Why did you focus your clinical and research work on epilepsy?

Epilepsy is a unique model disease that allows us to examine human brain function on different levels. While I understand this statement now, it was an intuitive attraction thought led me to the field early on. Epilepsy stands exactly at the border between neurology and psychiatry; the study of it unifies two of my main interests in brain and behavior relationship. My other two interests are in neuroimaging and neurophysiology of the central nervous system, subspecialties that also play a central role in the practice of epileptology and related research work.

What are the biggest changes in our understanding of epilepsy and its treatment?

In terms of diagnostic developments that can help us in treatment, there is a tremendous advancement in technology. High-resolution imaging with post processing of magnetic resonance imaging is very helpful for studying the brain of patients with epilepsy. Digital long-term video electroencephalograph (EEG) monitoring has become increasingly available. Functional imaging studies and advanced neurophysiologic techniques are in development or in use now. Patients with medically refractory epilepsy may be candidates for surgical therapy. Epilepsy surgery itself has become more widely accepted as an effective and potentially curative means of treatment.

Currently available medications more or less suppress seizures and are targeted toward relieving symptoms. However, we do not yet have disease-modifying therapies for epilepsy. Therefore, understanding the pathophysiology and mechanisms of epileptogenesis is extremely important. Much work is being conducted in the laboratory, including using in vitro and in vivo models in animal studies, that needs to be translated to the human condition.

The other aspect is better understanding of pharmacoresistance in intractability. Why do people present or develop intractable epilepsy in the course of their disease? Interestingly, intractability is not particular to epilepsy; there is intractability in psychiatry, with treatment-resistant depression (TRD) and treatment-resistant psychosis, as well as in other medical diseases. Thus, shared mechanisms have been postulated. We are developing animal models that are specifically geared toward intractable epilepsies, because the way we have been screening antiepileptic medications so far has not taken into account the sizeable and challenging population of patients with medically refractory epilepsies. Clearly, this is an area where we need to focus more.
Is there a delay in some people being diagnosed with epilepsy?

Yes, there is a significant delay. Excellent psychiatrists and neurologists may miss the diagnosis. Epileptologists, however, have the advantage of access to a surrogate clinical marker—the EEG. More importantly, now we have access to continuous video EEG recordings, which are geared toward capturing the patient’s typical spell and characterizing the correlate on the EEG at the same time. That helps diagnostically, especially with atypical spells and other paroxysmal behaviors that cannot be classified based on history alone.

Depending on the type of seizures, the delay to the diagnosis is variable. Patients with more commonly understood seizures, such as generalized tonic-clonic seizures, usually receive proper diagnosis early on. However, delay in diagnosis can be significant for complex partial or simple partial seizures. Often, families, caretakers, or even patients are not aware of the patient’s seizures. Episodes in children may be misconstrued as daydreaming. The same applies for the elderly, who may present with new-onset seizures. In fact, the incidence of epilepsy has a bimodal distribution in the very young and the very old. Spells in the elderly may be difficult to diagnose. They do not exactly follow the book. It may take several months (on average 1–2 years) to identify these cases of epilepsy.

Once the diagnosis is made, appropriate treatment must be instituted. Unfortunately, in approximately one-third of patients diagnosed with epilepsy, medications will not work well or will be associated with unacceptable side effects. Therefore, seizures are not well controlled, even if the patient is quite adherent to the prescribed treatment. There is a tremendous delay from the time of the diagnosis to the time that intractability is recognized. Thus, it is important to identify these patients early on. These patients need to be referred to fourth-level epilepsy centers where comprehensive evaluations can be conducted. If they are surgical candidates, epilepsy surgery can be offered early on in the course of the patient’s epilepsy. This is important because of the detrimental effects of uncontrolled seizures, in terms of quality of life, lack of independence, and progression of disease.

Other common type of spells, the so-called “psychogenic nonepileptic seizures,” are often mistaken for seizure-like activity. However, the pathophysiology between psychogenic seizure and epileptic seizure is fundamentally different. Misdiagnosis is quite common, and patients are often subjected to long-term treatment with antiepileptic medications and unneeded side effects. Potentially harmful interventions, including intubation and pharmacologically induced coma, have also been reported in a subset of these patients for so-called non-epileptic seizures.

When a patient is evaluated with an EEG or continuous monitoring, is diagnosis based exclusively on clinical aspects?

When confronted with a potential diagnosis of psychogenic nonepileptic seizures, the gold standard is to refer the patient early on for video EEG recording. This is cost effective as it can avoid many years of unnecessary treatment. Video EEG is useful in making the correct diagnosis, but there may be uncertainty at times. For example, if the patient comes into the monitoring unit and stays there for 1 week and the typical episode is not captured, the physician must go by the history and available information. If the patient has episodes that lead to loss of consciousness, even if these are really nonepileptic, restrictions in the patient’s lifestyle related to seizure precautions must be applied, including driving restrictions.

On other occasions, a patient may exhibit a paroxysmal behavior but there is no signature of seizure activity on the EEG. Then the behavior has to be analyzed systematically by looking at the video of the episode, which can either be recorded in the hospital or at home. These videos must be reviewed by experienced interpreters, who will focus on the pathophysiological underpinnings and evolution of recorded manifestations. Thus, documentation of seizures can be made even in the absence of any EEG abnormalities or when EEG is inconclusive. It is important to remember here that the diagnosis of epilepsy is first and foremost a clinical one that relies heavily on a careful history and description of the patient’s spells. EEG is a quite helpful tool, but needs to always be viewed from within the clinical context. In addition, we are interested in developing screening questionnaires that can be available to primary care physicians so that they are attuned to the possibility of nonepileptic seizures. These screening instruments would also suggest when a patient should be referred for video EEG evaluation.

Is there a scientific basis for the United States Food and Drug Administration labeling all antiepileptic drugs with a suicide warning?

I think there are several criticisms about the methodology and results of the meta-analysis conducted by the FDA, pooling data from 200 clinical studies of several antiepileptic medications, which were studied not only in patients with
epilepsy, but rather in a number of heterogeneous conditions (eg, treatment of chronic pain, migraine, and psychiatric indications such as anxiety and bipolar disorder). Currently, I believe the FDA is trying to come up with a class warning for all antiepileptics because some were not included in their initial warning in 2008.

However, the issue is more complex than what appears at the surface. For example, psychiatrists are also familiar with warnings that relate to the initial introduction of antidepressants and the relationship to suicide. Depression is a very common comorbidity in patients who have epilepsy. Depression and epilepsy share common pathophysiologic mechanisms. In adults, epilepsy commonly arises from the limbic system, which is at the center of mechanisms that control emotions and that may underlie depression. In addition, uncontrolled seizures, their unpredictability, and restrictions related to seizures also create a significant burden and frustration in patients. There is also the stigma associated with epilepsy that can have major psychosocial implications.

I would think that ~50% or more of our patients attending the outpatient epilepsy clinic at a tertiary epilepsy center have comorbid mood disorders. Recently, we have instituted screening methods where all of our patients are asked to complete questionnaires, including a suicide screen, a patient healthcare questionnaire, and a depression severity questionnaire. This occurs before medication is prescribed. Rarely a full day at the epilepsy clinic goes by without encountering a patient with a moderate to severe depression based on these measures. Ever so often one of these patients will present with a high risk of suicide, as assessed by suicidal ideation in the past 3 months or prior suicide attempt at any time, and positive responses to emotional items that are consistent with serious depression. Thus, screening for suicide and discussing it openly with patients is extremely important. In this respect, I think that the FDA warning may in fact help clinicians pay more attention to this important facet of epilepsy care. It is increasingly recognized that the impact of comorbid psychiatric conditions like depression and anxiety on quality of life can be worse than the effect of epilepsy. Lastly, I should emphasize that nonadherence to antiepileptic drug therapy can lead to a significant increase in accidents and deaths. This fact is well-documented, and therefore treatment with antiepileptic medications should not be withheld even in patients with suicidal risks. Rather, these patients should be managed closely by both neurology and psychiatry. Good communication between the treating neurologist and psychiatrist is essential.

Is suicide screening as a mode for suicide prevention effective?

I wish it were. However, it does make clinicians more sensitive to the existence of an underlying mood disorder in patients who voice their frustration and feelings about suicide. Being acutely suicidal upon screening merits immediate referral to a psychiatrist who initiates appropriate treatment. Many of our patients with epilepsy also receive treatment with antidepressants. It is of course important to understand the need for concurrent antidepressant therapy because even if the seizures are controlled, the quality of life, in general, is not improved unless the mood is also improved.

Given that several of the anticonvulsants are also effective in treating bipolar disorder, do bipolar disorder and epilepsy share a common pathophysiology?

One possibility why these medications have efficacy in both conditions is that these conditions have a shared underlying pathophysiology. Further, the biochemistry, neurotransmitter, or network abnormalities in both conditions can be modified by the same medical interventions. Take electrical stimulation, for example, which is being explored not only for epilepsy but also for mood disorders and other psychiatric and neurologic conditions. Organic psychiatry plays an important role in understanding and treating these conditions.

However, it should also be remembered that medications that are effective in the treatment of epilepsy have a variety of mechanisms of action. Few, if any, antiepileptics have a single well-characterized action that targets the expression of abnormal hyperexcitability and/or hypersynchrony. Although rational development of antiepileptics is a desirable goal, it should be recognized that most medications currently on the market are not the product of rational drug design. Most available antiepileptics have multiple and unknown mechanisms of action. Even in cases where we have been able to identify the relevant molecular target or pathway, we still cannot exactly explain how modulation of this pathway can result in seizure suppression.

Is vagus nerve stimulation (VNS) effective in treating epilepsy?

When seizures are not well controlled we often rely on combination therapy. By increasing doses and adding more medication the burden of side effects is inevitably high. Thus, development of nonpharmacologic treatments is important. VNS has been a welcome addition to our armamentarium in treating epilepsy, though it is intended for the treatment of medically refractory epilepsy. The premarketing data that led to FDA approval of VNS were fairly convincing, though more systemic and control studies are needed for VNS treatment in TRD.

Approximately one-third of patients with epilepsy will derive an appreciable benefit from VNS, but it has not been possible to predict, before implantation, which patients will benefit. Therefore, prior to VNS implantation, it is important to conduct a thorough preimplantation workup. This should be done by physicians who are used to evaluating treatment-resistant epilepsy. The same should apply for patients with
TRD, and I would think that a similar approach would be necessary for patients with TRD, although I have no personal experience with the use of VNS in this patient population.

In our practice, we first need to confirm that the diagnosis of epilepsy is correct. I sometimes see patients with nonepileptic seizures who have already had a VNS implanted. This is, of course, inappropriate and results in poor utilization of our resources. Before implanting the VNS we need to establish that there are no other curative options available for this patient. For example, the a patient may be a candidate for potentially curative resective epilepsy surgery. VNS, in contrast, may be beneficial but rarely eliminates seizures long-term; therefore, it is considered more of a palliative intervention. There may be an additional benefit in terms of mood, attentiveness, and overall cognitive function, independent of seizure control. Lastly, VNS for the treatment of epilepsy is attractive because it is less invasive compared to direct or deep brain stimulation. At this time, studies are ongoing to examine the utility of electrically stimulating other brain targets for the treatment of intractable epilepsy, as well as TRD. Deep brain stimulation for epilepsy may be around the corner.

At the recent annual meeting of the American Epilepsy Society in December 2008, the results of a prospective, randomized, double-blind study examining the effectiveness of bilateral deep brain stimulation of the anterior nucleus of the thalamus were released. The Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy study showed that stimulating the left and right anterior nucleus of the thalamus produced a modest, but statistically significant median percent reduction in seizures compared to a no stimulation control group at the end of the blinded phase of observation. These results have not yet been published.

Another device-based trial for the treatment of epilepsy is currently ongoing. This study utilizes a responsive brain stimulation approach to directly target/stimulate the putative epileptogenic focus. Enrollment in this study was just completed; results should be anticipated sometime in 2010 after completion of the blinded period of observation for all enrolled subjects.

What are the major side effects of VNS?

Stimulation-related side effects occur only at the time of stimulation, such as hoarseness, discomfort in the throat, shortness of breath, changes in speech, and coughing. These are usually self-limited and can also be modified by changing the parameters of stimulation. There are no known major side effects. However, it should be pointed out that long-term studies are lacking because VNS for epilepsy was only approved in the US the past decade.

There are situations where VNS may not be ideal. For one, VNS may worsen obstructive sleep apnea; the manufacturer also recommends that the device should be used with caution in patients with underlying pulmonary diseases like chronic obstructive airway disease. There are also safety issues related to MRI, where the VNS scan must only be conducted under specific conditions, with the device turned off, and with the use of specific coils and MRI sequences, which are known to be safe in this setting. This remains a problematic issue, especially for patients who have a chronic condition and may need sequential imaging. That is a major issue; that is, at least until the technology advances and MRI-compatible devices become available.

REFERENCES
