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## The Electrochemical Brain: Lessons from The Bell Jar and Interventional Psychiatry

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...because wherever I sat—on the deck of a ship or at a street café in Paris or Bangkok—I would be sitting under the same glass bell jar, stewing in my own sour air.

- “Esther Greenwood” in Sylvia Plath’s The Bell Jar

The Bell Jar, a haunting first-person narrative about depression and suicide, debuted in January 1963 under the pseudonym Victoria Lucas (1). Sylvia Plath told confidants that she disguised her identity because she questioned the literary value of the novel. One month later, Plath committed suicide via carbon monoxide poisoning; she was found in a carefully-sealed kitchen with her head in an oven. Plath’s suicide suggests that The Bell Jar is actually a *roman à clef*, or non-fiction with a veneer of fiction.

The novel opens on a sweltering summer day in 1953. Esther Greenwood, a witty college student from a Boston suburb, has begun a highly coveted internship at *Ladies Day* magazine in New York City. Unfortunately, the aspiring author is not herself; an insidious depression is slowly spoiling her experience and her normally-vivid worldview. As the summer continues, Esther struggles to conceal morose moods and cognitive distortions. When the internship ends, she returns home to focus on writing but succumbs to mounting hopelessness and perceptual disturbances. After two brief psychiatric evaluations, Esther is prescribed an antiquated, anesthesia-free version of electroconvulsive therapy (ECT). It only takes one traumatic “treatment” for Esther to drop out of care. After several suicidal gestures, she pens a suicide note and attempts to overdose on sleeping pills. Esther survives the attempt, and ultimately remits following a modernized version of ECT during a subsequent hospitalization.

Esther’s treatment course mirrors that of Sylvia Plath’s, and highlights the limitations of psychiatry at the time. Acutely ill patients had few treatment options, and psychiatry had yet to define itself as an evidence-based medical specialty. Four years earlier, the neurologist who developed the lobotomy had won a Nobel Prize. Some psychiatrists were still using this form of psychosurgery as a treatment for troubled descendants of “schizophrenogenic mothers.” Indeed, many of the available interventions were used to control patients rather

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than treat them. ECT initially fit this description until it was improved, validated, and ethically practiced.

The central tenant of ECT is that electricity can be used to alter neurotransmission for therapeutic purposes. Shockingly, this idea dates back to ancient civilizations that used electric rays and eels as medical devices. In the mid 18<sup>th</sup> century, capacitors replaced bioelectric sea creatures as brain stimulation tools. With this new-found tool, researchers attempted to reanimate decapitated livestock and cadavers in order to understand how the brain moves the body. These macabre methods spurred decades of neurophysiology research that ultimately established foundational brain-behavior relationships and revealed how neurons wire into synapses and networks. By the early 20<sup>th</sup> century, psychiatry was deeply invested in “the electric brain.” Even Sigmund Freud conducted electrophysiological research as a young neurologist, and then wrote extensively about human behavior as a means of discharging energy in order to maintain psychodynamic equilibrium.

Then, everything changed. The rapid and unexpected discovery of chlorpromazine shook psychiatry, releasing seismic waves through Europe right around the time that Esther received her first course of ECT. Medications suddenly became treatments rather than sedatives. Shortly thereafter, the serendipitous discovery of the antidepressant effects of monoamine-oxidase inhibitors and tricyclics further reinforced the notion that medications were the future of psychiatry. These early successes contributed to the re-conceptualization of psychiatric illness in terms of disordered neurotransmitter systems. Selective serotonin reuptake inhibitors emerged during the peak of this phenomenon. By the late 20<sup>th</sup> century, psychiatry was deeply invested in “the chemical brain.”

In a 21<sup>st</sup> century remake of The Bell Jar, Esther would probably have a cartoon understanding of the monoamine hypothesis of depression long before she meets a psychiatrist. Data suggest that direct-to-consumer “telepharmevangelism” (2) increases medication requests from patients, which in turn increases prescription rates and drug company profits (3). Esther might request an “antidepressant,” an on- or off-label medication from one of several classes that targets one or many neurotransmitter systems. Her clinician would be likely to oblige, thus starting a trial-and-error medication odyssey.

Unfortunately, remakes are rarely as compelling as originals, and the thought of The Bell Jar 2018 is particularly unappealing because it would spotlight the limitations of modern psychiatry. “Antidepressants” remain the most frequently prescribed class of psychiatric medications (5), despite offering relatively modest response and remission rates, as well as inconsistent effect sizes when compared to placebo (4). If the first drug fails, the second and third drug are also quite likely to fail. Indeed, study after study has shown that only a fraction of patients with depression remit with medications. Prescription rates remain high and more than 80% of those who take psychiatric medications report long-term use. Yet depression remains the leading cause of disability worldwide.

Despite the fact that current psychiatric medications are inadequate for most patients, novel medications remain rare. For a host of reasons, pharmaceutical companies have reduced or abandoned psychiatric drug development. Most “new” medications are only new in name,

not in class or mechanism. Ultimately, it may be that neurotransmitter models are intrinsically flawed, and that chemical reductionism cannot capture the complexity of psychiatric disorders.

One way forward may be to look backward. What often gets lost in this chemical era is the basic principle that neurotransmission also requires electrical signals. Medications do not always work, but when they do it is because they ultimately modulate both the electrical and the chemical properties of the brain. Interventional Psychiatry (IP) is an emerging branch of medicine that embraces this electrochemical dualism. The term “interventional” has been used in cardiology and other medical disciplines to describe procedures along the spectrum between standard care and surgery. Using a similar conceptual framework, the nascent field of IP features an array of electrical, electromagnetic, and chemical interventions for patients whose symptoms are refractory to standard care. These treatments are often used to augment psychotherapies and medications, and are thought to alter both electrical and chemical aspects of neurotransmission. IP treatments have their own set of side effects, risks, and efficacy limitations, but they offer evidence-based hope for patients who fail to remit with routine treatments.

The goal of IP is to use brain stimulation techniques or acutely acting drug infusions to modulate the neural systems thought to be associated with refractory psychiatric symptoms (6). Data suggest that patients who fail 2–3 medications for depression are more likely to benefit from IP treatments than they are from serial on- and off-label medication trials that are highly unlikely to work. Two of the most common IP treatments are transcranial magnetic stimulation (TMS) and ECT. In TMS, a staccato magnetic field induces electricity in neurons, causing changes in neurotransmission and promoting plasticity in targeted circuits. In ECT, a therapeutic seizure leads to a large release of neurotransmitters and a rapid induction of neurogenesis. TMS is less efficacious than ECT but causes fewer side effects and is performed without anesthesia. Severely ill patients are most likely to benefit from ECT, a treatment that remains deeply stigmatized and underutilized despite being one of the most efficacious treatments in all of medicine (7). If these interventions fail, patients might be evaluated for experimental treatments such as ketamine, vagus nerve stimulation, and others.

One of the most exciting aspects of IP is that its electrochemical treatments can also be used as powerful research tools. Aside from their therapeutic effects, brain stimulation techniques are also useful for investigating clinical symptoms and neural systems. For example, researchers have paired TMS with electrophysiological and neuroimaging techniques in order to make causal inferences about cognitive processes and the neural systems and networks that instantiate them (8). Such studies have already provided insights into depression biotypes as well as the tantalizing possibility of optimizing treatment selection with biomarkers or predictive algorithms (9).

The field of psychiatry has come a long way since The Bell Jar, but Plath’s life and fictionalized autobiography remain stark testimonies to the inadequacy of psychiatric models and treatments. Looking back, ECT may have saved Plath’s life had it been used to augment the medication prescribed during her relapse (10). Looking forward, psychiatric models and

treatments should be guided by both the electrical and the chemical properties of neurotransmission. Rooting psychiatry in neuroscience will ensure that more patient stories mirror the end of Plath's novel rather than her life: with cathartic remission. As Plath wrote: "All the heat and fear had purged itself. I felt surprisingly at peace. The bell jar hung suspended a few feet above my head. I was open to the circulating air."

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