Do early seizures beget seizures later in life? Clinical data and experimental observations seem to answer that question differently, with a no and a yes, respectively, which may stem from an inadequate readout of what experimental data actually do tell us and a possible simplification of what clinical data indicate. Using specific experimental examples, it is possible to show that in the developing brain, seizures do produce long-lasting alterations of neuronal excitability, although ongoing seizures are not observed in adults. The findings suggest that the long-lasting changes in developmental programs and network activity that seizures induce do not necessarily lead to epilepsy, unless other events that remain to be identified occur.

Are experimental observations of epilepsies in the developing animal brain relevant to clinical data? Relying on epidemiological and clinical observations, it has been claimed that animal data are of limited value to clinicians, as these studies fail to adequately mimic the clinical condition and thus provide little insight into treatment and outcome (1); other authors opine that this is a rather narrow view of the animal literature (2,3). Animal studies have provided enormous information about the mechanisms underlying seizures and the pathophysiological consequences of seizures on the developing brain. Much of the angst from clinicians, particularly those treating childhood epilepsy, seemingly comes from the lack of animal models that parallel the ictal semiology, interictal and ictal EEG patterns, and behavioral consequences of the human epileptic syndromes. For the most part, rodent animal models do not closely mimic the heterogeneous behavioral and electroencephalographic features of the majority of human epilepsies. However, the strength of animal research comes from the information gained about the pathophysiological mechanisms of seizures and the sequelae of such events, which often can be nicely extrapolated to the human condition, rather than paralleling every nuance of the human condition. While the human brain clearly will have a different repertoire of epileptic behaviors than the rodent brain, the fundamental physiological basis of seizures and their sequelae are conserved across species.

What conclusions can be drawn from animal data concerning seizures and epilepsies that are applicable to early human life? Do animal models tell us anything about how seizures are generated in humans and whether and how they trigger lifelong sequelae? If drugs block seizures in experimental animals, does this imply that they are promising tools to treat one or another type of human epilepsy? If the term “animal model” is taken literally, in its simple interpretation, then the answer should be positive, otherwise animal data are not a suitable or useful model.

It is reasonable for clinicians to question the value of screening potential antiepileptic drugs in animal models. Indeed, most antiepileptic agents have been discovered using primitive animal models that bear little resemblance to human conditions. Putative antiepileptic drugs are typically screened in adult, male rats that do not have epilepsy, using seizure-inducing models, such as electroshock or pentylentetrazol. Even the kindling model has limitations when compared with human epilepsies. Although kindling is championed as a model of epileptogenesis, spontaneous seizures (epilepsy) rarely occur. More relevant models, in which the animals have epilepsy, are used infrequently because of time constraints and costs. Virtually no drug screening has been performed in young animals, despite the high incidence of epilepsy in the first decade of human life. This practice is clearly debatable, considering the unique neurobiology of the developing brain.

Do Seizures Beget Seizures in the Developing Brain?

Clinicians question the applicability of animal data that suggest each seizure alters the brain, that is, “seizures beget seizures,” because a large percentage of children with epilepsy outgrow their epilepsy and few patients show a progressive increase in severity or duration of their seizures over time. If each seizure increases the likelihood of another seizure, why do so many patients undergo remission? To take this clinical observation
and suggest that seizures are inconsequential and have no effect on the developing brain, again, seems shortsighted. Why some patients’ epilepsy remits is certainly not clear from clinical studies; but, it is likely to be secondary to the overall decrease in excitability of the brain that occurs with age as well as with age-specific effects of gene activation and deactivation. The absence of explanations as to why some epilepsies go into remission and others do not, limits the relevance of the information to the issue of whether seizures beget other seizures. Rather, clinical observation indicates that there are likely to be a number of factors that determine which children with early life seizures will or will not go on to develop chronic epilepsy.

Perhaps, there is much less discrepancy between clinical and experimental data regarding whether seizures early in life beget seizures in adulthood than has been suggested. An abundance of animal studies indicate that seizures change the developing brain in a way that increases excitability and hence, heightens seizure susceptibility. There is no compelling clinical data to indicate that similar changes do not occur in the human brain. Indeed, parallels drawn from both in vivo and in vitro studies support the contention that the immature rodent brain acts very much like the immature human brain. The information available on this issue from relevant in vivo and in vitro studies follows:

In Vivo Studies

Evidence that long-lasting seizures produce long-lasting alterations in the threshold for later seizures appears across several types of experiments. Early-life seizures in rodents induce a lifelong reduction in seizure threshold but do not necessarily result in epilepsy (4,5,6). Seizure-induced changes in the young brain substantially increase the risk of subsequent injury by a second, induced seizure—the so-called “two-hit model” (7,8). Similarly, while the incidence is low, children with early-life seizures have an increased risk of developing epilepsy (9–11). Whether the increased risk for the development of epilepsy in children is related to the early seizures, per se, or to an etiology (e.g., resulting from the initial seizures, genetic predisposition, or some other “second-hit”) cannot be adequately addressed in clinical studies.

It has been known for several decades that kainate triggers hippocampal status epilepticus seizures in rodents at an early stage but does no discernible damage until the end of the second postnatal week, when the entire limbic system becomes connected and activated by the seizures (12–14). The occurrence of seizures that involve the entire limbic system, notably the perforant pathway input to the hippocampus, as well as the maturation of the mossy fibers links are required for seizures to beget damage. Similarly, the occurrence of febrile status epilepticus, in otherwise normal young children, is associated with a very low incidence of brain damage or subsequent epilepsy (15). However, the observation that prolonged seizures induced by convulsive agents, like kainate, beget seizures in certain brain regions in older rodents (16) suggests that severe seizures with the same properties, in the same structures, and at the same age in humans will activate similar cascades. Again, clinical data parallel the animal data well (17–19). Certainly, exceptions occur in both animals and humans. In rare situations, very prolonged human febrile seizures can lead to hippocampal damage (20). Also, prolonged febrile seizures in rat pups can alter hippocampal excitability and lead to epilepsy (21). The point is that animal studies are remarkably predictive of what happens in humans.

It is important to note that seizures in the immature rodent brain result in a number of functional changes, including reduced expression of glutamate receptor 2 (GluR2) expression and increased expression of excitatory amino acid carrier 1 (EAAC1) (22), decrease the kainate GluR6 receptor (23), or alter hyperpolarization-activation and cyclic nucleotide-gated channels (24)—some of these factors clearly facilitate the occurrence of seizures, while others may constitute a failed attempt to reduce excitability. While some seizure-induced changes may predispose the brain to seizures, other changes such as increases in the α-1 subunit of the GABA A receptor (25), may put the breaks on seizure development. A greater understanding of these functional changes and how they alter oscillatory patterns in the developing brain will likely provide additional insights into how seizure-induced changes may lead to epilepsy.

In Vitro Studies

Probably the most compelling data in favor of the concept that seizures beget seizures comes from in vitro experiments. One series of experiments used a special preparation composed of a triple chamber with three independent compartments that accommodate the intact immature hippocampi and their connecting commissures (26,27). Field and patch clamp recording electrodes were placed on each hemisphere, and a convulsive agent was applied to one chamber. The effects of the propagation of seizures to the other naïve, untreated side were investigated (see Figure 1). Using the preparation, three fundamental observations have been made:

1. Recurrent (5–10) seizures, but not single seizures, with ictal components that propagate from the treated to the naïve side, transform the latter to an epileptogenic mirror focus capable of generating spontaneous seizures. In other words, the hippocampal network becomes “epileptic.” This state remains for the life of the preparation (i.e., 3 days).

2. The transformation only occurs when the propagated seizure includes high-frequency oscillations above 40 Hz.
Lower-frequency events that take place repeatedly will not produce a similar outcome.

(3) Functional NMDA and GABA receptors are required for the generation of high-frequency oscillations and the formation of an epileptogenic mirror focus. The recurrent seizures activate NMDA receptors, leading to a large influx of calcium that in turn activates a cascade of signaling, which induces long-lasting alterations in synaptic efficacy. This finding is in keeping with extensive observations suggesting that long-term alterations of synaptic efficacy play a crucial role in epilepsy. Similarly, the requirement that there be operative GABA receptors is consistent with numerous studies indicating that GABAergic interneurons play a central role in the generation of behaviorally relevant high-frequency oscillations.

What can be concluded from these observations? If seizures, similar in characteristic to the initial seizures, occur in the hippocampus of the developing brain during the same developmental stage (i.e., early postnatal), the effect will lead to long-lasting alterations. The similarity of these changes with alterations that can occur in humans is reinforced by the observation that, in both cases, there is an inhibitory to excitatory alteration that can occur in humans is reinforced by the observation that, in both cases, there is an inhibitory to excitatory alteration that can occur in humans.

What cannot be concluded from these observations? First, the findings cannot be generalized to the neocortex, as the neocortex is far less epileptogenic than the hippocampus. In the developing rodent neocortex, a cocktail of convulsive agents are needed to trigger seizures in the neocortex and must be applied at concentrations that would literally “blow up” the hippocampus. Also, at present, it is not known whether recurrent seizures generate a mirror focus with spontaneous seizures in vivo, which is due in part to the paucity of information on the excitability of immature neocortical neurons and network patterns. The lack of data severely handicaps the range of conclusions that can be drawn from animal studies.

How do these observations accord with the crucial role of etiology in determining both the incidence of seizures and their subsequent outcome? Currently, there are no relevant experimental data to answer this question. Resolving the issue of great importance, as studying naive animals may provide only a partial picture of the sequence of events that occur following neonatal seizures. But, here also there are clues and means to bridge the knowledge gap. The identification of human mutations involved in familial forms of epilepsies and migration disorders provides a powerful tool to directly ablate or knock out a gene in situ, using in utero transfection techniques (29).

Using this tool, we can determine how and why mutation renews neuronal migration and how this event, in turn, results in a substantial proportion of early intractable seizures. Thus, with double cortin transfections, some neurons do not migrate but rather remain as a mass of cells that then can be studied in an otherwise normal environment, of the behavior of neurons in adult brains that have this mutation. The approach relies on the transfection of a construct that functionally knocks out a given gene in embryonic neurons in situ and allows study, in an otherwise normal environment, of the behavior of neurons in adult brains that have this mutation.
hypothesis—an early subclinical insult and an additional general insult, such as fever—could be performed followed by testing of the consequences of these manipulations. By understanding the science, strategies can be developed to target those changes that are harmful versus those that are compensatory.

In summary, trying to mimic clinical signs in rodents is not a productive strategy because of the interspecies differences and the large spectrum of seizures types in humans. More systematic investigations of mechanisms and alterations of synaptic efficacy are needed, rather than more animal models that reproduce one or another aspect of human epilepsies. The conceptual advances in understanding basic mechanisms of epilepsies, such as the loss of certain types of interneurons, the excitatory actions of glutamatergic actions of GABA and fast oscillations in the developing hippocampal cells, and the large spectrum of seizures types in humans. More systematic investigations of mechanisms and alterations of synaptic efficacy are needed, rather than more animal models that reproduce one or another aspect of human epilepsies. The conceptual advances in understanding basic mechanisms of epilepsies, such as the loss of certain types of interneurons, the excitatory actions of glutamatergic actions of GABA and fast oscillations in the developing hippocampal cells, and the excitatory actions of GABA and fast oscillations in the developing hippocampal cells. By understanding the science, strategies can be developed to target those changes that are harmful versus those that are compensatory.

By understanding the science, strategies can be developed to target those changes that are harmful versus those that are compensatory.

References