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## Pathophysiology of Acute Symptomatic Seizures

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### Introduction

Seizures may arise through the direct or indirect effects of disease on the central nervous system (CNS). Drugs used to treat a variety of systemic illnesses may alter the seizure threshold and cause seizures, and illness may also unmask an underlying tendency to seizures in a stressed patient. In this chapter, we explore the pathogenesis of acute symptomatic seizures in patients who are systemically ill. In some circumstances, much is already known about the mechanisms underlying the development of seizures. However, in many instances these remain speculative and are not completely understood. We will attempt to present putative mechanisms that lead to seizures, based on our current understanding of specific disease processes and their interplay with neuronal excitability. Many of the diseases described in this chapter will be discussed in greater detail in subsequent chapters. This chapter serves to highlight both the general and specific mechanisms responsible for seizure development in a variety of medical illnesses. We have chosen a number of prototypic disorders (i.e., hyponatremia, alcohol withdrawal syndrome, hepatic failure, drug toxicity, and infectious disease) to illustrate particular pathophysiologic processes that orchestrate the development of seizures. We will also focus on the complex and clinically important interplay of discrete pathophysiologic processes, which may aggregate to produce seizures in critically ill patients.

Although seizures may complicate a variety of chronic medical illnesses (**Table 1**), seizures are seen most commonly in patients who are critically ill. In a study of 55 patients with new-onset seizures admitted to an intensive care unit (*1*), seizures were associated with narcotic drug withdrawal in approximately one-third of patients. In a further one-third, the cause was an acute

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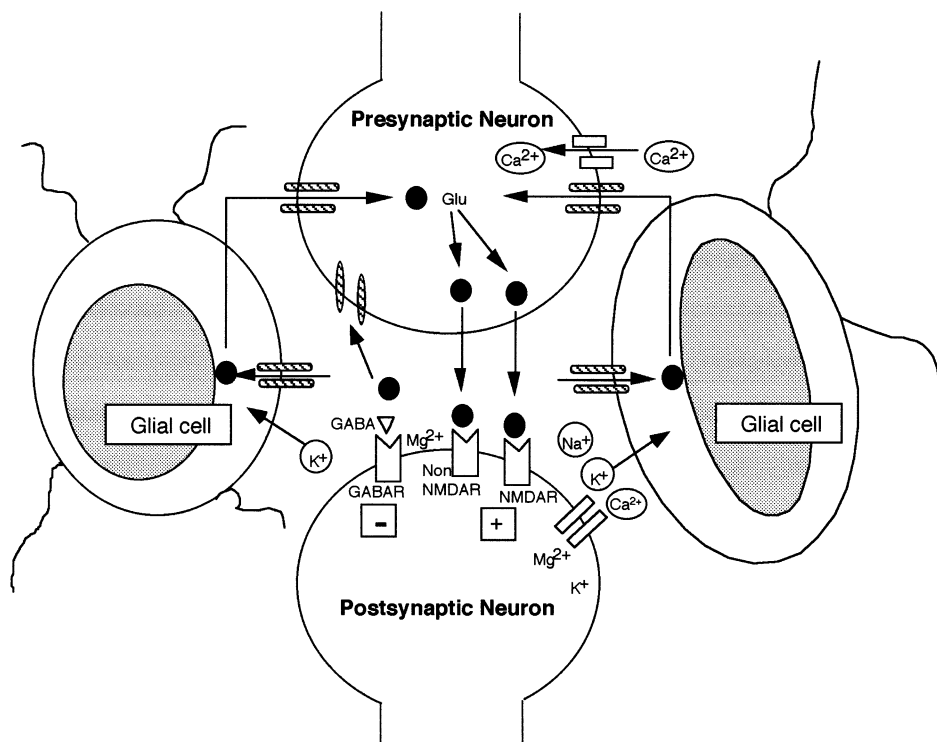
**Table 1**  
**Examples of Medical Causes of Seizures**

Cerebrovascular disease	Metabolic ( <i>cont.</i> )
Thrombosis	Hypomagnesemia
Embolism	Alkalosis
Hemorrhage	Organ Failure
Vasculitis	Hepatic failure
Cerebral infection	Renal failure
Meningitis	Endocrine
Encephalitis	Hypothyroidism
Abscess	Thyrotoxicosis
Neurosyphilis	Vitamin deficiency
Hypoxic-ischaemic encephalopathy	(e.g., pyridoxine deficiency)
Hypotensive syndromes (shock, Stokes-Adams attacks, vasodepressor syncope)	Drugs- Therapeutic (e.g., penicillins, imipenem, isoniazid, phenothiazines, meperidine, theophylline, cyclosporine, FK506 [tacrolimus])
Hypertensive encephalopathy	Drugs- Recreational (e.g., cocaine)
Eclampsia	Alcohol withdrawal
Fever	Sedative drug withdrawal
Metabolic	Environmental toxins (e.g., lead, mercury, arsenic, strychnine, thallium)
Hypoglycemia	
Hyponatremia/hyponatremia	
Hypocalcemia	

metabolic disorder, predominantly significant hyponatremia ( $<125$  mmol/L serum sodium). In eight patients seizures were attributed to drug toxicity (mainly the use of antiarrhythmic or antibiotic agents). Less than 10% of patients in this study had previously unrecognized structural abnormalities of the CNS that were manifest by focal or generalized tonic-clonic seizures. In 10%, the cause of the seizures remained unknown.

## General Mechanisms of Seizure Development

A seizure is produced when neurons within an area of the brain are activated in an unusually synchronous manner. Focal activation of a group of neurons may subsequently spread to involve nearby or distant neurons in an abnormal activation pattern. Any event, or combination of events, that disturbs the delicate balance between neuronal excitation and inhibition can produce a seizure. Many different cellular or biochemical changes such as alterations in ion channel function, neurotransmitter level, neurotransmitter receptor function, or energy metabolism may affect the excitability of neurons and produce seizures. In general, depolarization is mediated by synaptic currents generated by the excitatory neurotransmitters glutamate and aspartate (**Fig. 1**) (2). Neuronal synchronization occurs through local enhancement of excitatory circuits. An increase in synaptic efficacy is thought to be due to recruitment of



**Fig. 1.** Neuroexcitability: the presynaptic and postsynaptic neuron. Excitatory amino acids are released from the presynaptic terminal and act on postsynaptic NMDA and non-NMDA receptors (NMDAR) to cause excitation. GABA is an inhibitory neurotransmitter and acts on postsynaptic GABA receptors (GABAR). The glial cells play a central homeostatic role in the control of neuroexcitation by controlling extraneuronal potassium concentration and by removing excitatory neurotransmitters such as glutamate (Glu). Neuronal excitability may also be influenced by ions such as magnesium.

*N*-methyl-D-aspartate (NMDA) receptors (3) (**Fig. 1**). As more NMDA receptors are activated, further depolarization occurs, additional calcium enters the cell, and excitability is enhanced. As these excitatory processes increase, there may be a simultaneous reduction in the activity of inhibitory circuits that are downregulated during high-frequency activation. Neurons can also be synchronized by extracellular currents that may reflect changes in the perineuronal environment, such as local edema, or changes in the extracellular potassium, calcium, or magnesium concentration (4). Finally, neurons may also be synchronized by local ephaptic (nonsynaptic) contacts, which facilitate the development of excitatory circuits (5,6).

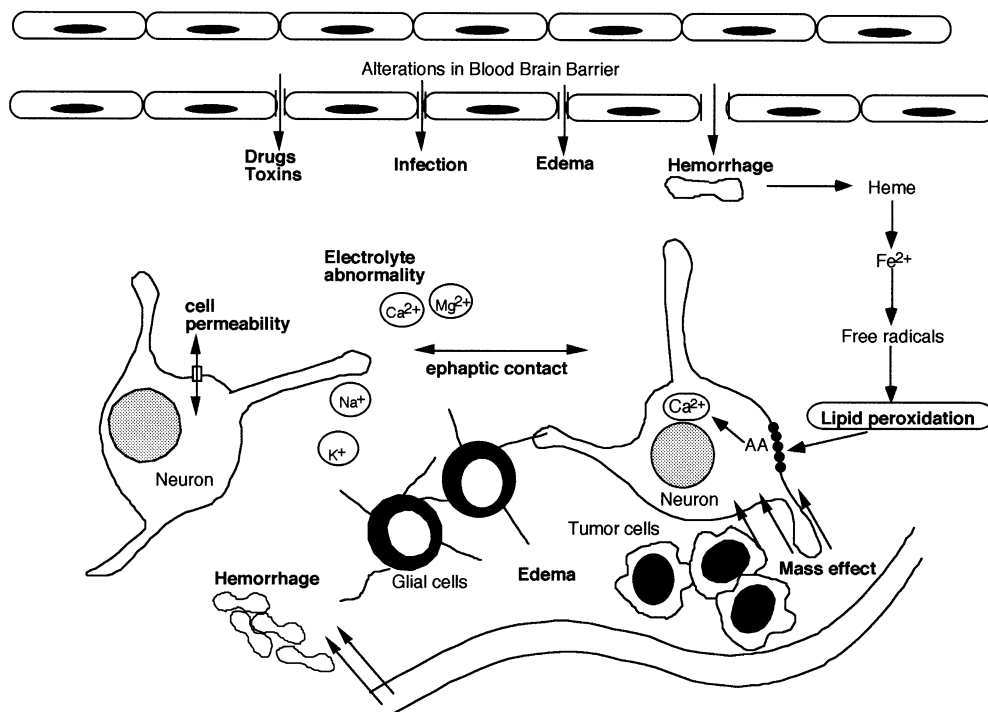
In many instances, the precise sequence of events leading to the development of seizures in patients with acute illness remains speculative. However, several pathophysiologic processes appear crucial in the pathogenesis of seizures in the acutely ill (**Table 2**). Changes in the permeability of the

**Table 2**  
**Pathophysiologic Mechanisms Producing Seizures in Acutely Ill Patients**

<b>Vascular</b>	Changes in the blood brain barrier Changes in intracranial pressure Hemorrhage Cerebral infarction Change in cerebral blood flow autoregulation Cerebral microhemorrhage and $\text{Fe}^{2+}$ liberation
<b>Metabolic</b>	Glucose or electrolyte disturbance (sodium, potassium, calcium, magnesium) Endocrine dysfunction (thyroid, adrenal, pituitary)
<b>Neuronal</b>	Neuronal excitotoxicity Glial cell dysfunction GABA neuronal loss Free radical damage
<b>Infection</b>	Central nervous system or systemic infections Fever
<b>Drugs and compounds</b>	Drug toxicity Drug or alcohol withdrawal Recreational drug use
<b>Autoimmune</b>	Systemic inflammatory or autoimmune states i.e. systemic lupus erythematosus
<b>Cardiovascular</b>	Arrhythmias Loss of blood pressure homeostasis Emboli
<b>Hematologic</b>	Thrombotic or hemorrhagic states
<b>Genetic</b>	

blood–brain barrier due to infection, hypoxia, or alterations in cerebral blood flow autoregulation may allow passage of drugs and toxins into the CNS, thus influencing neuronal excitability (**Fig. 2**). Changes in the integrity of the blood–brain barrier may also influence homeostasis within the neuronal microenvironment that is normally tightly regulated by the glial cell (**Fig. 1**). For example, glial cells normally maintain a low concentration of extracellular potassium (7). Interruption of the blood–brain barrier may directly cause glial cell dysfunction or change the extracellular environment beyond its regulatory capacity. Glial cell dysfunction may lead to seizures by permitting a high ratio of extracellular to intracellular potassium, which depolarizes the neuronal membrane and increases neuronal excitability (8).

Cerebral hemorrhage has been strongly associated with seizure development. For example, this may occur in the setting of spontaneous intracerebral or subarachnoid hemorrhage, which may be associated with hypertension.



**Fig. 2.** Pathophysiology of seizures in the systemically ill. A number of pathophysiologic processes may lead to seizures, including alterations in the integrity of the blood–brain barrier, electrolyte abnormalities, changes in neuronal permeability, ephaptic (nonsynaptic) contact between neurons in the setting of edema or infiltrative processes, and hemorrhage or mass effects caused by tumors or infections. The liberation of  $\text{Fe}^{2+}$  from hemosiderin in areas of hemorrhage may lead to the production of free radicals, lipid peroxidation, and activation of the arachidonic acid cascade. This may elevate intracellular calcium concentration and mediate neuronal excitability, excitotoxicity, and neuronal death.

More subtle alterations in cerebrovascular endothelial cell permeability and integrity as a result of disorders such as hypertensive encephalopathy can lead to the formation of small areas of edema or hemorrhage (**Fig. 2**). The liberation of iron from hemoglobin may be an important inciting mechanism for seizure development. The presence of free iron within the CNS may lead to the production of free radicals, lipid peroxidation, and activation of the arachidonic acid cascade (9,10). These processes may promote the formation of inositol triphosphate and diacylglycerol, which elevate intracellular calcium concentration; this, in turn, may mediate neuronal excitability, excitotoxicity, and ultimately neuronal death.

In critically ill patients, glucose and/or electrolyte abnormalities are important in the pathophysiology of seizures (**Fig. 2**). Hypoglycemia is a common cause of both coma and seizures and should be excluded in any patient

presenting with a seizure. Disturbances of electrolyte homeostasis are common and may arise in the setting of intravenous fluid therapy, diuretic use, or activation of the hypothalamic/pituitary/adrenal axis. Of particular importance is abnormal central potassium homeostasis. In animal models of epilepsy, increased extracellular potassium decreases neuronal hyperpolarization and promotes seizure activity (4,7,8). Similarly, low extraneuronal concentrations of calcium or magnesium may increase synaptic excitability predisposing to seizures (11,12,13). Low magnesium concentration leads to activation of NMDA receptors, which are normally inhibited by voltage-dependent magnesium blockade. Moreover, changes in the concentration of other ions within the neuronal extracellular environment may also have important influences on the activity of voltage-gated ion channels.

Structural changes in the brain parenchyma that accompany systemic illnesses may produce seizures. A variety of vascular disease processes may produce seizures, and stroke is a common cause of seizures in older people. Seizures may accompany an acute stroke or occur later as a result of a scar formation in brain tissue. This occurs when neurons in the affected area die, and glial cells, mainly astrocytes, cause a glial reaction, which may produce a seizure focus. Altered blood flow may affect neurotransmitter concentration by causing ischemic damage to neurons responsible for production and release of neurotransmitters;  $\gamma$ -aminobutyric acid (GABA) neurons are particularly susceptible to ischemic damage due to their high intrinsic metabolic rate (14). GABA is an inhibitory neurotransmitter that acts on populations of GABA receptors to reduce synaptic excitability (**Fig. 1**). Factors that compromise neurons that produce GABA may increase the likelihood of seizures.

Cardiac disease may also lead to seizures. Patients with structural heart disease and/or atrial fibrillation have an increased tendency to develop thromboembolic stroke that may present with or cause seizures. Patients with a variety of different congenital heart defects have a propensity to develop cerebral emboli or infarction that may also present with a seizure. A patent foramen ovale may present in this manner with emboli arising in the venous circulation, which cross to the left heart through the patent foramen. Although exceptionally rare, cardiac myxomas have been reported to present with a seizure (15).

Abscesses or tumors may have a number of direct and indirect seizure-provoking effects (**Fig. 2**). Mass lesions may disturb cerebral blood flow (16) or cerebrospinal fluid (CSF) production/flow and alter the integrity of the blood-brain barrier. In addition, tumors or foci of infection produce local inflammation and lead to the production of pro-inflammatory cytokines. Tumors have a propensity to cause cerebral edema and hemorrhage. Brain edema associated with these pathophysiologic processes may cause neuronal and neuroglial swelling and reduce the relative space between cells. This may

increase neuronal excitation because of ephaptic interactions between different groups of neurons (5,6) (**Fig. 2**).

An imbalance of neurotransmitters may predispose to seizure activity. Depletion of inhibitory neurotransmitters or accumulation of excitatory neurotransmitters in ailing patients may cause seizures (**Fig. 1**). Increased amounts of excitatory amino acids such as glutamate and aspartate, formed during hypoxic-ischemic injury, may increase neuronal excitability (17). Conversely, depletion of the inhibitory neurotransmitter GABA may also trigger seizures (18). In addition, the formation of free radicals during acute illness may putatively predispose to both seizures and exacerbate neuronal injury (19) (**Fig. 2**).

Genetic alterations affecting ion channel or receptor function may predispose to seizures. It is being increasingly recognized that many idiopathic types of epilepsy have a genetic basis (20). Similarly, individuals without a history of epilepsy may have molecular genetic defects that make seizures more likely when homeostasis is disturbed. Subclinical defects in mitochondrial DNA could also predispose to seizures in critically ill patients (21).

A seizure may directly promote further seizure activity through its effects on the brain. Increased excitability may also independently lead to neuronal damage (excitotoxicity). Resting neurons depend on continuously synthesized adenosine triphosphate (ATP) to maintain an electrochemical gradient across the neuronal membrane. During seizures, ATP requirements increase (22), and this may exceed the capacity of cerebral blood flow to deliver additional substrate. Convulsive seizures are also often associated with hypoxia and acidosis that may further exacerbate the energy-depleted state (23).

Sleep deprivation is common in hospitalized critically ill patients, and this may further predispose to the occurrence of acute symptomatic seizures. Sleep deprivation itself is well recognized as a precipitant of seizures in those with and without epilepsy (24). It is thus not uncommon for a student doing frequent “all-nighters” prior to examination time to present to the Emergency Room following a convulsion. In addition, the seizures of the genetic idiopathic epilepsies (e.g., juvenile myoclonic epilepsy) are particularly vulnerable to sleep deprivation. The causes of sleep deprivation in hospitalized patients are many and include undertreated pain and discomfort, environmental noise pollution, frequent disruption by staff during intensive physiologic monitoring, and disease or medication-induced alteration in sleep architecture (25). In one survey of patients’ perceptions of intensive care, 46 of 76 patients (61%) reported subjective complaints of sleep deprivation (26). In another study of environmental noise in an intensive care unit, noise levels above 80 decibels were most likely to cause sleep deprivation, and patients identified staff noise as the most disturbing (27). Television and talking accounted for half of sound peaks and were amenable to behavior modification. Further



study of this problem is warranted, and in the future, improved engineering design of hospital critical care units may help to alleviate some aspects of noise pollution and thus reduce sleep deprivation and risk of seizures.

## **Specific Disease Processes and Seizure Pathogenesis**

### ***Hyponatremia and Electrolyte Disturbances***

Acute hyponatremia (<48-h duration) is generally hospital-acquired and occurs mainly in the postoperative state and/or after excessive fluid administration. Chronic hyponatremia (>48-h duration) usually develops outside the hospital and is generally better tolerated. Some factors appear to aggravate hyponatremic encephalopathy, including female gender (menstruating women) (28), and young age. Hyponatremia produces brain edema, and increased intracranial pressure that may lead to seizures and other neuropathological sequelae, including death (29,30). Hyponatremia is compounded by the tendency of neuronal tissue to undergo demyelination during rapid correction of hyponatremia (central pontine or extrapontine myelinolysis) (31). The mechanisms through which hyponatremia produce neurologic dysfunction and seizures have been studied extensively. Normally, when serum sodium decreases, the brain is protected from edema by actively extruding electrolytes and organic osmolytes. Conversely, during a subsequent increase in serum sodium, re-establishment of intracerebral electrolyte balance occurs but in a delayed manner (often requiring 5 d). In both circumstances the protective mechanisms that normally prevent the development of cerebral edema can be overwhelmed (29,30). The concurrence of both hyponatremia and hypoxia can be particularly problematic and frequently leads to refractory seizures. Hyponatremia aggravates hypoxic brain injury by further reducing the pH after a hypoxic insult. This occurs through a reduction in the availability of sodium for use in the proton exchange pump. As protons build up in the cytoplasm the limited amount of sodium renders the cell unable to restore normal pH (32).

### ***Alcohol Withdrawal Seizure***

Alcohol withdrawal seizure (AWS) refers to the seizures that occur secondary to the withdrawal of alcohol after a period of chronic alcohol administration (33). A growing body of evidence indicates that ethanol increases the effect of GABA at GABA<sub>A</sub> receptors and contemporaneously blocks the NMDA receptor (34). These events lead to a down-regulation of the GABA system and up-regulation of the NMDA receptor system, which promotes increases in neuronal excitability when ethanol withdrawal occurs. Another mechanism that has been proposed to explain the pathogenesis of AWS is the



modified lipid-protein interaction (35). This hypothesis proposes that acute ethanol ingestion modulates the neuronal cell membrane phospholipid that leads to altered protein handling or insertion within the membrane. It is proposed that this alters the relative contribution of GABA<sub>A</sub> receptors, NMDA receptors, and voltage-gated Ca<sup>2+</sup> channels in a manner that promotes neuronal excitability upon withdrawal of alcohol. Low-dose alcohol has been shown to inhibit calcium influx through the NMDA receptor/ionophore, and alcohol has also been shown experimentally to increase the expression of NMDA receptors in the hippocampus. These data suggest that upregulation of the NMDA receptor/ionophore complex plays a role in AWS (36). Other possible mechanisms may relate to the direct effects of unopposed metabolites of alcohol such as aldehydes on nervous tissue, which predominate during the withdrawal period.

### ***Hepatic Encephalopathy***

Hepatic encephalopathy is complex neurologic syndrome associated with acute or chronic liver failure. The pathophysiologic basis of hepatic encephalopathy has been investigated extensively (37). Ammonia is considered to play an important role in the onset of hepatic encephalopathy. Seizures in fulminant hepatic failure may be caused by acute ammonia neurotoxicity. Ammonia is directly excitotoxic and is associated with increased synaptic release of glutamate, activation of NMDA receptors, and increased neuroexcitability (38). In contrast, hepatic encephalopathy complicating chronic liver failure is associated with a shift toward a net increase of inhibitory neurotransmitters owing to downregulation of NMDA receptors and inactivation of the glutamate transporter GLT-1 in astrocytes (37). In addition, chronic liver failure is associated with increased inhibitory GABA activity caused by elevated brain levels of GABA, and the direct interaction of increased levels of ammonia with the GABA<sub>A</sub> receptor complex. Patients with liver failure are particularly prone to develop drug toxicity, as many drugs undergo extensive hepatic metabolism. Additionally, reduced hepatic synthetic function may reduce serum plasma protein concentration and increase free levels of drugs that are normally highly protein-bound. These changes in drug metabolism and handling may predispose to drug toxicity and seizures.

### ***Febrile Seizures and the Genetic Milieu***

Febrile convulsions affect 2–5% of children under age 5. Although these seizures have a variety of causes, it is increasingly recognized that many have a familial component. Genetic linkage analysis in families with febrile seizures inherited as an autosomal dominant trait have revealed that the disease genes responsible for these disorders are located on chromosome

8q13-21 and chromosome 19p13.3 (39,40). To date, the genes responsible for febrile convulsions in these families have not been isolated. These genes are of great interest, as they may have a pivotal role in neuronal responses to fever and other neurologic insults. Febrile convulsions are age-related acute symptomatic seizures in which there is a large genetic background, but one that depend on the occurrence of an additional stressor (i.e., fever) before seizures are manifest. This disorder may therefore be a prototype of many other acute symptomatic seizures that occur in the setting of systemic illness.

Recently, molecular studies in animals have uncovered a number of genetic abnormalities that predispose to seizure activity. Mice harboring a mutation in the gene encoding the  $\alpha_{1A}$ -subunit of the voltage-dependent calcium channel are seizure prone (41). Similarly, a mutation in the *Nhe-1* gene, which encodes a sodium-hydrogen exchanger, is responsible for seizures in the slow-wave epilepsy mutant mouse (42). The *Nhe-1* exchanger has a prominent homeostatic role in virtually all cells of the CNS by extruding a hydrogen ion in exchange for sodium, thereby maintaining intracellular pH and cell volume. Molecular genetic studies of human epilepsy have unveiled a number of inherited defects, predominantly in genes coding ion channel subunits (20). In the absence of epilepsy, mutations or polymorphisms in these or other human genes that regulate neuronal homeostasis may produce a subclinical predisposition to seizures that may only become manifest during the stress of an acute illness.

### ***Infectious Agents and AIDS***

Many bacterial, viral, fungal, and parasitic infections produce seizures. A spectrum of pathophysiologic processes accompany different infections to produce CNS dysfunction that leads to seizures. Cortical damage may accompany infection with a number of viruses, including herpes, rubella, measles, and human immunodeficiency virus (HIV) (43). Conspicuous cerebral edema and inflammation occurs in varicella-zoster virus infection. Cerebral malaria is very frequently accompanied by seizures. The pathogenesis of cerebral malaria is characterized by capillary thrombosis caused by intravascular aggregation of parasitized red cells, predominantly within the cerebral white matter. Aspergillosis, tuberculosis, hydatosis, cysticercosis, and trypanosomiasis generally produce CNS disease and seizures through the formation of vasculitis, infarction, necrosis, and granuloma or abscess formation. Infection with *Candida* species often leads to meningitis, whereas infection with *Aspergillus* generally leads to hyphal vasculitis, infarction, or abscess formation (44).

Although a seizure may be the presenting symptom in a patient with AIDS, seizures are more common in advanced stages of the disease (45,46). Seizures are usually generalized; however, partial seizures may also occur. Intracranial mass lesions are responsible for over 50% of neurologic disorders in AIDS

patients, and seizures are a common presentation of such lesions (47). Mass lesions promote seizure development through local irritation of the brain parenchyma, enhanced ephaptic contact between neurons facilitated by invading inflammatory or neoplastic cells, compression of brain structures, or disruption of blood flow. Venous drainage or CSF circulation in the brain adjacent to a space-occupying lesion may also be disrupted. Toxoplasmosis and primary CNS lymphoma are the most common mass lesions encountered among patients with AIDS (47). Other causes of intracranial lesions that may precipitate seizures include tuberculomas, tuberculous abscesses, and cryptococcal abscesses. Meningitis and encephalitis are also common and may present with seizures. Cryptococcal meningitis is the most frequent meningitis provoking seizures in AIDS (46,48). Meningoencephalitis may lead to the development of seizures through a variety of pathophysiologic processes such as focal irritation and inflammation of the brain parenchyma, disruption of the blood–brain barrier, and through alterations in intracranial pressure and CSF production or flow. Progressive multifocal leukoencephalopathy (PML) may also cause new-onset seizures among patients with AIDS (49). This process does not produce an intracranial mass effect, but it has been postulated that PML precipitates seizures by producing demyelinating foci near the cerebral cortex, which lead to cortical irritability, and/or by interrupting axonal conduction.

Although mass lesions and infections may have a florid presentation with new-onset seizures, the etiology of seizures remains unknown in over 50% of cases. In these patients a number of pathophysiologic processes have been proposed to contribute to the development of seizures. These putative factors include HIV- or immune-mediated neuronal cell death and the production of neurotoxic substances such as eicosanoids, cytokines, or free radicals, which enhance glutamate availability and lead to the activation of voltage-gated calcium channels and NMDA receptors. Patients with AIDS may have a variety of other electrolyte, endocrine, or metabolic abnormalities that may contribute to the development of seizures, including hyponatremia, hypomagnesemia, hypoadrenalism, and renal failure (50,51). Finally, the milieu in patients with AIDS is further complicated by the increasing use of multiple drugs (i.e., antimicrobial drugs and protease inhibitors) with many side effects and the potential for a myriad of drug interactions.

### ***Drugs and Toxins***

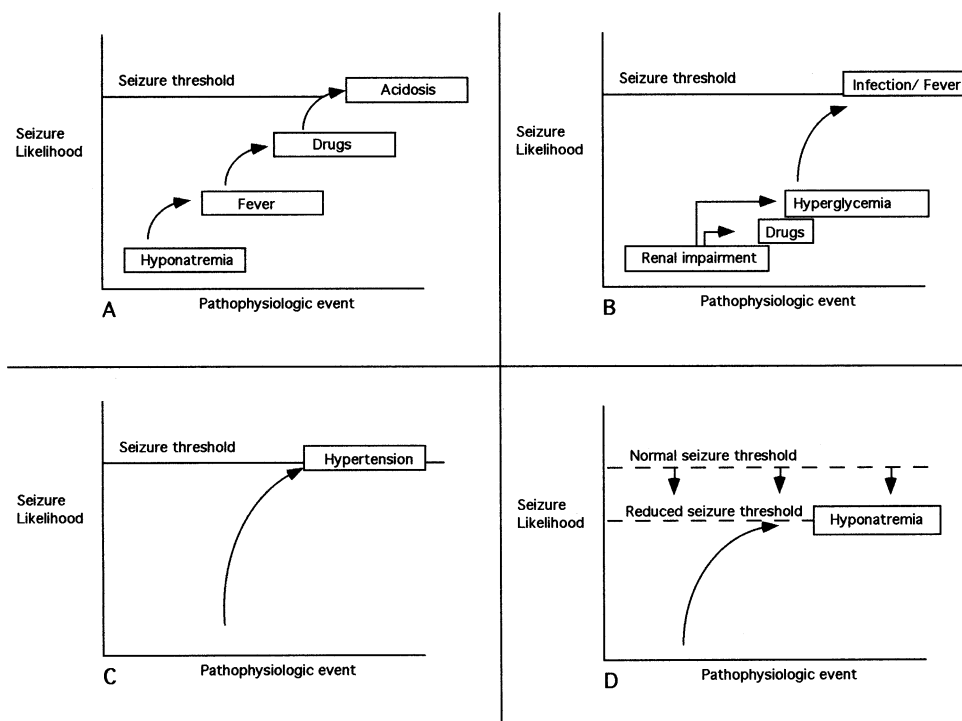
A variety of drugs and toxins are known to cause seizures. The list of drugs outlined in **Table 1** is a representative sample of a much larger list of compounds that have been associated with the development of seizures (52,53). The most common causes of drug- or toxin-induced seizures are medications, such as the tricyclic antidepressants, theophylline, and isoniazid, or the recreational abuse of drugs such as cocaine, phenylcyclidine, and amphetamines

(54). Cocaine-induced seizures have been documented after a single dose and are often generalized tonic-clonic, and self-limiting (55). However, cocaine may be associated with other serious pathologies including severe hypertension, intracranial hemorrhage, stroke, aortic dissection, and spinal cord injuries. Administration of large doses of penicillin may cause seizures, including status epilepticus, through disinhibition of the GABA<sub>A</sub> receptor by allosteric modulation of the receptor by the penicillin molecule (56). The mechanisms of isoniazid-induced seizures appears to be through depletion of pyridoxine (vitamin B<sub>6</sub>) through the formation of isoniazid–pyridoxal hydrazones (57). These hydrazones inhibit the enzyme pyridoxal phosphate, leading to additional depletion of pyridoxine. Depletion of pyridoxine in the CNS depletes GABA. It has been shown that in this setting seizures can be prevented by administering large doses of pyridoxine. Theophylline is commonly used in the management of patients with a variety of pulmonary disorders, and theophylline toxicity is frequently associated with the development of seizures (58). Recent data from an animal model suggest that theophylline-induced seizures are mediated by GABA<sub>A</sub> and NMDA receptors (59). The pathophysiologic mechanisms of seizures accompanying salicylate overdose are unclear. A high concentration of salicylate in the CNS is associated with low CNS glucose levels and enhanced CNS oxygen consumption (60,61). The high anion-gap metabolic acidosis seen in salicylate poisoning may also contribute to the development of seizures. Seizures may occur after deliberate or accidental exposure to carbon monoxide (CO). This gas binds to hemoglobin to form carboxyhemoglobin, resulting in a reduced tissue oxygen content and cellular hypoxia (62). The brain is particularly sensitive to hypoxia, leading to cerebral dysfunction and injury (63). Putative mechanisms of neuronal injury accompanying CO poisoning include direct cellular toxicity, hypoxia, lipid peroxidation (64), free radical damage (54), altered neurotransmitter release, acidosis, and hypotension.

The accidental ingestion of toxins is associated with seizure development. For example, mussels contaminated with the neurotoxin domoic acid, a structural analog of glutamate and kainate, has been reported to cause encephalopathy and prolonged seizures in some patients (65,66). Although a large number of other exogenous drugs and toxins may cause seizures (**Table 1**), the molecular and biochemical bases through which these compounds induce seizures are not completely understood.

### **Interplay Between Different Pathophysiologic Factors and the Genesis of Seizures**

In many acutely ill patients who seize, no specific single cause can be found. In these circumstances, it is likely that a number of synergistic subcritical insults aggregate to promote seizure development (67). **Figure 3** rep-



**Fig. 3.** Putative models of initiating factors and seizure development. **(A)** The acute disease model: A number of cumulative insults are required before seizures develop. **(B)** The chronic disease model: Seizures develop as a consequence of a single insult superimposed on a background of chronic disease. **(C)** The single insult model: A single insult of sufficient magnitude produces seizures in the absence of other precipitants. **(D)** The genetic predisposition model: The genetic constitution of the individual is such that seizures occur in the setting of a relatively minor insult that would not normally cause a seizure.

resents this concept schematically. In **Figure 3A** a number of cumulative insults are required before seizures develop. This is an acute disease model and is common among critically ill patients who develop progressive organ dysfunction and multiorgan failure. The case illustrated in **Figure 3B** is a chronic disease model; and in contrast to the acute disease model, seizures develop as a consequence of a single insult superimposed on a background of chronic disease. Examples of chronic disease models in which seizures occur with an increased frequency are chronic renal failure and in patients with cerebrovascular disease. The single insult model is represented in **Figure 3C**; an example of this model is eclampsia. In eclampsia the rate of blood pressure rise is usually sufficient to produce seizures in the absence of other pathologies. Finally, the genetic predisposition model (**Fig. 3D**) conceptualizes the occurrence of seizures in a subject with a latent seizure tendency but one who

does not have epilepsy. This is similar to the single insult model, but in this model the genetic constitution of the individual is such that seizures occur in the setting of a relatively minor insult that would not normally cause a seizure. This model best explains interindividual differences in seizure tendency.

The concept of cumulative synergistic insults (**Fig. 3A**) and seizure development has important therapeutic implications. The therapy of symptomatic seizures in the acutely ill often requires antiepileptic drug therapy. However, it is important to pay close attention to the patient's physiologic milieu at the time of seizure development to determine the presence of one or more reversible factors that perturb CNS homeostasis. Reversal of one or more homeostatic abnormalities in a critically ill patient may prevent seizures from occurring by interrupting the cumulative insults as depicted in **Figure 3A**.

## Conclusion

Systemic illnesses often cause seizures. A seizure is produced when neurons are activated in a synchronous manner. The mechanisms causing seizures in the systemically ill patient are incompletely understood. Seizures often reflect an imbalance between neuronal excitation and inhibition and may be due to a variety of cellular or biochemical changes that affect neuronal excitability. The neurotransmitters glutamate and aspartate mediate excitation, and inhibition is mediated by the prominent GABA system. Neurons can be synchronized by changes in the neuronal environment due to alterations in the blood-brain barrier, brain edema, electrolyte disturbance, or through non-synaptic neuronal contact. Seizures are a prominent feature in a number of diseases, including disorders of electrolyte homeostasis, particularly in hyponatremia, and AWS. Seizures are also a conspicuous and important manifestation of many infectious diseases, including HIV. In many patients who seize, there may be no single etiologic factor that accounts for seizure development. Seizures in this setting may be caused by cumulative synergistic insults. Pre-emptive reversal of one or more discrete homeostatic abnormalities in a critically ill patient may prevent their synergism and their culmination in a seizure.

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