Neuroprotection and antiepileptogenesis

Where are we now?

Marc A. Dichter, MD, PhD, and Andrew J. Cole, MD, FRCP(C)

Current epilepsy treatment is focused on suppressing seizures and ameliorating secondary effects of seizures. Essentially, all available therapy is symptomatic. In most other areas of medicine, however, treatments are increasingly focused on preventing the development of the disease (e.g., vaccination), in curing the disease once it appears or, at least, preventing the progression of a disease at an early stage. Attention is finally being focused on these issues with regard to epilepsy, but progress remains slow.

This supplement has reviewed several important issues that must be addressed for new therapies to be developed that will either prevent the development of epilepsy for those at risk, arrest the progression of brain dysfunction that is often a part of the epileptic process, or cure individuals who have developed epilepsy. For any or all of these issues to be addressed, fundamental knowledge about the epileptic process itself, from the perspective of the concept that epilepsy is, in fact, a progressive neurodegenerative disease, must be delineated and the scientific underpinnings of the process must be defined.

It has long been known that many forms of congenital and acquired brain injury produce brain hyperexcitability that results in epilepsy. The precise changes in the brain that underlie hyperexcitability are being identified and the mechanisms responsible for these changes are also being elucidated. This remains a work in progress, as reviewed by Dr. White. Many changes in the epileptic brain have been identified. However, distinguishing alterations that are compensatory and protective from those that produce epilepsy has not yet been possible. Similarly, identifying the key alterations, starting at the time of "injury" and occurring during subsequent "latent" periods still needs to be accomplished. This is a particularly important endeavor because it is probable that effective intervention will be directed against these processes to prevent epileptogenesis after different forms of brain injury and that strategies directed against such processes may not involve standard antiepileptic drugs (AEDs).

Dr. Herman reviewed the data with regard to human patients who experience various forms of brain "insult" that lead to epilepsy. This clearly happens, and modern epidemiologic studies are revealing relative risks for many different forms of acute and chronic injury. These are the individuals who will need to be treated to prevent epilepsy, once they can be identified and appropriate treatments are discovered. These are also the individuals who will need to be recruited into clinical trials to test putative antiepileptogenic agents once they emerge from the laboratory. Data discussed by Drs. Pitkanen and Schachter indicate that efforts in both the laboratory and clinical domains to prevent the development of epilepsy after experimental or natural injuries have thus far been unsuccessful. To date, the overwhelming majority of the limited number of studies performed have used a few of the older AEDs in the clinical setting and more of the newer drugs in the laboratory. However, studies of this kind remain limited, and judgment should be reserved about the ultimate success of such treatments. Of particular significance is the absence of any validated surrogate marker for the brain changes associated with epileptogenesis that can be used in either the laboratory or the clinic.

If we are currently unable to prevent the development of epilepsy after brain injuries, can we modulate the potential deleterious effects of the epileptic process in patients who already have epilepsy? First, we must determine whether, in fact, ongoing brain damage occurs in the context of intractable seizures. Dr. Holmes reviews this area and makes a compelling case that at least some forms of seizures induce brain damage and further epileptogenesis. However, not all seizures appear to have similar "toxic" properties, and the long-term effects of various kinds of seizures are clearly age-related. In many cases, very young animals are more resistant to the usual forms of seizure-induced brain damage, even damage that occurs after severe status epilepticus. However, it is also clear that absence of cell loss and obvious injury does not mean absence of deleterious effect. Animals that sustain seizures at a very young age appear more susceptible to brain damage later in life from "second hits," seizures or otherwise, and also have cognitive and behavioral changes that require subtle

From the Departments of Neurology and Pharmacology, University of Pennsylvania School of Medicine and the David Mahoney Institute of Neurological Sciences and Penn Epilepsy Center, Philadelphia, PA (Dr. Dichter), and the MGH Epilepsy Service, Massachusetts General Hospital, Department of Neurology, Harvard Medical School, Boston, MA (Dr. Cole).

Publication of this supplement was supported by an educational grant from GlaxoSmithKline. The sponsor has provided A.J.C. with honorarium during his professional career.

Address correspondence and reprint requests to Dr. Marc A. Dichter, Department of Neurology, University of Pennsylvania, 3 West Gates, 3400 Spruce St., Philadelphia, PA 19104; e-mail: dichter@mail.med.upenn.edu

testing to reveal. Therefore, the animal data indicate that recurrent seizures are bad for the brain.

What about the human data? Dr. Duncan addresses this issue from a different but equally compelling perspective. Although acknowledging the difficulties inherent in rigorously addressing the issue of whether seizures induce brain damage in humans, he cites several important studies demonstrating that, in some patients, recurring generalized seizures are associated with identifiable and quantifiable changes in brain anatomy, as measured most precisely by MRI. He points out the difficulty in determining whether the seizures themselves are the injurious agents or whether an ongoing neurodegenerative process could be simultaneously responsible for both intractable seizures and altered anatomy. He also discusses a number of studies that fail to show major anatomic deterioration in populations of people with epilepsy, although within such populations there may be subgroups that demonstrate altered anatomy over time. Finally, he discusses the use of imaging techniques and other potential surrogate markers in possible future studies of antiepileptogenesis and of neuroprotection in epilepsy.

Finally, once it has been ascertained that a specific epileptogenic process occurs after various brain injuries and that seizures themselves may injure the brain, causing both secondary effects on cognition and behavior, and more seizures, one can ask whether there are any data to suggest that any of the drugs currently available are effective either for preventing epilepsy or for neuroprotection. Dr. Pitkanen reviews currently available literature from laboratory experimentation. In several experimental models of seizure-induced brain damage (severe status epilepticus or continuous electrical stimulation), drugs that suppress the seizures have been shown to protect against damage. The fact that none of these treatments administered directly after the status epilepticus is effective indicates that they work by suppressing the seizures and seizure-induced excitotoxicity rather than by modifying subsequent brain reactions. Unfortunately, as discussed in Dr. Schachter's chapter, treatment of patients with AEDs that suppress ongoing seizures has not been shown to modulate the course of the epilepsy or the development of intractable seizures in a significant fraction of patients who present with epilepsy. It should be noted, however, that the animal experiments demonstrating a positive effect of AEDs are conducted with either status epilepticus or other severe forms of seizures, whereas the human data are from studies of patients with much more "benign" forms of seizures.

Dr. Pitkanen also points out that there are no data indicating that treatment during the "latent period" after status epilepticus can prevent epileptogenesis. However, there are a number of reports that treatment with agents not commonly thought of as AEDs can alter the kindling process. Whether these will ever be useful in a clinical setting remains to be seen. Dr. Pitkanen also raises another important issue about disease modification after the appearance of a first seizure or in established epilepsy. Once again, the data are disappointing. However, she raises an important issue that is not often considered: could modulation of seizure severity affect the degree of seizure-induced damage? Shortening the duration of seizures or limiting their spread might prevent some of the damage induced by recurrent seizures. This is an issue that will require further exploration when clinical trials of antiepileptogenic agents or neuroprotective strategies are formulated.

The data presented by Dr. Schachter with regard to available human studies designed either to prevent epilepsy or to cure it can only be described as disappointing. To date, even when we can identify individuals at great risk for development of epilepsy, there are no effective strategies for prevention. Similarly, there is no evidence that treating patients to suppress seizures has a secondary effect of preventing the degenerative process or of preventing the conversion of relatively easily controlled seizures into severely disabling, intractable epilepsy.

The objective of this supplement was not to induce a state of despair among the neurologic community. Epilepsy is one of the oldest, most disabling, and most common neurologic disorders. Physicians have been trying to treat seizures from the beginning of medical history, and in recent years have been relatively successful in suppressing seizures in 50—65% of patients with epilepsy. However, for more than 3,000 years, the focus of any therapeutic intervention has been on suppressing the seizures themselves after the individual develops epilepsy. Some people are cured by surgery, but no other curative therapy exists for those for whom surgery is inappropriate. In the modern era of medicine, it is time to treat the epilepsy and not merely the symptoms of the disorder.

One of the objectives of compiling this supplement was to point to future directions in epilepsy research that will fulfill our goal of preventing or curing epilepsy. New animal models and screening procedures are clearly needed—for testing antiepileptogenic strategies, for protecting the brain against ongoing damage produced by seizures, and for developing new drugs to treat currently pharmacoresistant seizures. Some of this is being done through the NINDS-sponsored antiepileptic drug screening program, as discussed by Dr. White. In addition, much more information is needed about the basic underlying mechanisms of epileptogenesis after brain injury, and this has also become the focus of attention in a number of laboratories. The problem of pharmacoresistance remains more elusive, but in both the laboratory and in the clinic, new approaches to defining this condition and to eliciting the underlying mechanisms responsible for it are being developed.

Ultimately, clinical trials in antiepileptogenesis and neuroprotection must be designed and implemented before any new therapy can be demonstrated to be effective. Given the relatively poor results in this field thus far, not only in epilepsy but in almost every aspect of neuroprotection, this area needs a lot of attention. Defining neuroprotection and measuring it, especially in patients, are difficult tasks. Determining how long to treat a patient at risk, what the nature of the treatment should be, and how best to measure outcome are all issues that need to be addressed. It is hard not to imagine that in the near future we will have treatments that prevent epilepsy after multiple forms of brain "insult" and that we will have drugs that prevent brain damage after a variety of injuries or encourage regeneration. The challenge for us now is to figure out how to get from here to there!