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Is Epilepsy a Progressive Disease? The Neurobiological Consequences of Epilepsy

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Summary: While primary, or idiopathic, epilepsies may exist, in the vast majority of cases epilepsy is a symptom of an underlying brain disease or injury. In these cases, it is difficult if not impossible to dissociate the consequences of epilepsy from the consequences of the underlying disease, the treatment of either the disease or the epilepsy, or the actual seizures themselves. Several cases of apparent complications of epilepsy are presented to illustrate the range of consequences encountered in clinical practice and the difficulty in assigning blame for progressive symptomatology in individual cases. Because of the difficulty in interpreting clinical material, many investigators have turned to epilepsy models in order to address the potential progressive consequences of recurrent seizures. The authors review experimental data, mainly from animal models, that illustrate short-, medium-, and long-term morphological and biochemical changes in the brain occurring after seizures, and attempt to relate these observations to the human condition. **Key Words:** Neuronal injury—Signal transduction—Second messenger—Gene expression—Synaptic reorganization—Plasticity.

INTRODUCTION

Is epilepsy a progressive disease? Are there complications of recurrent seizures? Clinical experience suggests that the answer to both of these questions is "sometimes," but a thoughtful response requires a definition of the term "progressive." To describe epilepsy as a progressive disease, one might demand strict evidence that seizures cause additional and worsening seizures, or one might approach the issue more broadly to consider whether seizures associated with epilepsy cause progressive neurological dysfunction, whether it be epileptic, cognitive, or even psychological. For the sake of this discussion, we will adopt the broader definition of "progressive disease" to encompass diverse potential neurological sequelae of recurrent seizures. Consider, for example, the following case histories:

Patient 1: L.G. was a 28-year-old beautician who was in good health until her first seizure. She suddenly turned to her husband and said, "What's that smell?" As he responded he noted a blank stare and chewing automatisms. She then developed a secondarily generalized convulsion. Recurrent events, initially occurring every few hours, accelerated in frequency over the next three days in spite of aggressive treatment. On transfer to Massachusetts General Hospital, the patient was lucid, without fever or neurological signs. A typical event was witnessed in the Emergency Room. An electroencephalogram (EEG) demonstrated right temporal spikes and recurrent seizures arising from the right temporal region. Cerebrospinal fluid, computed tomography, and magnetic resonance imaging (MRI) were all negative, as was a polymerase chain reaction test for herpes simplex virus. Aggressive treatment, including midazolam and then pentobarbital, suppressed the events, but recurrent seizures occurred each time anesthetics were withdrawn. A right temporal biopsy was performed during the second week of her illness. Pathological examination disclosed only modest gliosis without diagnostic features. There was no evidence of encephalitis. During the sixth hospital week anesthetic agents were successfully discontinued. The patient was able to recognize family but had poor memory and limited language function and was fully dependent on others for daily care. Two years later, she remains dependent with severe cognitive deficits. Seizures have recurred only rarely, but the patient remains on anticonvulsant medications.

Patient 2: J.S. is a 73-year-old retired executive who formerly ran a multimillion-dollar business. He has had seizures since age 30, but no cause was ever identified.

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He functioned well until his mid-60s when memory loss became disabling. He was initially thought to have Alzheimer's disease, but over the past eight years there has been no significant change in his memory, and he has developed no other signs of cortical dysfunction. Whereas he used to have 2–3 seizures a month, during the past several years he has had only 1–2 attacks each year. EEG examinations have consistently demonstrated left temporal spikes, and several recorded seizures clearly arose from the left anterior sylvian region. MRI examination, however, demonstrated bilateral hippocampal atrophy (Figure 1). He appears to have an isolated amnestic syndrome, likely related to his chronic seizures, without evidence of a progressive dementing illness.

Patient 3: J.W., a 47-year-old travel agent, had a febrile convulsion as a youngster and began having recurrent complex partial seizures at age 12. On average she was aware of 3–4 events each week, in spite of treatment with multiple medications alone and in combination. Growing frustration with her illness led her to seek surgical evaluation, which revealed right temporal interictal spikes and seizure onsets from the right mid-temporal region. Her right hippocampus was atrophic and gliotic, and an FDG-PET scan (positron emission tomography with ^{18}fluorodeoxyglucose) revealed right temporal hypometabolism. Neuropsychological testing revealed a Full-Scale Intelligence Quotient of 96 (Verbal Intelligence Quotient 98, Performance Intelligence Quotient 92). In spite of her illness she has been happily married and successful in the workplace all of her life, without evidence of cognitive decline.

Patient 4: K.W. is a 45-year-old attorney who had a single nocturnal generalized convulsion. When seen six weeks later, she had not been treated. She complained vigorously that since her event, her memory had not returned to normal, and she gave concrete examples substantiated by associates in her firm. Investigations including EEG and MRI were entirely negative, though memory complaints persisted six months later.

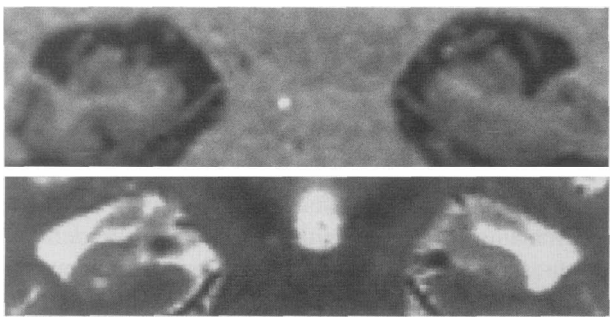

FIG. 1. High resolution MRI (Patient 2) illustrating bilateral hippocampal atrophy. Upper panel illustrates tissue loss (SPGR sequence). Lower panel illustrates dilation of the ventricular horns and minimal increased t_2 signal intensity.

These cases illustrate several points:

- Status epilepticus can have devastating consequences.
- Recurrent seizures over many years may be associated with delayed neurocognitive dysfunction.
- Seizures may go on for many years without evidence of progressive neurological symptoms.
- Even a single seizure may be sufficient to cause injury and prolonged consequences.

Of course, each of these cases can be criticized. Could the first patient have had encephalitis, with seizures only as a secondary phenomenon? Could the amnestic syndrome manifest in the second case be the result of something other than his epilepsy? Is the patient described in the third vignette truly functioning normally, or would her cognitive performance have been better had she never had seizures? Does the lawyer K.W. have genuine memory dysfunction as she claims, or is she really suffering from depression and anxiety in response to her seizure and its associated implications? These questions exemplify some of the difficulties one encounters when trying to answer the question of whether epilepsy is a progressive disease by relying on clinical observation alone.

In the face of such variability, how can we begin to address the question of whether epilepsy is a progressive disease? Moreover, in the midst of continued seizures, treatment, and the underlying pathological processes, how can we unravel the contribution of seizures themselves to progressive neurological syndromes? For these reasons, it seems worthwhile to address the question experimentally. After developing a framework for thinking about the question of whether epilepsy is a progressive disease, we will concentrate on data obtained in experimental studies, mainly using whole animal epilepsy models, that address the possibility that epilepsy is a progressive disease and that highlight potential mechanisms underlying its progressivity. We will review some existing data on the neuropathological and neurobehavioral consequences of human epilepsy, along with the experimental neuropathological literature, and then consider characteristics of the human disease that may determine its progressive nature.

FRAMEWORK FOR ANALYSIS

At a conceptual level, the idea that recurrent brief events such as epileptic seizures may result in progressive pathological and functional change in the nervous system implies the existence of a mechanism to transduce short-term activity into long-term change. This concept, when applied to advantageous phenomena such as learning or memory, is often labeled activity-dependent neuronal plasticity. Plasticity need not be solely a posi-

tive or advantageous characteristic, however; it is possible to conceptualize the progressive pathological changes that might be associated with epilepsy as an alternative example of neuronal plasticity. In this manner, the tools that have been developed to study plasticity should be readily applicable to the study of progressive pathology. For example, the idea that intracellular signal transduction systems convert brief surface receptor activation into altered gene expression in neurons, as in fibroblasts (1), is likely to be key to understanding progressive pathology in epilepsy.

Do seizures per se lead to long-term neurological changes?

Because epileptic seizures are complex events, involving not just abnormal neuronal activity but also supportive and compensatory physiological responses within and outside the nervous system, an important but difficult question arises as to what aspect of the epileptic activity might underlie progressive disease. This concept is illustrated in Figure 2. Seizures may induce long-term change directly or indirectly. If abnormal activity *directly* results in progressive neurological disease, we should be able to trace the long-term consequences of recurrent seizures back to events that are initiated by the abnormal activity per se. An alternative possibility is that seizures, by some *indirect* mechanism such as seizure-associated hypoxemia, ischemia, or substrate insufficiency, cause neurological injury.

Is there a signal transduction system with the characteristics necessary to underlie long-lasting neurological consequences of single or repeated seizures?

If we hypothesize that epilepsy is a progressive disease, there must exist a transduction system that can convert brief episodes of neuronal dysfunction into long-term functional change in the nervous system. If the hypothesis is true, we should be able to find evidence for both a transduction process and an end result. What are the characteristics of a signal transduction system that might serve to convert episodic seizures into progressive dysfunction?

- Signaling must be activated by seizures.
- Acute events must be transduced into long-lasting or permanent modification, either anatomic, biochemical, or functional.
- Blockade of the critical transduction components should prevent long-term sequelae of individual seizures.
- Activation might display threshold properties.

One would predict that a transduction system capable of mediating the conversion of short-term activity into long-term events would encompass a series of effectors deployed over an overlapping but expanded time course. In the course of depolarization, ionic shifts, including calcium fluxes, occur. There is now a substantial body of evidence that second messenger systems are activated by ictal activity. Early after seizures, gene activation with increased messenger RNA (mRNA) transcription can be documented, and waves of protein synthesis have been demonstrated in the ensuing hours. Finally, morphological and anatomic changes appear to occur over hours to weeks after experimental seizures, including both sprouting, synaptic reorganization, and neuronal loss and gliosis. This time course is represented in schematic form in Figure 3. In the following section we will review each of these events in the context of experimental seizure models. It is important to remember, however, that although various phenomena are distributed over a wide time course, this cannot be taken as evidence that early

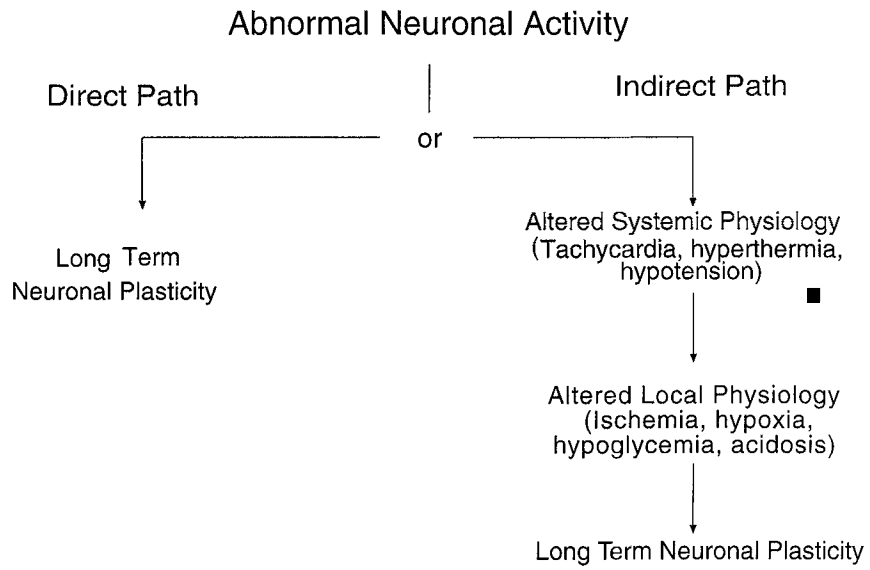

FIG. 2. Representation of direct and indirect pathways underlying seizure-induced neurological changes.

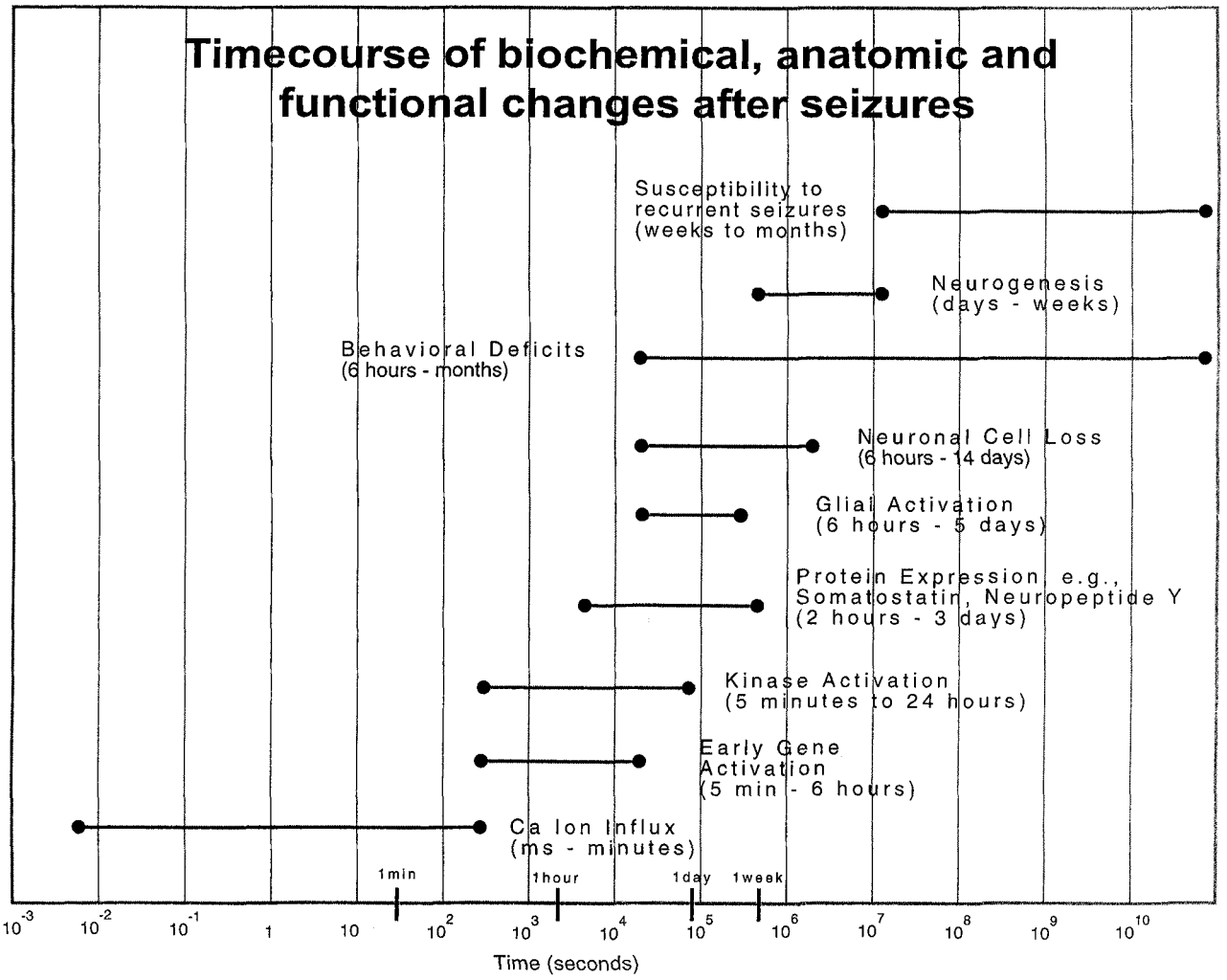

FIG. 3. Time course of seizure-induced biochemical, anatomic, and functional changes in the central nervous system.

changes are required to mediate later events. Signal transduction may theoretically occur in either a series or a parallel fashion, as illustrated in Figure 4.

CONSEQUENCES OF SEIZURES

We will now review a spectrum of neurobiological consequences of single or repeated seizures described mainly in animal models. The goal of this review is not to provide an encyclopedic list of consequences of epilepsy but to highlight the time course and range of phenomena that have been encountered and described.

- *Ionic fluxes.* By definition, seizures involve the repeated depolarization of populations of neurons, often synchronously, during the time of the ictus. Depolarization, of course, is mediated by sodium influx and potassium efflux, mainly through voltage-sensitive channels. Transmitters, interacting with receptors, activate ionic fluxes through inotropic channels. Not only sodium and potassium, but calcium may enter neurons this way (2). Additionally, calcium may be mobilized from intracellular stores due to both depolarization and activation of intracellular signaling systems, some coupled to metabotropic receptors. Considerable study using ultrastructural techniques (3) and calcium imaging technologies has demonstrated robust changes in intracellular free calcium concentration after seizure-like bursts of depolarization (4).
- *Kinase activation.* Within minutes of a brief electroconvulsive seizure, increased phosphorylation and activation of the neuronal form of mitogen-activated protein kinase, p44/42-MAP kinase (also known as extracellular signal regulated kinase, or Erk 1/2), is seen in hippocampal neurons and specific cortical neuronal populations (5,6). In a cell culture model of seizure-like activity in which primary hippocampal neurons chronically deprived of synaptic activity undergo brief bursts of depolarization, robust phosphorylation and activation of Erk

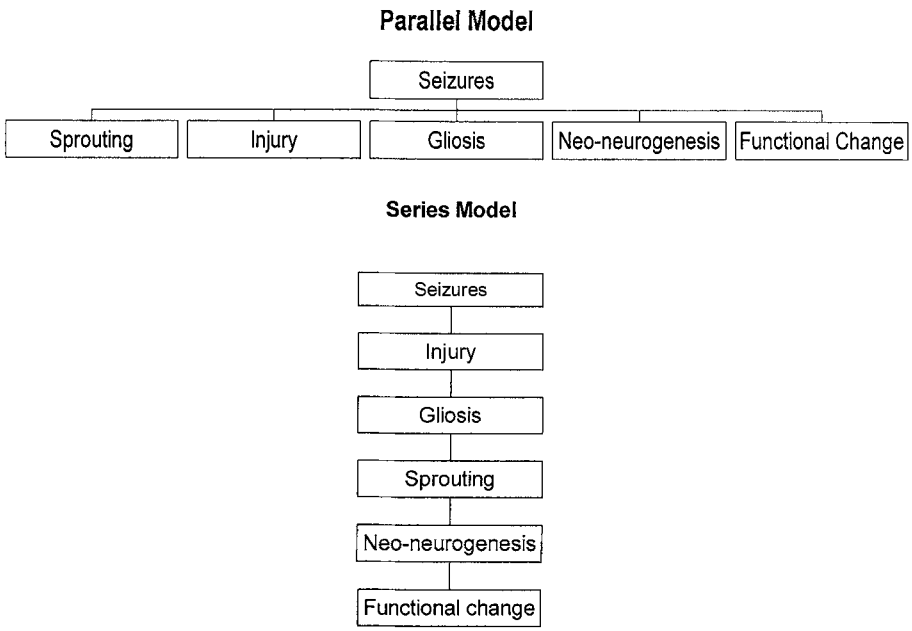

FIG. 4. Representation of series and parallel models of seizure-induced signal transduction.

1/2 is observed (7). Interestingly, activated kinase is localized to synaptic terminals as well as cell bodies, suggesting a presynaptic role in modulating transmitter releases. Moreover, blockade of kinase activation using the specific inhibitor PD98059 abolishes activity-induced neuronal injury and cell death in this culture model (7). In recent whole animal studies using kainate-induced seizures, we have demonstrated activation of Erk 1/2 in dentate gyrus hilar neurons, mossy fibers, and occasional pyramidal neurons mainly in CA3 (8). Many of the hilar neurons in which activated Erk 1/2 is found appear to be somatostatin positive. In complementary studies using the chronic perforant path stimulation model, which replicates both loss of inhibition and hilar injury seen in epilepsy, we have shown Erk 1/2 activation within hours of the initiation of stimulation in dentate granule cells, subgranular layer neurons and mossy fibers (9). Together, these studies indicate that at least one major intracellular signaling pathway is activated in specific neuronal populations after experimentally induced seizure activity in a variety of models. This pathway seems optimally positioned to modify neurotransmitter release, and may be important in regulating a variety of cellular responses to seizures .

- *Immediate early gene (IEG) expression.* In 1987 Morgan et al. (10) demonstrated induction of c-*fos* mRNA after pentylenetetrazol-induced seizures in rodents. Soon thereafter, we and others showed the induction of a host of mRNAs, most coding for IEGs in rat brains after seizures induced by chemoconvulsants (11) or electroconvulsive shock (12). Numerous investigators have confirmed and extended these findings. IEGs were initially defined in models of viral replication as genes that could be induced in the absence of new protein synthesis (13,14). As such, they were thought to be critical regulators of post-stimulation responses, either proliferation or differentiation. Many of the IEGs studied in seizure models encode known transcription factors, that is, proteins that bind DNA in a sequence-specific manner and regulate the transcription of additional messages (15–17). As such, it has been tremendously seductive to imagine these activity-induced messages as critical regulators of long-term cellular responses. Unfortunately, convincing evidence to support this notion, e.g. examples of target genes in brain that are regulated by specific IEGs, has remained elusive.
- *Late gene expression.* A variety of mRNAs, encoding peptides, receptors, cytokines, glial fibrillary acid proteins (GFAPs) and even cytoskeletal proteins can be induced by seizures resulting from chemoconvulsant treatment, kindling stimuli, and electroconvulsive therapy (18–26).
- *Protein expression.* Messenger RNA expression, whether for IEGs or later effector genes, would be of limited interest unless those messages expressed were translated in protein. While there has been some tendency to equate mRNA expression with increased synthesis of encoded proteins, numerous examples of regulated but apparently untranslated mRNAs can be found. After experimentally induced seizures, however, numerous changes in protein expression and abundance have been documented. Immunoblot studies and immunohistochemical analyses have documented increased expression of IEGs,

a host of peptides, proteins involved in putative cell-death pathways, cytoskeletal elements, and signal transduction molecules.

- *Protein modification.* As indicated in the discussion of kinase activation above, there is considerable precedent for the notion that seizures lead to protein modification, which likely determines the physiological role of the regulated molecule. It seems likely that a variety of protein-processing pathways can be activated by seizures. For example, increased synthesis of the processing enzyme peptidylglycine α-amidating monooxygenase that converts peptidylglycine substrates into α-amidated products has been documented after a single electroconvulsive seizure (27).
- *Mossy fiber sprouting and synaptic reorganization.* The previously described biochemical consequences of experimental seizures may have broad significance, but the concrete or tangible importance of seizure-induced nervous system responses is perhaps nowhere more dramatic than in the observation that prolonged or repeated seizures lead to anatomic change. Numerous anatomic studies, most using the Timm's stain, have convincingly demonstrated robust sprouting of apparent mossy fibers with extension into the supragranular cell layer, a region in which mossy fiber endings are not normally found (28–30). Interestingly, blockade of nerve growth factor using a selective antibody does not attenuate the sprouting phenomenon (31). While the anatomic observation strongly implies a functional connection between newly sprouted fibers and existing neurons, to date no convincing evidence of a functional connection has been presented. This is perhaps due to the technical difficulty of the necessary experiment, but leaves open to question the significance of the anatomic finding for the time being.
- *Cell loss.* There is overwhelming experimental evidence of selective neuronal injury after seizures induced by some (but not all) experimental stimuli. Kainate-, pilocarpine-, and bicuculline-induced status, along with chronic perforant path stimulation, kindling stimuli, and hypoxia-ischemia–induced seizures, all result in easily observable cell loss in varying regions of the limbic system, including granule cells, hilar interneurons, CA3, CA1, subicular pyramidal cells, amygdala, hypothalamus, entorhinal cortex, septum, dorso-medial thalamus, and cingulate gyrus (32–37). A major focus of current research is to determine the mechanism of cell death following experimental seizures. While this issue remains controversial, it seems likely that diverse mechanisms are involved, perhaps varying with both region and model, and including necrosis, apoptosis, other forms of active cell death, and in some areas combinations of multiple mechanisms (34,38,39).
- *Gliosis.* Prominent glial responses have been described after experimentally induced seizures, including glial activation (defined by morphological change and increases expression of GFAP) (40,41), and glial proliferation (42,43). Whether glial responses are independent of neuronal loss or secondary to it remains uncertain. Recent increases in our understanding of glial function, including roles in transmitter re-uptake and catabolism (44), glucose transport (45), and perhaps trophic support (46,47) all support the notion that glial responses to seizures may have important effects on the long-term consequences of epileptic activity.
- *Neo-neurogenesis.* Another dramatic response to brief episodes of epileptic activity has recently been described by Parent and Lowenstein. Neo-neurogenesis in hippocampus appears to occur within hours to days of pilocarpine-induced seizures or perforant path stimulation (48) and is likely to be a more generalized phenomenon. Using bromodeoxyuridine labeling, these investigators have shown convincing evidence of the formation of new neurons with the appearance of granule cells in dentate hilus. These neurons appear to migrate toward the granule cell layer. It remains unclear whether these cells form functional connections and just what their functional role might be. An important negative observation is that blockade of neo-neurogenesis by ionizing radiation does not block mossy fiber sprouting (49).
- *Increased susceptibility to recurrent seizures.* Impressive as they may be, biochemical and anatomic consequences of experimental seizures would be of limited interest if they did not result in changes in the function of the nervous system. What, then, is the evidence to support the idea of seizure-induced functional modification? In recent studies in our lab, we have shown that early life seizures increase the susceptibility to and severity of later life epileptic events in rodents (50). Similar findings after early life hypoxic-ischemic attacks (51,52) and flurothyl-induced status (53) have been documented by others. Others have shown that in some models, even seizures occurring during adulthood lead to recurrent spontaneous events (54).
- *Memory/learning/behavioral deficits.* Behavioral studies have provided compelling evidence for seizure-induced neurobehavioral deficits, including spatial learning difficulties and memory deficits. We and others have found deficits in performance in the Morris water maze after kainate- (50) or

pilocarpine-induced (Brisman, unpublished observation) seizures, which appear to correlate well with hippocampal injury (55). Interestingly, in recent studies we have examined the effect of unilateral hippocampal injury and can find no clear evidence of behavioral disturbance (Brisman, unpublished observation).

What are the limitations of animal studies?

Animal models have significant limitations that must not be overlooked.

- *Most models are acute.* By their nature most animal models are acute, whereas human epilepsy is typically chronic. Logistical problems make chronic animal studies difficult to perform. Some deficits seen after experimental seizures may resolve over longer time intervals, making extension to the human condition problematic.
- *Many models incorporate status, rather than isolated brief seizures.* Many of the models used to develop the data presented above rely on single, often relatively prolonged seizures. While these may fairly represent the events associated with status epilepticus, they may not recapitulate the events that occur after repeated brief seizures in humans.
- *It may be difficult to separate effect of convulsant agent from seizure itself.* The question invariably arises as to what is the effect of the convulsant agent (e.g. kainate or pilocarpine) versus what is the effect of the seizures themselves. While this issue can never be completely addressed, some experimental approaches are helpful in addressing it. In the case of kainate, the finding that many of the consequences of systemic kainate-induced seizures are reproduced after seizures induced by direct intra-amygdaloid injection of kainate, even at sites distant from the amygdala, increases our confidence that the seizures and not the kainate are mainly responsible for the late effects. Similarity between the pathological and biochemical consequences of various models (e.g. kainate, pilocarpine, and perforant path stimulation) support the interpretation that the abnormal activity, and not the means of its induction, is the critical underlying element.
- *It can be difficult to demonstrate causation, e.g. separate epiphenomena from pathophysiologically relevant events.* A major problem in interpreting both human and experimental data is to identify causation in the face of correlation.

What do we know about the consequences of acute or chronic seizures in human beings?

The anatomic and neuropathological literature is filled with studies of the pathology of human epilepsy. The literature is plagued, however, by the problems of separating effects of seizures from effects of treatment and underlying disease, and of separating primary effects of seizures from secondary effects mediated by associated ischemia, hypoxia, and the like. Because the majority of attention has focused on the hippocampus and temporal structures (presumably due to their relatively common availability from surgical resections), we will outline three major well-documented pathological consequences of recurrent focal seizures.

- *Documented neuronal loss in cases of mesial temporal sclerosis, especially in hippocampus and entorrhinal cortex.* Since the 1880's neuropathologists have recognized neuronal loss in the hippocampus as a hallmark of chronic epilepsy (56–59). Ample confirmation and extension of these early descriptions has come from numerous members of this society.
- *Documented glial activation and gliosis in epileptic tissue.* Concomitant with neuronal loss, gliosis manifest by increase reactive astrocytes is commonly seen in epileptic tissue (60–62).
- *Documented mossy fiber sprouting in human tissue.* Convincing evidence of mossy fiber sprouting and apparent synaptic reorganization has now been demonstrated in the human hippocampus in patients with chronic focal seizures (63,64). Recent studies have begun to correlate the expression of various neuroactive peptides such as nerve growth factor, neurotrophin-3, and brain-derived neurotrophic factor with the phenomenon of sprouting (65). It remains to be determined whether trophic factor expression induces sprouting in humans.

These pathological findings in patients with chronic epilepsy have a striking similarity to those elucidated in animal models as described above. While the finding of specific pathology does not establish whether epilepsy is a progressive disease, they certainly support the notion that many key elements of a hypothetical signal transduction process are available in human brain. It is likely, however, given the heterogeneity of human epilepsy, that a number of factors will contribute to determine whether a specific individual will suffer from progressive seizure-induced neurological dysfunction.

What factors might determine whether a particular human epileptic syndrome has lasting consequences/progressive features?

- *Seizure/epilepsy type.* Clinical experience indicates that not all seizures or epilepsy syndromes are alike in their associated neurological morbidity. For example, there seems to be little residual effect of childhood absence seizures on cognitive or neurological function (66,67), though even this point may

be debated (68). One might argue that these attacks are nonconvulsive, but if that were the critical characteristic, one would not expect the cognitive decline often seen in association with recurrent complex partial attacks. Moreover, if convulsive activity were the critical element, it would be surprising that the benign focal epilepsies of childhood, such as benign rolandic epilepsy, are not associated with detectable neurological injury (69).

- *Seizure frequency.* It seems likely that seizure frequency contributes to the associated neurological morbidity encountered in clinical practice. It remains unclear whether injury and progressive symptomatology are directly related to seizure "dose," or whether seizure frequency and liability to progressive disease are both markers of a more severe underlying condition.
- *Seizure severity.* Status epilepticus can be clearly associated with neurological residua in many cases (70,71). It seems likely that repeated severe seizures are more likely to induce progressive pathology than rare mild attacks; however, objective data to support this contention are difficult to develop.
- *Host characteristics.* We can speculate that host characteristics, presently undefined, interact with seizures to determine long-term consequences.

CONCLUSIONS

From this survey of clinical experience, clinical study, and experimental data, we can draw several conclusions. First, an answer to the question of whether epilepsy is a progressive disease is complicated and ultimately depends on strict definitions and rigorous analysis. Numerous confounding variables exist in both the clinical and experimental environments that are difficult to completely control. In spite of these issues, it seems increasingly clear that some epilepsy syndromes manifest progressive features that are unlikely to be secondary to treatment. Similarly, some epilepsy syndromes, in particular nonconvulsive primary generalized epilepsies, appear to have little long-term significance that can be detected either biochemically, anatomically, or functionally. A startling variety of mechanisms exist that may underlie the progressive features of epilepsy syndromes. While some putative mechanisms may represent "bystander" phenomena, e.g. local hypoxemia, many of the likely mechanisms depend on activity-induced biochemical events. Whether direct effects of activity or indirect effects secondary to seizures, each of these mechanisms should be effectively blocked by improved seizure control. Identifying and characterizing the key molecular mechanisms of progressive consequences of epilepsy will likely offer new and important targets for therapeutic intervention.

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