

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Neurological Disorders and Stroke

**EPILEPSY RESEARCH COORDINATION AND PROGRESS IN
IMPLEMENTING THE EPILEPSY RESEARCH BENCHMARKS**

A handwritten signature in black ink, appearing to read 'Elias Zerhouni', written over a horizontal line.

Elias Zerhouni, M.D.
Director, NIH

March 2005

Department of Health and Human Services

National Institutes of Health

National Institute of Neurological Disorders and Stroke

EPILEPSY RESEARCH COORDINATION AND PROGRESS

Table of Contents

Executive Summary	1
Introduction.....	2
Background.....	2
Coordination of Epilepsy Research at NIH	2
Epilepsy Research Benchmarks.....	5
Progress in Implementing the Benchmarks	6
Conclusions.....	10

EPILEPSY RESEARCH COORDINATION AND PROGRESS

Executive Summary

In Senate Report No. 108-345, the Senate Committee on Appropriations requested that the National Institutes Health (NIH) report on efforts to coordinate epilepsy research activities across NIH and on progress made to implement the Epilepsy Research Benchmarks (p. 166). The following report is submitted in response to this request.

Epilepsy is a chronic neurological disorder characterized by spontaneous, recurring seizures. The National Institute of Neurological Disorders and Stroke (NINDS) is the lead NIH Institute for epilepsy research. Several other NIH Institutes also fund epilepsy related projects, including the National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the NIH John E. Fogarty International Center (FIC). Representatives from these Institutes and Centers (ICs) and from the Centers for Disease Control and Prevention (CDC) have formed an Interagency Epilepsy Working Group. The purpose of this group is to increase communication among institutes and agencies sponsoring epilepsy-related research and explore opportunities for increased coordination. For example, representatives from other NIH ICs have participated in NINDS-sponsored epilepsy conferences and workshops in the past, and plans for joint workshops are under discussion for the future.

The NINDS, working together with the epilepsy research and voluntary communities continues to support progress toward the milestones outlined in the Epilepsy Research Benchmarks. The Benchmarks evolved from a White House initiated international scientific conference entitled “Curing Epilepsy: Focus on the Future,” held in March 2000. This conference, for the first time, focused the epilepsy research community on the concept of a cure for epilepsy, defined as “preventing epilepsy in those at risk and no seizures, no side effects in those who develop the disorder.” The research plan includes seventeen specific research “benchmarks” for the epilepsy community to achieve in the search for a cure for epilepsy. The NINDS continues to make progress in implementing the Benchmarks, as evidenced in Institute initiatives and workshops and in the large number of investigator-initiated research projects related to the Benchmarks goals.

Introduction

In its report on the Fiscal Year 2005 budget for the Department of Health and Human Services, the Senate Committee on Appropriations stated:

“The Committee recognizes that while the NINDS is the primary Institute for addressing epilepsy, several other Institutes are also involved in related research. They include the NICHD, the NHGRI, the NIMH, and the NIA. The Committee requests the Director to provide a report by April 1, 2005, on the progress made in the coordination of research efforts in epilepsy among these Institutes, and on the progress made in implementing the NINDS research benchmarks resulting from the March 2000 conference ‘Curing Epilepsy: Focus on the Future.’” (Senate Report No. 108-345, page 166)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

Background

Epilepsy is a neurological disorder of spontaneous, recurrent seizures caused by uncontrolled electrical activity in the brain. Epilepsy may result from head injuries, brain tumors, cerebrovascular events (e.g., strokes), lead poisoning, neurodevelopmental problems, certain genetic conditions, and infectious illnesses. In the majority of cases, however, no cause is ever found. Epileptic seizures can take many forms, ranging from brief attention lapses (absence seizures) to minor motor, sensory, or psychological changes (partial seizures) to prolonged losses of consciousness with convulsions (tonic-clonic seizures).

Epilepsy is estimated to affect approximately 2.3 million Americans¹, and strikes all ages and ethnic groups. For a majority of those diagnosed with epilepsy, seizures can be controlled with medicines and/or surgical interventions. However, about twenty-five percent of people with epilepsy will continue to experience seizures even with the best available treatment. Many anti-epileptic medicines have significant side effects that have an impact on quality of life. Some side effects can be of particular concern for women, children, and the elderly.

Coordination of Epilepsy Research at NIH

The National Institute of Neurological Disorders and Stroke (NINDS) is the lead NIH Institute for epilepsy research and is the predominant funding source for studies of seizure disorders. Several other NIH Institutes also fund epilepsy related projects, including the National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the NIH John E. Fogarty International Center (FIC). Representatives from these ICs and from the National Center for Chronic Disease

¹ Begley CE et al., The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. *Epilepsia*. 2000 Mar;41(3):342-51.

Prevention and Health Promotion at the Centers for Disease Control and Prevention (CDC) formed an Interagency Epilepsy Working Group. The purpose of this group is to increase communication among institutes and agencies sponsoring epilepsy-related research and explore opportunities for increased coordination. Members of the Working Group participate in NINDS-sponsored conferences and workshops; this is one way the NIH ICs maintain on-going coordination of epilepsy research activities. For example, both NIA and NINDS representatives assisted in the organization and proceedings of the International Geriatric Epilepsy Symposium in September 2003, and staff from NICHD attended the NINDS-sponsored “Animal Models of the Childhood Epilepsies” workshop in May 2004.

The members of the Interagency Epilepsy Working Group are primarily extramural program staff who administer epilepsy research grants and develop program activities to facilitate research efforts. The Working Group members communicate with each other in several ways. An NIH email distribution list has been established to alert members to epilepsy program activities through the year. An epilepsy research website (<http://www.ninds.nih.gov/funding/research/epilepsyweb/index.htm>) hosted by NINDS provides information on epilepsy-related funding opportunities and workshops supported by NIH. The website also features the Epilepsy Research Benchmarks, milestones developed by the epilepsy community in 2001 to measure progress in epilepsy research. Finally, meetings of the Working Group are scheduled on a regular basis; the most recent meeting was held in October 2004 and the next meeting will be held in spring 2005.

The Institutes and Centers represented on the Epilepsy Working Group meeting support, both individually and collaboratively, a diverse range of research related to epilepsy and seizures. Some selected examples are described below.

- The NINDS supports a number of large, Phase III clinical trials to directly compare the efficacy of standard epilepsy therapies, including a trial comparing surgery to medical management of one type of epilepsy, and a trial to compare the efficacy, toxicity, and pharmacogenomic profile of three anti-epileptic drugs commonly used to treat absence epilepsy in children.
- The NICHD and the NINDS support epilepsy prevention research in children who are at-risk for developing epilepsy as a result of very low birth weight, traumatic brain injury, viral infection, exposure to drugs of abuse, or certain rare diseases of childhood. In some cases, Mental Retardation and Developmental Disabilities Research Centers funded by the NICHD provide infrastructure for NINDS-funded, investigator-initiated epilepsy research.
- The NIMH and the NINDS support basic research to understand the underlying cellular and molecular mechanisms of seizure generation and the anti-epileptic action of drugs used to treat epilepsy.
- The NIA supports clinical studies to identify anticonvulsant drug treatment issues that are unique to elderly individuals, such as the risk of hip fractures associated with benzodiazepine use and age as a risk factor for phenytoin toxicity.

- The NIA also funds basic research studies to further understand and clarify the mechanism of action of several anticonvulsants – carbamazepine, valproate, and topiramate – either alone or in combination with the mood-stabilizer lithium, which has been reported as having “proconvulsant” action when chronically administered to rats.
- The NHGRI sponsors large scale efforts to understand complex disease genomics, such as the International HapMap project to map patterns of unique sequences in the human genome, so that genes associated with complex disease susceptibility can be identified more rapidly.
- The NIBIB supports studies to combine the use of magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) analysis of neuronal activity to adequately localize a seizure event in the brain, as well as to better understand the biochemical mechanisms and general pathology of epilepsy. Other research includes neuronal interfaces for diagnosis and therapy, data analysis software to quantify EEG signals, deep brain stimulation probes, and a novel method to predict and prevent seizures.
- The NINDS and the FIC collaborate to support international projects to develop culturally appropriate programs to decrease the burden of epilepsy-related stigma in sub-Saharan Africa, China and Vietnam.
- The NINDS supports a pre-clinical drug development program called the Anticonvulsant Screening Program (ASP) to annually screen hundreds of compounds in various epilepsy models. Recently the ASP and the NIAAA-sponsored therapeutics development program have begun to assess whether some anticonvulsant compounds might have dual-uses in other indications, like pain or alcoholism.
- The NIMH funds research to understand the mechanisms, outcomes, and beneficial effects of seizures induced by electroconvulsive shock therapy for treatment of depression.
- The NIAAA supports studies to better understand and to prevent alcohol-induced withdrawal seizures.
- The CDC supports population-based studies of epilepsy incidence and prevalence, health disparities, and burden of illness in communities. The CDC is supporting two new research projects to assess the relationships between demographic variables, socioeconomic status, health care use, cost, and outcomes in a diverse population of people with epilepsy: one project in Texas and New York City, the other in South Carolina. In cooperation with the national Epilepsy Foundation (EF), CDC also promotes the inclusion of questions regarding epilepsy prevalence in population surveys of health status (such as the Behavioral Risk Factor Surveillance System) conducted by some state health departments.
- A cooperative agreement between the CDC and the EF has produced a high school curriculum on epilepsy. This is being pilot tested by EF affiliates in over 20 states. A reference guide for school nurses is being written in collaboration with the National Association of School Nurses and will be part of a training

program for school nurses. In addition, a toolkit on the CDC epilepsy website titled “You Are Not Alone” provides access to a set of materials developed specifically to support parents in encouraging and assisting their teens with epilepsy. This kit was developed by CDC in collaboration with the EF. Using the toolkit, the EF will develop facilitated workshops for parents in 2005.

The Epilepsy Working Group members will continue to explore opportunities for collaboration and combined interest. For example, the NINDS and the NIMH share an interest in supporting research to understand and effectively treat non-epileptic seizures (NES), which have also been called pseudoseizures or psychogenic seizures. The diagnosis of NES is made when an individual has reoccurring seizures, but electroencephalogram (EEG) measurements of brain activity during the seizure show no obvious neurological abnormalities. Individuals with NES typically do not respond to anticonvulsant drug therapy, but often respond well to cognitive/behavioral interventions. Distinguishing patients with epileptic seizures from those with non-epileptic seizures is critical so that appropriate treatments are provided. The NINDS and the NIMH will jointly sponsor a workshop in May 2005 to better define diagnostic criteria for NES, develop outcome measures for clinical trials, and discuss a research strategy for this disorder.

Epilepsy Research Benchmarks

The NINDS, together with the American Epilepsy Society (AES), the Epilepsy Foundation (EF), Citizens United for Research in Epilepsy (CURE), and the National Association of Epilepsy Research Centers (NAEC), have developed an epilepsy research plan and are working together to implement the plan. This planning effort evolved from a White House initiated international scientific conference entitled “Curing Epilepsy: Focus on the Future,” held in March 2000. The conference focused the epilepsy research community on the search for a cure for epilepsy - defined as “preventing epilepsy in those at risk and no seizures, no side effects in those who develop the disorder,” instead of just treating the symptoms. The research plan includes seventeen specific research “benchmarks” for the epilepsy community to use to measure their progress towards finding a cure for epilepsy.²

The Benchmarks are divided into three broad categories; understanding the underlying mechanisms by which epilepsy develops, developing new therapies to prevent epilepsy in individuals at risk, and developing new therapies for those with epilepsy that will prevent seizures without producing side effects. The overall purpose of the Epilepsy Benchmarks is to help epilepsy researchers maximize the translation of basic science findings into improved clinical therapies. They are not meant to include all areas of epilepsy research, but rather represent significant research milestones to be achieved in order to find a cure for epilepsy. Many will require a better understanding of the causes of epilepsy, advances in technology to study these causes, and increased long-term collaboration among scientists, industry, and patient groups.

² The benchmarks were published on the NINDS website in January 2001 and are currently available at <http://www.ninds.nih.gov/funding/research/epilepsyweb/benchmarks.htm>.

A major feature of the Benchmarks is that their implementation is the shared responsibility of the entire epilepsy community, including the NIH, the extramural research community, epilepsy professional organizations, and the epilepsy patient community. Benchmarks “stewards,” senior well-established individuals in the epilepsy community, monitor the status of existing and planned research that advances the goals of the specific benchmark. Benchmark stewards also advise NINDS and other organizations on progress in implementing the Benchmarks. The next regular meeting of the Benchmark stewards will be held in February 2005, where stewards will review recent progress and consider ideas for future research efforts. The meeting will also include discussions about preliminary plans for a second “Curing Epilepsy” conference in March 2007. Representatives from the epilepsy organizations who were involved as co-sponsors of the first Curing Epilepsy conference have been invited to attend this planning meeting, as have the members of the NIH Interagency Epilepsy Working Group.

Progress in Implementing the Benchmarks

Working with the scientific and patient voluntary communities, the NINDS has continued its efforts related to the Epilepsy Research Benchmarks. Some of the recent activities that advance the Benchmark goals, including a number of NINDS-supported research projects and initiatives are highlighted below.

Benchmarks Area I: Understanding basic mechanisms of epileptogenesis

The specific milestones within the first area of the Benchmarks plan all focus on developing a better understanding of where, how, when, and why neurons begin to display the abnormal firing patterns that cause epileptic seizures (the process known as *epileptogenesis*). Epilepsy researchers are applying advances in genetics and neuroimaging techniques to the study of these fundamental questions about how epilepsy develops and persists as a chronic disease.

Although inherited epilepsy syndromes are relatively rare, studying the process that causes seizures in an inherited form of epilepsy can sometimes help to explain more common forms of unexplained, or idiopathic, epilepsy. Idiopathic epilepsies are not clearly caused by a single genetic mutation, but are more likely to be a result of complex interactions between susceptibility genes and the environment. Several efforts to identify the genetic contributions to epilepsy are underway. Selected examples of these projects are below:

- An administrative supplement program provides extra funds to NINDS-sponsored clinical trials for the collection of blood samples and clinical data to submit to the NINDS Human Genetics Resource Center: DNA and Cell Line Repository³. Epilepsy is one of three disorders initially included in the Registry. As of mid-January 2005, over 100 samples from 16 families with epilepsy have been submitted to the Registry.
- A number of investigator-initiated research projects are currently underway to map genes contributing to human epilepsy syndromes, such as idiopathic generalized epilepsy, familial adult myoclonic epilepsy and autosomal dominant partial epilepsy

³ <http://ccr.coriell.org/ninds/>

with auditory features. Other investigators are working to identify genetic factors that cause seizures in various animal models of inherited epilepsy, including fruit flies, mice, dogs, and baboons. These studies will help researchers uncover the steps that lead from the mutated gene to protein malfunctions that cause abnormal neuronal firing that in turn, leads to seizures.

- Several epilepsy researchers are continuing to discuss a large-scale, national, collaborative epilepsy phenotype/genotype project that will take advantage of advances in pharmacogenomics, genetics and bioinformatics. These discussions are an outcome of the 2002 workshop on “Molecular Analysis of Complex Genetic Epilepsies” sponsored by NINDS, the AES, and the International League against Epilepsy.

In addition to these efforts to identify gene mutations that can lead to epilepsy, NINDS-supported investigators are using DNA microarray technology to pinpoint the molecular effects of seizures on the brain. DNA microarrays measure the activity of large numbers of genes simultaneously. The technique allows researchers to study changes in gene expression caused by seizures or anti-epileptic medications in animal models of epilepsy. Clinically, DNA microarray technology is being used to identify pharmacogenomic profiles of patients who respond particularly well or poorly to a given medication. NINDS and NIMH jointly fund three DNA microarray resource centers to facilitate the application of this technology to neurological and psychiatric disorders.

In addition to genetic analysis, neuroimaging techniques such as fMRI and PET are beginning to produce clinical information about epileptic brain activity that complements the EEG, the traditional measure of neuronal activity. The NIH supports many investigators who are working to develop methods to use these dynamic, non-invasive imaging techniques to reliably identify regions of the brain that function abnormally before and during an epileptic seizure. While these techniques are critical for basic research studies of seizure mechanisms, they can also be used clinically to more accurately identify discrete epileptic foci in the brain prior to epilepsy surgery, or perhaps in the future, to deliver targeted anti-epileptic therapies directly to the brain.

Benchmarks Area II: Preventing epilepsy in individuals at-risk

It has been known for some time that certain conditions, including traumatic brain injury, stroke, very low birth weight, and some infections or inherited diseases can predispose an individual to develop recurring seizures. Currently, however, there are no effective methods to prevent epilepsy in those at-risk. One of the Epilepsy Benchmark stewards was instrumental in organizing a conference to discuss clinical trials in neuroprotection, since prevention remains an unmet goal for many neurological disorders. The conference brought together clinical researchers and basic scientists with representatives of the pharmaceutical industry, the NIH, and the Food and Drug Administration (FDA) to discuss how to evaluate pharmacological agents that may protect the brain from injury in a variety of closely related neurological conditions, including epilepsy.

Prior NINDS-sponsored trials and outcome studies have found that epileptic seizures, serious cognitive difficulties, high unemployment, and inability to live independently are common among survivors of moderate or severe head injury. For many years, the NINDS has supported clinical studies to evaluate treatments for preventing seizures

following head injury. Currently, researchers are conducting a randomized, double-blind, placebo-controlled Phase III trial to test whether magnesium sulfate, a widely used and well-tolerated compound, can improve functional outcomes and protect against developing epilepsy following moderate or severe head injury.

In addition, a pilot clinical study has been initiated to evaluate the feasibility of conducting an epilepsy neuroprotection trial in individuals with traumatic brain injury using a new generation anti-epileptic drug, levetiracetam. The study will investigate the safety, tolerability, and pharmacokinetics of levetiracetam in preventing the development of post-traumatic epilepsy. If the pilot study demonstrates that it is both feasible and safe to administer the drug within eight hours after injury and to continue treatment for six months, the results will be used to design a large Phase III study to determine if levetiracetam effectively protects against the development of epilepsy after traumatic brain injury.

NINDS-supported researchers are also investigating epilepsy prevention methods in animal models of post-stroke epilepsy and chemically-induced development of epilepsy. A small, high risk, high pay-off grant has been awarded to evaluate the value of MRI to detect epileptogenic brain regions in a rodent model of epilepsy. The ultimate goal of these studies in animal models is to establish potential therapeutics and diagnostic imaging techniques that can move forward to human testing to prevent epilepsy in those at risk.

Benchmarks Area III: Developing new therapies to stop seizures without side effects

Individuals with recurrent seizures that are intractable, that is, not controlled by current medications or surgery, make up approximately twenty-five percent of the epilepsy patient population. Even when seizures are controlled, the quality of life for some patients with epilepsy can be severely affected by the long- and short-term side effects of drug or surgical therapy. Milestones in the third area of the Benchmarks plan focus on developing interventions that stop seizures without negative side effects.

The NINDS Anticonvulsant Screening Program (ASP) is an avenue for developing anti-epileptic therapies without adverse side effects or with decreased side effects. The ASP is a long-standing and highly successful translational component of the NINDS epilepsy program that was established to identify and develop safer and more efficacious epilepsy therapies. A public-private partnership, the ASP has worked with over 160 pharmaceutical companies and 250 academic institutions throughout the world to test over 25,000 compounds for anticonvulsant potential. In 2004, NINDS established 19 new partnerships through the ASP. These efforts have most recently resulted in seven new ASP compounds being advanced through animal evaluations into human testing. The focus for the next five years is to develop novel agents for intractable forms of epilepsy and to find agents that prevent the development of epilepsy in those at risk for the disease.

Another approach to this Benchmark goal is to determine whether having surgery earlier in the course of the disease is more effective than medication at controlling seizures and in improving quality of life. Although patients with intractable epilepsy are oftentimes candidates for surgery, most patients are not referred for surgery until decades after their seizures become intractable, by which time they may have developed serious

neurological and psychosocial problems. NINDS is funding a multi-center randomized controlled clinical trial to determine whether early surgical treatment is superior to aggressive medication management in reducing seizure frequency and improving quality of life.

Physicians currently select a particular anti-epileptic drug for a newly diagnosed patient based on the seizure type and the side effect profile of the medication, but individual responses to the same medication can be very different. The NINDS is supporting a large, Phase III study to directly compare the efficacy of three commonly prescribed anti-epileptic drugs used in the treatment of absence epilepsy in children. The trial will also assess whether there are unique patterns of gene expression that correlate with treatment success; if so, these biomarkers may be useful in predicting which patients will respond best to a particular medication.

The NINDS also supports investigators working to develop new neurological devices for epilepsy. A consortium of investigators with expertise in diverse fields, such as bioengineering, computer science, neuroimaging, cellular and molecular neuroscience, and pediatric and clinical epileptology, is developing an implantable “closed loop” device for epilepsy therapy. If successful, this project will produce a device capable of detecting epileptic activity in the brain and delivering targeted therapy before the behavioral expression of the seizure can occur.

Developing validated models of epilepsy and epileptogenesis

The development and characterization of animal models of epilepsy is related to all three areas of the Epilepsy Research Benchmarks, since much of the basic and translational research required to produce new therapies ready for human safety and efficacy testing is carried out in animal models of the disorder. Although existing epilepsy models have been pivotal to the development of currently approved therapies, they are not appropriate models for all patient populations or for all forms of epilepsy. More relevant, reliable, and predictive epilepsy animal models should greatly enhance progress in the search to find preventive therapies and cures.

The NINDS, in collaboration with the epilepsy research and patient voluntary community, has held a series of workshops on improving animal models for testing epilepsy prevention approaches and new interventions for treatment-resistant forms of epilepsy. These workshops have included “Models for Epilepsy and Epileptogenesis” (Models I) in March 2001⁴, and a follow up meeting called “Models II - Identification and Validation of Epileptogenesis and Resistant Models Predictive of Human Efficacy” in September 2002⁵. Based on the recommendations of the Models I and II workshops, the NINDS issued a Request for Applications on "Model Validation for Antiepileptogenic and Resistant Epilepsy Therapies" in August 2003. Six new projects have been awarded through this initiative. In May 2004, NINDS held a workshop on “Animal Models of the Childhood Epilepsies,” since many of the current epilepsy animal models are not appropriate for the study of childhood epilepsies. The goal of the workshop was to identify the minimal criteria a model should meet to be considered a

⁴ Stables JP et al., 2002. Models for epilepsy and epileptogenesis: report from the NIH workshop, Bethesda, Maryland. *Epilepsia* 43(11):1410-20.

⁵ Stables JP et al., 2003. Therapy discovery for pharmaco-resistant epilepsy and for disease-modifying therapeutics: summary of the NIH/NINDS/AES models II workshop. *Epilepsia* 44(12):1472-8.

validated animal model of pediatric epilepsy. Workshop organizers presented the outcomes of the meeting to the larger epilepsy research community at the 2004 Annual Meeting of the AES in order to stimulate discussion of these issues in the field. A manuscript is also being prepared for publication in a prominent journal focused on epilepsy research so that the information is disseminated to the wider epilepsy community.

Conclusions

Although great strides have been made in the treatment of epilepsy since the “Decade of the Brain” (1990-2000), a significant number of individuals continue to struggle with seizures and their consequences. Another sizable population is known to be at risk of developing epilepsy because of injury, infection, or inherited disease, although prevention strategies are still not available. The NINDS and the other members of the Interagency Epilepsy Working Group are working together to support research that addresses the ongoing challenges presented by seizure disorders. The Epilepsy Research Benchmarks, a plan developed by the entire epilepsy research community, outlines milestones for the community to achieve in the search for a cure for epilepsy. The NINDS continues to place a high priority on working with the research and voluntary communities to facilitate the goal of “no seizures, no side effects” for all those affected by epilepsy.