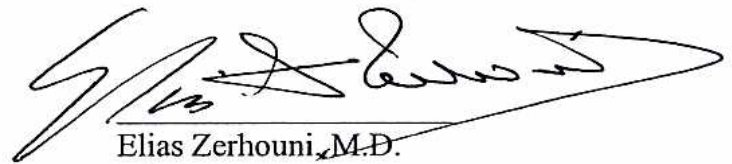


DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Neurological Disorders and Stroke

PROGRESS IN IMPLEMENTING EPILEPSY RESEARCH BENCHMARKS
AND COORDINATING RESEARCH EFFORTS

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

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Director, NIH

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Department of Health and Human Services

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National Institute of Neurological Disorders and Stroke

EPILEPSY RESEARCH BENCHMARKS
IMPLEMENTATION PLAN

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Epilepsy Research Benchmarks Implementation Plan

Executive Summary

In Senate Report No. 107-216, the Senate Committee on Appropriations requested that the National Institutes Health (NIH) report on progress made to implement the Epilepsy Research Benchmarks and to coordinate research efforts across NIH (p. 149 - 150). The following report is submitted in response to the request.

In March 2000, the National Institute of Neurological Disorders and Stroke (NINDS) and several epilepsy patient and professional groups jointly sponsored a White House-initiated international scientific conference entitled “Curing Epilepsy: Focus on the Future.” An epilepsy planning group formed after the conference developed a set of seventeen specific research “benchmarks” for the epilepsy research community to use as milestones to measure their progress towards finding a cure for epilepsy. A major feature of the Benchmarks is that their implementation is the shared responsibility of the entire epilepsy community.

In order to emphasize this responsibility, the planning group developed the concept of “stewardship”; that is, the active involvement by senior well-established individuals in the epilepsy community in the status of existing and planned research that advances the goals of the specific benchmark.

Significant progress has been made during the past year in implementing the Benchmarks. NINDS, together with the Benchmark stewards and the patient advocacy community, have held a number of workshops, conferences, and meetings and begun several other initiatives that address many different benchmark areas. A non-technical or “lay” version of the Benchmarks is being finalized, and an Epilepsy Benchmarks website is being developed.

The individual NIH Institutes that support epilepsy research continue to explore opportunities for collaboration and cooperation but, based on a review showing that NINDS funds over 90 percent of NIH epilepsy research, the NIH Director has determined that a formal Interagency Epilepsy Coordinating Committee is not appropriate at this time. Extramural and intramural program staff from NINDS, the National Institute of Child Health and Human Development (NICHD), the

National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Human Genome Research Institute (NHGRI), and the John E. Fogarty International Center (FIC) met recently to discuss their epilepsy research activities, areas of common interest, and possible collaboration, and plan to meet throughout the year. In addition, a NIH Epilepsy Special Interest Group (SIG) has been formed. The NIH will continue to build on its significant efforts in epilepsy, and, through the concept of stewardship continue to work closely with the research and advocacy communities to achieve the Epilepsy Benchmarks.

Introduction

In its report on the Fiscal Year 2003 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. As 75 percent of epilepsy cases begin in childhood, the NICHD has an important role to play in studying this disease. So, too, does the NHGRI, which is urged to assist the NINDS in the search for a genetic fingerprint diagnostic test aimed at improving drug therapy for epilepsy. The NIMH is encouraged to explore a potential link between epilepsy and mood disorders, both of which are often treated with anti-convulsant medications. Finally, the NIA is encouraged to examine epilepsy in patients over age 65. The Committee urges the Director to continue an Interagency Epilepsy Coordinating Committee that includes agency scientists and industry and patient representatives. It requests the Director to provide a report to Congress by April 1, 2003, on the progress made in the coordination of research efforts in epilepsy among these Institutes, and on the progress made to implement the NINDS research benchmarks resulting from the March 2000 conference “Curing Epilepsy: Focus on the Future.” (Senate Report No. 107-216, pages 149 - 150)

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 chronic brain disorder characterized by spontaneous, recurrent seizures that are caused by uncontrolled electrical activity of nerve cells in the brain. Epilepsy may result from several events, including head injuries, brain tumors, cerebrovascular events (e.g., strokes), lead poisoning, neurodevelopmental problems, certain genetic conditions, and infectious illnesses. However, in over 50 percent of cases, 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). The consequences of seizures, especially in children, can be serious or even fatal.

Epilepsy is estimated to affect 2.5 million Americans, and strikes all ages and ethnic groups. According to the 1990 NIH Cost of Illness report, epilepsy costs

the nation more than \$3 billion per year in direct medical costs. More recent estimates by the Epilepsy Foundation put the total annual cost at close to \$12.5 billion, including indirect costs. For a majority of those diagnosed with epilepsy, seizures can be controlled with medicines and/or surgical techniques. Many of these medicines, though, have significant side effects, which are especially of concern for women and children. About 20 percent of people with epilepsy will continue to experience seizures even with the best available treatment.

In March 2000, the National Institute of Neurological Disorders and Stroke (NINDS), together with the American Epilepsy Society (AES), Citizens United for Research in Epilepsy (CURE), the Epilepsy Foundation (EF), and the National Association of Epilepsy Centers (NAEC), jointly sponsored a two-day White House initiated international scientific conference entitled “Curing Epilepsy: Focus on the Future.” The conference energized the epilepsy research community to focus on a cure for epilepsy - defined as “preventing epilepsy in those at risk and no seizures, no side effects in those who develop the disorder” – rather than just treating the symptoms. The proceedings of the conference were published in the journal *Neurology* in October 2001.

An epilepsy planning group was formed after the “Curing Epilepsy” conference to develop a research plan for the next five to ten years. The group, made up of researchers, clinicians, representatives of the advocacy community, and NINDS professional staff developed seventeen specific research “benchmarks” for the epilepsy research community to use to measure their progress towards finding a cure for epilepsy. The benchmarks were published on the NINDS website in January 2001 at http://www.ninds.nih.gov/about_ninds/epilepsybenchmarks.htm.

Epilepsy Research Benchmarks

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.

The Benchmarks are divided into three broad categories. The first of these categories involves understanding the underlying mechanisms by which epilepsy develops. The second broad category focuses on the creation and implementation of new therapies aimed at preventing epilepsy in individuals at risk. The last category seeks to create and implement new therapies for patients with epilepsy that will prevent seizures without producing side effects.

Stewardship of the Epilepsy Benchmarks

A major feature of the Benchmarks is that their implementation is the shared responsibility of the entire epilepsy community, including NIH, the research community, the epilepsy professional organizations, and the epilepsy patient community. All of these groups must work together if the Benchmarks are to be achieved.

In order to emphasize this collaborative relationship, the planning group developed the concept of “stewardship.” This refers to active involvement by senior well-established individuals in the epilepsy community in the status of existing and planned research that advances the goals of the specific benchmark.

Stewards’ responsibilities include monitoring relevant research efforts, making the research community aware of the benchmark and related funding programs or opportunities, acting as a catalyst for new initiatives, and providing regular progress reports to the NINDS. Examples of specific activities that stewards have participated in include writing updates or reviews for journals and newsletters; discussing benchmarks at seminars, symposia, or other forums; organizing workshops and conferences; and acting in an advisory capacity to NINDS and other organizations.

Progress in Implementing Epilepsy Research Benchmarks

The 2000 “Curing Epilepsy: Focus on the Future” conference was a landmark event, in that, for the first time, the epilepsy community began to focus on curing epilepsy. The creation of the Epilepsy Benchmarks has been a catalyst for the community. Progress towards their implementation was reviewed at a meeting of the Benchmark stewards on December 9, 2002, in conjunction with the annual meeting of the AES. Benchmark stewards, along with other epilepsy researchers and the NINDS, have been involved in several workshops and other meetings during this past year to address the benchmarks. These activities, together with a number of NINDS initiatives, and patient community activities, are highlighted

below:

- On January 31- February 1, 2002, NINDS, together with the American Epilepsy Society and the International League against Epilepsy, sponsored a workshop on “Molecular Analysis of Complex Genetic Epilepsies.” While approximately 24 genes have been discovered so far that play a role in human epilepsy (including seven discovered in 2002), epilepsy researchers believe that most forms of epilepsy are due to the complex interaction of multiple genes. This workshop brought together epilepsy researchers with geneticists to establish a scientific basis for analyzing these complex genetic forms, including discussions of the best molecular and statistical methods for studying them. A report of the meeting was published in the journal *Epilepsia* in December 2002. As a result of the meeting, several epilepsy researchers are discussing a large-scale, national, collaborative epilepsy phenotype/genotype project, which will take advantage of advances in pharmacogenomics, genetics and bioinformatics.

NINDS is further facilitating genetic efforts with the establishment of a contract for a Human Genetics Repository to collect and distribute DNA cell lines and related clinical information; epilepsy is one of three disorders initially included in the Registry.

Also of relevance to this research, the Epilepsy Foundation sponsors the Epilepsy Gene Discovery Project, which is the only nationwide effort to recruit families with epilepsy to participate in genetic research studies. Five NINDS-supported researchers have applied for, and been granted, access to the project.

The above activities all directly address several Benchmarks associated with epilepsy genetics.

- Despite the introduction of several new anti-epileptic medications over the last decade, a significant percentage of epilepsy patients continue to have seizures that are resistant to medication. In addition, none of the current medications prevent the development of seizures in susceptible individuals. In March 2001, NINDS and several Benchmark stewards, together with AES, EF, and CURE, hosted the first of a series of workshops on “Models for Epilepsy and Epileptogenesis.” (Models I) The purpose of the March 2001 workshop was to explore new methods for developing more effective epilepsy therapies for both adults and children. A report of the meeting was published in the journal *Epilepsia* in November 2002.

As a follow-up to the Models I workshop, experts in anti-epileptic drug (AED) development independently convened a workshop in Philadelphia in November of 2001 to review and critically evaluate the current state of AED development efforts and discuss strategies for moving the field forward. The workshop discussions were summarized in a special issue of the journal *Epilepsia* in June of 2002.

A major recommendation of the Models I workshop specified that, in order to expedite the discovery of new treatments, development and validation of better animal models for the acquisition of epilepsy and for therapy-resistant forms of epilepsy were required. The AES and NINDS appointed a task force to examine how best to address this recommendation. The task force met in Toronto in July 2002 to plan another workshop, "Models II - Identification and Validation of Epileptogenesis and Resistant Models Predictive of Human Efficacy." The goal of this workshop, held on September 19-20, 2002, and sponsored by NINDS, AES, EF, and CURE, was to propose a number of promising candidate animal models for studying the development of epilepsy and therapy resistance; to establish criteria for evaluating their validity; and to apply these criteria to the proposed models. A summary of the meeting is currently being prepared for publication.

In addition, several Benchmark stewards are currently discussing plans to hold a workshop on models of pediatric (in particular infantile and early childhood) epilepsy. Such a workshop would explore the difficulties and challenges in developing treatments for epilepsy in children, including the lack of appropriate models of pediatric epilepsy, with special emphasis on the development of epilepsy in the immature brain and on therapy-resistant epilepsy.

The above activities all directly address several Benchmarks related to identifying and validating improved models as test systems for novel anti-epileptic therapies.

- On October 4, 2002, NINDS, working with a Benchmark steward, held a workshop on "DNA Microarrays and Epilepsy." The purpose of this workshop was to discuss the application of this new technology to epilepsy research. NINDS, together with the National Institute of Mental Health (NIMH), has recently funded three DNA microarray resource centers to facilitate the application of this technology to neurological and psychiatric disorders. DNA

microarrays are research tools that allow researchers to easily measure the activity of large numbers of genes simultaneously. Epilepsy researchers are interested in using this technology in animal models of epilepsy to measure gene activity in brain areas during seizures in order to better understand the molecular mechanisms of epilepsy. Clinically, DNA microarrays may also be useful for predicting which patients are likely responders to a given treatment, as well as identifying those who might experience adverse side effects.

A major outcome of the workshop was the formation of a task force to plan for a multi-laboratory collaboration to facilitate the distribution and integration of DNA microarray technology into the epilepsy research community, and to identify genes that may contribute to the development of epilepsy, first in animal models, and ultimately, in humans. This workshop is relevant to several benchmarks aimed at understanding the anatomical, physiological, and molecular mechanisms of epilepsy, and to developing a genetic fingerprint diagnostic test for tailoring an individualized treatment based on a patient's genetic makeup.

- In January 2003, a conference was held on clinical trials in neuroprotection. Initiated by one of the benchmark stewards, the aim was to address how to evaluate pharmacological agents that may protect the brain from injury in a variety of closely related neurological conditions. The conference took a multidisciplinary approach by bringing together clinical researchers and basic scientists with representatives of the pharmaceutical industry, the NIH, and the FDA. Rather than focus on one neurodegenerative disorder, the purpose was to identify common features among a variety of neurological disorders, including epilepsy, and discuss how to develop new treatment strategies and clinical trial designs. This workshop is relevant to the benchmark to develop clinical trials for potential neuroprotective agents in individuals at the highest risk of developing epilepsy.

- On April 10-11, 2003, NINDS held a workshop on "Imaging Markers of Epileptogenesis: New Research Directions." The purpose of this workshop was to discuss the potential role of imaging technology in studying the development and neurobiology of epilepsy. In particular, it focused on technical advances in neuroimaging that can be applied to the study of epilepsy, and brought together epilepsy basic scientists and clinical investigators with imaging scientists who have not worked primarily in the field. This workshop is relevant to several benchmarks aimed at understanding the anatomical, physiological, and molecular mechanisms of epilepsy.

- Patients with intractable epilepsy are oftentimes candidates for surgery, but most patients are not referred for surgery until decades after their seizures become intractable, i.e., not controlled by medication, by which time patients may have developed serious neurological and psychosocial problems. NINDS is currently funding a new multi-center randomized controlled clinical trial to determine whether early surgical treatment of mesial temporal lobe epilepsy, a certain type of epilepsy, is superior to aggressive medication management in reducing seizure frequency and improving quality of life. This trial is relevant to the benchmark to widen the use of surgery to treat epilepsy, including as an early form of treatment.

Lay Version of the Benchmarks and Epilepsy Benchmark Website.

Since the Epilepsy Benchmarks are geared towards the entire epilepsy community, the planning group felt it important that the Benchmarks be understandable to the patient community. NINDS program staff are working with representatives of patient advocacy groups to develop the non-technical or “lay” version of the Benchmarks. A draft of this effort is currently being reviewed by the Benchmark stewards for scientific accuracy. This summary should be completed in late Spring 2003, and will be posted on the NINDS Epilepsy Benchmarks website, which is currently being developed.

Coordination of Epilepsy Research at NIH

Although NINDS is the lead NIH Institute for epilepsy research, several other NIH Institutes also fund epilepsy related projects, including the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD), and the National Human Genome Research Institute (NHGRI). In FY2002, NIH received Senate congressional appropriations language urging the Director of NIH coordinate NIH epilepsy research efforts through an Interagency Epilepsy Coordinating Committee, to include NINDS, NHGRI, NIA, NICHD, and NIMH. Representatives from these Institutes met with epilepsy patient advocates and Congressional staff to discuss the purpose of such a committee, which would be to identify common areas of research interest in epilepsy between the Institutes and initiate collaborative and cooperative activities in epilepsy research. NIH staff discussed the many mechanisms and activities that were already available, and the initial steps that the Institutes were taking to increase cooperation and collaboration. For example, NHGRI participated in the NINDS workshop on “Molecular Analysis of Complex Epilepsy Genetics”; representatives from both the NHGRI intramural and extramural programs gave presentations at the workshop.

NINDS collected and confirmed for the NIH Director the reported FY1998 – FY2001 epilepsy funding of the relevant Institutes. The data showed that NINDS funds greater than 90 percent of NIH epilepsy research. After considering the distribution and type of epilepsy research reported by these Institutes, the NIH Director determined that a formal Interagency Epilepsy Coordinating Committee was not appropriate, but encouraged the named Institutes to continue to explore opportunities for collaboration and cooperation. In response to this, staff from the five NIH Institutes named in the report language (NINDS, NICHD, NIMH, NIA, and NHGRI) met to discuss epilepsy research endeavors. The meeting was attended by both extramural program staff, who administer epilepsy research grants, and intramural scientists with an interest in epilepsy research. In addition, a representative from the NIH John E. Fogarty International Center (FIC) participated. The meeting attendees reviewed the epilepsy research interests of the different Institutes, and discussed areas of common interest that could be explored for possible collaborative activities. Outcomes of the meeting included a decision by the participants to meet at least twice a year, to develop better methods for alerting meeting participants to epilepsy program activities through the year (i.e., through the development of a web page or Listserv), and to invite representatives from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the Centers for Disease Control and Prevention (CDC) to participate in future meetings. NINDS will coordinate these meetings. In addition, NINDS intramural scientists invited the participants to join the newly formed NIH Epilepsy Special Interest Group (SIG), composed of both NIH intramural research and extramural program staff, which will meet on a regular basis to stimulate communication and collaboration among NIH scientists and administrators who are interested in clinical and basic epilepsy research.

Conclusions

The March 2000 “Curing Epilepsy: Focus on the Future” conference was a landmark event for the epilepsy field. For the first time, the epilepsy community began to focus on curing epilepsy, instead of treating its symptoms. The Epilepsy Research Benchmarks are a direct result of this new vision, and provide milestones to measure progress towards the cure.

NIH, working closely with the Benchmark stewards and the epilepsy research and advocacy communities, have made significant progress during the past year in implementing many of the Benchmark areas. In addition, the NIH Institutes who

support epilepsy research have begun to collaborate more closely to review their activities and identify areas of common interest.

The Epilepsy Benchmarks represent research milestones, but are not meant to encompass all areas of epilepsy research. NIH is committed to building on its ongoing significant efforts in all areas of epilepsy, and to working closely with the research and advocacy communities to achieve the Epilepsy Benchmarks and move the field closer to the ultimate goal of curing epilepsy.