Interview

The National Institute of Neurological Diseases and Stroke/American Epilepsy Society benchmarks and research priorities for epilepsy research

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■ What led to the convening of the ‘Curing Epilepsy: Focus on the Future’ conference in 2000 & what were its primary aims?

The fundamental driving force was a sense of frustration within the patient advocate community about the inadequacy of epilepsy care, and the sense that more needed to be done to translate research efforts into tangible benefits for the patients and their families, who had to struggle with the disorder. Of course, this focus is not dissimilar to the impetus of many of the organizations aligned with other disease areas – the public has been demanding that we push as hard as we possibly can to make progress to better the lives of people who are suffering from these different diseases, and epilepsy is a prime example of this. The original conference was a result of a confluence of interest and attention by the lay organizations, including Citizens United for Research and Epilepsy (CURE), the Epilepsy Foundation of America (EFA), and other groups, the National Institute of Neurological Diseases and Stroke (NINDS), and the professional communities led primarily by the American Epilepsy Society (AES).

In the early discussions of the design of the conference, the organizers agreed that the focus needed to be on the quest for cures for epilepsy. We defined this as ‘no seizures and no side effects’ in people with epilepsy, and preventing epilepsy from occurring in the first place in those

people who are at risk [101]. I believe that most people felt that the conference was a spectacular success; the program covered a wide range of basic and translational neuroscience research that was presented in a way that could be understood by both trained scientists and the lay public. During the meeting, there was a group of us who felt that it would be important to take note of where the field currently stood and try to predict what areas in epilepsy research might be the most likely to lead to improvements in the lives of patients. We thought it would be interesting to try to identify what we felt should be the highest priorities for research efforts going forward, given our current state of knowledge, and recognizing that it is always impossible to predict the course of science. That led to a hastily convened, noon-time, *ad hoc* meeting of anyone who was interested in sharing ideas about how to define the research agenda going forward. There were some 75–100 people at the meeting, and we had an extremely lively discussion as to whether or how one could predict what the priorities should be. Ultimately, we came up with three overall areas of inquiry:

- Understanding how epilepsy develops;
- Finding ways to prevent seizures from developing in at-risk individuals;
- Finding better ways to stop seizures without side effects in those who have epilepsy.

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These became the three general categories of the so-called ‘Epilepsy Research Benchmarks’, which were further developed through a series of follow-up meetings and publicized on the NINDS website and in various published articles [10].

■ How forward-looking are the benchmarks?

When the benchmarks were first conceived, my colleagues and I thought it would be important to consider them as applying to a long-term timeframe of roughly 5 years, since there were plans for a follow-up conference to be held approximately 5 years later. That is, we wanted to be able to determine whether or not some of the areas of emphasis that we felt were important in 2000 would actually prove to be so over subsequent years. Thus, rather than creating nebulous, albeit important, areas of priority that might be open-ended and unanswerable over the short term, we attempted to come up with goals that were reasonably specific. If you look at the benchmarks that originated in 2000, as well as those revised in 2007, many are quite explicit. Following the second Curing Epilepsy conference, held in 2007, we came up with the idea of specifying both short- and long-term goals. In the published 2007 benchmarks, short-term goals were thought to be achievable in less than 5 years, while longer-term goals were deemed feasibly achievable in approximately 5–10 years [1].

■ What roles do biomarkers play in the ongoing research priorities?

I think that Dr Jerome Engel (Brain Research Institute, UCLA, USA) has done a beautiful job of describing the concept of biomarkers and identifying what their roles are, and the many aspects within epilepsy; this can be found in the article by Engel in this issue of *Biomarkers in Medicine* [2].

The official NIH definition of a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. The identification of biomarkers in epilepsy is critical because, analogous to other diseases, we need to have better measures of the presence of epileptogenesis in those people who

are at risk of developing epilepsy. We also need markers of the degree of severity of epilepsy in people who have the disease, markers of the progression or remission of the disease, and markers of the likely therapeutic response given the many treatment options that exist. Unfortunately, our ability to assess these various aspects of epilepsy in patients is woefully inadequate. Patients with epilepsy come to us with three questions, which I consider the three universal questions for people who are seeking help because of an illness:

- What is wrong with me?
- What can you do to help me?
- What does my future hold?

Unfortunately, we continue to be unable to answer any of these questions in the vast majority of patients with epilepsy. The research community has made many significant advances in understanding the basic biology of epilepsy, but there remain tremendous gaps in our knowledge. For example, we have a very limited understanding of the basic mechanisms underlying epilepsy that develops after traumatic brain injury or stroke, or in the setting of a brain tumor or infection. There have been great strides in identifying the genes that can cause epilepsy [3–5], but in most cases those are relatively rare forms of familial epilepsy and we don’t understand the multigenic effects for the more common forms of so-called ‘nonacquired’ epilepsies. Thus, for most patients we really do not know why they have developed their seizure disorder. For the second question, ‘what can we do to help?’, we have a whole array of medications, surgical treatments and, most recently, various forms of brain stimulation that have been shown to be effective in epilepsy in general. However, we really have very little guidance with regards to which particular therapy is going to be the most effective for a given patient. This is a prime example of how the lack of biomarkers results in an inability to know which treatment is best for a given patient. In most cases, the choice of a particular medication remains, at best, a partially educated guess. Similarly, we have very little to go on for predicting whether or not a drug may cause side effects, which are relatively common and, in some cases, quite

serious. Again, this is another example where the lack of biomarkers is limiting us in our ability to help our patients. Finally, with regard to the question, ‘what does my future hold, will my epilepsy ever go away and will there be a day when I can come off of these medications and feel certain that I’m cured?’ Unfortunately, because of our limited understanding of the basic biology of epilepsy and epileptogenesis, and the lack of biomarkers, in most cases we are unable to determine whether the epilepsy has gone into remission or been fully cured.

■ How promising are current research efforts in the quest to meet the benchmarks?

Despite the limitations that we continue to face in clinical care; I think there is great hope for some substantial progress in both the short and the long term. If we look at the latest set of benchmarks that were a result of the ‘Curing Epilepsy 2007’ conference [1], we can see that, although it is still early, some significant advances are being made. In the area of understanding basic mechanisms of epileptogenesis, there has been very interesting work investigating the role of inflammatory factors that affect the excitability of neural networks, which has opened up new avenues for therapeutic intervention [6]. Studies of basic mechanisms of post-traumatic epilepsy, a relatively neglected field despite the importance of the clinical problem, have also been very promising [7]. There has been some very good work in the area of models of infantile spasms and other epileptic encephalopathies of infancy and childhood [8].

In addition, research in diseases of neurodevelopment, such as tuberous sclerosis, has led to remarkable new insights into the molecular pathways involved in pathogenesis and, as a result, the identification of drugs or agents that can actually interrupt the abnormal pathway [9]. These are all great examples where efforts in the laboratory aimed at understanding basic mechanisms can translate into therapies for our patients. In the area of biomarkers, there’s been very exciting work looking at electroencephalographic biomarkers. For example, recent studies have demonstrated that high-frequency oscillations appear to identify the region of neuronal networks that

are most likely to be the source of seizures, and very recent reports suggest that the targeting of high-frequency oscillations in surgical treatment may improve outcome [10]. A nice example of a biomarker that has had a very clear, direct, impact on the care of patients is a genetic marker (a polymorphism in a HLA gene), identified in 2004, that is associated with an exceptionally high risk of developing a severe pathological immune response called Stevens–Johnson syndrome in patients treated with the antiseizure drug carbamazepine [11]. The marker is significantly more common in individuals of Han Chinese descent, which means that practitioners should avoid prescribing this drug in at-risk individuals. There are substantial efforts underway to determine whether there are other ethnic populations with increased risk and other markers for susceptibility to other medications. I think this is a clear example of pharmacogenomics and its potential impact on patients with epilepsy, and just the beginning of things to come.

In the second benchmark area – developing new therapeutic strategies and optimizing approaches to cure epilepsy – progress appears to be a bit more limited. There have had some interesting results in the field of brain stimulation. Two recent clinical trials have demonstrated that focal brain stimulation, in either the anterior nucleus of the thalamus [12] or through electrodes placed on or near the presumed seizure focus [13], can decrease seizure burden in patients, although I think the extent of beneficial effect was not quite as dramatic as many people had hoped. Related to this is work looking at seizure prediction and seizure detection that could give the patient a warning of when a seizure is likely to occur, so that the patient or caregiver could intervene with a fast-acting medication. Another intriguing avenue of research related to therapeutics is in the use of vectors, such as adenovirus or stem cells, for introducing seizure-suppressing molecules or anti-epileptogenesis molecules into the brain [14]. So, again, there are efforts related to these benchmarks that hold great promise.

Finally, comparing the initial benchmarks in 2000 to those that were developed in 2007, a new area was added to bring focus to the important issue of the comorbidities associated with epilepsy

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and its treatment. I think it's actually been quite remarkable how this addition to the benchmarks has galvanized the research community to pay much more attention to an area of epilepsy that previously was relatively disregarded. These comorbidities include psychiatric illness, sudden unexpected death in epilepsy, sleep disorders and a whole host of other forms of suffering that many patients with epilepsy have in addition to the experience of having seizures. This has actually gained a lot of traction among researchers, and there are many individuals and groups of investigators who are now submitting grant proposals to study these comorbidities. With regard to sudden unexpected death in epilepsy, there has been some very exciting progress made in identifying specific molecular factors that appear to place an organism at risk for both epilepsy and cardiac dysfunction, and work is going on now to see how these results apply to humans [15].

■ **Is there another future reappraisal planned & what are the main research priorities moving forward from 2007?**

I know that the NINDS is beginning to plan a third Curing Epilepsy conference, which is likely to occur in 2013. In terms of the priorities going forward, we'll have to see what the attendees at the 2013 conference feel, but I think there will be a renewed call for identifying biomarkers that will enable us to identify patients who are at risk in developing epilepsy after an acquired lesion, such as traumatic brain injury, stroke or encephalitis, so that we can know in advance that these are people who are likely to develop epilepsy and, therefore, apply an intervention that prevents epilepsy from occurring in the first place. There has already been much discussion, which I think will continue, about having a better idea of the reliability and validity of the animal models that are used to study epileptogenesis, and I suspect that the research community will attempt to reach a consensus as to which animal models are best to use for specific epileptic conditions. I think the area of defining the functional networks that cause seizure generation and then having targeted interventions that reverse that process will be a focus;

I alluded before to the somewhat limited results of the clinical trials with brain stimulation to date. The results emphasize the importance of having a better understanding of the fundamental properties of seizure foci and how they can be ablated with various kinds of targeted interventions. And with regard to the benchmark area of comorbidities, I think there's going to be a renewed call to increase our understanding of the natural history of the comorbidities and epilepsy, and to search for their genetic and environmental causes. Importantly, it is now thought that patients who are at risk of developing epilepsy may, in fact, have parallel or related abnormalities of network dysfunction that put the patients at risk of psychiatric comorbidities, even before the epilepsy has appeared. I think we will see great progress in this area in the not-too-distant future.

■ **Finally, which aspects of future epilepsy research hold particular interest and excitement for you personally, & what kind of timescale are these research efforts working on?**

I'm particularly interested in the genetic determinants of epilepsy in patients who have no other obvious cause for the development of their epilepsy. I've had the good fortune of working with colleagues from around the world who have organized two rather large-scale efforts. One is called the Epilepsy Phenome/Genome Project (EPGP) [102]. This is a project that was conceived almost 10 years ago and received funding from NINDS 5 years ago, and which is bringing together groups from around the world to collect and carefully phenotype a large number of patients with nonacquired epilepsy, and banking DNA samples at a central repository that will then be used for genomic analysis. The hope is that we can make useful contributions to the growing number of discoveries that are identifying the genes that cause the more common forms of epilepsy, and also identify markers (similar to the HLA story that I mentioned before) that would help guide the choice of therapy; that is, which medications are most likely to be effective and not be associated with side effects. The second project, still in its planning phase, is an international collaborative

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effort to apply cutting edge technologies and genomic analyses, including whole exome and whole-genome sequencing, to analyze the samples we've been collecting in the EPGP, as well as other large cohorts that have been assembled by various groups around the world. This project has been catalyzed in large part by the new NINDS-sponsored 'Epilepsy Center without Walls Program', which aims to engage the epilepsy research community in collaborations to solve challenges related to the Epilepsy Research Benchmarks [103]. I think that the possibility of seeing many thousands of whole genomes analyzed in patients with epilepsy within the next 3–5 years is now a reality. What we'll discover out of that level of analysis remains

to be determined, but clearly the opportunity for understanding the contribution to common forms of epilepsy at the genetic level is certainly within our reach.

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