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# Introduction and Symposium Overview

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Status epilepticus (SE) is a medical emergency that requires immediate identification and treatment. Despite extensive research, it continues to be a major clinical problem throughout the world, with high rates of incidence (approximately 40 per 100,000) and mortality (approximately 26% in adults and 3% in children) (1). However, a number of new insights into the pathogenesis and treatment of SE have improved our understanding and overall clinical management of this condition. This supplement reviews the most up-to-date experimental and clinical research on the diagnosis and treatment of SE in children and adults.

Several important and complex issues relative to the definition of status epilepticus must be addressed if we are to understand its underlying pathogenesis and develop effective treatments. In an overview, Dr. Daniel Lowenstein describes the history of SE and the evolution of its definition. For many years, investigators have struggled to identify a specific seizure duration parameter that defines the onset of SE. The "textbook" definition of SE cites seizure duration of ≥30 min, indicating the point at which seizure-induced neuronal injury begins. However, there are currently no data that clearly support this time interval. The exact duration of seizures that establishes SE remains uncertain and difficult to ascertain. Therefore, Dr. Lowenstein discusses the rationale for using an operational definition of SE that is distinct from a mechanistic definition. The role of underlying etiology, duration of seizures, and age as significant determinants of outcome of SE are reviewed as well.

Under normal circumstances, individuals will have a seizure that is self-terminating, but when the mechanisms of termination fail the seizure becomes prolonged. My article examines the pathophysiologic mechanisms occurring in the hippocampus during an acute episode of SE. Although the mechanisms at work during the transition between a self-terminating seizure and the prolonged duration of SE remain unknown, several theories on the pathophysiology of SE have evolved: (a) the hippocampus is consistently activated during SE; (b) loss of γ-aminobutyric acid (GABA)-mediated inhibitory synaptic transmission in the hippocampus is a crucial component in the emergence of SE; and (c) glutamatergic excitatory synaptic transmission is an important factor during SE. The focal point of this discussion will be on the alteration of GABAergic inhibition in the hippocampus and other areas of the brain that occurs during the prolonged seizures of SE.

Because SE is not a singular entity, it is often followed by severe forms of morbidity, the most common of which is the development of seizures. The long-term consequences of SE are the topic of two presentations. First, Dr. Douglas Coulter discusses the chronic changes that occur in experimental animals after prolonged seizures. An association between seizures originating from or involving the limbic system and an ensuing partial epilepsy has been demonstrated through the development of animal models of temporal lobe epilepsy. These models involve triggering an episode of SE in an experimental animal, leading to the eventual development of recurrent spontaneous seizures of limbic origin. Dr. Coulter reviews the distinct patterns of cell loss, circuit rearrangements, alterations in GABAergic function, and other changes that are evident in the epileptic hippocampus of experimental animals. In addition, Dr. Coulter explores the implications of duplicating experiments involving animal models of temporal lobe epilepsy by conducting studies of the limbic tissue of humans with epilepsy.

Dr. Robert Sloviter then discusses the potential role of SE-induced neuronal injury and network reorganization in the subsequent development of mesial temporal sclerosis. Episodes of SE or prolonged febrile seizures in childhood may be a contributing factor in the epileptogenic process leading to temporal lobe epilepsy. It is possible that an unidentified preexisting defect is responsible for both SE and epilepsy, and that no causal relationship exists between the two events. However, the mechanisms by which prolonged seizures trigger epileptogenesis, if in fact they do, are not yet clear and present a challenge for future studies.

Issues that must be addressed concerning the occurrence of prolonged seizures in the pediatric population differ from those in adults. Dr. Eli Mizrahi discusses clinical issues associated with the acute and chronic effects of SE on the developing brain, using the neonate as an example. Seizures in the neonate are frequently considered a form of SE because of their prolonged duration, the difficulty involved in controlling them with antiepi-

leptic drugs, and their association with severe morbidity and mortality due to underlying brain disorders. There remains to be a clear understanding of how seizures affect the developing brain, even though basic neuroscience and clinical research have addressed these issues. Current clinical studies indicate that there are several predominant factors in determining long-term outcome of neonates with prolonged seizures. However, the effects of CNS injury that accompany the onset of neonatal seizures may be difficult to distinguish from the effects of the seizures themselves or their treatment. Therefore, clinical studies must be designed to apply methodology that is sensitive enough to identify seizure-induced injury.

Dr. Frances Jensen explores the acute and chronic effects of prolonged seizures on the developing brain of experimental models. This article reviews recent experimental data that may provide answers to questions concerning clinical epileptology, as well as new insights into possible mechanisms of seizure-induced injury in the developing brain.

Lastly, Dr. Thomas Bleck discusses the problem of treating SE, providing up-to-date results of ongoing clinical trials and describing his approach to treating SE in the hospital setting.

Future studies and research will, in all likelihood, identify accurate methods for recognizing the important factors that differentiate a single seizure from SE. A thorough understanding of the events that lead to the development, preservation, and cytotoxicity of status epilepticus should result in more effective treatment strategies and reduced mortality and morbidity in the future.

## REFERENCES

1. Delorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology* 1996;46:1029–35.