ECT is making something of a comeback because it remains a paragon of efficacy amidst other relatively disappointing treatments. The dexamethasone suppression test (DST), once the poster child for a laboratory test in psychiatry, is of minor theoretical and historical interest. Edward Shorter and Max Fink\(^1\) intertwine the stories of ECT, DST, and the hypothalamic-pituitary-adrenal (HPA) axis in their recently published book, *Endocrine Psychiatry: Solving the Riddle of Melancholia*. The book chronicles the rise and fall of the HPA axis in psychiatry and offers some lessons relevant to the practice of ECT today.

Shorter and Fink’s fast-paced medical history gives the reader a ringside seat to the breakthroughs that led to an understanding of the best replicated finding in biological psychiatry—namely, hypercortisolemia in melancholic depression. Starting from discoveries in the early 19th century about the basics of the endocrine system, it traces the identification of adrenal steroids in the early 20th century and finally the landmark clinical studies of the 1970s and 1980s that almost resulted in the DST becoming a standard of psychiatric diagnosis. Unfortunately, DSM-III diagnostic criteria did not reliably identify patients with positive DST results. Instead of questioning the DSM criteria, the DST was discarded as faulty.

This extremely detailed book gives both comprehensive citations and fascinating quotes from interviews with the main protagonists in this real-life scientific drama. As you read, you want more—more science in clinical psychiatry and more rational explanations for what we deem useful and discard as irrelevant in our field. It is an eye-opening revelation of how politics, personalities, and science can collide, with unfortunate results.

Many experts, including Fink, would say that the DST and ECT are for the severely, “melancholically” depressed.\(^2\) This distinction is important because it is possible to be severely dysfunctional and dysphoric on the basis of a type of depressive syndrome that is characterized by neither hypercortisolemia nor ECT responsiveness. Such a condition has been labeled neurotic depression, characterological depression, reactive depression, or any number of terms that indicate something other than the clear-cut, inherited, biological/clinical depression for which somatic treatments are necessary.\(^3\) Shorter and Fink argue that the DSM construct of “major” depression is flawed because it includes such heterogeneous variants.
In general, however, there is significant overlap between the severely depressed and the melancholically depressed. The more severe the depressive symptoms, the more likely the patient is to have the neurovegetative depressive signs and symptoms that constitute melancholia, a dysregulated HPA axis, and the likelihood of response to ECT. The most severe subtype of depression—psychotic depression—is both particularly ECT-responsive and likely to be characterized by HPA axis abnormalities.4-6

**The Holy Grail of biological psychiatry**

Severity of illness is not exactly the same as treatment resistance. While that may seem obvious, the two are very often confounded. Just as melancholia and severity of depressive symptoms overlap, so do treatment resistance and severity of illness, but certainly not completely.7 Treatment resistance is at least partly a function of prescribing the weakest treatments first, even for the most severely ill patients. Is it reasonable to give a psychologically depressed patient a trial of an SSRI (with or without an antipsychotic) instead of recommending ECT as a first-line treatment? Such a patient would not be classified as treatment-resistant if he or she responded quickly to a course of ECT (a very likely outcome).

If the likelihood of response is 80% with ECT and 30% with an SSRI, are we doing patients a favor by allowing them to remain seriously ill for additional weeks or months by first giving them a trial, or multiple trials, of an SSRI? If a patient is in the group of responders to SSRIs, then no time would be wasted. For the remaining majority of patients, the risks of postponing effective treatment are not trivial. The consequences include undue suffering, risk of suicide, and financial burdens (eg, cost of inpatient hospitalization, inability to work).

The solution to this dilemma is the Holy Grail of biological psychiatry: finding biological markers that would serve as sensitive and specific predictors of treatment response to a particular treatment for a given patient. Since the majority of patients respond to ECT,8 the need for predictors of response is actually less urgent than for other treatments. A positive DST result could, however, encourage earlier recommendation of ECT.

There is also an issue in ECT about predicting what type of ECT will be best for a particular patient. Bilateral electrode placement may work more quickly and reliably, but at the cost of increased cognitive impairment in some patients, compared with right unilateral electrode placement.9 An additional, more recent technical refinement, ultrabrief pulse stimuli, may be an option to decrease the risk of further cognitive impairment.10 It would be very helpful to know with certainty that a particular patient would respond to either right unilateral or bilateral electrode placement from the start. In practice, some patients who start ECT with right unilateral electrode placement need to be switched to bilateral electrode placement if there is no adequate response after several treatments.11 This practice puts the patient at additional unnecessary risk, incurs extra cost, and means that he will remain depressed longer.

An additional important function of a predictor would be to inform the practitioner of when a patient has had enough treatment. This, too, was an application for which the DST almost made it into clinical use. As reviewed by Shorter and Fink, the DST normalized in patients who had had enough treatment to remain well; for patients whose DST results remained abnormal despite apparent good treatment response, there was a high rate of early relapse.12 This information could be used to help determine not only how many ECT treatments a patient might need but also how long patients treated with antidepressant medications would need to keep taking them.

Finally, the DST may have an important function in detecting the risk of future suicidal behavior. Shorter and Fink highlight this neglected aspect in the DST literature. They note that a study by Coryell and Schlesser13 demonstrated a 10-fold greater rate of suicide in the 15-year follow-up of depressed patients with persistently positive DST results.

**The earlier, the better**

The treatment of the severely, melancholically depressed patient can be optimized by correct and early diagnosis; early recommendation of proven, definitive treatment modalities; and continuation of those treatments long enough to ensure protection against early relapse. A biological marker laboratory test could be helpful in determining diagnostic categorization, in determining treatment adequacy, and possibly in predicting suicide risk; we nearly had that with the DST, but we abandoned it because it was not perfect.

In this case, as argued by Shorter and Fink, perfection was the enemy of the good.

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