

Management of Medically Intractable Epilepsy

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Many patients are referred to my Epilepsy Clinic because their seizures recur with an unacceptable frequency despite faithfully taking their anti-convulsant medications. Such patients are said to have “medically intractable epilepsy”. The guidelines which I have found most useful in managing such patients are:

1. Establish the type of epilepsy that the patient has (most patients and their referring physicians don't know !)
2. Choose medications which are best suited for the management of the epileptic syndrome in question.
3. Maintain a seizure diary
4. Improve quality of life of patient by lowering anticonvulsants while maintaining same seizure frequency.

Seizure diary:

A useful way to monitor the progress of a patient with medically intractable epilepsy is to plot their cumulative number of seizures versus time. In preparing these plots no distinction is made between “big” and “little” seizures. For most patients such a graph is linear (see Figure 1). The slope of the straight line is the average seizure frequency and is a characteristic unique to each patient. From a mathematical point of view the linear relationship implies that seizures recur randomly (and are distributed by a Poisson distribution). Response to treatment is reflected by a decrease in the slope of the line (the slope would become zero if the patient had no more seizures), whereas a worsening would be reflected by an increase in the slope.

A common scenario is shown in Figure 2. This figure shows the seizure diary for two patients. The black squares indicate the points at which a physician made a change in the patients anti-convulsant regimen (e.g. a change in timing of medications, dose, or switch to a new anti-convulsant). Clearly these changes made no difference in the patient's seizure frequency.

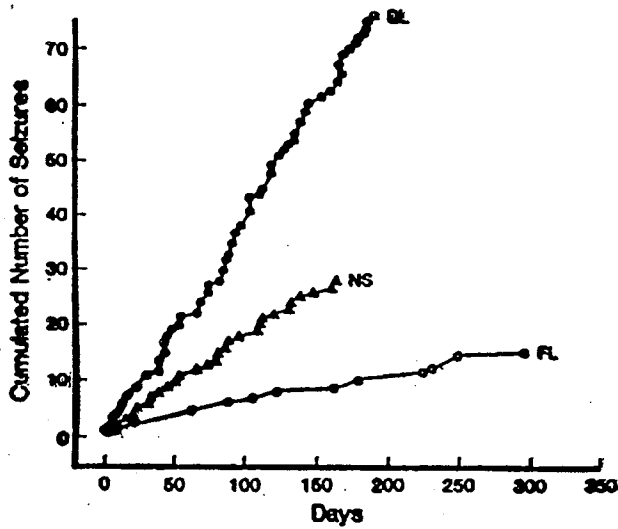


Figure 1

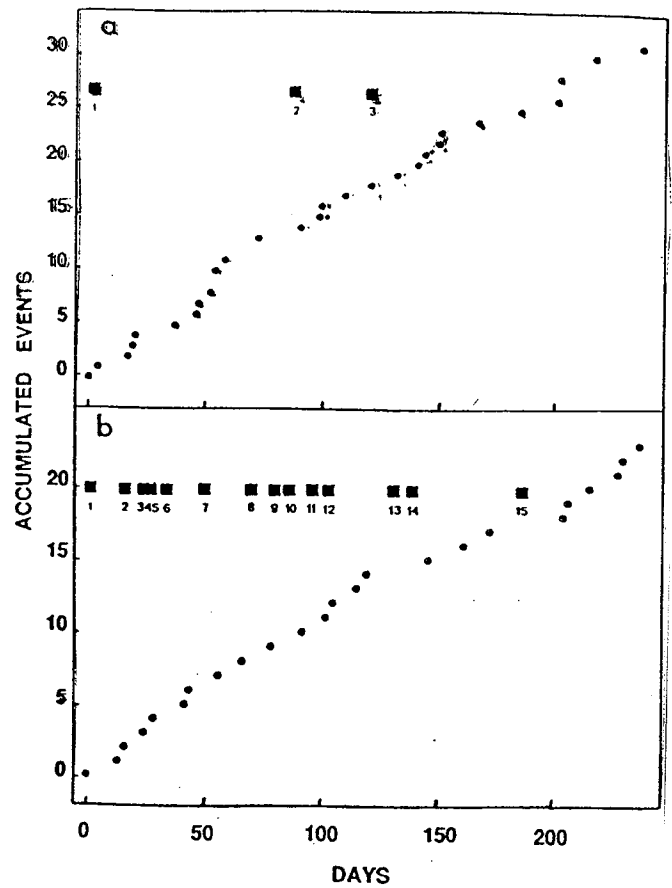


Figure 2

● seizures
 ■ medication changes

The take home message is that changes should be made in a patient's anti-convulsant regimen in response to changes in seizure frequency, not in response to the occurrence of a single seizure. Conversely, if an increase in medications has been made or a second anti-convulsant has been added and there is no change in seizure frequency, then change the medications back to where they were before the therapeutic trial was started.

Illustrative Example:

A 74 year old right-handed female presents with simple partial motor seizures involving the right face which began following the removal of a left frontal meningioma. The seizure frequency has been one episode every two days for the last year. When first seen her daily dose of medication was 180 mg phenobarbital, 700 mg Topamax and 5200 mg Neurontin. She complains of excessive fatigue, confusion, difficulty speaking, and feeling drugged. She has not left her home since the operation and explains that she is depressed.

Management:

Simple partial seizures are typically refractory to anti-convulsant medications. The management goal is directed towards preventing secondary generalized seizures and towards optimizing the patient's quality of life. The medications of choice are Dilantin and phenobarbital (low dose: 45-60 mg qhs) principally since both can be given as a single dose per day at bedtime.

Over the next few months Neurontin was discontinued, Topamax was reduced to 50 mg BID and phenobarbital was reduced to 45 mg. When the patient returned to clinic she was alert and spoke clearly. Even her friends had noted the marked improvement in her. She is planning to go to California with her husband on a second honeymoon. By the way her current seizure frequency is one every two to three days.

Brain Defibrillators:

The recent advent of the vagal nerve stimulator is important for two reasons:

1. It reminds us that the only seizure frequency which makes a major impact on someone's life is zero.
2. Non-pharmacological approaches to epilepsy are also possible.

At present the vagal nerve stimulator functions independently of feedback concerning the state of the brain. In other words, it turns on and off independently of whether the brain is having a seizure or not. An alternate approach would be to construct a device ("brain defibrillator") which continuously monitors brain activity and then delivers an appropriate stimulus (electrical or chemical) to a localized area of the brain to abort the seizure. Such devices would function much in the manner as an implantable cardiac defibrillator. The major advantage of this therapeutic approach is that it is called upon only when needed.

Although the development of a brain defibrillator for the treatment of patients with medically intractable epilepsy seems like science fiction, recent theoretical developments have suggested that such devices may be possible (Glanz, 1997; Milton, 1998). Present emphasis is being devoted to determining the nature of the stimulus that would have to be delivered. Two ideas are being actively investigated:

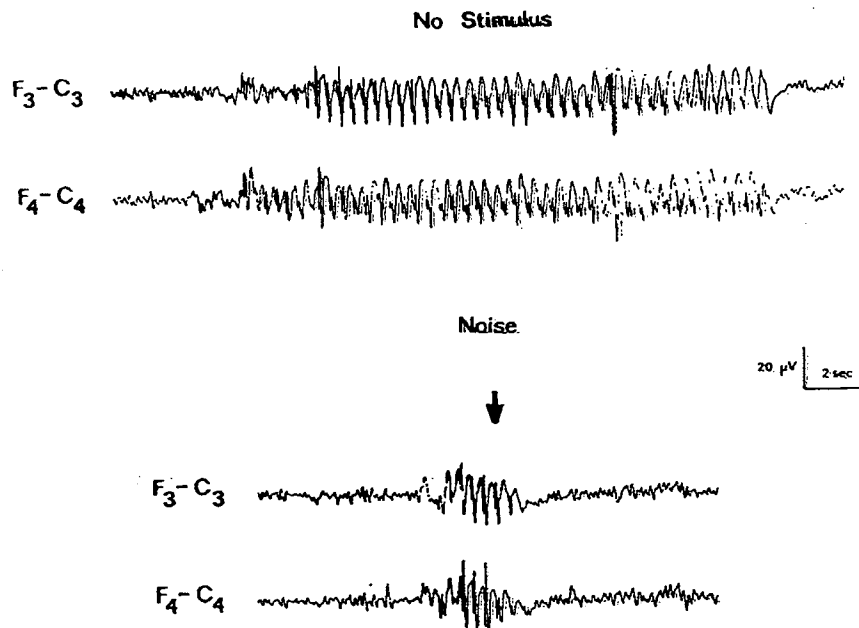


Figure 3

1). Multistability:

It has long been known a brief sensory stimulus, such as a noise, given close to seizure onset can stop a seizure (Figure 3). This observation is very suggestive of an underlying multistable dynamical system (Foss, et al, 1996, 1997; Milton and Foss, 1997). Multistability refers to the coexistence of multiple attractors (for example two or more qualitatively different oscillations). In such dynamical systems brief perturbations can cause sudden changes in dynamics because a switch between basins of attraction occurs.

There is over 25 years of experimental and theoretical work to indicate that the onset of oscillations in neurons (Figure 4) and in neural populations is characterized by multistability. Recent direct evidence for switching between attractors in the brains of epileptic patients has been obtained from intracranial EEG recordings (Manuca, et al, 1997). In these studies, time series analysis suggested that the time variation of the EEG signals could be characterized by changes in a single variable. The observations were most consistent with a model

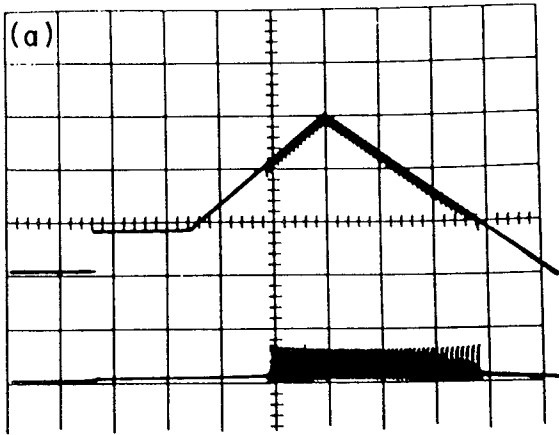
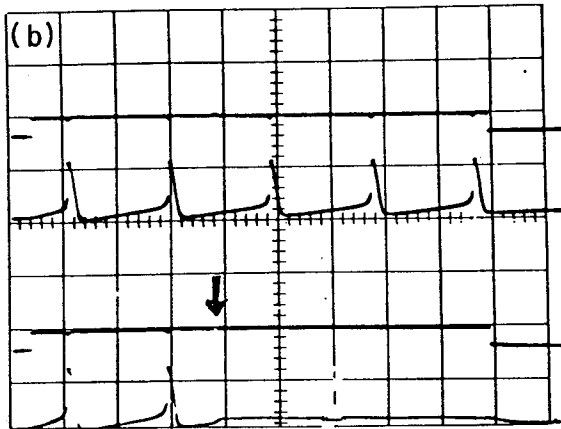


Figure 4:

Guttmann, et al (1980)



of bistability in which large collections of neurons flip between two collective states. In this context the time variation in the EEG corresponds to time variations in the switching probabilities between the two states.

2). Control of Chaos

In a chaotic dynamical system there are an infinite number of unstable periodic orbits. Suppose we know that one of these orbits would be the “non-seizure” state. Now we could choose the initial conditions to that we were on this orbit; however, since the orbit is unstable we would quickly diverge from it. However, if we were clever we might carefully follow the dynamics and when they diverge from the period 5 orbit we could apply a carefully honed perturbation designed to knock the system back onto the period 5 orbit. This is the basic idea behind controlling chaos with small perturbations.

The possibility of using this strategy to control the dynamics of an epileptic hippocampal slice has already been demonstrated (Schiff, et al, 1994).

The role of pencil and paper in the development of therapeutic strategies for application at the bedside receives little attention in modern day clinical research. Indeed medical students are not even required to know the simplest concepts of control. In contrast, work directed towards the design of brain defibrillators emphasizes that the performance of critically important experiments requires a theoretical knowledge of the response of the underlying control mechanisms to perturbations. Only through the efforts of dedicated teams involving theorists, basic scientists, and bedside clinicians, will the scourge called epilepsy be defeated.

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