Forecasting brain storms

Nonlinear mathematical techniques can be used to analyze the EEG patterns of epilepsy patients enabling the prediction of seizures prior to the onset of symptoms (pages 1173–1176).

STEVEN J. SCHIFF

CAN EPILEPTIC SEIZURES be predicted? If so then, unlike hurricanes, something might be done to prevent them. Two recent reports, one in *Physical Review Letters*[1] and the other on page 1173 of this issue[2], use nonlinear mathematical analyses of electrical signals (electroencephalogram, EEG) from the brains of epilepsy patients to predict seizures minutes before their onset.

Chronic epilepsy is a common condition, affecting about one percent of the population. Despite the availability of many new anti-seizure medications, about one-third of epilepsy patients remain refractory to drug therapy. For these individuals (although a few can achieve control through diet), the best alternative is often surgery. If the seizures are localized to portions of the brain that are separate from eloquent cortex (the parts we really miss if damaged), then surgical resection of the epileptic foci can be very effective. But the substantial risks involved limit surgery to only the best candidate patients. Furthermore, from a technical standpoint (apart from improvements in imaging and anesthesia) surgical resection to treat epilepsy has advanced little in four decades[3].

Attempts to predict seizures are not new. Traditional linear statistics (which sum the local frequency content of the signals) applied to continuous EEG recorded from the scalp enable anticipation of seizures by several (1–6) seconds[4]. However, scalp EEG is noisy and laden with artifact compared with EEG collected from intracranial (depth or subdural) electrodes implanted within the brain. It has been difficult to detect consistent rate changes prior to seizure if one counts and bins in time the interictal (between seizure) epileptic spikes from intracranial EEG; however, examining the linear correlations between the spikes from spatially separated electrodes suggested that prediction of seizures several minutes before onset was feasible[5]. Comparison of these results with those from more recent nonlinear studies seems a bit unfair—linear and nonlinear techniques are seldom tested head-to-head on the same data sets and, when they are, the success of linear versus nonlinear predictors may differ considerably from patient to patient[6]. From a practical standpoint, perhaps a warning of several seconds would be sufficient to implement certain seizure control strategies. In any case, these days linear analysis of EEG is not terribly fashionable.

During the last two decades, we have become fascinated with the realization that some nonlinear systems have very complex behaviors. Nonlinear systems obey rules where superposition breaks down—you do not just add up the activities of small responses to get the big picture. We apply the term *dimension* to the number of parts (or, equivalently, the number of variables or degrees of freedom) needed to specify the state of a dynamical system. One extreme in the spectrum of deterministic behaviors for nonlinear systems is *chaos*, in which the system shows no evidence of settling down to any stable state, and shows extreme (exponential) sensitivity to small perturbations. A hallmark of chaotic systems is that the dimension seems fractional or *fractal*, that is 1.26 rather than 1 or 2. Nonlinear dynamics and chaos have their own subspecialty within physics and mathematics, yet application of such theory to the workings of the brain has been slow. Despite a plethora of papers in the scientific literature attempting to estimate the fractal dimension of brain activity, many of us are left in doubt about the interpretability of such calculations[7].

What the two new reports demonstrate is that a tool from chaos theory (an estimator of dimension) can be used as a discriminator to predict a preseizure time window of minutes. In both reports, the authors are very careful not to claim that they are measuring the actual system's dimension—one report completes the standard calculation of dimension[1] whereas the other[2] does a variant of the calculation and uses a geometric method (seizure route plot), which in essence tests for a form of bistability (seizure versus nonseizure) in the EEG (ref. 8). The result is a statistic termed D that, although not interpretable in terms of a physical quantity, is a nonlinear measure that (we hope) reflects the state of the system. The conclusions are almost identical in these studies: prediction of an impending seizure with sufficient warning to permit nonsurgical intervention.

What might be done with such information? At a basic level, patients could prepare themselves for an imminent event by moving to a safe location. Because some patients can alter their seizures with cognitive or physical maneuvers, an early warning (before any auras that they may experience) might be useful. Recent research into drug delivery systems suggests that it might be possible to design a device to inject a small quantity of medication into the seizure focus[9] to prevent a seizure. The ability to reliably predict seizures would benefit the implementation of such a drug device.

For many of us who treat diseases of the brain, the ease with which the cardiologist employs electrical stimulation to control aberrant heartbeats seems an unfair monopoly of pacemaker technology. So far, the results of indirect electrical pacing of human epilepsy using electrodes implanted at sites distant from the focus (whether in the cerebellum, thalamus or vagal nerve) have not been effective enough to challenge traditional surgical resection. Direct pacing of epileptic foci in laboratory experiments has been explored[10], and oriented electric fields have been studied for their ability to directly suppress epileptic activity[11]. Although intriguing, experiments using chaos control techniques to pace neuronal activity[12] are still too primitive for human application. Nevertheless, recent research into the rigorous detection of neuronal electrical patterns[13] and into the delivery of electric fields to neurons, offers optimism that some of the current implementation issues will eventually be overcome.

One speculates that if we could create seizure control devices with a sufficiently high benefit-to-risk ratio, they would not have to be restricted to only the most pharmacologically resistant patients. The two new reports offer further encouragement that, for many patients with epilepsy, a substantial preseizure time window exists within which more effective and less intrusive methods of seizure control could be applied.

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Krasnow Institute for Advanced Studies
and Department of Psychology
George Mason University
Fairfax, Virginia 22030, USA

The fascinating life of hematopoietic stem cells

Elucidation of stem cell biology and of the unique gene products that promote stem cell self renewal and differentiation should lead to improvements in stem cell transplantation.

SAUL SHARKIS[1], LOTHAR KANZ[2], WOLFRAM BRUGGER[2] & DONALD ORLIC[3]

AT THE SECOND international workshop on hematopoietic stem cells* (HSC), 36 experts came together to report the latest results on: self renewal, mobilization and homing of HSC, cell cycle activity, gene expression, responses to cytokines and chemokines, and gene therapy and stem cell transplantation. For example, Metcalf (Walter and Eliza Hall Institute, Australia) reported on the novel SOCS (suppressors-of-cytokine-signaling) proteins, which might regulate HSC self renewal. Bodine (NIH) told us about a cDNA found exclusively in human bone marrow HSC that encodes a new receptor tyrosine kinase, the ligand for which may prove to be a new stem cell cytokine. These research approaches may enable us to dissect the molecular events that control the onset of specific gene expression in HSC and the 'decision' to either self renew or differentiate.

In addition to reports on intracellular control pathways, data were presented on the influence of the bone marrow microenvironment on HSC behavior. Broxmeyer (U. Indiana) observed chemotaxis of hematopoietic progenitor cells exposed to 16 new chemokines. Möhle (U. Tübingen) suggested that downregulation of the chemokine receptor CXCR4 (which binds to stroma derived factor-1, SDF-1) is a prerequisite for progenitor cell mobilization. Work from Papayannopolou's laboratory (U. Washington, Seattle) pointed to expression of VLA-4 (an adhesion molecule) by cells of the hematopoietic microenvironment as a major trigger of stem cell migration.

The several sites of hematopoietic activity in the embryo have prompted investigators to search for HSC at different developmental stages using a bone marrow repopulation assay (Fig. 1). Dzierzak (Erasmus University) showed that HSC from the aorta-gonad-mesonephros region of early mouse embryos engraft and self renew in adult mice. These HSC express CD34, c-*kit*, and MAC-1. Using mouse embryonic stem cells as yolk sac equivalents (another early site of hematopoiesis), Keller (U. Colorado) reported that early precursors called transitional cells could respond to both VEGF (vascular endothelial growth factor) and hematopoietic cytokines *in vitro* suggesting a common origin for endothelial and hematopoietic cells.

A number of investigators presented findings on HSC proliferation. Eaves (Terry Fox, Vancouver) told us that *in vitro* exposure to the cytokines interleukin (IL)-11 and hyper IL-6 (engineered to be highly potent) resulted in a 30-fold expansion of HSC in the murine competitive repopulation assay. In addition, Quesenberry (U. Massachusetts) found that HSC enter the cell cycle within the first 12 hours after transplant. However, others indicated that stem cells can remain quiescent for 48 hours after transplant, based upon selection with PKH26 and propidium iodide staining (Sharkis, Johns Hopkins). Clearly the controversy regarding the quiescent nature of HSC and the signals that trigger HSC to enter the cell cycle have yet to be resolved.

Improvements in methods for rapid expansion of HSC may present an opportunity for high efficiency insertion of therapeutic genes into stem cells (Fig. 2). Sorrentino (St. Jude Children's Research Hospital, Memphis) showed that when mice transplanted with HSC carrying the dihydrofolate reductase transgene were subjected to a drug-based regimen, the genetically modified HSC expanded whereas the host's endogenous HSC pool was depleted (see page 1136). This approach could result in the correction of blood cell disorders such as the hemoglobinopathies through gene therapy.

Controversy arose over the CD34 antigen as a marker of the earliest HSC.

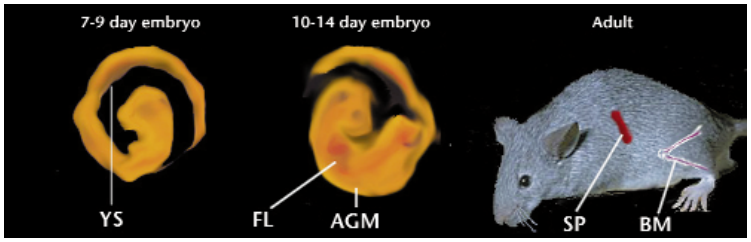

Fig. 1 Hematopoiesis originates on day 7 in the yolk sac (YS) blood islands perhaps generated by a precursor cell with the potential to give rise to both the endothelial and hematopoietic lineages. Initiation of hematopoietic stem cells (HSC) in the aorta-gonad-mesonephros (AGM) region in 10 day embryos is observed with additional expansion and migration to the fetal liver (FL). In the adult mouse, both the spleen (SP) and bone marrow (BM) have hematopoietic activity.

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