladonna, digitalis, mistletoe, cotyledon umbilicus and indigo. He ended his long chapter on treatment by referring readers to the complete lists of therapies in the works of Tissot, Fraser, Cooke, Copland and others, and by his now famous remark:

> In fact, there is not a substance in the material medica, there is scarcely a substance in the world, capable of passing through the gullet of man, that has not at one time or other enjoyed a reputation of being an anti-epileptic.

Hughlings Jackson also took a negative view of drug therapy, writing in 1888: 'It is notorious that our treatment of epilepsy is deplorably unsatisfactory' (cited in [6]), and he recommended for the first time, consideration of surgical treatment. Despite the pessimism of these leading doctors, it was nevertheless quite clear that bromide had changed the way physicians approached therapy in epilepsy. These drugs ushered in the modern age of antiepileptics, with its emphasis on efficacy, side-effects, mechanism of action and clinical therapeutics. This revolution started with bromide in its formulation as a potassium salt, but was soon followed by other formulations (notably as sodium, ammonium, strontium or lithium salt, and by combination products) but no consensus was ever reached about their relative merits. This was the start of a trend for the production of 'me-too' drugs which has continued to this day.

In this period, medicaments fell into three categories (Table 1): plant derivatives, animal derivatives and simple chemicals. Therapy also was often divided into therapy for the acute seizures (or impending seizures) and chronic therapy. The plant and animal extracts were produced largely in local pharmacies and dispensaries, but the chemicals were increasingly the province of the growing chemical industry, particularly in those companies involved in making dyes. These were the birth pangs of the pharmaceutical industry which was to so dominate therapy in the next century.

William Gowers was the most celebrated writer on epilepsy therapeutics in the late nineteenth century. His superb text *Epilepsy and Other Chronic Convulsive Disorders* [7] contained 50 pages on

Drug treatment for epilepsy

1857 Sir Charles Locock reported the effectiveness of bromide in hysterical catamenial epilepsy

1861 Samuel Wilks reported the effectiveness of bromide (combined with iodide) in ordinary epilepsy

1865 Chloroform and ether used for acute seizures

1871 Amyl nitrite and later nitroglycerin used for acute convulsions

1872 Cannabis recommended for the headache and restlessness after an epileptic fit

1873 Ergot reported to be useful in epilepsy

1874 Chloral used for acute seizures

1880 Borax introduced for epilepsy by Sir William Gowers

Strychnine reported to be useful in epilepsy

1884 Coal tar products used in epilepsy

Beta-naphthol used to cleanse the bowel in epilepsy

1887 Paraldehyde used for epilepsy (the drug was entered into the formulary in 1874)

1892 Sulphonmethane (Sulphonal) used in epilepsy

1893 Paul Gibier recommended injection of extract of sheep cerebrum

1895 *Adonis vernalis* recommended for epilepsy by Bernard Sachs and Vladimir Bekhterev

1898 Erysipelas antiserum used to treat epilepsy by Hessler

1901 Ceni recommended injection of serum from other epileptic patients on the basis that this contained autocytotoxin

1906 First Food and Drug Act in the USA

Other treatments for epilepsy

1854 Publication of *Traité de l'épilepsie* by Louis Delasiauve

1857 Publication of *On Epilepsy and Epileptiform Seizures: Their Cases, Pathology and Treatment* by E.H. Sieveking

1859 Publication of *On the Origin of Species* by Charles Darwin and modern theories of inheritance of disease were born

1860 Foundation of the National Hospital for the Relief and Cure of Epilepsy and Paralysis in London

1866 Gregor Mendel published his theory of inheritance, widely recognized only in 1902 when his work was translated into English by William Bateson

Cliterodectomy reported to be effective in epilepsy

1881 Ligation of carotid artery reported to be effective in epilepsy

Publication of first edition of *Epilepsy and Other Chronic Convulsive Disorders* by Sir William Gowers

1883 Cervical sympathectomy described for use in epilepsy

1886 Sir Victor Horsley carried out first cortical resective surgery for epilepsy, an operation that opened the modern era of epilepsy surgery, and published work on cerebral localization and brain mapping

1889 Francis Galton proposed his law of ancestral inheritance whereby offspring receive half of their inherited characteristics from each parent

1899 Low salt diet recommended for epilepsy and to reduce the dose of bromides

1904 Publication of *Epilepsy and its Treatment* by William Spratling

1905 William Bateson coined the term genetics

1906 First Food and Drug Act in the USA

1908 Sir Victor Horsley and Robert Clarke designed a stereotactic frame

1907 Indiana became the first US state to enact a eugenic compulsory sterilization law for persons with mental deficiency and included patients with epilepsy

Publication of *Epilepsy: a Study of the Idiopathic Disease* by W. Aldren Turner

1909 Foundation of the International League Against Epilepsy (ILAE) in Budapest

Launch of first series of *Epilepsia* which continued publication until 1914

1910 Eugenic record office opened at Cold Spring Harbor under the leadership of Charles Davenport and engaged in genetic studies of epilepsy

1911 First report that fasting improves epilepsy

treatment, and his recommendations for drug therapy are summarized in Table 2. He wrote in the second edition in 1901 that apart from therapies aimed at the underlying cause, and general and surgical measures:

> The treatment of epilepsy is purely medicinal. It has always been so, but in a far more pronounced degree since the almost accidental discovery, more than forty years ago, of the influence on the disease exerted by the combinations of bromine.

Gowers considered all other therapies as 'adjuncts' to bromide, and he also criticized many of the medicaments used in contemporary therapy as being of little if any value. One adjunct though that did impress him was borax, which Gowers himself first introduced in his Goulstonian lecture of 1879, and this continued to have a place in therapy right up until the 1950s.

Bromide dominated therapy until the 1920s, but it was clear that, by 1890, enthusiasm for medicinal therapies was waning. No new effective therapies were launched in the next 20 years and the transient nature of improvement on therapy was also recognized. As Gray wrote in 1895:

> Epileptics, are very readily influenced by slight changes in the environment and in … treatment … [they] do well for a time upon any change in treatment, whether that treatment be medical or surgical, whether it consists of cutting off the prepuce, removing the clitoris, extirpating the ovaries … using the hot iron ... cutting the eye muscles … or etherizing the patient and cutting a piece of skin out of the buttock. I have even seem improvement effected in a patient for months by mere change of locality. (cited in [7])

In 1907, the next major figure in epilepsy therapeutics, William Aldren Turner, published his classic book *Epilepsy: A Study of the Idiopathic Disease* [8]. This was a text that defined advanced thinking of the time. In the book, he considered that only a few drugs were of definite benefit and his lists of effective and ineffective drugs are shown in Table 3.

William Philip Spratling, the leading US epileptologist of the time, published his book *Epilepsy and its Treatment* in 1904 [9]. His recommendations regarding drug treatment were very similar to those of Gowers. He expounded in detail on the bromides, and their various formulations, and also recommended their combination with opium or codein. Other drugs he thought efficacious, in line with Gowers and Turner, were borax, chloral, amylene hydrate, nitroglycerin, zinc, iron and chloroform. He also recommended chloretone (trichloro-2-methyl-2-propanol, a hypnotic similar to chloral), urethan, solanum carolinense, simulo, trional (a GABAergic sedative), serum therapy of Ceni and the coal tar derivatives (antipyrin, phenacetin and acetanilide).

The therapy of status epilepticus also evolved during these years (for sources see [10]). In 1874, Bourneville, in his classic account of status epilepticus, related the case of Marie Lamb who was treated at the Salpêtrière with sinapisme (a topical remedy with a base of mustard flour), lavement purgative and quinine sulphate – to no effect. Amyl nitrite was introduced in 1876, and Gowers in 1881 recommended morphia. Other drugs used were apomorphine, hyoscine hydrobromate and chloroform. In 1903, Clark and Prout advocated chloroform, bromide and chloral. Turner suggested at the onset of status epilepticus that the dose of bromide salt should be doubled, and chloral hydrate, but that at the height of an episode 'nothing will arrest the seizures except the inhalation of chloroform' and that

in the stage of stupor what was needed was careful nursing, abundance of light nourishment and tonics.

By the end of the nineteenth century, the side-effects of bromides were recognized ('bromism'), and much of the therapeutic efforts were focused on reducing these. This included the use of low salt diets to reduce the requirement for bromide (so that the body would replace chloride with bromide; dechloridization), the use of combination therapies and the use of lower doses. With the advent of bromides many previously widely used compounds fell from favour (including most herbal and many chemical remedies such as zinc and iron) and the range of therapies greatly narrowed.

1912–1988

In 1912, the hegemony of bromides was challenged for the first time by a totally new medicament. This newcomer, a new chemical compound manufactured in the laboratories of Bayer, the German pharmaceutical company, was phenobarbitone (Luminal). It been synthesized in 1904, and joined a group of barbiturates then being used as sedatives and hypnotics. Its antiepileptic properties were discovered in 1912 by chance by Alfred Hauptmann, a young psychiatrist in Freiburg, who wrote a long and detailed account of its actions. The importance of this discovery was not initially widely recognized, partly because of its publication in an obscure German language journal and also the greater medical priorities of the 1914–1918 war. However, by 1920 its use was being reported in England and a year later in the USA, and very rapidly after this it entered general prescribing.

Until about 1940, bromide and phenobarbital remained the first-line drugs for epilepsy, with some authorities favouring each. It is curious to see how opinion was divided about their relative merits, but what it does seem clear that when bromide therapy was used skillfully, it matched the outcomes of phenobarbitone in the eyes of many of the leading neurological figures. Kinnier Wilson [11], for instance, could still write in the late 1930s in his standard neurological textbook that: 'although phenobarbital was at first thought likely to supplant bromides as a remedy of choice', it was 'not its equal in general applicability', and bromide 'remains the drug of first choice – the sheet-anchor on which everyone relies'. Wilson listed other drugs that he found helpful (Table 4) but wrote that 'no useful purpose would be served by further comment on the list of drugs vaunted at one time or another: all must stand the test of experience, and … those which have successfully done so can be numbered on the fingers of one hand'.

In the 1950s, the absorption, distribution, metabolism and excretion of phenobarbital was first clearly identified when serum phenobarbital levels were possible to measure in clinical practice (in 1952). This improved its therapeutic effectiveness and phenobarbital remains today one of the most prescribed medications for epilepsy globally, with a high uptake especially in the developing world because of its remarkable cheapness. Furthermore, its efficacy has never been shown to be significantly worse than any other drug, and its fall in popularity in contemporary Western medicine is largely because of its side-effect profile, and its lack of marketing backing by any of the major players in the pharmaceutical industry who see little profit in the promotion of such an inexpensive drug.

Intravenous phenobarbital was introduced in 1926 for status epilepticus, and was sometimes mixed with chloroform, enemata and bromides. Other drugs recommended for status epilepticus at the time [10] included scopolamine and atropine, amyline hydrate ('Alt') and paraldehyde (first used in 1914). Non-pharmacological therapies included irrigation of the bowel. Kinnier Wilson [11]

Drug treatment for epilepsy

1912 Discovery of the anticonvulsant effects of phenobarbitone by Alfred Hauptmann

1913 Publication of a large series of epileptic patients treated with crotalin – rattlesnake venom – by Ralph Spangler

1914 Paraldehyde first used for status epilepticus

1915 William Shanahan stated that irrigation of the bowel was the most urgently indicated procedure to treat status epilepticus

1920 Positive effect of the ketogenic diet on epilepsy was first documented critically

Borotartrate introduced by Pierre Marie

1922 Introduction of allobarbital with allylparacetaminophenol (Dialacetin; Ciba) for epilepsy (approx. date)

1926 Intravenous phenobarbital reported to be used in status epilepticus

Other treatments for epilepsy

1912 Fedor Krause reported 96 operated patients with focal epilepsy and brain mapping by electrical stimulation

1914 ILAE went into hibernation with the outbreak of the First World War

1915 William Shanahan stated that irrigation of the bowel was the most urgently indicated procedure to treat status epilepticus

1916 *Bacillus epilepticus* isolated from stools of epileptic patients and identified as the cause of epilepsy and the theoretical justification of colectomy

1917 Publication of an influential series of cases of right-sided colectomy for the control of epilepsy from Boston

1918 Air ventriculography devised by Walter Dandy

1919 Air encephalography first carried our via the lumbar route by Dandy

1921 Ketogenic diet proposed as a possible treatment for epilepsy

1922 Resection of adrenal gland used as treatment for epilepsy

1923 Dandy carried out the first hemispherectomy in a human patient

1924 Hans Berger recorded the first human EEG

Publication of the first edition (in Dutch) of L.J.J. Musken's book *Epilepsy: Comparative Pathogenesis, Symptoms and Treatment*

1926 Cerebral angiography first attempted by Egas Moniz

1927 *Buck* v. *Bell* case in US Supreme Court ruled in favour of forced sterilization of epileptic patients

1929 Penfield's first 'temporal lobectomy' (a cortical resection)

Berger published a recording of human EEG

1930 Foester and Penfield's paper on the surgical treatment of post-traumatic epilepsy published in *Brain*

1931 Dandy carried out the first corpus callosal section to remove a congenital cyst

1934 Adrian and Matthews published their renowned paper in *Brain* corroborating Berger's EEG findings

J.D. Bernal and Dorothy Hodgkin developed X-ray crystallography

1935 Gibbs, Davis and Lennox described the interictal spike waves and the 3/s pattern of absence seizures

The first intraoperative electrocortigram carried out by Foester and Altenburger

A group of neurologists met at Lingfield Epilepsy Centre and relaunched the ILAE

1936 First clinical EEG laboratory was set up at Massachusetts General Hospital

Moniz published the first human frontal lobotomy

realized that status was often caused by too rapid drug withdrawal and in these cases large doses of bromide and chloral per rectum every 4–6 hours should be used. Other methods of treatment included the hypodermic injection of Luminal sodium, bromide (including intrathecal bromide), repeated drainage of the spinal fluid by lumbar puncture, hyoscine hydrobromide, paraldehyde and, he also commented, 'venesection and saline injections may also be used in the robust'.

In 1910–1939, many of the other traditional herbal, animal and simple chemical remedies still continued to be widely used, although one senses from the literature that these were applied with little hope of success. A small number of other novel therapeutic options were also launched in this period. Perhaps the most important of these was the ketogenic diet, and although not strictly speaking a 'drug' it is included here as it was thought to exert its effects through biochemical changes similar to those induced by drugs. The diet was first mooted in 1921, based on the observations that starvation, and also the 'water diet', improved epilepsy (first made in 1911). After a few years of experimentation with different fat : carbohydrate and protein ratios, the standard diet was in widespread use in the 1930s with many reports of its value. Another introduction was that of borotartrate, first mentioned by Marie in 1926. This was notable for the fact that it was antiepileptic without being sedative (a property not shared with bromide or phenobarbital) but its effectiveness seems to have been modest at best.

A snapshot of the most popular drug treatments in the period was given by the Dutch neurologist Muskens in his book of 1926 [12]. He divided therapy according to the stage of the disease. He emphasized prophylaxis in the prodromal stage, where therapy should be aimed at preventing the development of epilepsy by elaborate social hygiene methods and good nutrition but without medication. In early epilepsy he used bromide, phenobarbital and borax as the three main therapies, and also zinc oxide, nitroglyerine and cannabis indica; in inveterate cases, he prescribed iodide of mercury, according to a method 'very similar to the mercurial treatment used for lues'.

Although this survey is primarily concerned with drug therapy, a brief word on non-drug approaches to the treatment of epilepsy needs to be added, as from the mid-nineteenth century right up until the 1950s there was also a strong emphasis on what was initially included broadly under the designation of hygiene and advice on other broad aspects. These included the importance of regular habits, enough sleep, sufficient exercise, massage, attention to bowel habits, the avoidance of masturbation, the avoidance of stress and the use of tonics. Hydrotherapy and detoxication were frequently proposed. Turner wrote in 1910: 'We have, therefore, in every case of epilepsy to treat the individual and not solely the disease' [13]. Turner recognized six headings under which the treatment of epilepsy should be considered: prophylaxis, management and treatment of young epileptics, hygiene, education of epileptic children, care of confirmed epileptics (epileptic colonies) and surgical treatment. There was great attention paid to diet, with emphasis on balance, often with low protein and or low salt diets promoted, and the omission of a seemingly random selection of foods and drinks by different authorities. Lengthy dissertations on these various measures were to be found in the texts of the period. Physical therapies included counter-irritation with cautery, blistering or setons, for example. This was popular too in the nineteenth century although seems to have faded from fashion in the early twentieth century, as did galvanism, magnetism and other electrical therapies. Another interesting trend in the late nineteenth and early twentieth centuries

was a vogue for institutionalization and the establishment of epilepsy colonies for promoting good health. Indeed, the promotion of research into institutional care was one of the main reasons proposed for the establishment of the International League Against Epilepsy (ILAE) in 1909 [14]. Surgical therapy was also made possible by the introduction of Listerian antisepsis, general anaesthesia with ether (1846) and especially chloroform (1847) and local anaesthesia (initially with cocaine, 1877). Horsley introduced resective cortical surgery on the basis of meticulous brain mapping in primates, and his pioneering work, with Jackson and Ferrier, on cerebral localization. His first epilepsy operations were carried out in 1886 to international acclaim. Other operations also performed around this time, almost certainly totally ineffectively, included ligation of the carotid artery (1881), cervical sympathectomy (1883), circumcision, cliteridectomy (1866), oophorectomy, testectomy, adrenalectomy and bilateral vertebral artery occlusion. Oophorectomy, orchidectomy and castration were used as eugenic methods, especially in the early twentieth century. Interest waned in cortical resection in the first four decades of the twentieth century, which was proving less successful than initially hoped, and the number of surgeries performed worldwide fell considerably. At the same time there developed a widespread vogue for colectomy and other bowel resections, on the basis that these would reduce autointoxication (for a consideration of the historical influences of aetiology on therapy see [15]).

In the early 1930s, especially in the USA, there was a new interest in trying novel compounds for epilepsy. These included the use of vital dyes – notably brilliant vital red and methyl blue – and for a time there was a vogue for these treatments. Vasodilator therapy was also being tried with a variety of substances, including acetylcholine, amyl nitrite, carbaminoylcholine (one of the most powerful parasympathomimetic drugs known), and the 'fourth substance of the arteriolenstaff', reflecting the then current interest in alterations in cerebral blood flow as a pathogenic mechanism of epilepsy. Other new medicinal therapies included thyroid extract, pancreatic extract, vitamin B, strychnine, boric acid, pyridine, ammonium chloride, ethyl phenyl sulphone and glutamic acid. Benzedrine and caffeine were widely used to counteract the sedative effects of the barbiturate, bromide and hydantoin drugs. Other physical treatments were explored including insufflation of the cerebrospinal fluid space with air, X-irradiation, metrazol-induced or electrically induced convulsions. Paraldehyde too, introduced into clinical practice in 1882, was first recognized to be have useful anticonvulsant action in 1940.

The big news of the period though of course was the discovery of phenytoin, by Merritt and Putnam, who were given the chemical by the US pharmaceutical company, Parke Davis, and who for the first time used an animal model for systematically screening chemicals for their antiepileptic action. The use of experimental models was not new, and camphor- and metrazol-induced models had been in use for many years, but the systematic use of screening, using an electrical convulsant model, was a novel step. The clinical development of phenytoin was impressively fast. It was first tried experimentally in the cat in 1936, eight patients had been treated by August 1937, the first clinical trial was reported in June 1938 and by September 1938 the results in 200 patients were published. In 1939, the drug was added to the 'New and Nonofficial Remedies list of the American Medical Association', on the basis of 13 different trials in 595 patients for 'epileptic patients who are not benefitted by Phenobarbital or bromides and in those in whom these drugs induced disagreeable side reactions'. By 1940, it was in widespread use as a first choice medication and remained so in epilepsy treatment worldwide at least until the late 1980s, when it was slowly

Drug treatment for epilepsy

1937 First report of the anticonvulsant effects of the vital dyes (Brilliant Red) in epilepsy

1938 Amendment to the Food and Drugs Act in the USA

First use of phenytoin in epilepsy (Dilantoin, Epanutin; Parke, Davis)

1941 Acetazolamide (Diamox; Lederle) introduced for the treatment of epilepsy

1946 Trimethadione (Tridione; Abbott) introduced into clinical practice

1947 Mephenytoin (Mesantoin; Sandoz) introduced into clinical practice

First randomized controlled trial carried out – the Medical Research Council study of streptomycin in tuberculosis

1949 Paramethadione (Paradione; Abbott) introduced into clinical practice

Intravenous paraldehyde first used in status epilepticus

1950 First use of corticosteroids and ACTH in epilepsy

Phenthenylate (Thiantoin; Lilly) introduced into clinical practice

1951 Phenacemide (Phenurone; Abbott) introduced into clinical practice

1952 Metharbital (Gemonil; Abbott) introduced into clinical practice

Benzchlorpropamide (Hibicon; Lederle) introduced into clinical practice and then withdrawn

1953 Phensuximide (Milontin; Parke, Davis) introduced into clinical practice

1954 Primidone (Mysoline; ICI) introduced into clinical practice

1956 Intravenous phenytoin first used in status epilepticus

1957 Ethotoin (Peganone; Abbott) introduced into clinical practice

Methsuximide (Celontin; Parke, Davis) introduced into clinical practice

1958 Ethosuximide (Zarontin; Parke, Davis) introduced into clinical practice

1960 Intravenous lignocaine reported to be effective in status epilepticus

Other treatments for epilepsy

1937 Second series of *Epilepsia* was launched and continued publication until 1950

J.B.S. Haldane and Julia Bell published the first evidence of genetic linkage in humans

1938 McKenzie carried out the first human hemispherectory

1939 Action T4 – the mass murder of handicapped persons with epilepsy began in Nazi Germany

Hodgkin and Huxley published their first paper on the membrane theory of nerve transmission

1940 First corpus callosectomy for epilepsy was reported by William van Wagenen and Yorke Herren

Publication of three-volume textbook *Neurology* by S.A. Kinnier Wilson

1941 Principle that one gene codes for one enzyme established by George Beadle and Edward Tatum

1942 ECT used in the treatment of epilepsy

1947 George Dawson recorded cerebral evoked potentials for the first time

Stereotactic methods introduced into neurosurgery by Spiegel *et al.*

1948 Around this time, the first temporal lobectomy with removal of the mesial structures was performed, by either Arthur Morris in Georgetown or Wilder Penfield in Montreal

Gibbs *et al.* described the anterior temporal EEG spike

1949 First video and EEG monitoring introduced

GABA identified in the brain by Roberts and Fraenkel

Video-tape and EEG recorded simultaneously

1950 Second series of *Epilepsia* ceased publication

1951 Stereotactic radiosurgery introduced by L. Leksell

1952 Volume 2 of the *Atlas of Electroencephalography*, devoted to epilepsy, was published

Third series of *Epilepsia* inaugurated but ceased publication in 1956

Measurement of phenobarbital serum levels first achieved

1953 James Watson and Francis Crick identified the helical structure of DNA

1953 Fourth series of *Epilepsia* launched and continues to be published

1960 Publication of *Epilepsy and Related Disorders* by William G. Lennox

First description of the sodium amytal (Wada) test

displaced in most countries from its pinnacle by carbamazepine and valproate.

The promise of phenytoin was recognized early, as shown by an article in 1940 in which the history of drug treatment in epilepsy was said to be divisible into three epochs: the first of bromide, the second of phenobarbital and 'the third era is very recent in origin and is characterized by the introduction in 1938 of Dilantin Sodium'. Within a few years it had displaced bromide from the front line of therapy, and although phenobarbital continued to be widely used, bromide became a peripheral therapy, although a flurry of new papers on aspects of bromide; were published in the 1980s.

In the two decades that followed the discovery of phenytoin, new chemical derivatives began to be explored for their antiepileptic action on a massive scale by the burgeoning pharmaceutical industry. Putnam and Merritt screened a further 700 compounds, provided to them by Parke Davis and other companies, and listed the results on 618 of these chemicals in a paper in 1945. Seventy-six compounds were given a 4+ rating. They could be grouped into seven categories on the basis of their structure: barbiturates, benzoxazoles, hydantoins, ketones and phenyl ketones, oxazolidine diones, phenyl compounds with sulphur and phenyl glycol. Of these drugs, phenytoin and four others were selected for clinical trial. None of the other four (5-phenyl-5-isopropoxymethylhydantoin, ethyl-phenylsulphone, 5-methyl-5-phenylhydantoin, 5,5-diphenylenehydantoin) showed clinical benefits greater than phenytoin and so were not pursued after the initial trials. However, a further 13 new antiepileptic drugs were introduced into practice in 1940–1958, by six pharmaceutical companies, five of which were American and the sixth, ICI, from England. The drugs were produced mainly by manipulating the structure of the barbiturates and hydantoins using the newly refined principles of medicinal chemistry linked to methods of large-scale industrial production. Clinical testing was perfunctory and the drugs were introduced with minimal safety testing and as a result many were subsequently withdrawn because of severe side-effects.

An international list of antiepileptic drugs was published in 1955 by the ILAE (a total now of 23 licensed drugs) and this demonstrates the extent of structural manipulation (Table 5) comprising four barbiturates, four oxazolidines diones, six hydantoins and seven other types. In addition, there were eight combination tablets which were mainly combinations of hydantoins and barbiturate. Although a large number of medicines, these were largely 'me-too' drugs and none were a major advance. This period, following the discovery of phenytoin, was essentially arid and little fundamental improvement was achieved.

A striking feature of the post-war period, initially in the USA and then in Europe, was the enormous rise in the power of the pharmaceutical industry and the intense commercialization of the pharmaceutical market. This was a period of great optimism; drugs developed in the 1950s and 1960s included the first oral contraceptives, corticosteroids, antihypertensives, monoamine oxidase inhibitors, new antibiotics, antipsychotics (chlorpromazine, haloperidol) and the benzodiazepines (Valium became the most prescribed drug in history).

In the 1950s, in the field of antiepileptic drugs there was no really major advance, and epilepsy drug therapy in this period can best be ascertained from William Lennox's definitive textbook *Epilepsy and Related Disorders* published in 1960 [16]. Lennox listed 16 drugs (his 'therapeutic arsenal') licensed for epilepsy in the USA (Table 6). The first places were given to bromides, which he noted were 'little used today', and to phenobarbital. Lennox mentioned that 2500

barbiturate compounds had been synthesized and of these 50 compounds were marketed, of which phenobarbital was the most frequently used for epilepsy. The third drug that impressed Lennox was methylphenobarbital (mephobarbital) which he pronounced to be 'the only barbiturate besides phenobarbital effective against epilepsy' and the fourth was phenytoin. He rated the fifth drug, mephenytoin, as better than phenytoin in several situations, and indeed he favoured their combined use. The next drug was ethotoin which Lennox noted was one of the 1500 compounds screened by Abbott Laboratories in the previous 8 years.

The next decade, 1958–1968, was the most productive in the history of epilepsy therapeutics, and in these 10 years a crop of truly effective and novel new drugs was developed. First off was ethosuximide (α-ethyl-α-methylsuccinimide; PM 671), a drug that was very similar in structure to phensuximide and methsuximide which had been introduced by Parke Davis in the previous years; in this sense this was a drug of the old school. It was licensed in 1958 for petit mal, and remains a drug of first choice to this day. It acts by blocking the low-voltage T-type calcium channel, a mechanism that was identified only in 1984, some 16 years after licensing.

Further developments were of drugs originating almost entirely from Europe and not the USA, and which were not chemical derivatives of known antiepileptics. The first was carbamazepine, initially known as G32883, a compound developed in the Swiss pharmaceutical company Geigy in 1953. It had a tricyclic structure, and was first investigated for depression and psychosis and then licensed for trigeminal neuralgia in 1962. Its antiepileptic effects were investigated clinically in 1959 and first reported in 1963. The drug was licensed as an anticonvulsant in Britain in 1965, then in Europe and in 1974 in the USA. Its principal mechanism of action, the blockade of sodium channels, was not recognized until 1983 but by then carbamazepine had become the most prescribed antiepileptic drug in Europe, consigning barbiturate to the therapeutic periphery, and it remains the gold standard for comparative studies of antiepileptics and the drug to beat for any new compounds.

Sodium valproate was the next antiepileptic to be introduced and a drug that, like carbamazepine, completely changed the scope of prescribing. The first report of the antiepileptic effect of sodium valproate was published in 1964. This was discovered serendipitously in a small laboratory in Rennes where valproate was being used as the solvent for other experimental drugs, but its potential was quickly realized. In 1967 it was approved in France for epilepsy, and then over the next few years in other European countries (and in 1976 in the USA, albeit initially only for absence seizures). Valproate and carbamazepine have since become the most prescribed drugs worldwide. Valproate is highly effective in many types of epilepsy, and was recognized early to be the drug of choice in idiopathic generalized epilepsy, but is also a drug with significant adverse effects, in particular teratogenicity.

Another enormous development in the epilepsy pharmaceutical landscape of the 1960s was the introduction into clinical practice of the benzodiazepine drugs. The first licensed was chlordiazepoxide in 1960 and then diazepam in 1963. Over the next 15 years, over 4000 related compounds were synthesized and screened, and by 1978 23 different compounds had been licensed. Although the main focus of these drugs was on their anxiolytic and hypnotic properties, the anticonvulsant effect of chlordiazepoxide (Librium; Ro 5-0690) was first reported in 1960 and in 1962, a series of cases of epilepsy treated with chlordiazepoxide and diazepam (Valium; Ro 5-2807) were presented. In 1965, Gastaut reported the effects of clonazepam (Rivotril; Ro 05-4023) and, in 1977, the first double-blind study

Drug treatment for epilepsy

1962 Sulthiame (Ospolot; Bayer) launched in Europe into clinical practice

Intravenous urea used in status epilepticus with excellent results

1963 Kefauver–Harris amendments to FDA regulations

Benzodiazepines — in the form of diazepam (Valium; Roche) and chlordiazepoxide (Librium; Roche) — introduced into clinical practice and diazepam also used in status epilepticus

Chlormethiazole (Heminevrin; AstraZeneca) introduced into clinical practice

1965 Carbamazepine (Tegretol; Geigy) introduced as an antiepileptic, with first licensing in the UK

1966 First randomized controlled trial in epilepsy published – of carbamazepine

1967 Valproate (Epilim; Sanofi) approved for use first in France

1968 Clonazepam (Rivotril; Roche) licensed for treatment of epilepsy in Europe

1971 Gastaut reported excellent results of intravenous clonazepam in status epilepticus

1972 Publication of *Effectiveness and Efficiency: Random Reflections on Health Services* and start of Cochrane collaboration by Archie Cochrane

1975 Clobazam (Frisium; Roche) licensed in Europe for the treatment of epilepsy

1978 Antimyoclonic effect of piracetam demonstrated

First published reports of the advantages of antiepileptic drug monotherapy – and the beginning of the 'monotherapy age'

1980 Beginning of a period of intense study of first GABAergic and then glutaminergic mechanisms ('GABA wave' and 'glutamate wave')

1985 Progabide licensed in France, but not elsewhere

Other treatments for epilepsy

1961 First routine method for measuring blood levels of antiepileptic drugs introduced in clinical practice, and the beginning of therapeutic drug monitoring and intensive pharmacokinetic and interaction studies which continue to the present day

International Bureau Against Epilepsy (IBE) formed

Francis Crick and Sydney Brenner discovered that the genetic code is a triplet code (the sequence hypothesis was predicted by Crick in 1957)

Francis Crick and Sydney Brenner proposed that RNA is the messenger, transmitting code from DNA

1962 First congress devoted entirely to status epilepticus (Marseilles Colloquium)

1964 Gastaut produced the first draft of the ILAE Classification of Seizure Type

1965 Talairach, Bancaud and coworkers published *La stéréoélectroencéphalographie dans l'épilepsie*

1966 Epilepsy section formed at NIH with J. Kiffin Penry as chief

1967 Computerized X-ray tomography (CT scanning) devised by Godfrey Hounsfield (later awarded a Nobel Prize)

Microneurosurgical techniques (and the operating microscope) introduced by Mahmut Yaşargil

1968 Laboratory of Prince in Stanford began to elucidate many of the electrophysiological characteristics of experimental epilepsy

First Gamma Knife introduced by Leksell

1969 ILAE Classification of Seizure Type approved

1970 Establishment of the ILAE Commission on Antiepileptic Drugs

1972 First CT scan carried out on a patient with epilepsy

First edition of *Antiepileptic Drugs* published. The fifth and last edition was published in 2002

1975 Ed Southern developed Southern blotting

1977 First MRI scan *in vivo* in man (of a finger) carried out in Nottingham by Peter Mansfield (later awarded a Nobel Prize)

A method for sequencing DNA developed by Frederick Sanger (later awarded a Nobel Prize)

1978 Publication of Commission for the Control of Epilepsy and Its Consequences, *Plan for Nationwide Action in Epilepsy,* by the US government

First clinical MRI brain scans carried out

First published reports of the use of PET scanning in epilepsy

1979 Recognition that barbiturates act by modulating GABA reception function

comparing clonazepam and ethosuximide in absence seizures was published. The mechanism of action — agonist action at the GABA receptor — was discovered. Clobazam was then licensed in Europe in 1975, but not until 2012 in the USA.

Amongst the more minor discoveries of the period was sulthiame, first launched in Europe in the early 1960s, but never licensed in the USA. Soon after its launch, its major interaction with phenytoin was recognized and it was postulated that its effects were due simply to the increasing levels of phenytoin when used in comedication. Because of this, in 1986 sulthiame was withdrawn from the market in the UK and then in other European countries. The ownership was transferred to Desitin in 1993 and it is available now in a few European countries. Progabide was licensed in France in 1985 and by 1992 used in over 2500 persons, where it remains to this day on the Gallic fringe of therapy. It was never licensed in any other European country nor in the USA.

Corticosteroids and particularly adrenocorticotrophic hormone (ACTH) were introduced into clinical epilepsy practice in 1950. In 1958 the dramatic effect of these drugs in infantile spasms was first reported, and they have remained first-line therapy for this indication. ACTH and cortisone were shown in the 1950s also to have value in occasional cases of other types of childhood epilepsy and in status epilepticus. The first report of the use of chlormethiazole in status epilepticus was in 1963 and it became a standard second-line therapy in the treatment of epilepsy in 1970s and of acute seizures and status epilepticus.

The treatment of status epilepticus (Table 7) [10] was also greatly influenced by the introduction of intravenous phenytoin, first used in 1956. Intravenous paraldehyde had also become popular after the first report of its use in 1949, and was favoured by many above phenytoin. Intravenous lignocaine was first reported in 1960 and intravenous urea was reported in 1962 to be highly effective in severe status epilepticus. All these drugs were eclipsed by the benzodiazepines. In 1965, Gastaut said of diazepam in status epilepticus, that it was:

> Outstanding for the reliability and rapidity of action, which together make it a more effective drug than others we have used in the past, amongst which have been: injectable Phenobarbital, Somnifene, Chloral hydrate, Eunoctal, Sodium Bromide, Rectanol, Novocain and Hemineurin … We have never obtained such results in the past, although we have used a variety of drugs, including: Tridione, Pentothal, Eunoctal, Hemineurin, ACTH and aldosterone.

Then, in 1971, Gastaut reported the use of clonazepam (Rivotril; Ro 5-4023):

> 'a new benzodiazepine – more active than diazepam … we do not hesitate to affirm that Ro 05-4023 is by far the most effective agent which we have at present for the treatment of status epilepticus of whatever form or aetiology'.

The application of pharmacokinetic principles to epilepsy therapy was a most important clinical advance in the 1960s and 1970s. The measurement of antiepileptic drug serum levels began to be studied systematically only in the late 1950s, although the technologies had been available for some years before. This early development was both methodology-driven and also stimulated by the regulatory requirement for pharmacological information. Extensive studies of bromide, ethosuximide, phenytoin and phenobarbital were conducted initially, and within a decade or so the clinical pharmacokinetic properties of all the antiepileptic drugs — their absorption, distribution, metabolism and excretion — were quite

fully documented. In the 1960s, too, the measurement of serum levels of drugs entered clinical practice (known as therapeutic drug monitoring), and soon laboratories were routinely measuring levels. By the early 1980s, the characterization of the hepatic enzyme systems was largely complete, and the relevant factors, both environmental and genetic, were intensively studied. A veritable industry arose, related to drug interactions, led by the study of phenytoin (a drug with uniquely complex interactions), in the mid-1960s.

The emphasis on single-drug therapy (monotherapy) was an influential change in treatment strategy dated from the late 1970s. Monotherapy became feasible, paradoxically, because of the introduction of a wider choice of new effective drugs, especially carbamazepine and valproate, and also because of the adoption of the therapeutic drug monitoring which refined and improved individual dosing. There rapidly followed a marked swing to monotherapy protocols in patients with epilepsy, and the nearly universal recommendation that antiepileptic monotherapy be initiated in new patients. By the late 1980s, the regulatory authorities had began to request monotherapy trials.

1989–2014

The impact of molecular medicine began to be felt in this period, initially particularly in relation to studies of inhibitory GABAergic brain function (the 'GABA wave') and then excitatory brain function (the 'glutamate wave'). Between 1989 and 1994, five major antiepileptic drugs were licensed in Europe and introduced into clinical practice. Vigabatrin, a product of the 'GABA wave' was the first. It was a designer drug, produced to be a 'suicidal inhibitor' of GABA transaminase. The first trials were in 1983 and it was launched first, in the UK, in 1989 and then in Europe but not in the USA. In 1997, severe visual side-effects were first reported and the drug, once widely prescribed, is now used in a very small number of patients. Lamotrigine was developed, in the UK, as an antifolate drug and found to have antiepileptic effects by chance. It was licensed in Britain in 1991 and then in Europe, and in 1994 in the USA, and is now a first-line medication. Felbamate, a drug developed by Carter Wallace Laboratories, was launched in the USA in 1993. It was not licensed in Europe and in 1994 was withdrawn because of the risk of hepatic failure. It has since been reintroduced to be used as a last-resort therapy with special precautions, and has a very small place in contemporary prescribing. Gabapentin was developed as a GABA analogue to act at the GABA receptor as a GABA agonist. In fact, it has no action at the GABA receptor and its mechanism of action is due to binding to the α2δ subunit of the neuronal voltage-dependent calcium channel (a fact discovered a decade or more after licensing). It was licensed in 1994 in the USA and UK and by 2003 was one of the 50 most-prescribed drugs in the USA (its sales of nearly $2.7 billion in 2003) due largely to non-epilepsy indications. It is still used as a second-line drug in epilepsy. Oxcarbazepine was licensed in Denmark in 1990 and then in most EU countries in 1999 and in the USA in 2000. It is now widely used as a first or second-line therapy.

Between 1995 and 2014, a further 10 antiepileptic drugs were licensed — topiramate, tiagabine, levetiracetam, zonisamide (although earlier licensed in Japan), pregablin, stiripentol, rufinamide, lacosamide, retigabine and perampanel. Of these, topiramate and levetiracetam are widely used as first-line agents, retigabine and tiagabine have been largely abandoned, and stiripentol and rufinamide licensed only for niche indications (in Dravet and the Lennox–Gastaut syndromes, respectively). In addition, buccal midazolam has been licensed for emergency therapy, initially as midazolam hydrochloride in a preparation approved under a special licence in

Drug treatment for epilepsy

1989 Licensing of a flurry of new drugs begins (third generation drugs) initially with vigabatrin in Europe and zonisamide in Japan

Vigabatrin (Sabril; Marion Merrell Dow) licensed in the UK for epilepsy

Zonisamide licensed in Japan and South Korea (Excegran; Dainippon) and then in 2000 relicensed for epilepsy in the USA and Europe in (Zonegran; Elan)

1990 Lamotrigine (Lamictal; Burroughs Wellcome) licensed first in Ireland and a year later in the UK

Oxcarbazepine (Trileptal; Novartis) licensed first in Denmark, then in EU generally in 1999 and in the USA in 2000

1992 First biannual Eilat Conference on New Antiepileptic Drugs held

1993 Felbamate (Felbatol; Carter-Wallace) licensed in the USA, but not in Europe, and then rapidly withdrawn

1994 Gabapentin (Neurontin; Parke-Davis) licensed in the USA and UK

1995 Topiramate (Topamax; Johnson & Johnson) licensed in the UK and subsequently in Europe and USA

Foundation of European Agency for the Evaluation of Medicinal Products (EMEA). Name changed to European Medicines Agency in 2004

1996 Tiagabine (Gabatril; Novo Nordisk) licensed first in France and then widely in Europe and the USA

Cochrane epilepsy group registered in the Cochrane collaboration

1999 Levetiracetam (Keppra; UCB) licensed as a treatment for epilepsy in the USA and in Europe a year later

2004 Pregabalin (Lyrica; Pfizer) licensed in Europe for epilepsy

Buccal midazolam, as midazolam maleate (Epistatus; Special Products) permitted under special license in the UK

2007 Stiripentol (Diacomit; Biocodex) licensed for use in severe myoclonic epilepsy of infancy in Europe

Rufinamide (Inovelon (Europe) and Banzel (USA); Eisai) licensed for use in Lennox–Gastaut syndrome in Europe

2008 Lacosamide (Vimpat; UCB) licensed in Europe, and in the USA in 2009

2010 Retigabine (ezogabine) (Trobalt; Glaxo Smith Kline in Europe, and Potiga; Valeant in USA) licensed 2010 in USA and 2011 in Europe

2011 Buccal midazolam in the form of midazolam hydrochloride (Buccolam; ViroPharma) licensed in Europe under PUMA scheme

2012 Perampanel (Fycompa; Eisai) licensed in Europe and USA in 2012

Other treatments for epilepsy

1981 Revision of the ILAE Classification of Epileptic Seizures approved

1982 Morrell and Whisler reported the first case treated by multiple subpial transection

First investigations of SPECT scanning in epilepsy

Clinical MRI introduced and first large published series of neurological patients, some with epilepsy

1984 MRS studies of epilepsy initiated

1993 Discovery of micro RNAs

1995 First epilepsy gene published

1997 Launch of the Global Campaign Against Epilepsy (entitled *Out of the Shadows*)

Vagal nerve stimulation received a US regulatory approval as a treatment for partial onset epilepsy

2000 First draft of the human genome published

2002 HapMap project launched

2008 RCT of trigeminal nerve stimulation in epilepsy initiated

2010 TMS trial reported favourable results in epilepsy

Publication of SANTE trial (bilateral anterior thalamic stimulation)

EMA approved Medronics Deep Brain Stimulation Therapy for treatment of epilepsy

2011 Publication of the NeuroPace trial (responsive cortical stimulation)

2012 EMA approved NeuroSigma external Trigeminal Nerve Stimulation (eTNS) system in epilepsy

2013 Publication of seizure prediction studies using implanted Neurovista device

NeuroPace RNS stimulator approved by FDA for treatment of epilepsy

Britain, and then as midazolam maleate in a preparation approved by the European Medicines Agency (EMA) under the PUMA (paediatric use marketing authorization) scheme in September 2011, for use in patients under the age of 18 years; in fact this is the only antiepileptic drug ever to be licensed in children but not in adults.

There have been, in addition, a range of further drugs under development. The drugs discussed at the Eilat conferences on New Antiepileptic Drugs are a rough guide to those that were closest to licensing and these are listed in Table 8. Other drugs in earlier clinical trials were listed in various periods between 1992 and 2014 and in Table 9 other additional drugs in early clinical development, listed in the various editions of this book, are given. Although the number of drugs is large, as will be very evident, many do not progress to licensing even though clinical trials have been undertaken.

It is clear that the most important scientific developments in this period have not been in the discovery of these novel drugs, but in the basic science of pharmaceutical medicine. The enormous developments in molecular science in the past three decades are outside the scope of this chapter, but suffice to say that the advances in knowledge about the molecular mechanisms and regulation of brain function and epilepsy are the key to future drug development, and these hold the promise of new drugs specifically targeted at previously unknown molecular processes. This is an exciting prospect, but one not yet realized in clinical practice, or indeed in most drugs currently under clinical investigation (Table 8). In this sense, epilepsy therapeutics is lagging behind therapeutics in other areas such as immunology and oncology. A clinical area in which there has been particular disappointment in that of pharmacogenetics. The promise of individualized 'tailored drug therapy' has been trumpeted, and over-hyped, for the last 15 years, but has singularly failed to materialize. Perhaps this is not surprising given the complexity of cerebral mechanisms, the importance of brain maturation and the inherent limitations of the approach, but it nevertheless is disappointing. This topic too has to date wasted large amounts of money and time, and whether more will be delivered in the future remains to be seen. Currently, the only practical result, in the routine epilepsy clinic, has been the ability to identify patients at increased risk of a Stevens–Johnson reaction (which is a very small risk anyway), in certain populations although there are different genetic bases for different populations (this is an immunological mechanism; cerebral epilepsy mechanisms have remained untouched in any practical sense by pharmacogenetics). This finding resulted in the over-reaction of the US Food and Drug Administration (FDA), and its main consequence in practice has been to limit carbamazepine prescribing to the detriment of most patients, and to drive up costs for very little gain.

One of the striking phenomena of the post-war years, and particularly in the last 50 years, has been the rise in the size, profits and power of the pharmaceutical industry. As a result of the profitability of the pharmaceutical section, drug discovery moved in large part from a university environment to in-house company laboratories, and drug development has become a commercial enterprise kept under conditions of tight secrecy to protect commercial interests. Particularly since the mid-1980s, the value of the antiepileptic drug market has increased dramatically and the total sales of antiepileptic drugs in the USA, for instance, rose from $400 million in 1990 to $3 billion in 2000. This is in part due to increased numbers of treated persons (for reasons that are not entirely clear) and also the greatly increased cost of medication and the use of the drugs in non-epilepsy indications. Despite this, none of the newer expensive antiepileptics have proven to be strikingly more efficacious in controlled clinical trials than the older drugs, nor generally has there been a paradigm shift in side-effect profile, although most (but not all) of the newer drugs have some pharmacokinetic advantages.

The regulatory environment has grown *pari passu* with the power of the pharmaceutical industry. In the USA, for instance, the first major legislation was the Federal Pure Food and Drugs Act, enacted in 1906. This required accurate labelling and was in response to public concern about excessive misbranding and adulteration of food, but this had little practical effect in the field of antiepileptics. The next significant development was the 1938 Food, Drug and Cosmetic Act, framed in response to public anger over the deaths of more than 100 people caused by 'elixir of sulfanilamide'. This required evidence of safety to be submitted to the FDA prior to marketing. Many of the raft of new drugs that were licensed following the discovery of phenytoin were then shown to be quite toxic, and it seems, at least in the field of antiepileptics, that this legal dog had little teeth. Then, in 1962, the Drugs Amendment Act, the Kefauver–Harris Amendment, was signed into law, in response to the thalidomide tragedy in Europe. This totally changed the regulatory environment. For the first time, evidence of efficacy was required as well as safety, and a retrospective programme of evaluation of drugs introduced between 1938 and 1962 was undertaken. The Act also required the disclosure of accurate information about side-effects and efficacy in drug advertising, and also placed on the FDA an obligation to establish guidelines for testing all classes of drugs, including antiepileptics. A new system of licensing was devised by which the FDA required each company to obtain an IND before it was permitted to use the drug in human subjects. Complete chemical and manufacturing information, preclinical screening and animal investigation, including toxicology, teratogenicity and safety, had to be submitted before the IND was granted. Clinical testing was divided into three phases and only after the completion of this battery of studies could a drug be licensed. These new regulations no doubt protected the public from dangerous compounds, but there were also immediate negative consequences. The cost of developing antiepileptic drugs increased greatly because of the huge increase in the number of animals and procedures needed in preclinical testing, and in the complexity and scope of this testing. Large controlled clinical trials were also required, and the immediate effect was a rapid fall-off in the number of drugs being developed.

Carbamazepine and valproate and some benzodiazepine drugs were licensed in Europe for many years before being given a US licence and patients in the USA were therefore disadvantaged. The US epilepsy community became very concerned and, in 1972, the US NINDS set up an Ad Hoc Committee on Anticonvulsant Drugs in conjunction, and with the ILAE and FDA, formulated a procedure in 1973 for design, patient selection and protocols for new drug trials which has been the framework for drug development right up until the present day.

In 1980, the FDA further tightened clinical trial methodology and made randomized controlled trials a necessary prerequisite of licensing. They also made the momentous decision that the new drugs had to demonstrate superiority over a comparator compound rather than equivalence, and so almost all the studies compared the new drug with placebo rather than a conventional therapy. This decision resulted in a lamentable lack of head-to-head randomized controlled trials, and the existing pattern of studies with small numbers of patients in a cross-over design had to be replaced by the early 1990s by the requirement to carry out parallel group studies in increasingly large numbers of patients. Over the past decades, the

laws have been interpreted with mounting stringency, and higher levels of evidence of efficacy and lack of toxicity are required now than even 20 years ago. In the past decade, a further layer of bureaucracy has been added in many countries, which assesses the cost-effectiveness of therapy. Whether, in the light of all these new regulatory hurdles, the balance between protecting the public and stimulating new therapies is appropriate is a matter of opinion but there is a strong sense that the development of AEDs is now being hampered by over-regulation.

Although this survey focuses on drug treatment, a brief note on non-pharmaceutical approaches in this period is in order. There has in the past 30 years been great interest in surgical therapy. This has been fuelled by the advent of CT and particularly MRI, which provides a method of identifying structural defects as the target of resective surgery. The increased sensitivity of MRI has demonstrated lesions such as hippocampal sclerosis, small cavernoma and development disorders which were previously not possible to visualize directly. Other investigatory modalities also (see Section 4) have improved surgical selection. Surgical technique has also improved in the last 50 years, with better anaesthesia and postoperative care, and surgical morbidity has fallen. The technology of surgery has improved, and in relation to epilepsy surgery the two most important developments were the introduction of the operating microscope, in 1967, which has allowed microsurgical techniques to be developed and, more recently, improved computerized stereotactic methods.

However, the theoretical basis of surgery has not changed at all. The fundamental basis of most surgery is the 'resection of epileptic tissue in focal epilepsies' in the hope that this will halt seizures without leaving large cerebral deficits. This is exactly the same basis of surgery that was expounded by Horsley and others in the 1880s. Indeed, the types of operation have also not changed fundamentally in the last 50 years (e.g. temporal lobectomy, lesionectomy, tailored resections, collosotomy, hemispherectomy, awake craniotomy). The non-resective approaches (e.g. cortical stimulation, ablation of pathways) also have a long history stretching back to the early twentieth century, and although technology has changed, the principles and, indeed to a large degree, the outcomes of non-resective operations have not. Nevertheless, in the last 10 years or so, the major focus of surgical research has been on stimulation both invasive and external. The first therapy to gain wide acceptance has been vagal nerve stimulation, on the basis of trials which have been criticized in various ways, and certainly the routine clinical experience of vagal nerve stimulation is less positive than the trials have indicated. More recently, a series of invasive stimulation technologies have been studied; divided into 'scheduled stimulation' (e.g. bilateral stimulation of the anterior thalamus and hippocampal stimulation) and 'responsive stimulation' (e.g. of the cortical epileptic focus or hippocampus). External non-invasive stimulation methods through the trigeminal nerve, and via transmagnetic cranial stimulation, have also been explored. In these areas, it has been possible to perform randomized controlled trials (uniquely in epilepsy surgery) and several systems have been licensed by the EMA and FDA. It must be admitted though, the results of stimulation generally on epilepsy control have been modest.

Much of the current emphasis of surgery is fuelled by economic factors in market-driven medical systems, where surgical activity brings in large monetary reward, rather than on clinical factors. The current reality is that although epilepsy surgery is a fashionable and much-promoted topic, it remains a marginal treatment, unsuitable for the vast majority of patients and with often suboptimal outcomes.

Non-pharmaceutical, non-surgical approaches to treatment (i.e., lifestyle, nutrition, socio-psychological factors, etc.) have been almost totally ignored in orthodox medicine in the post-war years, as the technologies of modern medicine and surgery and of pharmaceutical science have dominated thought. This perhaps is the biggest change in the past 100 years.

The drug treatment in common use in 1996–2014, as reflected in the four editions of this book, are shown in Table 9. As can be seen, one very obvious development in the past 50 years has been the narrowing of treatment options in professional practice to only those drugs that have been assessed in blinded and randomized trials and that have shown superiority over placebo (i.e. have biological action). Patients are often not satisfied with this, and alternative and complementary medicines are widely sought (for the common remedies used see Chapter 22) as well as other physical non-medicinal approaches. Furthermore, orthodox medicine has removed its focus from consideration of diet, hygiene and modes of living which were so much part of conventional therapy, and which were a large component of the medical consultation at least until the period of the Second World War. It is interesting to speculate on the degree to which the much more evidence-based approach of today has improved overall outcome (there is little synoptical study of this) or alleviated suffering. Therapy has undoubtedly improved, but the focus on drugs and surgery, to a significant extent commercially fuelled, has tended to protocolize medicine and to dehumanize therapy. What has been gained on one hand might have been lost on the other, and I suspect the picture is more complicated than often believed.

Acknowledgement

Table 1 Non-bromide medicinal products used in the treatment of epilepsy 1857–1910.

Plant-based (herbals)	Aconite (wolf's bane), adonis vernalis, bryonia, cannabis, calabar bean, conium (hemlock), cotyledon umbilicus (penny wort), ergot, digitalis, gelseminum sempervirens (yellow jasmine), hydrastine, indigo, mistletoe, opium (and codeia), picrotoxin (from connulus indicus), piscidia erthrina (fishfuddle) rue, santonin (artemisia), selenum (marsh parsley), simulo (hyssop), strophanthus, strychnine, valerian. Extracts of the solanaceae (nightshade) family were also widely used: atropine, belladonna, hyoscine, stromonium
Animal-based extracts	Bufo rana crotalin (rattlesnake venom), curare, thyroidin, toxins and antiserum
Simple chemicals	amylene hydrate, borax, caustium, coal tar (acetanilide, phenacetin, acetophenetidin), chinolin (quinoline), copper, copper sulphate, chloral hydrate, chloralamide, chloretone, iron, lead, nitroglycerine, osmic acid, pepto-mangan, potassium iodide, resorcin, sodium eosinate, silver nitrate, sulphonal, urethane, zinc (oxide, sulphate, acetate, valerianate, lactate, nitrate)

Source: Lists derived from [1,5,6,7,8,9,19].
Most of the above were used for chronic therapy. For the treatment of acute seizures in the nineteenth century, various compounds were widely used such as amyl nitrite, atropine, chloral, chloroform, ether, nitroglycerine, paraldehyde. Others less frequently recommended included some by inhalation: alcohol, ammonia, assafoetida (inhalation or enema), camphor, curare (by injection), hydrocyanic acid, lavender, musk, turpentine, veratrum (American hellebore).

Table 2 Antiepileptic drugs listed by Gowers in 1881 and 1901.

Drugs of 'definite benefit'	Drugs of 'doubtful value'
Bromide (ammonium, potassium, sodium, lithium, strontium)	Camphor
Digitalis	Aconite
Belladonna	Hydrocyanic acid
Atropine	Iodide of potassium
Stramonium	Mistletoe
Cannabis indica	Turpentine
Gelsemium sempervirens	Cocculus indicus (picrotoxin)
Opium	Choral
Nitroglyerine	Amylene hydrate
Zinc	Nitrate of silver
Borax (sodium biborate)	Sulphate of copper
Iron	Benzoate of soda
Hyoscine	Piscidia erthrina
Strophanthus	Codeia
(Of this list, bromide was seen by Gowers as the primary treatment,	Calabar bean
and all the others 'adjuncts')	Ergot
	Sclerotic acid
	Nitrite of amyl
	Bromide of aluminium, nickel, camphor, rubidium and ammonium, iodine, chorine, bromaline (bromine and formaldehyde derivatives), bromapin (bromine and sesame oil), hydrobromic acid
	Osmic acid
	Curare
	Hydrastin
	Chinolin
	Resorcin
	Antipyrine
	Acetanilide
	Thyroidin

Source: Data from Gowers 1881 [7].
Gowers also notes that zinc and opium were generally of not much use but good in hysteroid convulsions; digitalis, cannabis, belladonna, atropine were thought useful only in combination with bromide.

Table 3 Therapy in 1907: drugs recommended by William Aldren Turner.

Drugs of definite benefit	Drugs of limited benefit	Drugs of no special benefit
Bromide — sodium and potassium primarily or Gélineau's formula	Zinc salts (oxide, valerianate, lactate)	Monobromate of camphor
Other synthetic formulations (e.g. bromipin, bromaline, bromocarpine) or salts (e.g. strontium or ammonium) had, in Turner's view, little advantage	Opium	Eosinate of sodium
	Strychnine	Chloretone
	Chloride of calcium	Antipyrin
Chloral hydrate	Atropine	Atropine
Borax	Glycerophosphates[a]	Intestinal antiseptics[b]
Belladonna		

Source: Data from Turner 1907 [8].

For status epilepticus, Turner recommended chloral, chloroform, morphia and bromides (including intrathecal bromide solutions).

[a] For neurasthenic symptoms.

[b] In view of the theories of autointoxication (which Turner found unconvincing).

Other drugs that Turner found of no value included sulpho-carbonate of soda, salol (phenyl salicylate), beta naphthol, salicylate of bismuth and 'a host of other remedies of this character'.

Table 4 Drugs listed in the treatment of epilepsy by SAK Wilson in 1940.[*]

Drugs of definite benefit
Bromide (in any of the following salts: sodium, potassium, ammonium, lithium, calcium, calcium bromine galactogluconate)
Bromide combinations
Phenobarbitone (Luminal)
N methylethylphenylmalonyl urea (Prominal)
Borax
Belladonna (sometimes with bromide or bromide and caffeine)
Nitroglycerine (sometimes with strychnine and bromide)
Dialacetin (a mixture of the hypnotic allobarbital (Dial) with allylparacetaminophenol)

Source: Data from Wilson 1940 [11].

*Although Wilson [11] was published in 1940, this was after his death and the draft manuscript was completed (in 1937), edited and published posthumously.

Table 5 The drugs used in the treatment of epilepsy in 1955, derived from the international list of antiepileptic drugs published in *Epilepsia*.

Chemical composition	Common or trade name
Barbiturates	
Phenylethyl barbituric acid	Gardenal
Phenylethyl malonylurea	Luminal, Phenobarbital, Phenobarbitone
Methylphenyl barbituric acid	Mephebarbital, Rutonal
Methylphenylethyl barbituric acid	Isonal, Meberal, Prominal
Methyldiethyl barbituric acid	Gemonil
Combinations with barbiturate	
Phenylethyl barbituric acid, belladonna and caffeine	Alepsal
Phenylethyl barbituric acid and amphetamine	Ortenal
Oxazolidine diones	
Trimethyl oxazolidine dione	Absentol, Epidione, Minoaleviatin, Petilep, Trimethadione, Tridione
Dimethylethyl oxazolidine dione	Paramethadione, Paradione
Diphenyl oxazolidine dione	Epidon
Allylmethyl oxazolidine dione	Malidone
Hydantoins	
Diphenyl hydantoin (or diphenyl hydantoin sodium)	Alleviatin, Alepsin, Antipil, Antisacer, Comitiona, Convulsin, Dihydan, Dilantin, Diphentoin, Ditoinate, Epamin, Epanutin, Eptoin, Phenytoine, Solantyl
Methyldiphenyl hydantoin	Melantoine
Methylphenylethyl hydantoin	Mesantoin, Phenantoin, Sedantoinal
Methyldibromophenylethyl hydantoin	Anirrit
Dimethyldithio hydantoin	Thiomedan
Sodium phenylthienyl hydantoin	Thiantoin, Phethenylate
Methylphenyl hydantoin	Nuarone
Combinations with hydantoins	
Diphenyl hydantoin and phenobarbital	Hydantoinal, comitoina compound
Diphenyl hydantoin, phenobarbital and caffeine	Antisacer compound, Apilep
Diphenyl hydantoin, phenobarbital and desoxyephedrine	Isosolantyl, Phelantin
Methylphenylethylhydantoin and phenobarbital	Hydantal
Diphenyl hydantoin and methylphenylethyl barbituric acid	Comital, Mebaroin
Diphenyl hydantoin, methylphenylethyl barbituric acid and phenobarbital	Comital L
Other types	
Phenylacetylurea	Epiclase, Fenilep, Phenacemide, Phenurone
Phenylethylhexahydropyrimidine dione	Mysoline, Primidone
Benzchlorpropamide	Hibicon, Posedrine
Methylalphaphenyl succinimide	Lifene, Milontin
Acetazolamide	Diamox
Alkaline borotartrates	Several preparations
Glutamic acid (or glutamic acid-HCl)	Acidulin, Glutan-HCl, Glutamicol
Bromides	Large numbers of preparations (in three categories: alkaline bromides and alkaline earths: polybromide; organic bromides; bromide in combination with other agents)

Source: *Epilepsia* 1955; 4: 121–123. Reproduced with permission from John Wiley & Sons.

Table 6 Lennox's 'therapeutic arsenal': drugs in common use in the USA around 1960.

Non-commercial official name	Patented trade name
Grand mal and psychomotor seizures	
Bromides	Bromides
Phenobarbital[a]	Luminal
Methobarbital	Mebaral
Diphenylhydantoin[a]	Dilantin
Mesantoin	Mesantoin
Ethotoin	Peganone
Primidone[a]	Mysoline
Phenacemide	Phenurone
Methsuximide[a]	Celontin
Acetazolamide[b]	Diamox
Petit mal	
Trimethadione[b]	Tridione
Paramethadione[a]	Paradione
Phensuximide[a]	Milontin
Ethylmethylsuccinimide	Zarontin
Quinacrine hydrochloride	Atabrine
Metharbital	Gemonil

Source: From Lennox 1960 [16]. Reproduced by permission of Wolters Kluwer Health.
[a]Drugs of initial choice.
[b]Drugs of second choice.
Phenurone and Diamox were noted to be often effective against petit mal as well, and phensuximide to be often effective against grand mal.

Table 7 Drug treatments reported to be used in status epilepticus 1857–1973.

ACTH	Hyoscine hydrobromate
Aldosterone	Lignocaine
Amyl nitrate	Morphia/apomorphine
Amylene hydrate	Oxygen inhalation
Amyline choral	Paraldehyde
Amylobarbital	Pentobarbital
Atropine sulphate	Phenobarbital
Bromide of potassium	Phenytoin
Bromide salts (various) intrathecal	Procaine
Camphor (subcutaneous)	Quinine sulphate
Chlordiazepoxide	Scopolamine (hydodermic)
Chlomethiazole	Sinapismes
Chloral hydrate	Strophanthus
Chloroform	Suxamethonium
Clonazepam	Tribromethanol
Diazepam	Tridione
Diethyl barbituric acid	D-Tubocuraine
Digitalis	Urea
Donath's solution	

Source: Data from Neligan and Shorvon 2009 [10].
In addition to these drugs, physical treatments were also strongly recommended including: cold douches or baths, darkened room, rest and quiet, lumbar puncture/CSF drainage, multiple enemata and irrigation of the bowel, saline infusions and venesection.

Table 8 Drugs in clinical trial development (presented at the biannual Eilat Conference on New Antiepileptic Drugs 1992–2014).

Eilat II, 1992	Eilat II, 1994	Eilat III, 1996	Eilat IV, 1998	Eilat V, 2000	Eilat VI, 2002
Flunarizine	CGP33 101 (rufinamide)	Clobazam	534U87 (a lamotrigine derivative)	AWD 131–138 (imepitoin)	Carabersat (SB-204269)
Felbamate	Desinamide	Dezinamide	ADCI	DP-VPA (DP16)	Conantokin-G (CGX-1007)
Gabapentin	Fluzinamide	Felbamate	AWD 131–138 (imepitoin)	Harkeroside (lacosamide: SPM 92 7)[e]	Fluorofelbamate
Lamotrigine	Gabapentin	Fosphenytoin	DP16 (DP-VPA)	LY 300164 (talampanel)	Lacosamide (SPM 927)
Oxcarbazpine	Lamotrigine	Gabapentin	Ganaxolone (CCD 1042)	NPS 1776	Pregabalin
Remacemide hydrochloride	Losigamone[a]	Lamotrigine	Levetiracetam (UCB LO59)	NW-1015	Retigabine
Stiripentol	Oxcarbazepine	Levetiracetam (UCB L059)	Losigamone	Pregabalin (CI-1008)	Safinamide
Tiagabine	Remacemide hydrochloride	Oxcarbazepine	Pregabalin (CI-1008; isobutyl GABA)	Remacemide	SPD421 (DP-VPA)
Topiramate	Stiripentol	Remacemide hydrocholride	Remacemide hydrochloride	Retigabine (D-23129)	Talampanel
Vigabatrin	Tiagabine	Retigabine (D-23129)	Retigabine (D-29129)	Rufinamide	Valrocemide (TV 1901)
	Topiramate	Ralitoline	Rufinamide (CGP 33101)	Valrocemide (TV 1901)	
	UCB L059 (levetiracetam)	Rufinamide (CGP 33101)	Soretolide (D2916)		
	Vigabatrin	Tiagabine	Valrocemide (TV 1901)		
		Valrocemide (TV 1901O)			

Source: Data from Eilat Conferences [21,22,23,24,25,26,27,28,29,30].

Drugs highlighted in green are those that were subsequently licensed.

[a]Losigamone was mentioned in programme but not the publication.

[b]RWJ-333369 was mentioned in programme but not the publication.

[c]NS1209 was mentioned in the publication but not the programme.

[d]Section on 'Emergency therapy' for drugs used in the first time; details from programme, not yet published.

[e]Harkeroside was sold on in various steps eventually to UCB and renamed lacosamide.

[f]Imepitoin is licensed for use in veterinary medicine for dogs.

Eilat II, 1992	Eilat II, 1994	Eilat III, 1996	Eilat IV, 1998	Eilat V, 2000	Eilat VI, 2002

Eilat VII, 2004	Eilat VIII, 2006	Eilat IX, 2008	Eilat X, 2010	Eilat XI, 2012	Eilat XII, 2014[d]
Atipamezole	Brivaracetam (UCB 34714)	2-Deoxy-glucose	D-deoxy-glucose	D-deoxy-glucose	D-deoxy-glucose
BIA 2-093 (eslicarbazepine acetate)	Eslicarbazepine acetate (BIA 2-093)	Brivaracetam (UCB 34714)	Brivaracetam	Brivaracetam	Adenosine-releasing silk
Fluorofelbamate	Fluorofebamate	Carisbamate (RWJ-333369)	Carisbamate	Ganaxolone	Allopregnanolone SAGE547)
NPS 1776	Ganaxolene	CSC700-008	Ganaxolone	ICA-105665	AMP-X-0079
Pregabalin	Huperzine A	Eslicarbazepine acetate (BIA 2-093)	Huperzine A	Imepitoin[f]	BGG492
Retigabine	JZP-4	Fluorofebamate	ICA-105665	NAX-810-2	Brivaracetam
RWJ-333369 (carisbamate)[b]	Lacosamide	Ganaxolene	NAX-5055	Perampanel	Bumetamide
Safinamide	NS1209[c]	Huperzine	Perampanel	Propylisopropyl acetamide (PID)	Butylpropylacetamide (SPD)
SPM 927 (lacosamide)	Propylisopropyl acetamide (PID)	JZP-4	Propylisopropyl acetamide (PID)	Tonabersat	Cannabidiol
Stiripentol	Retigabine	Lacosamide (SPM 927)	Retigabine	VK-765	Cannabidivarin (GWP 420006)
Talampanel	Rufinamide	NAX 5055	T2007 (sodium 5,5-diphenylbarbiturate)	Valnoctamide (VCD) and sec-Butylpropylacetamide (SPD)	Everolimus
UCB 34714 (brivaracetam)	RWJ-333369 (carisbamate)	Propylisopropyl acetamide (PID)	Valnoctamide (VCD)	YKP3089	Ganaxolone
Valrocemide	Seletracetam (UCB 44212)	Retigabine	YKP3089		Huperzine A
	Stiripentol	T2000			Imepitoin[f]
	Talampanel	Tonabersat			Micocycline
	Valrocemide	Valrocemide			NAX-810-2
		Valnoctamide			Pitolisant (tiprolisant)
		YKP3089			Propofol hemisuccinate
					Propylisopropyl acetamide (PID)
					PRX 0023 (naluzotan)
					SAGE-217
					Valnoctamide (VCD)
					VLB-01
					YKP3089

Table 9 Drugs used in the treatment of epilepsy 1996–2014 as taken from the four editions of the *Treatment of Epilepsy*.

First edition, 1996	Second edition, 2004	Third edition, 2009	Fourth edition
Clobazam	Acetazolamide	Acetazolamide	Acetazolamide
Clonazepam	Carbamazepine	ACTH and corticosteroids	ACTH and corticosteroids
Other benzodiazpines (clorazepate, diazepam, lorazepam, midazolam, nitrazepam)	Clobazam	Benzodiazepines used primarily for chronic treatment (clobazam, clonazepam, clorazepate, nitrazepam)	Benzodiazepines used in epilepsy (clobazam, clonazepam, clorazepate, diazepam, lorazepam, midazolam, nitrazepam)
Carbamazepine and oxcarbazepine	Clonazepam	Benzodiazpines used primarily for emergency treatment (diazepam, lorazepam, midazolam)	Brivaracetam[a]
Ethosuximide and methsuximide	Short-acting and other benzodiazepines (diazepam, lorazepam, midazolam, clorazepate, nitrazepam)	Brivaracetam[a]	Carbamazepine
Felbamate	Ethosuximide	Carisbamate[a]	Eslicarbazapine acetate
Gabapentin	Felbamate	Carbamazepine	Ethosuximide
Lamotrigine	Fosphenytoin	Eslicarbazapine acetate[a]	Felbamate
Phenobarbitone	Gabapentin	Ethosuximide	Gabapentin
Phenytoin	Lamotrigine	Felbamate	Lacosamide
Piracetam	Levetiracetam	Gabapentin	Lamotrigine
Topiramate	Oxcarbazepine	Lacosamide	Levetiracetam
Valproate	Phenobarbital, primidone and other barbiturates (metharbital, methylphenobarbital, barbexaclone)	Lamotrigine	Oxcarbazepine
Vigabatrin	Phenytoin	Levetiracetam	Perampanel
Other drugs used in the treatment of epilepsy (acetazolamide, ACTH, allopurinol, ethotoin, bromides, mephenytoin, paraldehyde, phenacemide, trimethadione)	Piracetam	Oxcarbazepine	Phenobarbital, primidone and other barbiturates
	Pregabalin	Phenobarbital, primidone and other barbiturates	Phenytoin
	Rufinamide	Phenytoin	Piracetam
	Tiagabine	Piracetam	Pregabalin
	Topiramate	Pregabalin	Retigabine
	Valproate	Retigabine[a]	Rufinamide
	Vigabatrin	Rufinamide	Stiripentol
	Zonisamide	Stiripentol	Tiagabine
	Other drugs more rarely used in the treatment of epilepsy (ACTH, allopurinol, bromide, ethotoin, mephenytoin, paraldehyde, phenacemide, trimethadione)	Tiagabine	Topiramate
		Topiramate	Valproate
		Valproate	Vigabatrin
		Vigabatrin	Zonisamide
		Zonisamide	Other drugs rarely used (bromide, lidocaine, methsuximide, paraldehyde, sulthiame)
		Other drugs rarely used (allopurinol, bromide, ethotoin, furosemide, mephenytoin, phenacemide, trimethadione — oral use)	

Source: Lists derived from Shorvon [1,2,3] and the current book.

In addition to the above licensed drugs, each edition of the book has listed drugs in early clinical development:

1st edition: eterobarb, levetiracetam, losigamone, ralitoline, remacemide, stiripentol, taltrimide, tiagabine, zonisamide.

2nd edition: AWD 131-138, carabersat (SB-204269), conantokin-G (CGX-1007), ganaxolone, harkoseride (SPM 927; ADD 234037), NPS 1776, retigabine (D-23129), safinamide (NW-1015; PNU-151774E). SPD421 (DP16; DP-VPA). talampanel (LY300164; GIKY 53773), valrocemide (TV 1901).

3rd edition: 2-deoxy-o-glucose, fluorofelbamate, ganaxolone, JZP-4, safinamide, seletracetam, T2000, talampanel, tonabersat, valrocemide, YKP3089.

4th edition: allopregnanolone (SAGE-547), cannabinoids, 2-deoxy-D-glucose, everolimus, ganaxolone, huperzine A (INS-001), NAX 810-2, pitolisant, PRX00023 (naluzotan), selurampanel, tonabersat, YKP3089.

[a]Drug not licensed but in late-stage clinical development.

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