Grand mal convulsive seizures are characterized by the sudden loss of consciousness and motor inhibition, followed by tonic flexion and extension, repetitive clonic movements, and motor relaxation and lassitude. Seizures are elicited in all vertebrates that have been tested. The loss of both vigilance and the defenses of fight or flight incur life-threatening risks to the individual. In evolutionary history, we would expect this behavior to be extinguished. Its persistence prompts the query: What are the benefits of seizures?

Despite the ingrained fear that accompanies each seizure, the repeated induction of grand mal seizures has been clinically accepted for use in patients with severe psychiatric disorders for more than eight decades. Melancholia, mania, catatonia, preoccupation with suicide, and florid psychosis are quickly relieved. Its efficacy and speed sustain its use. How do grand mal seizures relieve intractable psychiatric disorders? What brain or systemic functions are altered by these seizures?

Clinical benefit
Seizures must be induced repeatedly to yield therapeutic benefit. Nonconvulsive brain stimulation, as in transcranial magnetic stimulation or vagus nerve stimulation, do not offer comparable benefits. The stimulus of induction, whether chemical (as with pentylentetrazol [Metrazol] or flurothyl [Indoklon]) or electrical (as in electroconvulsive therapy [ECT]), has little effect on outcome as long as full grand mal seizures are induced. A single induced seizure is rarely clinically effective. Nor are seizures effective when administered at long intervals. To sustain the benefit, seizures are induced weekly or at greater intervals for four to six months, or longer.

Modifiable clinical syndromes
Diverse behaviors are modified. Although introduced for the relief of psychosis, the first studies reported benefits in catatonia, melancholia, and mania. The breadth of effects is disturbing to clinicians and neuroscientists, because it questions the present classification systems that see these syndromes as unique biological entities. Melancholia is the disorder of mood, motor, and homeostatic functions. Disturbances in all three dimensions are necessary. These are identified by clinical signs using a depression rating scale, by tests of neuroendocrine functions, and validated by the rapid treatment response to tricyclic antidepressants or ECT. Mania and depression occur frequently in patients with melancholia, and both are equally responsive to treatment, which encourages the view that depression and mania are features of a single disorder.

Catatonia is the motor disorder diagnosed by clinical examination using a catatonia rating scale to identify typical signs, verified by the immediate relief afforded by intravenous benzodiazepine, and validated by the rapid treatment response to ECT. Catatonia is found in about 10% of patients admitted to academic psychiatric treatment facilities. Labels such as psychotic depression, delirious mania, mixed mania, postpartum psychosis, malignant catatonia, and neuroleptic malignant syndrome identify melancholia and catatonia. Patients are commonly relieved of symptoms within four weeks of treatment. Trials of ECT in patients with schizophrenia, dysthymia, depression secondary to character pathology, and other disorders defined by DSM criteria have varied results with low predictability of outcome and poor specificity.

Studied mechanisms
Explanations of how seizures modify behavior are focused on brain structure, brain chemistry,
Electroshock works. Why?

Brain structure. In the late 19th century, studies of cellular neuropathology found low brain glia amounts in patients with dementia praecox and high amounts in patients with epilepsy. Reports that the psychosis of dementia praecox could be relieved with seizures following accidental head injury or systemic infections excited interest in a possible antagonism between seizures and psychosis. Could seizure induction increase glia? Would such proliferation relieve psychosis? The first experiments, in a patient with catatonic schizophrenia in 1934, found chemically induced seizures to be well tolerated. The treatments did relieve his illness, and within a year the safety and efficacy of the treatment were widely heralded. The ease and safety of the treatments led to trials in other psychiatric disorders, finding efficacy in manic-depressive illness and relief of suicidal risk. While glial proliferation was not confirmed at that time, recent experimental studies report hippocampal neurogenesis with increased mossy fibers following induced seizures. Both hippocampal cell loss and hypometabolism normalize, and levels of brain-derived neurotrophic factors increase with successful treatment.

Catecholamine enhancement. Studies of psychoactive drugs have focused on the drugs effects on catecholamines and their receptors, especially serotonin and epinephrine in depression and dopamine in psychosis. The antidepressant effects of seizures led to comparisons with the effects of antidepressant medications. Each seizure releases a flood of catecholamines, but systematic studies fail to find associations between these releases and clinical outcome. The translation from psychopharmacology to convulsive therapy is even more difficult for the antipsychotic effects that are ascribed to the blockade of dopamine receptors with lowered levels of brain dopamine. An argument against this formulation is the relief patients with the "on-off phenomenon" of parkinsonism experience, a relief that is accompanied by increased cerebrospinal fluid (CSF) and brain levels of dopamine. In patients with clinical psychosis, especially those with positive symptom psychosis (the variety best treated with typical and atypical antipsychotic agents), the benefits following induced seizures are not predicted by the present biochemical theories of antipsychotic drug action.

Normalization of neuroendocrine abnormalities. Hypothalamic and pituitary peptides (prolactin, adrenocorticotropic hormone, thyrotropin-releasing hormone, corticotropin-releasing factor and cortisol, growth hormone, neurophysins, and endorphins) surge into the serum and CSF with each seizure. Serum and CSF calcium concentrations fall. The integrity of the blood-brain barrier is temporarily compromised, allowing for greater transfer of substances between blood and CSF. Hypercortisolemia is frequent in all forms of melancholia. Serum cortisol levels are elevated, diurnal rhythmicity is lost, and the expected feedback suppression by steroid administration is blunted. The dexamethasone suppression test is a measure of this phenomenon. With effective treatment, cortisol functions normalize. Persistent abnormality is an early sign of relapse. Other measures of neuroendocrine dysfunction, such as the thyroid-stimulating hormone response to thyrotropin and the growth hormone response to growth hormone-releasing factor, are also abnormal during illness and normalize with remission.

Patients with the severe forms of psychotic depression respond more quickly and more fully to treatment than do patients without psychosis. This difference is matched by the hormonal dysfunction in the hypothalamic-pituitary and growth hormone axes. Serum prolactin rises quickly following every seizure. The extent of release varies depending on the dose, stimulus form, electrode placement, and frequency of inductions. These variables reflect a direct impact of the stimulus on centrencephalic structures. Greater endocrine releases accompanying seizures that are induced with higher energies and bilateral electrode placement are associated with greater clinical efficacy. Neuroendocrine systems are central to human development, maturation, senescence, and vegetative functions. The periods of greatest neuroendocrine hormonal flux during adolescence, involution, and aging are also the periods of the greatest incidence of mood disorders. Abnormal hypothalamic functions affect downstream endocrine glands and functions. With each seizure, sudden discharges of hypothalamic and pituitary gland products flood the CSF and serum, restoring endocrine homeostasis. How more normal hormone functions are restored is the enigma. While homeostasis is momentarily restored, the underlying deficiency persists, requiring repeated stimulations to sustain remission. Neuroendocrine studies are fruitful targets for understanding a mechanism of action of the behavioral effects of induced seizures.

Electrophysiology. The electroencephalogram (EEG) is a noninvasive and accessible measure of the brain's neurochemical balance. Psychoactive agents alter EEG patterns, with specific signatures for
compounds that have a common brain chemical or clinical behavioral effect. The association of EEG and human behavior offers an opportunity to study the effects of induced seizures. Not only is a characteristic ictal EEG essential to behavioral effects, but changes in the interictal EEG characterize an effective course of treatment. Interseizure EEG records, monitored 24 to 30 hours after an induced seizure, exhibit high-amplitude slow-wave activity and persistent bursts that increase with greater numbers of seizures. Such changes normalize in the weeks following treatment. While these associations are well demonstrated and verified, the EEG is an untapped source of study of mechanism in ECT.

**Anticonvulsant effects.** The point at which a seizure is induced by a calibrated electrical stimulus is defined as the "seizure threshold." This arbitrary measure is highly dependent on the parameters of the stimulus and is unstable. When measured before the first treatment, and again late in the course, the threshold rises modestly in a small number of patients whose condition remits with treatment. This limited change is one of the many measurable changes that occur during treatment and does not explain a clinical relationship.

**Cerebroversion.** In cardioversion, a heart that is in a dysrhythmic state is restored to normal rhythm by a very large electrical stimulus. In some views, the persistent mood states of depression and mania reflect hypothalamic-pituitary hyperactivity, a breakdown in the feedback mechanisms in the stress response. Both seizures and cardioversion have similar initial effects on hypothalamic-pituitary-adrenal function. The analogy of cardioversion and cerebroversion is an interesting target for study.

Severe forms of melancholia, mania, catatonia, and psychosis rapidly remit with convulsive therapy. The rapid response of melancholia and catatonia to this treatment is so secure that it is offered as a validating criterion for clinical diagnosis. How such benefits come about is a riddle for neuroscience. Can seizures, as risky as they may be for the organism, reestablish normal neuroendocrine functions when they are awry? Such a benefit would counterbalance the risks and sustain this peculiar reflex in nature.

Of the many hypotheses, neuroendocrine functions offer the best opportunities for quantitative measurement of brain and systemic physiology. The structural, neurohumoral, electrophysiological, and seizure threshold images are interesting features of the process, with lesser probability of being explanatory. Our formulations for the pathophysiology of psychiatric disorders lack biological bases. An understanding of the mode of action of induced seizures would lead to a more productive classification of psychiatric disorders. It will also encourage their replacement by less intrusive procedures.

**References: References**

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