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CRITICAL REVIEW

The right and the wrong with epilepsy and her science

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Summary

This is a commentary and an opinion paper attempting a critical reassessment of the methods and practices of epilepsy research as we see it. The enormous progress in the field of epilepsy in recent years is a cause of celebration. Advances have been made on most fronts, and the position of patients with epilepsy in society has greatly improved. However, there have also been culs-de-sac and dead ends of modern science and clinical practice which are also intriguing. It may be true that we can learn more from our mistakes than from our successes. In this opinion paper, we have listed some of the successes and some of the failures of past epilepsy practice, and also areas of current practice and theory which we feel are likely to prove mistaken. The underlying reasons for misdirected practices and theories include, in our view, the influence of fashion, bad science, and the bureaucracies of practice and academic medicine. As a result, some findings are far from objective. Recognition is the first step to remediation, and hopefully future research will minimize some of the pitfalls mentioned in this article and bring the "End of Epilepsy," as defined and predicted by Oswei Temkin, closer than it is today.

KEY WORDS: Epilepsy research, Scientific progress, End of epilepsy?, Anatomy of errors, Clinical practice, Bureaucracies of epilepsy, Dark side of epilepsy.

When we were invited to write this article for *Epilepsia Open,* the new International League Against Epilepsy (ILAE) journal, we felt apprehensive. We have just completed a book entitled *The End of Epilepsy?* which is an account and critique of the history of epilepsy since 1860.[1] In this, we outlined what we believe are landmarks in the tremendous progress that epilepsy has made in these 150 years and the negative aspects of this history. The title of our book is based on the final chapter of Oswei Temkin's definitive text on the history of epilepsy,[2] in which he wondered whether the advance of science and of culture, in the post-Jackson era, would mean that epilepsy would cease to be "a paradigm of the suffering of both body and soul in disease."

The positives certainly greatly outweigh the negatives, and the result is that epilepsy now holds a privileged position in the pantheon of neurology. Epilepsy is, at least in societies that offer their citizens sufficient health care resources, the most treatable of the severe chronic brain diseases. Around 80% of all patients will become and remain free of seizures after a course of usually well-tolerated drugs, as a series of long-term studies have shown[3] (Fig. 1).

Admittedly, not all patients become completely seizure free, but of those who do not, many have fewer or less-severe seizures during continued treatment. Emergency care is readily available in kindergartens, in schools, and at work and elsewhere. Compare these good outcomes with the outcomes of people with stroke, encephalitis, brain tumors, traumatic brain injury, Parkinson's disease, or Alzheimer's dementia, which are all common severe brain diseases, and which have less satisfactory treatment and a poorer chance of recovery or longevity. It is clear that, over the period reviewed in the book, enormous advances have been made. Identifying which have been the most important steps is obviously to an extent subjective. In Table 1, we list

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Key Points

- The anatomy of the progress in epilepsy in the past century
- The history of errors in the practice and the science of epilepsy
- The change in public attitude and societal practice in the last century
- The role of economics, fashion, and bureaucracies in epilepsy and its research

medical therapeutic and investigatory advances in the 20th and 21st centuries that we believe have had the most impact for treatment.

Our purpose is not to provide a fully referenced medical review, but a critical commentary on the methods and practices of current and past epilepsy research. We have only sparsely added key references for what we think are the most important facts mentioned. The purpose of critical reassessment is not to negate research and attempts to progress but to redirect them in possibly more useful directions.

Another point, worth stressing, is that social changes have also been very impressive, and indeed in our book we suggest—perhaps to some, provocatively—that the achievements on the social side have in fact been more important than those in medicine. It is these social aspects that Temkin emphasized, and they are as important a component as the medical advances are in "ending the falling sickness." Society now has a more sympathetic understanding of the plight of patients with severe epilepsy; there is less stigma, better integration, better opportunities, better social care, including rehabilitation, and far fewer social restrictions and prejudices. These societal aspects and attitudes have improved but are certainly not fully resolved, and they still have a daily impact on people with epilepsy that should not be underestimated.

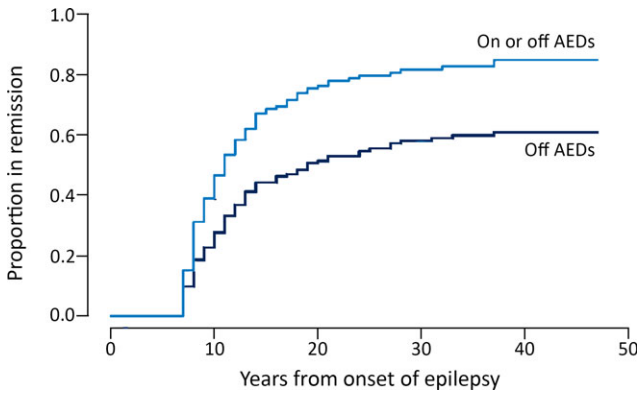

Figure 1.
Complete seizure remission in epilepsy. About 60% of people with new-onset epilepsy enter a remission of at least 5 years after stopping AEDs. Roughly 80% enter a remission of at least 5 years on or off AEDs. Unfortunately, the 20% with persistent seizures and often additional brain disease that is responsible for the epilepsy have created the public image of an incurable condition (personal communication: Matti Sillanpää and Maiju Saarinen).
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However, in writing our book, we also came to realize that many medical theories and practices strongly held in the past have lost much of their appeal in later years and have become discredited. These were furthermore not all "prescientific" topics, but in fact many were made in the name of science. Illustrative examples of such theories and practices, which were widely accepted during some periods of time in the last 100 years but then were much less appreciated by later generations, are shown in Table 2.

Today's Theories and Practices Which May Not Withstand the Test of Time

It is also clear that, even in our scientific era, we are not immune to erroneous theories or practices and that inevitably areas of our contemporary practice will be proved incorrect in future decades. We have listed 10 theories or practices that are, in our view, good candidates for being rejected as erroneous in the future (Table 3). Of course, this is a speculative list, and illustrative only, and certainly not comprehensive; notwithstanding these cautions, our outline justification for inclusion in the list is as follows.

Current drug discovery

Many drugs have been and continue to be based on physicochemical manipulation of current drug structure, often with the primary goal of maintaining patent protection and commercial advantage. These manipulations result largely in "me-too" drugs with similar efficacy rather than in a fundamental change to much-needed, substantially more effective or better-tolerated drugs compared with current medications.[4,5] A much more promising method, currently gaining momentum, is to design drugs to modify a molecular target presumed to be involved in seizure generation.[4,5] Such target-based strategies offer the potential for more fundamental advance than simply manipulating the structure of existing drugs. However, in practice, there have been some notable problems. Target-based design depends on the validity of the target. Theories of seizure generation have often been shown to be overly simplistic at best or completely false at worse. It has also been clear that, to date at least, drugs designed to act at one simple target have not proved more useful in clinical practice. Finally, the targets have often been determined after the antiseizure effect of a drug has been noticed. In practice, most current drugs are discovered by screening and their mechanisms identified post hoc. It is

Table 1. Some notable steps in the investigation and treatment of epilepsy, 1911–2013

1911	Fasting noted to improve seizure control, leading to the ketogenic diet
1912	The effect of phenobarbital on epilepsy reported
1918	Air ventriculography introduced into clinical practice
1921	First trial of the ketogenic diet
1923	First hemispherectomy for epilepsy
1926	IV phenobarbital used in status epilepticus
	Cerebral angiography introduced into clinical practice
1929	First human electroencephalogram published
1935	First intraoperative electrocardiogram using an EEG published
1936	First clinical EEG laboratory established
1938	First reports of the use of phenytoin
1940	First corpus callosectomy for epilepsy reported
1941	Acetazolamide introduced into clinical practice for epilepsy
1948	First temporal lobectomy with removal of the mesial structures
1953	First en bloc anterior temporal lobectomy
1954	Primidone introduced into clinical practice
1956	IV phenytoin used in status epilepticus
1957	Stereotactic atlas introduced for use in epilepsy
	Operating microscope introduced into practice
1958	Ethosuximide introduced into clinical practice
1962	Depth EEG introduced into clinical practice
1963	Benzodiazepines (diazepam, chlordiazepoxide) introduced into clinical practice
	IV diazepam used in status epilepticus
	Acetazolamide introduced into clinical practice for epilepsy
1965	Carbamazepine introduced into clinical practice for epilepsy
1967	Valproate approved for use in clinical practice
1968	Clonazepam approved for use in clinical practice
	Gamma knife used in clinical practice
1972	CT introduced into clinical practice for epilepsy
1975	Clobazam approved for use in clinical practice
1978	Piracetam approved for use in clinical practice
	Antiepileptic drug monotherapy first postulated
	PET scanning introduced into clinical practice for epilepsy
1982	Multiple subpial transection introduced into clinical practice
	SPECT introduced into clinical practice for epilepsy
	MRI introduced into clinical practice for epilepsy
1984	MRS introduced into clinical practice for epilepsy
	Linac-based neurosurgery introduced
1989	A range of new drugs, licensed for clinical use over the next 25 years, based on increasingly strict regulatory framework and data from randomized clinical trials: vigabatrin (1989), zonisamide (1989), lamotrigine (1990), oxcarbazepine (1990), felbamate (1993), gabapentin (1994), topiramate (1995), levetiracetam (1999), pregabalin (2004), stiripentol (2007), rufinamide (2007), lacosamide (2008), retigabine (2010), perampanel (2012)
1995	First "epilepsy gene" discovered and the beginning of genetic investigation
1996	Cochrane epilepsy group registered in the Cochrane collaboration
1997	Vagal nerve stimulation introduced into clinical practice for epilepsy
2004	Buccal midazolam introduced into clinical practice for epilepsy
2008	RCT of trigeminal nerve stimulation in epilepsy initiated
2010	TMS trial reported favorable results in epilepsy
	Deep-brain stimulation therapy for treatment of epilepsy
2011	Buccal midazolam licensed in Europe under PUMA scheme
	Responsive cortical stimulation introduced into clinical practice for epilepsy
2012	eTNS system introduced into clinical practice for epilepsy
2013	Closed-loop deep-brain stimulator introduced into clinical practice for epilepsy

CT, computed tomography; EEG, electroencephalography; eTNS, external trigeminal nerve stimulation; Linac, linear accelerator; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; PUMA, paediatric-use marketing authorisation; RCT, randomized controlled trial; SPECT, single-photon emission computed tomography; TMS, transcranial magnetic stimulation.

reasonable to expect that the discovery of specific targets makes precision research and medicine in epilepsy possible as opposed to relying on a limited armamentarium of mostly acute-seizure mass screening tests in a nonspecific way as we often do now. Another important issue is that our current drugs are "antiseizure," not "antiepilepsy," medications, and there has been no progress in finding medications that prevent epileptogenesis.

Table 2. Areas of theory widely held or practices widely accepted at some time in the last century that are now discredited or fallen out of favor

Theories of pathogenesis and causation of epilepsy	Discredited theories/practices that were widely held/accepted: • Genetic theories of inherited degenerative trait suggesting that there are families in whom a wide variety of neurological disorders are inherited together and which lead to increasing degeneration over generations • Autointoxication suggesting that epilepsy is due to toxins from, for instance, infection, dental decay, or fermentation from gastrointestinal bacteria • Reflex causes of epilepsy suggesting seizures are caused by sensory-motor triggers, pain in limbs, pathology in ear or nose, or genital stimulation • Psychoanalytical theories of epilepsy suggesting that epilepsy is the result of egocentricity, supersensitivity, emotional poverty, or an inherent defect of adaptability to normal life, and the epileptic attack as a regression to an infantile mentality • Vascular theories of epilepsy suggesting epilepsy is due to vascular congestion or insufficiency
Clinical theory	Epileptic personality traits, such as viscosity, adhesiveness, circumlocutory, aggressivity, enechetic, ixoid, glischroid, mental obliquity
Drug treatment	Drugs now rarely used or abandoned as either too toxic or ineffective: mesantoin, phenacemide, trimethadione, paramethodione, quinacrine hydrochloride, methsuximide, ethotoin, phensuximide, progabide, felbamate, tiagabine, vigabatrin, retigabine
Surgical treatment	Surgical operations previously widely used and now abandoned as ineffective: • *Related to theories of autointoxication:* colectomy, nasal polypectomy, adenoidectomy, removal of teeth • *Related to theories of sexual or hormonal disturbance:* castration, hysterectomy, oophorectomy, adrenalectomy • *Related to theories of reflex causation:* treatment of disease of the ears or nasopharynx, ophthalmic operations, operations on eye muscles, the removal of tight prepuce, resection of peripheral nerve lesions • *Related to vascular theories:* carotid artery occlusion, bilateral vertebral artery occlusion, cervical sympathectomy
Other treatment	Treatments recommended but for which there is very little evidence: • Diets (except ketogenic diet) • Rest • Dyes (such as brilliant red) • Lifestyle changes such as open-air work, quiet environment, lack of sexual activity
Prevention of epilepsy	Eugenics

Table 3. Ten current areas of theory and practice that are candidates for being rejected or revised in the future

Current approaches to drug discovery
Current animal screening methods
Clinical trial methodology
Overinvestigation and overdiagnosis
Theory that the failure of response to a first and second AED implies drug resistance
Drug resistance is a result of simple variants in drug transporter or target genes
Pharmacogenomics is making a big impact on epilepsy
Surgical resection removes the "epileptic focus"
Surgical procedures (such as multiple subpial transection, corpus callosotomy, some types of extracortical resection, cortical stimulation)
Postulation that the prognosis for seizure control has not been improved by the introduction of new AEDs

Animal screening tests

The common screening tests used for drug screening at the Antiepileptic Drug Development (ADD) program and related programs have a number of significant drawbacks. First, and most important, most models are acute-seizure models that test the antiseizure potential of a drug rather than its antiepilepsy potential (for instance, the maximal electroshock seizure [MES] and pentylenetetrazole [PTZ] seizure tests). Acute seizures induced by convulsants such as in MES and PTZ experiments do not mirror epilepsy because they are seldom provoked and do not occur in "normal," nonepileptic brains. Screening drugs using the

small number of current seizure models is also a process that inevitably identifies me-too drugs and that will probably fail to identify drugs with completely novel antiepilepsy effects. More recently, however, recognizing the limitations of earlier testing methods, the ADD program has been revised and renamed Epilepsy Therapy Screening Project (ETSP). Newer and more laborious models in animals with chronic spontaneous seizures are increasingly used by the ETSP, industry, and academic groups for screening purposes. These models test different actions, but still old-fashioned screening predominates, at least for initial mass screening. We believe fresh approaches are needed.

Clinical trials

Current trial designs are also compromised in a number of important ways, of which we sketch out some briefly here. First, although all trials rely on changes in seizure frequency (the seizure diary) as an outcome parameter, unfortunately this is a most inaccurate measure. In a study by Bonn in which the patients' diaries were compared to video electroencephalogram (EEG) telemetry, patients recorded only 44% of partial seizures, and even major seizures were missed, as were four out of five seizures at night.[6] In a study using long-term intracranial monitoring, 8 out of the 11 patients studied underestimated the real seizure rate by at least threefold.[7] One patient, who had 126 seizures recorded per month, considered none to have occurred, and another recorded a monthly seizure rate of 11 per month when in fact the true figure was 102 per month. Some improvements have been made, and small electronic wristband devices for detecting seizures and increasing the accuracy of seizure counts might be used in future trials, but these are not a complete solution. A second fundamental problem is that drugs are compared to placebo rather than to each other. Although this may allow short-term biological effects to be recognized, such studies provide little information to the physician who wishes to know the drugs' relative value. Placebo control is now also questioned from an ethical point of view when trials delay therapy and when the delay increases the risk of sudden unexpected death in epilepsy (SUDEP) or other adverse consequences.[8–10] Most trials have been of adjunctive therapy, whereas the clearest assessment of any drug would be in monotherapy, but monotherapy trials have significant ethical and methodological defects. The current requirement to license drugs separately as monotherapy or as adjunctive therapy also makes no scientific sense.[11] Another concern is that controlled trials generate results of low clinical value, where a positive outcome is usually defined as a 50% response rate, which in clinical practice would often be considered as a treatment failure. One reason for relying on a 50% seizure reduction is that current drugs cannot achieve better seizure reduction in sufficiently high numbers in formerly drug-resistant patients, which is needed for statistical evaluation. More effective drugs of the future may be able to achieve clinically more meaningful 75% or 100% seizure reductions in larger numbers of patients. Long-term retention studies after clinical trials also swamp the literature, but these almost always give inflated treatment estimates owing to progressive enrichment of the population (i.e., the inclusion of only those responding), regression to the mean, and changes in concomitant therapy. Of course, a regulatory clinical trial is not just a scholarly affair but a global, multibillion-dollar business enterprise. A variety of statistical and other problems, which are discussed below, have also arisen. Where enormous sums of money are at stake, ethical problems relating to the methodology, recording of results, analysis and interpretation of results, and marketing and communication can occur; and misdemeanors at all levels may occur.

Overinvestigation and overdiagnosis

In clinical practice, overinvestigation is common and wasteful, and it carries the risk of misdiagnosis.[12] Misinterpretation of EEG readings by nonepilepsy specialists and subsequent misdiagnosis of epilepsy is a case in point. The misdiagnosis of epilepsy is often unquestionably responsible for great human suffering. Misdiagnosis rates of epilepsy have been estimated to be around 30%, and this is the result of overinterpretation of clinical signs and misreading or misapplication of EEG findings, often by nonspecialists.[12] The multimedia approach to surgical investigation is another example of a wasteful protocol if not used properly. In a similar vein, the overapplication of advanced imaging carries the risk of nonspecialists diagnosing minor variations as pathological that are in fact incidental. Such overdiagnosis is also not necessarily misdiagnosis, but incidental or unimportant findings can lead to personal, financial, and social disadvantage. What is really needed in the application of all investigatory modalities is clear and concise health technology assessment, which balances the advantages and drawbacks of tests in different clinical settings.

Failure of response to a first and second AED implies drug resistance

It has become a recent mantra that, if epilepsy fails to respond to a first and second antiepileptic drug (AED), then the long-term prognosis of the epilepsy is poor, and that the epilepsy is "drug resistant."[13] This view is plainly too pessimistic. Careful long-term studies have shown that up to 50% of patients who did not become seizure free with their first two AEDs enter long-term seizure remission with a change of AED treatment.[14] It has been known for years that many cases of epilepsy remit early in the course of the condition and that the longer the condition remains active, the worse the prognosis. But to ascribe this to the "number of drugs taken" and to conflate this with "drug resistance" are errors. Short-lasting epilepsy is going to be treated with fewer drugs than long-lasting epilepsy, and the association of outcome and number of drugs is not likely to be causal.

Many types of epilepsy have a good inherent prognosis and remit regardless of treatment—this is true of benign syndromes and acute symptomatic seizures; on the other hand, other types fail to remit whichever treatment is applied—this is true of severe syndromes and the like. Prognosis and natural history are much more likely to be determined by these biological factors than a spurious factor such as the number of drugs tried. Misdiagnosis is another important factor at this early stage that affects these apparent statistics, and it has been estimated that up to 30% of early cases of apparent seizures are in fact not epileptic at all.[12] Furthermore, it makes no sense to believe that failure to respond to a drug with one mechanism of action has any influence on whether an epilepsy will respond to another with a different mechanism of action. Finally, it is common in clinical experience to see response to drug changes even in chronic epilepsy, and formal studies have repeatedly shown this, with very good responses obtained when rational approaches to the treatment of chronic epilepsy are applied.

Drug resistance is a genetic trait

One commonly mentioned theory is that drug resistance is a genetic trait and that variants (polymorphisms) in the genes coding for drug transporters, for instance for P-glycoprotein, or for drug targets, for instance for the GABA or sodium channel, are responsible for the lack of response in focal epilepsy.[15–17] In fact, no polymorphism of genes involved in regulating AED transporter activity across brain cell membranes has been shown consistently to have any marked effect on therapy. Moreover, there are a number of obvious and crucial objections to such theory. Many drugs are not transported, or are only weakly so, by P-glycoprotein, and there is also marked phenotypic variation, no known saturable kinetic effects, and the expression of the gene is under strong environmental influence. Not all drugs act at the same brain receptors, so the target hypothesis cannot be universally applied for this reason alone. Also, other aspects affect response but cannot have any relationship to drug target or transporters, for instance: etiology of the epilepsy, epilepsy syndrome, extent or position of a brain lesion, environmental factors such as nutrition, lack of sleep, hepatic enzyme induction, drug receptor regulation, drug dose, pharmacokinetics, and comedication. In fact, none of the commonly proposed theories is able to convincingly explain drug resistance in focal epilepsy.[4,5]

Pharmacogenomics is making a big impact on epilepsy

In 2000, the head of a major pharmaceutical company informed the epilepsy community that "pharmacogenetics will be widespread in epilepsy within 3 to 5 years." This was overoptimistic. Articles are still frequently written on the "promise of pharmacogenetics," but as yet the concrete benefits are conspicuous by their absence except perhaps in detecting hypersensitivity to individual AEDs, mostly carbamazepine in people from Asia.[18–24] In our view, the complexity and multifactorial nature of success or failure of antiepileptic drug treatment render it unlikely that simple single pharmacogenetic mechanisms, at least as they are currently conceived, do have any major impact on therapy. The widely hyped "tailoring" of drug therapy to an individual on the basis of that person's genetic makeup sadly seems a long way off.

Surgical resection removes the epileptic focus

Much of contemporary surgical practice is predicated on the thought that in partial epilepsy there is a discrete "focus" that is limited in anatomical range, and that fully resecting this focus can "remove" the epilepsy. In a minority of patients this is the case, for instance, in patients with small cortical lesions, particularly in the primary motor-sensory areas. However, in the majority of types of epilepsy, a large body of evidence demonstrates this to be a simplistic and erroneous view, which might be termed the *phenological fallacy* of epilepsy surgery. Neurophysiological evidence, both experimental and clinical, shows that the seizures of mesial temporal lobe epilepsy arise from activation of a whole network of cells (in the latest jargon—a neural network), starting sometimes simultaneously in different parts of the network or arising in varying alternative parts of the network. The fact that the clinical features of a temporal lobe seizure involve many aspects that are not part of temporal lobe function (motor aspects, loss of consciousness, etc), even when there is pathology in the hippocampus, is further evidence of involvement beyond the hippocampus. This is not caused by "spread" but by much more sophisticated reciprocal activation in the epileptogenic areas. Clinical depth electrode studies frequently show different seizure onsets in different parts of the limbic system. Widespread connectivity changes have been repeatedly demonstrated extending beyond the temporal lobe, and neurochemical changes are measurable in locations outside the temporal lobe. Furthermore, after temporal lobectomy, three clinical phenomena need explanation. Auras often remain even if complex partial seizures are suppressed. Seizures recur in an important minority of patients in the years after temporal lobectomy. Many patients require continued drug treatment after full surgical removal of the focus. The most parsimonious explanation of these phenomena is that seizures are a system phenomenon and that wide limbic areas, not a discrete focus, underpin the seizures. The temporal lobectomy simply removes part of this system, and resective surgery does not fully eliminate the widespread connectivity changes responsible for seizures. Successful surgery does degrade the ability of the system to generate seizures but certainly does not resect a focus. This is of obvious importance clinically, because increasingly complex multimedia investigations are directed at identifying the "epilepsy

focus." Despite these concerns, surgery is of course necessary and very valuable in selected circumstances, but by virtue of the complex mechanisms underlying seizure occurrence, the possibility exists of seizure recurrence on and off AEDs during follow-up,[25] and the concept of the discrete focus cannot be applied in many types of focal epilepsy.

Surgical procedures

Corpus callosotomy, multiple subpial transection, and some types of extratemporal resections are surgical procedures still carried out, but they have not been subject to any controlled assessment and they have significant drawbacks and risks. Randomizing patients to surgery plus medical treatment versus standard medical treatment alone would be one option, or delayed surgery. Wilder Penfield, a pioneer of epilepsy surgery, carried out a study in which patients were randomized to brain surgery or sham surgery,[26] but this would not meet modern ethical standards. Given the dramatic nature of surgery and the presurgical examinations, it is likely that surgical interventions in epilepsy will trigger a substantial placebo response similar to that seen in drug trials (as Penfield demonstrated). If one takes a very pessimistic and possibly too harsh view, it is likely that in the future some of our surgical treatments may be considered as obsolete as some of the operations mentioned in Table 2. The same might apply to more recent procedures such as certain forms of cerebral and peripheral stimulation. One recent well-performed trial of an implanted brain stimulator, for example, illustrates the issues of double-blind trials in cerebral stimulation. Following implantation of the stimulator and leads and prior to stimulation treatment in either the treatment or the sham group, both groups experienced a mean percent reduction in the observed number of seizures (25% treatment and 20% sham) and a median percent reduction in the observed number of seizures (33% treatment and 30% sham). Whether this is an effect of the surgical procedure or anesthesia, lead implantation, regression to the mean, or placebo is not known. While undergoing treatment in the next phase of the trial, 76% of subjects in the treatment group and 70% in the sham group reported a decrease in seizures during the blinded evaluation phase. A benefit in seizure reduction was, however, seen in the subsequent open-label long-term observation phase.[27] A double-blind trial of a new AED showing no difference in seizure outcome during the blinded evaluation period would not have been considered as evidence for efficacy.

The prognosis of epilepsy has not improved

It is often stated that the prognosis of epilepsy has not improved in recent decades. This is despite the fact that millions of dollars have been spent on demonstrating the antiseizure effect of modern drugs and that a range of new drugs has been licensed. It is true that no large-scale study has been carried out that confirms or refutes this proposition, but with the large number of new therapies made available in recent years, and the indisputable advances in the science of epileptology, including surgery and neuroimaging, it would be surprising if the medical prognosis has not improved. Even if individual drugs result in seizure control in only a small percentage of patients, the additive effect of a number of these drugs tried in turn results in a markedly improved overall prognosis.[28] Furthermore, there is plenty of anecdotal evidence that prognosis has been transformed. We are old enough to remember the common clinical experiences of 40 years ago at a time when there was widespread use of sedative drugs, when the treatment response was clearly worse than that now.

Why Do We Get It Sometimes Wrong?

Epilepsy has made tremendous progress in the past century. We have attempted to list in Table 1 some landmarks in the investigation and treatment of epilepsy, and because of these, there is no doubt that the prospects for persons with epilepsy have greatly improved. As we point out earlier, too, societal changes in recent years have greatly benefited people with epilepsy, and indeed the evolution of change in public attitude and societal practice can be considered even more important than the scientific and medical changes.

However, we hope also to show that theories and practices in the past are often later dismissed as misguided, and the same is likely to apply today. The examples we have chosen are perhaps particularly egregious, and many others could have been selected.

Compiling lists is less important than trying to understand the root causes of such solecisms. Sometimes, appropriate research has not been carried out (for instance, in relation to assessing the prognosis of epilepsy), but often practice or theory is based on inaccurate research. Identifying the cause of inaccuracy is not necessarily simple. Often various factors are relevant, and here we speculate briefly on some of the more fundamental root causes that promote the adoption of flawed theory and practice.

The first point to make is that scientific theory and practice are prone to fashion. They are strongly influenced by the societal beliefs and mores of the time. In other words, science is relative and certainly not objective—an important point to emphasize. The focus on degeneration in the early part of the 20th century is one example. The theories of the neurological trait and of degenerative genetic influences imply a manifestation of this fashion, which affected many different intellectual areas in social studies, art, and science. The same applied to a variety of fashionable psychological theories that were often shared between medicine, the arts, and politics. The more recent fashions for cerebral functional imaging and the related phrenological fallacy are partly the result of the public appetite for visual display and

visual imagery of what "the brain is like." Raymond Tallis has effectively criticized this as "neuromania."[29]

The overwhelming influence of economics, too, is another example of how the priorities of science are determined predominately by social forces—in the field of epilepsy, there are many examples of this in relation to the pharmaceutical industry, regulation, and the conduct of university research (see below). Funding issues and underfunding of epilepsy research push investigators toward small-sample studies with narrow foci. It is not fair to blame investigators for trying to do what they can with limited resources, and one should be thankful—and we are—for what has been done despite all the issues surrounding the practicalities of academic research. In the field of investigation and clinical practice, financial considerations are paramount. In the United States, a country of 300 million people with a largely free-market approach to medicine, 15 million nuclear medicine scans, 100 million computed tomography (CT) and magnetic resonance imaging (MRI) scans, and almost 10 billion laboratory tests are carried out each year.[30] Often, these are essentially fishing expeditions, and because no patient is perfectly "normal," clinicians tend to find a lot of fish. Societal fashion and trends are not necessarily detrimental to medicine, of course, and the liberal political climate has encouraged social advancement in epilepsy in many countries. That scientific knowledge is relative is an obvious truism, but one that is sometimes forgotten in overinflated claims of scientific neutrality.

A second point is that the mere application of scientific method does not imply accuracy. Many scientific theories, supported by scientific study, have produced "scientific" conclusions that later were shown to be utterly wrong —"bad science," as this has been dubbed.[31] Increasing criticism has been made, not least from the editors of scientific journals frustrated by the profusion of bad science. Richard Horton, editor of the *Lancet*, recently wrote that much of the scientific literature—indeed, perhaps half—is simply untrue.[32] The problem is often methodological, with poorly drafted scientific questions or poorly conducted scientific method. Horton mentions "small sample sizes, tiny effects, invalid exploratory analyses, flagrant conflicts of interest, an obsession in pursing fashionable trends of dubious importance. . .. The apparent endemicity of bad research behaviour is alarming. In their quest for telling a competing story, scientists too often sculpt data to fit their preferred theory of the world or they retrofit hypothesis to fit their data." John Ioannidis in a widely cited paper in 2005[33] analyzed 49 of the most highly regarded research findings in medicine over the previous 13 years and compared the 45 studies that claimed to have uncovered effective interventions with data from subsequent studies with larger sample sizes. He found that 16% were contradicted, 16% had effects that were smaller than in the initial study, and only 44% were replicated. This is not a good record. Another point concerns meta-analysis and other large data projects. Jeffrey Drazen, editor of the *New England Journal of Medicine*, has pointed out that a person not involved in the generation or collection of data may not understand the choices made in defining its parameters.[34] In joining up different studies, for instance, in meta-analysis, the data may be collected from heterogeneous study populations with different eligibility criteria, different methods of data collection and analysis, and different treatments. Drazen wrote that "a new class of research person has emerged," whom he calls provocatively "research parasites." These are "people who had nothing to do with the design and execution of the study but use another group's data for their own ends." In epilepsy, meta-analyses abound, and although the early analyses comparing clinical trials were important and justified, their proliferation into surgical and psychosocial fields, for instance, where studies are often extremely heterogeneous, has led to poor standards and poor methodology, much as Drazen, Ioannidis, and Horton describe.

The lack of reproducibility and reliability of results in biomedical research is another great concern. This has been thought to result from sloppy methodology of the sort listed above; wish fulfilment of researchers who are dedicated to finding one result and who retrofit, massage, or otherwise manipulate data; or, in some cases, actual fraud. We are aware of examples of each of these in the field of epilepsy. Where large datasets are involved, for instance, in genetics, the complexity of the statistical analysis lends itself to manipulation, and the lack of reproducibility of genetic data is a cause of particular concern. The issues of reliability of pharmaceutical drug trials, too, is worrisome, given the very large investment of time and money and the effects failed trials can have on companies and shareholders. Pharmaceutical medicine is just one area where science, marketing, and commercial factors are intimately intertwined, and their close relationships have been a matter of public disquiet.

It is also important to realize that the process of medicine, and the context in which it is practiced, determines its direction. The impact of context and bureaucracy should not be underestimated, and the consequences are sometime unintended or perverse. The strengthening of rules for drug trials in epilepsy is an example. Although changes were necessary to establish criteria for effect and safety, the pendulum of current regulations may have swung too far toward unnecessary overregulation (one example is the need to demonstrate efficacy in both monotherapy and polytherapy, when there is no scientific evidence of synergy). Drug discovery is now probably seriously hampered and possible to undertake only by the largest multinationals. The consequences are a lack of innovation and inflation of costs, and there is also no evidence that safety is enhanced, as some recent substantial adverse events involving new drugs, such as retigabine or vigabatrin for treatment of focal seizures, demonstrate. However, to be fair, vigabatrin is still a first-choice medication for children with epilepsy due to tuberous sclerosis and among the top choices in West syndrome, even if for lack of

better treatment. Another example is the extraordinary multiplication of medical journals, which has occurred primarily because journal publishing in the online age can make a quick profit. The result is that poorer work, which would not previously have passed muster, is able to find a home in a journal that will accept it. The academic world is now awash with inconsequential and often inaccurate science and a veritable barrage of white noise. Other issues relating to medical publishing, and to the gaming of medical authors in publishing their work, have recently been reviewed by the ex-editor of *The BMJ*.[35] The increasing tendency of universities to base their decisions about funding and about individual promotions on publication record fuels this gaming around medical publishing.

Finally, to impropriety

Medical scientists are assumed to have high standards, but in a small number of cases, this assumption has been shown to be unjustified.[36] We have come across individuals whose results seem untrustworthy and whose findings are never reproduced. Of course, not all unvalidated discoveries are dishonest or useless, and progress can only be made when there are both successes and failures. Yet, there is a spectrum of behaviors ranging from unconscious bias to deliberate fraud. In some cases, data massaging occurs, such as ignoring outliers or results that do not conform, or results are over interpreted, justified by the thought that "my theory must be right." In other cases, the fraud has been more conscious, often stimulated by the need to obtain more grant funding. We are aware of high-profile figures reporting results that seem highly unlikely and that are never replicated. In modern epileptology, this seems to occur especially in fields where big data are easy to misrepresent. A recent survey found that 0.3% of researchers falsified data, 6% failed to present data that contradicted their results, 8% circumvented minor aspects of human subject requirements, 13% overlooked others' questionable interpretation or flawed data, and 16% changed study methodology in response to funding source pressure.[36] It has also been estimated that approximately 10–20% of all research and development (R&D) funds are spent on questionable studies characterized by misrepresentation of data, inaccurate reporting, and fabrication of experimental results.[37] A meta-analysis of studies similarly showed that 2% of all scientists admitted to having fabricated, falsified, or modified data, and more than 33% admitted other questionable research practices.[38] The epilepsy journals, as with others, are littered with their fair share of reports of the success of surgical and medical treatments that cannot possibly be correct, and for these various reasons, it has been claimed that massive misinformation exists in the domain of scientific research. This has become of increasing public concern.[39–44] Goldacre wrote of a litany of dubious practices in relation to pharmaceutical trials including missing data from negative trials that were suppressed, the lack of transparency of data, the problems with outsourcing volunteer studies, statistical errors in trials, the medicalization of behaviors to create diseases that then can be treated, the sophistication of marketing of drugs, the nature of the connections between the academic medical community and commercial interests.[45] Many of these issues may have applied as much to epilepsy as to other conditions.

Disclosure

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References

1. Schmidt D, Shorvon S. *The end of epilepsy?*. Oxford: Oxford University Press; 2016.
2. Temkin O. *The falling sickness*. Baltimore, MD: The Johns Hopkins Press; 1945.
3. Shorvon S, Goodridge D. Longitudinal cohort studies of the prognosis of epilepsy: contribution of the National General Practice Study of Epilepsy and other studies. *Brain* 2013;136:497–510.
4. Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia* 2011;52:657–678.
5. Löscher W, Klitgaard H, Twyman RE, et al. New avenues for antiepileptic drug discovery and development. *Nat Rev Drug Discov* 2013;12:757–776.
6. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Arch Neurol* 2007;64:1595–1599.
7. Cook MJ, O'Brien TJ, Berkovic SF, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol* 2013;12:563–571.
8. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol* 2011;10:961–968.
9. Zaccara G, Giovannelli F, Schmidt D. Placebo and nocebo responses in drug trials of epilepsy. *Epilepsy Behav* 2015;43:128–134.
10. Kaptchuk TJ, Miller FG. Placebo effects in medicine. *N Engl J Med* 2015;373:8–9.
11. Mintzer S, French JA, Perucca E, et al. Is a separate monotherapy indication warranted for antiepileptic drugs. *Lancet Neurol* 2015;14:1229–1240.
12. Wiebe S, Jette N. Pharmacoresistance and the role of surgery in difficult to treat epilepsy. *Nat Rev Neurol* 2012;8:669–677.
13. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
14. Sillanpää M, Schmidt D. Is incident drug-resistance of childhood-onset epilepsy reversible? A long-term follow-up study. *Brain* 2012;135:2256–2262.
15. Löscher W, Sills GJ. Drug resistance in epilepsy: why is a simple explanation not enough? *Epilepsia* 2007;48:2370–2372.
16. Sisodiya SM, Lin WR, Harding BN, et al. Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy. *Brain* 2002;125:22–31.
17. Tate SK, Sisodiya SM. Multidrug resistance in epilepsy: a pharmacogenomics update. *Expert Opin Pharmacother* 2007;8:1441–1449.
18. Piana C, Antunes Nde J, Della Pasqua O. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. *Expert Opin Drug Metab Toxicol* 2014;10:341–358.
19. Cavalleri GL, McCormack M, Alhusaini S, et al. Pharmacogenomics and epilepsy: the road ahead. *Pharmacogenomics* 2011;12:1429–1447.

20. Reid CA, Jackson GD, Berkovic SF, et al. New therapeutic opportunities in epilepsy: a genetic perspective. *Pharmacol Ther* 2010;128: 274–280.
21. Sisodiya SM, Marini C. Genetics of antiepileptic drug resistance. *Curr Opin Neurol* 2009;22:150–156.
22. Kasperaviciūte D, Sisodiya SM. Epilepsy pharmacogenetics. *Pharmacogenomics* 2009;10:817–836.
23. Anderson GD. Pharmacokinetic, pharmacodynamic, and pharmacogenetic targeted therapy of antiepileptic drugs. *Ther Drug Monit* 2008;30:173–180.
24. Löscher W, Klotz U, Zimprich F, et al. The clinical impact of pharmacogenetics on the treatment of epilepsy. *Epilepsia* 2009;50:1–23.
25. Schmidt D, Baumgartner C, Löscher W. The chance of cure following surgery for drug-resistant temporal lobe epilepsy. What do we know and do we need to revise our expectations? *Epilepsy Res* 2004;60: 187–201.
26. Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain*. Boston, MA: Little, Brown and Company; 1954: 811–812.
27. RNS System, Summary of Safety and Effectiveness, P100026. U.S. Department of Health and Human Services, Food and Drug Administration. Available at: www.accessdata.fda.gov/cdrh_docs/pdf10/p100026b.pdf. Accessed May 6, 2016.
28. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 2007;62: 375–381.
29. Tallis R. *Aping mankind: neuromania, Darwinitis and the misrepresentation of humanity*. London: Routledge; 2011.
30. Gawande A. Overkill. *New Yorker* 2015; May 11 issue.
31. Goldacre B. *Bad science*. London: Fourth Estate; 2008.
32. Horton R. Offline: what is medicine's 5 sigma? *Lancet* 2015;385:1380.
33. Ioannidis J. Why most published research findings are false. *PLoS Med* 2: e124.
34. Drazen JM. Data sharing and the journal. *N Engl J Med* 2016;374: e24.
35. Smith R. *The trouble with medical journals*. London: Royal Society of Medicine; 2006.
36. Broad WJ, Wade N. *Betrayers of the truth: fraud and deceit in the halls of science*. New York, NY: Simon and Schuster; 1982.
37. Martinson B, Anderson M, De Vries R. Scientists behaving badly. *Nature* 2005;435:737–738.
38. Glick L. Scientific data audit—a key management tool. *Account Res* 1992;2:153–168.
39. Fanelli D. How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. *PLoS ONE* 2009;4: e5738.
40. Monrieff J. *The bitterest pills*. Basingstoke: Palgrave Macmillan; 2013.
41. Healy D. *Pharmageddon*. Berkeley: University of California Press; 2013.
42. Healy D. *Mania*. Baltimore, MD: Johns Hopkins Press; 2010.
43. Healy D. *Let them eat Prozac*. New York: University of New York Press; 2004.
44. Goldacre B. *Bad pharma*. London: Fourth Estate; 2014.
45. Goldacre B. *Bad pharma: how medicine is broken, and how we can fix it*. London: Fourth Estate; 2012.