RESEARCH PRIORITIES IN EPILEPSY FOR THE NEXT DECADE—A REPRESENTATIVE VIEW OF THE EUROPEAN SCIENTIFIC COMMUNITY

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This document expresses a representative view of the European scientific community involved in epilepsy research. It is the result of action taken by the International League Against Epilepsy (ILAE) and its Commission on European Affairs (CEA). The ILAE is the worldwide professional organization that represents scientists and clinicians working in epilepsy in more than 98 countries worldwide. This paper lists what scientists have achieved in epilepsy research so far and identifies further challenges in epilepsy research. It names the six most relevant and urgent priorities, discusses the problem in each of the six areas, and identifies the direction future research should take.

Epilepsy is a serious and common chronic neurologic disorder characterized by recurrent seizures, which are caused by abnormal synchronized neuronal discharges. As many as 6 million people in Europe currently have active epilepsy. This has major implications not only for health, but also for independent living, education and employment, mobility, and personal relationships. The term epilepsy encompasses a vast and heterogeneous ensemble of syndromes and diseases, differing in types of seizures, age at onset (with high incidence peaks in childhood and old age), and etiology, which can be acquired and/or genetic.

Epilepsy is an expensive disorder. The total European health costs associated with epilepsy have been estimated to be €15.5 billion, with indirect costs accounting for more than half (€8.6 billion) of this amount. From direct health care costs of €2.8 billion, the outpatient care comprised the largest part (€1.3 billion). Direct nonmedical cost of epilepsy was estimated to be €4.2 billion and that of antiepileptic drugs €400 million. The total cost per epilepsy patient was €2,000–11,500 and the estimated cost per European inhabitant was €33 (EUCARE, 2003; Andlin-Sobocki et al., 2005; Pugliatti et al., 2007).

The prognosis and quality of life of a person with epilepsy varies considerably. It depends on the type and severity of the person's seizures, response to drug treatment, coexisting developmental and cognitive disorders, other comorbidities, and the occurrence of episodes of status epilepticus.

Though a large number of antiepileptic drugs (AEDs) that suppress or prevent the seizures are now available, about 30–40% of the patients, children as well as adults, remain resistant to drug treatment. So far, we have no treatments that prevent the development of epilepsy ("antiepileptogenic drugs") or modify the detrimental course of the disorder ("disease-modifying agents").

We must invest in those research areas that will provide the required understanding of the fundamental mechanisms of epilepsy and advance the treatment of epilepsy to the next level. It is no longer enough to try to prevent the symptoms of the disease. We must now attempt to cure the disease and prevent its development in patients who are at risk.

We used the following method to identify the research priorities in epilepsy listed in this document. Initially, we asked all the 42 chapters in the European region of the ILAE and group leaders in clinical and basic epilepsy research what their most important research priorities were. Subsequently, a task force of the CEA met in Brussels in January 2008, discussed these, and identified the top research priorities. These top six priorities and the scientific reasons behind them are discussed herein.

ACHIEVEMENTS IN EPILEPSY RESEARCH

The most important advances that have improved the care of patients have been the discovery of the first epilepsy genes, the improved diagnosis of epilepsy because of better electroencephalographic techniques combined with video recordings, and the use of structural and functional brain imaging for the diagnosis of epilepsy and for research. A new generation of AEDs offers improved tolerability and better pharmacokinetic properties.

The benefits of epilepsy research have extended beyond epilepsy. Many AEDs have proven to have beneficial effects in conditions other than epilepsy. These include

neuropathic pain, depression, migraine, tremor, and anxiety. Epilepsy research also provides unique opportunities for research in neuroscience not otherwise possible. For example, intracerebral recordings from the brains of patients undergoing evaluation for epilepsy surgery and studies on postoperative epileptic brain tissue have helped to understand the fundamental mechanisms of the human brain.

CHALLENGES IN EPILEPSY RESEARCH

Unfortunately, the achievements of epilepsy research have so far not resulted in AEDs with superior efficacy. Many patients continue to experience severe adverse effects because of these drugs and memory disorders. A number of epilepsy syndromes, particularly, in children, remain resistant to drugs.

So far, drug discovery programs for new AEDs have relied primarily on a screening process that uses traditional animal models. This has resulted in the development of AEDs that act primarily on ion channels or on neurotransmitter receptors (Rogawski & Löscher, 2004). In some instances new AEDs have been discovered serendipitously—when new chemical entities were subjected to systematic testing and found by chance to have antiepileptic properties. In other instances, new molecules were rationally designed based on currently available agents in order to enhance their efficacy, or more commonly, to eliminate side effects.

To get better drugs we need to define new targets for drugs. This can be possible only if we further understand the neurobiology of the epileptogenic brain and the mechanisms that lead to the emergence of epileptic seizures. The required technologic platform for identifying new drug targets can be provided by developments in molecular and cellular analysis of tissue specimens, generation of genetically modified animals, gene transfer technology, and advanced imaging and electrophysiologic techniques.

PIVOTAL DOMAINS IN EPILEPSY RESEARCH

The most relevant and urgent priorities for research in epilepsy are:
1. Better understanding of childhood epilepsies and brain development
2. Preventing the development of epilepsy (epileptogenesis) after brain injury
3. Translating genetic knowledge to optimize the care of epilepsy
4. Reducing the life-compromising burden of seizures and epilepsy
5. Identifying the mechanisms of seizure-genesis (ictogenesis)
6. Improving treatments in epilepsy

PRIORITY 1—BETTER UNDERSTANDING OF CHILDHOOD EPILEPSIES AND BRAIN DEVELOPMENT

The problem

Epilepsies are far more frequent early in life than in adulthood, and they may have devastating cognitive and social consequences. In addition, epilepsies in children are often drug resistant because the developmental processes underlying epilepsy rely on signaling elements and cascades that are unique to brain maturation (Ben-Ari & Holmes, 2006). Therefore, childhood epilepsy is a specific problem that cannot be dealt with as a subset of adult epilepsies. Unfortunately, at present, clinical trials of novel AEDs in pediatrics are scarce, especially in a distinct group of infantile and childhood epilepsies—the epileptic encephalopathies. In these encephalopathies, the epileptic processes themselves are believed to contribute to the disturbance in brain function. These rare diseases require the use and the development of orphan drugs (http://www.emea.europa.eu/htms/human/orphans/intro.htm).[1]

One additional difficulty is that childhood epilepsies are heterogeneous in both their age dependence (neonates, infants, children, and adolescents) and their etiology. Therefore, they are not amenable to single models and one approach. Finally, translating basic research into the emergence of novel therapeutic compounds is difficult because only a few laboratories are involved in the basic research. Consequently, basic research has currently little impact on a clinical endpoint.

Current status, novel resources and information available

Why is it mandatory to invest now in childhood epilepsies? This is an opportune moment because a sudden convergence of concepts, data, networks, and technologic improvements has begun to emerge. First, huge advances have been made in determining the genetic basis of many forms of childhood epilepsy. These will have a limited impact unless they are translated into novel treatments. To do so, these advances need to be accompanied by powerful post genomic studies that will link the molecular findings to specific aspects of the disease process. We need to provide this missing link now. Second, recent data have shown that immature neurons are intrinsically more excitable and readily generate seizures. The mechanisms underlying these findings have only recently been clarified. Third, young animals that have seizures are particularly prone to have further seizures. These have been shown to

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[1]Medicines for rare diseases—so-called "orphan" medicinal products—are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the European Union, which, for economic reasons, would be unlikely to be developed without incentives.

have deleterious effects on cognitive development. Fourth, during development, when neuronal migration occurs, neurons express receptors that modulate their own migration. Research shows that drugs that interfere with the working of these receptors, including AEDs, can lead to subtle disorders of migration. Fifth, the pharmacologic properties of epileptic immature neurons have been shown to differ from those of adult neurons and these require further specific investigations. Sixth, the recent development of imaging and epilepsy surgery in small infants is now helping us to identify the epileptic network and allowing us to remove small subtle lesions. In addition, the development of statistically more rigorous designs for performing clinical trials in small populations now allows us to test new treatments for rare diseases. These methods will allow us to carry out research on some of the most severe childhood epilepsies with greater confidence. Finally, the timing is also very favorable in terms of EU regulations, as the EU Commission has recently implemented incentives for the early development of new AEDs in children.

What should be improved and investigated

There are two major issues—performing post genomic research and translating this to human use, and translating basic research to drug discovery and to clinical trials in children.

Recent technologic developments enable the transfection of genes in animal's utero to reproduce mutations at a neuronal level and allow the determination of the properties of transfected neurons and the nature of their connections with the rest of the brain. This has turned out to be a very fruitful technique to understand and possibly treat migration disorders, which are the cause of half the pharmacoresistant epilepsies in childhood. Subtle migration disorders are also produced by a variety of drugs (including AEDs) taken during pregnancy, suggesting that careful investigations are warranted to ensure the best risk-to-benefit ratio for using AEDs in pregnancy. Parallel studies assessing molecular and cellular characteristics of brain malformations in brain surgical specimens can complement these observations and confirm their relevance whenever possible.

Childhood epilepsies are specific to the developing brain, and the treatments resulting from adult clinical trials cannot be extrapolated to childhood epilepsies. Some drugs can even worsen the condition in children. There are very few clinical trials on infantile spasms and severe myoclonic epilepsy in infancy. Of the 10 new AEDs developed for adults in the last decade, only one is approved for use in infants. Novel drugs that are age and disease specific can best be discovered from the extrapolation of the basic research discussed previously.

Box 1. Research priorities—Childhood epilepsies and brain development

- Develop post genomic research on malformations of cortical development and perform parallel studies on surgical tissue
- Identify age- and disease-specific drug targets and translate these into drug discovery and new models for clinical trials
- Evaluate the effects of antiepileptic drugs (AEDs) on the developing brain in experimental models and perform trials in age-related epileptic encephalopathies in small patient populations using innovative trial designs

PRIORITY 2—PREVENTING THE DEVELOPMENT OF EPILEPSY AFTER BRAIN INJURY

The problem

Trauma and stroke are the most common brain injuries that result in epilepsy. Europe has about two million cases of traumatic brain injury and one million strokes in its population every year. About 17% of patients with severe closed head injury, and more than one-half of patients with penetrating brain injury go on to develop epilepsy. Epilepsy also occurs in 4% of patients with neocortical stroke. Understanding how and why epilepsy develops after brain injury, especially in some people but not in others, would provide novel strategies to prevent many new cases of epilepsy. This will have immense public health implications, prevent ill health, and reduce the cost to society.

In currently available experimental models, numerous changes have been documented at the molecular, cellular, and network levels during the development of epilepsy. To date, however, this understanding has not led to effective intervention strategies. A major obstacle is that the reported phenomena have not been clearly separated into causative changes that lead to a lowered seizure threshold and compensatory changes that support the beneficial recovery from injury.

Current status, novel resources and information available

Currently we have the tools that can be used in a translational manner to assess the molecular, cellular, and network alterations that differentiate between the people who will and will not develop epilepsy. These are the result of recent advances in the development of animal models, large scale molecular analysis, electrophysiologic techniques [invasive and noninvasive electroencephalography (EEG)], magentoencephalography (MEG), behavioral analysis, and multimodal imaging using magnetic resonance (MR) and isotopes.

What should be improved and investigated

Our current understanding of the risk factors associated with epileptogenesis originates from epidemiologic studies carried out in heterogeneous populations. To understand

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the specific variables that predispose humans to epileptogenesis we need to conduct a large-scale pan-European clinical study in carefully characterized patient populations, which includes genetic analysis, biomarkers, and imaging.

Studies on the mechanisms of epileptogenesis have so far been conducted in animal models in which the development of epilepsy is triggered by status epilepticus, which is not a major cause of epilepsy in humans. Therefore, we urgently need to broaden the armamentarium of animal models that can be used to investigate the major causes of epilepsy in humans, such as applying experimental manipulations that mimic traumatic brain injury and stroke and applying these injuries to genetically modified rodents.

We need to understand which mechanisms and processes during the recovery from brain injury contribute to the development of a lowered seizure threshold and which are compensatory in helping the brain to recover. For this, we have to do novel research with new drugs, perform studies on lesions in human and animal models, study focused delivery of pharmacologic agents or genes, and use genetically modified animals including conditional mutants.

Currently we lack validated biomarkers that reliably predict the risk of developing epilepsy, or which correlate with the progression of this process after brain injury in individual subjects. We need, therefore, to develop novel molecular and electrophysiologic techniques and cellular and noninvasive imaging to study and predict the process of epilepsy development in relevant animal models and then translate the method to a clinical setting.

To be able to interfere with the processes that lead to epilepsy, we have to use specific mechanistic knowledge to develop novel chemical entities that reduce or prevent the risk of epilepsy after brain injury by using high throughput screening methods in drug discovery.

Box 2. Research priorities—Preventing epilepsy development after brain injury

- To understand the genetic, environmental, and other variables that predispose to the development of epilepsy after brain injury
- To develop, test, and validate a broader range of relevant animal models for postinjury epilepsy
- To test which molecular, cellular, and network processes that occur following brain injury contribute to the development of epilepsy and which are compensatory in helping the brain recover
- To develop novel antiepileptogenic therapies that do not compromise recovery from brain injury
- To develop and use high-throughput screening methods in drug discovery for antiepileptogenic and disease-modifying therapies

PRIORITY 3—TRANSLATING GENETIC KNOWLEDGE TO OPTIMIZE EPILEPSY CARE

The problem

Up to 50% of all epilepsies have major genetic components. These can have direct causative effects, indirect secondary effects (which are the effects resulting in compensatory mechanisms that reorganize the brain), and effects on the response to drugs.

The identification of the first epilepsy genes was a major step in epilepsy research during the last decade. However, we still do not know how alterations in our genetic material led to the development of epilepsy; what are the causes of the more common genetically complex epilepsies in which multiple genes are involved; what are the genetic determinants of how we respond to drugs; and how to apply genetic information to clinical practice.

Current status, novel resources, and information available

Advances in genetics are leading to a wider and deeper knowledge of the basic mechanisms underlying the epilepsies. Genes associated with the idiopathic generalized epilepsies, now considered channelopathies, remain within the ion-channel family but mutations in nonchannel genes are also emerging as responsible for a form of idiopathic partial epilepsy, malformations of cortical development, the rare progressive myoclonus epilepsies, and X-linked mental retardation with epilepsy. Still, most epilepsies have a complex mode of inheritance, and genes identified so far account for only a minority of families and sporadic cases.

In the last few years, in vitro studies in nonneuronal systems have been used to analyze the effects of mutations, mainly in ion channels, as these proteins are the key players in the regulation of neuronal excitability and the major target for genetic epileptogenic changes. The combination of genetic and functional studies has contributed to the detection of molecular correlates of crucial mechanisms modulating neuronal excitability and the development of seizures, and to the provision of new targets for pharmacotherapy. However, although such investigations provide very useful information on the single gene and mutation level, we have to study the effects of many different genetic variants to identify their common pathways. Primary and secondary consequences on the behavior of neurons and neuronal networks have still to be investigated as a next step. Gene-targeted animals provide particularly interesting and powerful tools to develop living models for human genetic epilepsies. In addition, tools allowing the study of the effect of epilepsy mutations in humans in vivo need to be developed.

The funding of EPICURE, a collaborative FP6-funded European project that started in 2007 (http://www.epicure project.eu/home.aspx), is establishing a powerful network for the recruitment of large cohorts of subjects for specific types of epilepsy (including pharmacoresistant epilepsy) to perform the first genome-wide and large-scale single gene studies and to determine the functional consequences of some selected genetic variants.

What should be improved and investigated

The technology of high throughput whole genome analysis (both genotyping and sequencing) should be applied to determine the genetic basis of specific, common, and presumably homogeneous types of epilepsy, such as classical idiopathic generalized epilepsy, febrile seizures, temporal lobe epilepsy with hippocampal sclerosis, and epilepsy after defined types of brain injury (for example, stroke or head injury). In the same way, the genetic determinants of drug response and side effects need to be investigated. A prerequisite and major effort will be the recruitment of respective large, accurately diagnosed, standardized patient cohorts.

Methods for both high-throughput and in-depth analysis of the functional consequences of the detected genetic variations should be developed. A major priority will be the use of gene-targeted animal models to study how genetic variants directly lead to the development of epilepsy; how they induce secondary changes of neuronal networks; how they can lead to pharmacoresistance; and how known gene mutations lead to rare forms of epilepsy such as the progressive myoclonus epilepsies. Modern techniques allowing the production and analysis of many different animals should be established in parallel.

An important issue for the translation of genetic knowledge into clinical practice is to evaluate how genetic testing can improve health care to facilitate diagnosis of common and rare epilepsies; to optimize treatment in the common epilepsies; to develop treatment in rare epilepsies such as the progressive myoclonus epilepsies; to predict the development of epilepsy; and to develop strategies to prevent epilepsy in appropriate cases.

Box 3. Research priorities—Translating genetic knowledge to optimize epilepsy care

- Identify genetic factors that increase the risk for specific types of epilepsy and the development of refractoriness to antiepileptic drugs
- Recruit large cohorts of accurately diagnosed and classified patients with epilepsy necessary to identify these factors
- Study the effects of gene mutations in the common and rare epilepsies
- Focus on the development of novel animal models of human genetic epilepsies including time-conditional and cell-specific gene-targeted animals, genomic homeostasis, and imaging epilepsy mutations in patients
- Determine the impact of genetic testing on medical care and patient counseling

PRIORITY 4—REDUCING THE LIFE-COMPROMISING BURDEN OF SEIZURES AND EPILEPSY

The problem

Epilepsy is associated with serious consequences and impairments beyond seizures. For persons with epilepsy, life expectancy is reduced and mortality rates are increased 2–3 fold compared to the general population. Premature mortality is even higher in chronic epilepsy. There is an increased prevalence of psychiatric disorders (depression, psychoses, and anxiety disorders). These comorbidities have a marked impact on the quality of life for people with epilepsy. Cognitive impairment may occur in more than 30% of patients, adding significantly to the burden of epilepsy. These aspects associated with epilepsy need to be recognized, understood, and managed to reduce their burden.

Current status, what should be improved and investigated

In particular, premature mortality in chronic epilepsy is mainly caused by sudden unexpected death in epilepsy (SUDEP), which is 20 times more common in people with epilepsy than in the general population, and to an uncertain extent by suicide. Some risk factors for SUDEP have been identified in case-controlled studies, but these need to be confirmed and refined in larger prospective studies. Clinical studies and very limited experimental data have suggested different possible mechanisms for SUDEP, but the actual mechanisms remain unclear.

Psychiatric disorders, such as depression, are more prevalent among people with epilepsy. However, the nature of this association is unclear. Recent observations indicate that depression might be a risk factor for developing epilepsy, whereas others suggest that it might be a consequence of the seizure disorder, or that there exists a common underlying predisposition. In addition, the pharmacologic treatment of epilepsy could contribute to the aggravation of psychiatric disorders and, conversely, psychoactive drugs could trigger seizures. These interrelationships need to be clarified through population-based epidemiologic studies of psychiatric comorbidity.

Cognitive impairment is the most common disability associated with epilepsy. In children, this is particularly frequent as an expression of learning disability from birth—a comorbidity that is present in 40–50% of children with active epilepsy. Cognitive disabilities can also be acquired later in life, for example, in patients with epilepsy caused by stroke or dementia, but also in those with continuing seizures of any cause. Continuous seizure activity as well as treatment with AEDs or surgery can also have a negative impact on cognitive function. We need further studies to clarify the intricate interrelationships between seizures, treatment, preexisting disabilities, and comorbidities, and to identify and assess appropriate treatment strategies.

Box 4. Research priorities—Reducing the life-compromising burden of seizures and epilepsy

- Develop animal models and conduct basic research to unravel the impact of seizures on brain-controlled homoeostasis including respiratory, cardiovascular, and endocrine functions
- Develop and validate methods to predict high risk of seizure-related death, such as sudden unexpected death in epilepsy (SUDEP), by large-scale case-control studies and screening programs, which will study autonomic functions and genetic markers
- Develop and assess approaches to prevent seizure-related death in prospective collaborative studies in high-risk patients by interventions such as epilepsy surgery, pharmacotherapy, cardiac interventions, seizure-detecting devices, and any other methods identified as potentially effective in experimental models
- Experimentally analyze basic mechanisms of cognitive impairment, expanding research to include nonlimbic structures, surgical tissue, and the discovery of novel molecular targets
- Identify the cause and extent of cognitive impairment and psychiatric comorbidity and analyze associated risk factors using prospective and case-control studies in people with chronic epilepsy
- Develop and assess interventions to ameliorate cognitive impairment and psychiatric comorbidity

PRIORITY 5—DEFINITION OF THE MECHANISMS OF SEIZURE-GENESIS (ICTOGENESIS) TO SUPPORT RATIONAL DEVELOPMENT OF NOVEL THERAPEUTIC STRATEGIES TO CURE EPILEPSY

The problem

Currently, the main goal of any epilepsy treatment is to reduce the frequency of seizures by suppressing their onset and propagation with minimal disturbance to the patient's function. The main therapeutic option for drug-resistant patients remains neurosurgery, but this is not always possible and its success rate is 70%. To propose new therapeutic strategies we need to identify the mechanisms involved in ictogenesis—the transition from the interictal state to seizure—that remain elusive despite many studies.

In most patients with drug-resistant focal epilepsy, noninvasive diagnostic procedures help to identify the region to be removed surgically—the epileptogenic zone. Nevertheless, in 30–40% of patients, the cerebral areas responsible for generation of seizures cannot be accurately defined, and further analysis of interictal and ictal activity is required. This necessitates invasive neurophysiologic recordings and functional imaging. During the last decade, several milestones have been achieved using these diagnostic techniques, which have improved our understanding of the mechanisms that control seizure precipitation in the epileptic brain. Intracranial recording in humans with either stereo-EEG or grid electrodes is the presurgical diagnostic procedure used to identify the epileptogenic zone in patients with drug-resistant focal epilepsies. Surgical removal of the epileptogenic zone has proved to be curative in most of these patients, especially those with temporal lobe epilepsy.

Current status, novel resources and information available

Presurgical intracerebral recordings present a unique opportunity to explore the electrical correlate of preictal and ictal events during seizures. They have shown that the transition to seizure correlates with unexpected activation patterns. Contrary to previous assumptions, seizure onset in explored focal epilepsies originating from the neocortex and mesial temporal structures was often found to be associated with the appearance of low amplitude, fast activity, and EEG desynchronization that lasted several seconds before the appearance of large amplitude, synchronous potentials commonly considered as typical epileptiform discharges. The identification of these novel patterns of activity at seizure onset profoundly changed our understanding of epilepsy and opened a new window to study focal ictogenesis.

In parallel, noninvasive diagnostic procedures to identify and locate the epileptogenic region using functional imaging techniques, such as functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT), and diffusion-weighted MR showed that negative BOLD (blood oxygenation level–dependent) signals, hypoperfusions, and increased diffusion changes may be associated with the occurrence of seizures. These findings indicate that complex mechanisms associated with neurovascular coupling may be disturbed in the epileptic brain and may contribute to seizure generation and propagation, thereby opening new avenues of research. The contribution of extraneuronal brain compartments to seizure generation is also supported by experimental studies showing the crucial role played by astroglia and the blood–brain barrier in regulating neuronal excitability and the genesis of ictal discharges.

What should be improved and investigated

European epilepsy centers currently maintain a leading role in developing and using presurgical intracranial recordings in humans, defining the principles for seizure detection and prediction, and developing basic science structures dedicated to epilepsy in clinical settings.

The study of the mechanisms of transition to seizures in different experimental and clinical conditions is timely and has the potential to be of great value in the following ways.

- To understand network, cellular, and molecular changes involved in seizure generation by applying new basic science concepts to observations made in humans, and by reproducing in experimental models the ictal transition patterns observed in humans
- To validate the role in ictogenesis of nonconventional mechanisms that control neuronal excitability, such as inhibitory synchronizing mechanisms, neurovascular coupling, and neuron–glia interactions

- To provide a setting for the development of innovative therapeutic strategies, such as novel antiepileptic compounds or protocols for deep brain stimulation, to cure resistant forms of epilepsy

Box 5. Research priorities to understand mechanisms of seizure generation (ictogenesis)

- Identify seizure patterns and study the underlying mechanisms in different forms of human epilepsy by using advanced neurophysiologic and functional imaging tools
- Reproduce the ictal patterns observed in humans in animal models and in post-surgical human tissue in order to study network, cellular and molecular changes that correlate to the ictal transition (focus on neurons, glia, and neurovascular interactions)
- Utilize the identified mechanisms to develop novel strategies to detect or prevent progression to seizures—that is, either new drugs or functional interventions
- Organize and reinforce epilepsy surgery and functional interventional centers in Europe to improve presurgical diagnostic assessment and treatment of drug-resistant epilepsies, with particular emphasis on refractory pediatric forms

PRIORITY 6—IMPROVING TREATMENT OF EPILEPSY

The problem

Despite the availability of 13 new AEDs over the last 18 years, 30–40% of the adult epilepsy population with the common seizure types and epilepsy syndromes continue to have regular seizures (Kwan & Brodie, 2000). The situation is much worse for infants with a range of severe epilepsy syndromes. They can have daily seizures and drug treatment is palliative at best. Many of these children are left with physical and mental disabilities. Prolonged epileptic seizures or status epilepticus can present at any time in life as a consequence of many brain disorders and in patients with severe epilepsy. The mortality rate of 10–15% associated with status epilepticus has not changed over the last 25 years. No new treatments have been licensed in Europe for status epilepticus over the same time period.

Current status and what should be improved and investigated

An outcome study determining the epidemiology of refractory epilepsy in a Europe-wide newly diagnosed population would provide prospective data in assessing response to treatment, insight into the everyday lives of people with epilepsy, the influence of stigma, and a lever to influence political change for improving epilepsy care in individual countries.

Pharmacoresistance is the major problem in the treatment of epilepsy. This is defined as the persistence of seizures despite treatment with a range of AEDs with different mechanisms of action used singly or in combination at maximum tolerated doses. Consequently, a pressing need exists to develop more effective treatments and strat-

egies. To achieve this goal, we need to understand the mechanisms underlying drug resistance. A number of plausible hypotheses have been proposed including inadequate penetration of AEDs across the blood–brain barrier, acquired alterations to the structure and function of target ion channels and neurotransmitter receptors, and an inherent resistance governed by genetic variants of proteins involved in the pharmacokinetics and pharmacodynamics of AEDs. These potential mechanisms need to be explored in new models of pharmacoresistant epilepsy and in surgically acquired brain tissue. Innovative clinical approaches such as using positron emission tomography (PET) to enhance our understanding of how alterations in the blood–brain barrier and access to AED targets produce refractory epilepsy are needed.

The discovery and characterization of new targets is an essential strategy for developing more effective drugs with anticonvulsant and antiepileptogenic properties. This could also provide drugs with better tolerability. Novel strategies are needed for clinical trials to identify the most appropriate AED therapy for each individual person with epilepsy.

Immune and inflammatory processes have been shown to be activated in epileptogenic tissue obtained from patients affected by epilepsy of diverse causes. Studies in rodent models of epilepsy have also highlighted the possibility of inhibiting seizures and delaying epileptogenesis by targeting specific proinflammatory pathways. Neuromodulatory compounds (such as neuropeptides, neurotrophins, and neurosteroids), brain metabolites or transmitters released by glial cells, and cannabinoid receptors are among the most promising areas for drug development. The role of the blood–brain barrier in the mechanisms of epileptogenicity is increasingly acknowledged. Therefore, compounds affecting its permeability and transport properties or the functional interactions between its cellular components (astrocytes, microglia, and endothelial cells) are of particular interest.

A major prerequisite in addressing the question whether polymorphisms in genes contribute to drug resistance is the availability of large, well-defined European cohorts, with every individual being phenotyped with precision. Consensus definitions of pharmacoresistance and pharmacosensitivity are necessary to define both study and control populations in this cohort. We also need to proceed prospectively and try to identify genetic markers in newly diagnosed populations of patients who are followed up for a number of years.

Despite efforts made by the pharmaceutical industry and basic scientists working in epilepsy, no major breakthroughs in care have resulted in the past 20 years. Nanotechnology presents a wide technologic platform that could be used for local, regulated, and long-lasting drug delivery to the brain. Gene and cell therapies offer refined and efficient ways of targeting the epileptic focus. Genetic

and other studies can identify an increasing number of promising molecules in the brain that could be considered as endogenous antiepileptic agents. Progress in light-activated channel transduction can provide multiple and selective approaches to stimulate or inhibit neuronal activity in ways that are region or cell-type specific.

Box 6. Research priorities—Improving treatment of epilepsy

- Determine the epidemiology of refractory epilepsy in Europe by studying prospectively a Europe-wide newly diagnosed population over a number of years
- Explore mechanisms of pharmacoresistance and develop strategies for its prevention by using sophisticated experimental models and novel clinical approaches
- Identify novel targets for the prevention and treatment of refractory epilepsy by focusing on the basic processes involved in its development
- Investigate the pharmacogenetic basis of drug response and resistance in newly diagnosed and chronic epilepsy populations
- Develop innovative treatment strategies based on gene and cell therapies, nanotechnological drug delivery systems, and brain stimulation techniques that are cell population–specific

CONCLUSION

European research centers of epileptology have long occupied a leading and pioneering position in clinical epilepsy research. The results of this research now form the fundamental basis for optimizing the choice of treatment for patients with epilepsy and for the development of the strategies using intracerebral electrodes for surgical treatment. The pharmaceutical industry, including several European companies, continues to invest in new AEDs. An urgent need exists to improve the translation of epilepsy research for identification of novel molecular and cellular targets for rational drug discovery processes. Multilevel in vitro and in vivo electrophysiology, genomic and post genomic research, structural and functional brain imaging, and engineering of relevant animal models are indispensable for identifying and testing new drug targets. These translational and interdisciplinary strategies should be supported as horizontal tools across the main research domains that have been identified by the CEA task force. The epilepsy research infrastructure, strong European tradition in epilepsy surgery, acknowledged skills in phenotyping patients and familial cases, and the dense network of centers of excellence in clinical and basic research are the main assets for undertaking these research priorities,

which should be reinforced and promoted through European research funding.

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