**Necklace** *made of shells and pierced bear and lion teeth. [From Rocher de la Peine, Dordogne; courtesy of Beloit College, Wisconsin]*

pierced animal teeth." White believes that the importance that Upper Paleolithic people appeared to have placed on body ornamentation might indicate a degree of symbolism in human relations that is not obvious earlier in the archeological record.

In reconstructing beads and pierced teeth as necklaces White is careful to point out, however, that "we assume that the beads were worn in this way, but they may have been used quite differently." Conkey agrees that caution is necessary. "Once the necklace image is created, it is almost impossible to erase it from your mind. Once you call these things body ornamentation you evoke all kinds of images drawn from your own experience." Art, including body ornamentation, is by its nature so much a part of a particular culture as well as a product of that culture that interpretation of it from a distance, particularly a distance of some 20,000 years or so, is always potentially hazardous.

A good example of this, perhaps, comes from the paintings on rock shelters and caves, which were for a long time interpreted as some kind of hunting magic. It was a "natural" suggestion to make, especially as there are some ethnographic analogies to draw on. But, principally following the influence of the late André Leroi-Gourhan, there developed during the 1960's onward the view that the art in some way encapsulated the artists' world. It was a structured world, divided between maleness and femaleness, which was said to be represented in a common pattern throughout all the caves. However, Denis Vialou of the Musée de l'Homme in Paris has recently been documenting in great detail the distribution of images in some of the most important caves in France and does not see the kind of repeated pattern that Leroi-Gourhan predicted. Where Leroi-Gourhan talked of similarities between caves, Vialou sees differences. Each cave, he says, should be viewed as a separate expression.

Henri Delporte of the Musée des Antiquités Nationales near Paris has come to a similar conclusion but from a different direction. He and his colleagues have been experimentally recreating painted and engraved images as a way of trying to understand something of the technological context of the art. Delporte has also been documenting the Paleolithic images as well as examining more recent representations of animals, in pottery and sculpture, by way of comparison of the sort of subjects artists like to portray. One conclusion is that artists mostly paint or carve what they do not eat, which is a blow to the hunting magic idea. But most important is a sense of diversity, both in the production and the effect of the images. Esthetics, which is often left out of scholarly considerations of Ice Age art, must have been a factor, he says.

Delporte has also documented some fundamental differences between wall art and portable art, in such things as the types of images portayed in each medium and the pairing of the various images. His final conclusion, therefore, is that "there were probably many different reasons why people produced art of different kinds, and we shouldn't just think of single explanations."

Diversity, then, begins to come through as a more realistic interpretive lens for the Upper Paleolithic, a diversity of people, a diversity of cultures, and a diversity of the meaning of the art. And there is a shift from trying to understand what an individual image or set of images might mean to how one might understand the social context in which those images were produced. Most of all, there is an attempt to try to divest modern interpretations of the bias inherent in modern eyes and minds. As Conkey says, "Perhaps we have closed off certain lines of inquiry, simply by using the label 'art.' " ■

ROGER LEWIN

# Debate About Epilepsy: What Initiates Seizures?

*Theories about what causes nerve cells in the brain to fire in abnormal synchrony during a seizure include changes in synaptic communication or in the ionic environment and abnormalities in specific brain structures and circuits*

ONE of the most frustrating aspects of research in epilepsy has been the search for a common mechanism or brain abnormality that initiates seizures. Given the wide variety of seizures, it is not surprising that finding a common denominator has remained an elusive goal. It may turn out that no such common factor exists, but rather that different kinds of seizures are triggered in different ways. But irrespective of their diversity, seizures are similar in one critical aspect—during a seizure neurons in the brain fire together in unusual synchrony.

Participants at a recent meeting, "Mechanisms of Epileptogenesis: From Membranes to Man,"* discussed why neurons spontaneously begin to fire in abnormal synchrony. Neuroscientists agree that at least some of the mechanisms responsible for initiating seizures may also be important during normal brain processes—learning and memory, for example. But there is also clear evidence of abnormal electrical activity in the brain of an epileptic patient.

People with epilepsy have recurrent spontaneous seizures, not just one. But even in chronic epilepsy, which affects about 1% of the population, seizures vary widely in duration, intensity, behavioral manifestations, how much of the brain is involved, and sensitivity to drugs.

Although someone with epilepsy does not have seizures all the time, even between

*"Mechanisms of Epileptogenesis: From Membranes to Man" was held in Philadelphia, Pennsylvania, 25 to 26 September 1986. The meeting was sponsored by the Graduate Hospital in affiliation with the University of Pennsylvania School of Medicine.

seizures the brain often shows abnormal electrical activity. Somehow these brief intermittent abnormal discharges give way to a full seizure, in which neurons fire synchronously for longer periods of time. A key to understanding what initiates seizures is knowing what causes this transition from brief abnormal discharges to the sustained synchronous discharge that marks a seizure.

Current hypotheses include the roles of excitatory and inhibitory synaptic activity, ionic mechanisms that may be independent of synaptic communication between nerve cells, and specific brain structures or circuits. To sort out these possibile explanations, neuroscientists monitor biochemical and electrical events in the human brain and study animal and in vitro models of seizure disorders.

Jerome Engel of the UCLA School of Medicine hypothesizes that specifically timed inhibitory neuronal activity and excitatory activity is required for synchronous firing and the initiation of a seizure. On the basis of his clinical observations and the work of Thomas Babb, Charles Wilson, Masako Isokawa-Akesson, and Jeffrey Lieb, also of UCLA, Engel proposes that the firing of a small group of excitatory neurons may shut down a larger region of brain activity by stimulating inhibitory neurons that have synaptic connections through that region. Then, a second excitatory pulse, properly timed, could produce a synchronized discharge, because all the neurons begin firing at once. Thus, there is increased synchrony within the primary epileptic zone, which then serves to recruit adjacent and distant areas of the brain.

But many neuroscientists, including David Prince of Stanford University Medical Center, argue against this fundamental role for inhibitory neurons in seizure initiation. Prince makes the point that some drugs used to treat seizures, such as the benzodiazepine Valium, enhance the action of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the mammalian brain. According to Prince, the suppression of inhibitory events, not their dominance, leads to some kinds of seizures. And that is why drugs that enhance GABA-mediated inhibition are anticonvulsants and drugs that block inhibition are convulsants.

Engel sees the initiation of synchronous neuronal firing as a complex process requiring selective excitation, selective inhibition, and selective *dis*inhibition. He thinks that a combination of these events may be the basis for the transition to petit mal seizures, and possibly to some seizures that involve only part of the brain, but that it does not necessarily account for convulsive seizures that involve the entire brain.

Yoel Yaari of the Hebrew University Medical School in Jerusalem has a different explanation for cell synchrony. He proposes that changes in the concentration of certain ions in the space surrounding brain neurons, coupled with a shrinkage of this space, may induce the transition to seizure. The latter would bring neurons physically closer together and increase the likelihood of nonsynaptic communication, he says. But the most controversial aspect of Yaari's idea is that these changes could occur independently of synaptic transmission among neurons.

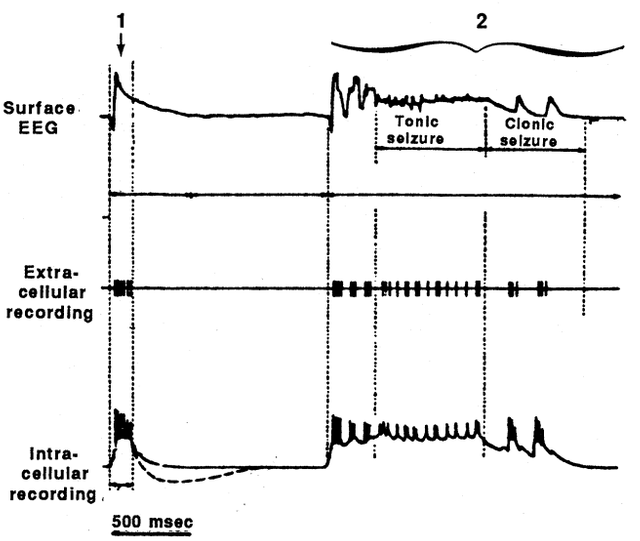
"The buildup of a seizure is associated with an increase in potassium and a decrease in calcium ion concentration in the extracellular space," says Yaari. He contends that the drop in calcium levels may increase neuronal excitability by decreasing synaptically mediated inhibition and also by decreasing the inhibitory influence of potassium efflux that is calcium-dependent.

Other neuroscientists, including James Ferrendelli of Washington University in St. Louis, think that occasional seizurelike discharges can be induced by and exacerbated by changes in extracellular potassium and calcium concentrations, but that epilepsy as a chronic condition cannot be explained solely by such nonsynaptic mechanisms.

Researchers generally agree that experimental models of seizures provide useful information about epilepsy, but they also caution against overinterpreting how an experimental model may relate to human epilepsy. Two current models are kindling in whole animals, which involves inducing seizures with low-intensity electrical stimuli given over a period of days, and generating seizurelike discharges in slices of brain tissue maintained in vitro.

James McNamara, Douglas Bonhaus, and Cheolsu Shin of Duke University Medical Center use electrical stimuli to kindle the brains of normal laboratory rats to develop motor seizures. Initially, the low-intensity stimuli have no obvious effect on the animal's brain activity or behavior, but if applied once a day for more than a week, the stimuli elicit seizures. According to McNamara, kindling may be a model of human seizures that begin in one part of the brain and then spread to include the entire brain.

Recent work on kindling from Duke and other laboratories shows that changes in the targets of kindled brain structures, rather than in the kindled areas themselves, may account for the development of seizures. Brain structures remote from the stimulated site, including the substantia nigra and pathways through the hippocampus, may participate in a "reverberating network that helps to sustain seizure activity," according to McNamara.




**Schematic diagram of abnormal epileptic activity.**

*Top trace shows typical electroencephalographic (EEG) recording from the brain surface during (1) an intermittent abnormal discharge and (2) a seizure. Middle trace shows electrical activity from a group of brain neurons and bottom trace shows activity of a single neuron.* [*Adapted from G. F. Ayala* et al., Brain Res. *52, 1 (1973)*]

The hippocampus, or slices of it, are often used to study seizure generation in vitro. Prince and David McCormick, also of Stanford, focus on synaptic mechanisms that participate in the transition to seizure, which in a tantalizing way, may be similar to mechanisms that seem to be basic to learning and memory. Citing work from his group and other laboratories, Prince notes that, in addition to changes in excitatory and inhibitory synaptic transmission, modulation of nerve cell activity by acetylcholine and norepinephrine can also contribute to seizurelike discharges in hippocampal slices.

But experimental models of epilepsy are limited in many respects and may resemble only certain aspects of the human disorder. For example, rats are much easier to kindle than animals higher on the evolutionary scale, such as rhesus monkeys. This leads some researchers to question the validity of kindling as a model of human epilepsy. Critics also point out that no one really knows if the human brain ever kindles itself.

The hippocampal slice model has certain drawbacks, too. By definition, it is only a piece of brain tissue, completely separated from its normal environment and connections with other brain regions. And the model mimics only some of the characteristics of the abnormal electrical discharges that occur between seizures, rather than the seizure discharges themselves.

Nevertheless, researchers are optimistic about the value of experimental models for epilepsy. McNamara predicts that within the next few years, neuroscientists will understand basic mechanisms underlying full seizures as well as those that underlie the abnormal discharges occurring between seizures. He foresees that the electrophysiological techniques now used to study brain slices will soon be applied to whole-animal models of epilepsy. "And that is a whole order of magnitude better than simply uncovering mechanisms for seizure events in the slice," he says.

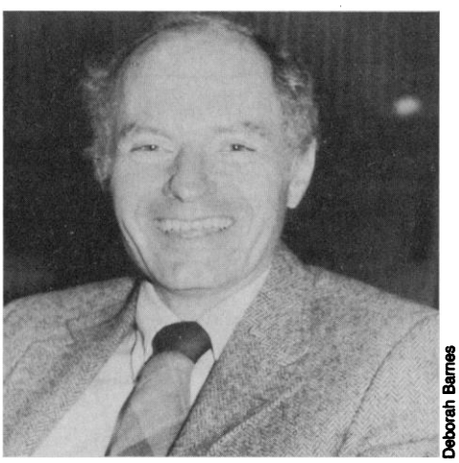
Another approach to understanding what initiates seizures is to identify specific brain regions or anatomical pathways that may be involved. Recent evidence suggests that some brain regions may trigger seizure activity whereas others may keep abnormal activity under control. Perhaps upsetting some balance between them is what precipitates a seizure.

"We don't know a lot about the functional anatomy of generalized seizures," says Ferrendelli. But he and his Washington University colleagues have recently found that a nerve fiber tract, leading from the mammillary bodies in the posterior part of the hypothalamus to the anterior nuclei of the thalamus, becomes specifically activated when rats are given a seizure-inducing drug, pentylenetetrazol.

Pentylenetetrazol-induced seizures have long served as a model for testing drugs that are effective against absence (petit mal) epilepsy in children. A patient with absence seizures loses awareness for varying periods of time, but may not show unusual movements. Identifying a specific anatomical pathway involved in absence seizures has been difficult, but in rats treated with pentylenetetrazol, Ferrendelli identifies a brain circuit that specifically becomes activated. He thinks that "synchronous, high-frequency discharges may begin in the upper brain stem, go to the mammillary bodies, and to the anterior nuclei of the thalamus. The anterior thalamus [two groups of nerve cells that underlie and ultimately project to the cerebral cortex], may act as a primary regulatory mechanism in seizures."

Karen Gale of Georgetown University School of Medicine and her co-workers study animal models of convulsive seizures that ultimately involve discharges throughout the brain. They define two distinct brain regions, the substantia nigra and the newly named area tempestus, as participating in these generalized convulsive seizures.

"There seem to be police stations in the brain that prevent seizures from occurring," says Gale. She describes the substantia nigra, a group of nerve cell bodies underlying the cerebral cortex that sends projections to the thalamus and the neostriatum, as capable of performing this function and blocking many kinds of seizure activity. "The substantia nigra is not a seizure initiation site," she says. "It seems to regulate the spread of seizures that are set up somewhere else in the brain."



Deborah Barnes

**James McNamara** *studies kindling as an experimental model of epileptic seizures.*

In contrast, the other site Gale and her coworkers study is the area tempestus, buried deep near the pyriform cortex. This part of the cortex "is a site for synchronous activity and setting up seizures," according to Gale.

Gale proposes that as more excitation comes out of the area tempestus, there will be a greater response in its targets, the hippocampus and other limbic structures. Then, if something alters the policing function of the substantia nigra, there will be less control over the seizures. Gale does not know if an area analogous to the rat area tempestus exists in the human brain, nor does she know why this area is so epileptogenic in rats.

"We now know things we didn't know 4 years ago," says Ferrendelli. "The data from animal models of epilepsy suggest that there is at least one initiation site for seizures in the brain, the area tempestus in rats, and at least two policing areas, the substantia nigra and the anterior thalamus." But whether the same brain regions regulate seizure activity in the human brain has yet to be determined.

Perhaps one of the most controversial and complex topics in epilepsy research today concerns the issue of brain abnormality in an epileptic patient. Clearly, some seizures occur as isolated events in a normal brain because of a head injury or other lesion, but whether a normal brain then supports the recurrent spontaneous seizures that constitute epilepsy is more controversial. "When epilepsy is generalized and probably inherited, it is likely that there is some diffuse abnormality in the brain," says Prince. "But between seizures, the brain of an epileptic patient works normally."

Engel takes the position that abnormalities in certain patients exist not only in the part of the brain that shows abnormal electrical discharges, but also in brain sites distant to this focus. "That does not mean that the brain functions abnormally, only that it is abnormally susceptible to epileptogenic input," he says. "But there is a reluctance to admit this. It makes epilepsy seem worse."

Engel cites the animal kindling model as an example. Early in the kindling process, the animal's brain shows an abnormal discharge that ends with no change in behavior. "But later it spreads and develops into a seizure," he says. "Does that mean that the recipient brain is still normal? I think it is ridiculous to believe that."

Marc Dichter of the University of Pennsylvania School of Medicine says, "I can't agree with that. In an epileptic patient it is the normal part of the brain that often becomes involved in a generalized seizure." Prince concurs. "There have to be mechanisms in the normal cortex for converting normal activity into epileptic activity."

The issue of whether a small brain region or the entire brain is abnormally excitable in a person with epilepsy is not likely to be resolved soon. But most researchers agree that it is important to define what brain structures and circuits initiate and support the spread of different kinds of seizures in order to target drugs more specifically to those regions.

Given the variety of pharmacological, electrical, and structural interventions that can induce seizures in a normal brain, it is perhaps amazing that the brain does not have seizures more often. Various animal models have yielded information about brain regions or circuits that may initiate or restrict seizures. In vitro models answer some questions about normal brain function and the cellular mechanisms of antiepileptic drug action. Nevertheless, basic questions remain about what causes the transition to seizure, questions that neuroscientists hope to answer as they refine techniques for measuring both the electrical and metabolic activity of the human brain. ■

DEBORAH M. BARNES