

Brown W A, Johnston R & Mayfield D. The 24-hour dexamethasone suppression test in a clinical setting: relationship to diagnosis, symptoms, and response to treatment. *Amer. J. Psychiat.* 136:543-7, 1979.
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We carried out dexamethasone suppression tests in 54 male psychiatric patients. Forty percent of those with major depression showed escape from suppression over the 24 hours after dexamethasone administration whereas all of the patients with other diagnoses—schizophrenia, neurosis, alcoholism, drug abuse—showed normal pituitary-adrenal suppression. There was no difference between depressed patients who did and did not show escape from suppression in previous episodes, family history, symptoms, or medication, but those who showed escape tended to have a more severe depression and responded better to treatment. [The *SCI*® and the *SSCI*® indicate that this paper has been cited in more than 285 publications.]

What Happened to the DST?

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In the 1960s a smattering of reports appeared describing elevated plasma cortisol in depressed patients. Through the 1970s a handful of psychiatric researchers continued to explore this matter. Their inquiries included assessment of pituitary-adrenal suppressibility in depressed patients using the dexamethasone suppression test (DST). I came into the picture after reading the 1976 paper by B.J. Carroll and his associates¹ that reported that 48 percent of depressed patients, but only 2 percent of those with other psychiatric diagnoses, show early escape from dexamethasone suppression. Apparently, the DST could discriminate depressed patients from those with other psychiatric diagnoses.

As a fledgling psychiatric researcher puttering about the wards and laboratory trying to figure out how to put hormones and psychiatry together, my attention was riveted by the possibility of an endocrine abnormality specific to depressive illness. As my first foray into clinical psychiatric research, I attempted to replicate Carroll's finding. I roped Robert Johnston and Demmie Mayfield, colleagues at the Providence Veterans Administration Medical Center and Brown University, into joining me, and together we conducted our psychiatric ward a study of DST results in relation to psychiatric diagnosis, symptoms,

and response to treatment. Our results, published in 1979, entirely replicated those of Carroll and his associates: 40 percent of the depressed patients but none of those with other psychiatric diagnoses showed early escape from dexamethasone suppression.

Others began to take notice and more replications followed. In 1981, Carroll and his associates hailed the DST as "A specific laboratory test for the diagnosis of melancholia."² For the next six years, psychiatrists the world over embraced the DST. There was an avalanche of DST papers—as one of the earlier reports, ours was frequently cited—and in psychiatric hospitals, clinics, and offices the DST became part of the "diagnostic" workup. Patients clamored for the test—a physician in Providence requested a DST so he would know whether or not he was depressed; and clinicians began to consider it essential. A thoroughly competent psychiatrist asked me if a patient with depressive symptoms, phobic about phlebotomy, could have enough blood drawn by skin puncture to perform a DST.

Today, it would be difficult to find any psychiatric setting where the DST is used other than as a test for Cushing's syndrome. DST research has decreased precipitously: The number of papers published on the DST and psychiatric illness rose from 5 in 1980 to a high of 100 in 1985. In 1989 there were only 22 such papers. What happened?

The fervor with which the DST was embraced is understandable. Psychiatry is bereft of gadgets—scopes, probes, scanners, assays—that offer up a diagnosis. Although we value our ability to detect the signs and symptoms of psychiatric illness through uncommon observation, we long for some hardware. So, when a simple blood test came along that looked like it confirmed the diagnosis of depression, we were enchanted. Like all infatuations, this one had little to do with reality. Despite scant evidence to support its clinical use—the DST has at best a diagnostic sensitivity for depression of about 50 percent, and its specificity remains unclear—the DST became widely used to both make and confirm a diagnosis of depression. Fueling the clinical use of the DST was a torrent of papers, many appearing in widely read journals, that initially confirmed the DST's "diagnostic usefulness." The onslaught of confirming, embellishing, and later disconfirming

reports was unique in the history of psychiatric research.

Why all the papers? The clinical importance of the original findings is not a sufficient explanation. After all, most "breakthroughs" in psychiatry are largely ignored and go on to expire without ceremony. My hunch is that a good deal of the paper deluge was because DST research can be quick and easy. The DST is inexpensive and noninvasive. Cortisol measurements are readily available. Collect a group of psychiatric patients, make a diagnosis, carry out DSTs, and, whatever the results, you had a paper.

As more DST studies were done, the specificity for depressive illness of early escape from dexamethasone suppression began to erode. Schizophrenic patients, patients with eating disorders, manic patients, and patients withdrawing from alcohol also resisted dexamethasone suppression, in some instances with a frequency approaching that of depressed patients. How come?

The specificity and diagnostic confidence of any laboratory test depend on the nature of the comparison, "no disease" group. As comparison groups begin to include more diverse and less healthy patients, the incidence of "false positive" test results usually increases. So it was with the DST. But there were some technical glitches as well. The earliest DST reports, ours included, that showed that escape from dexamethasone suppression had high specificity for depressive illness, used a 2 mg dexamethasone dose. In an attempt to increase the DST's sensitivity for depression, a 1 mg dexamethasone dose was suggested and became the "standard" DST protocol.² But a 2 mg DST may be a more valid indicator of pituitary-adrenocortical hyperfunction;³ the results of a 1 mg DST may be more vulnerable to extraneous influences. In patients given a 1 mg DST, for example, some instances of dexamethasone resistance are accounted for by low dexamethasone blood levels. Unfortunately, before these procedural matters could be sorted out, the DST was repudiated.

The erosion of the DST's specificity for depressive illness does not fully account for the

rapidity and completeness with which clinicians and researchers rejected it. When psychiatrists began to realize that the DST is not a perfect test—that, for example, many severely depressed patients suppress normally—they spurned the DST with a vengeance. They seemed to feel betrayed. But who had betrayed whom? The DST was applied as a diagnostic aid before there were sufficient data to support its clinical use. An American Psychiatric Association task force report on the DST, published in 1987, urged "the psychiatric community neither to accept the DST uncritically for clinical application nor to discard it at this time."⁴ But it was too late. The tide had turned.

To add to the confusion, we seem to have gotten our terms mixed up. Depression is defined in current parlance as a constellation of signs and symptoms having to do with how a person feels, looks, and acts. The diagnosis of depression requires the presence of these symptoms and signs and cannot be made by a laboratory test anymore than a diagnosis of dementia can be made by a CT scan or of angina pectoris by an EKG. Until we know more about the pathophysiology of depression and until we change our diagnostic criteria, no laboratory test alone can "diagnose" depression. We were asking ourselves the wrong question. The question should have been and still is: What can an endocrine abnormality such as that detected by the DST tell us about the pathophysiology, prognosis, and treatment of depressive illness?

It is indisputable that a subgroup of depressed patients have a state-dependent pituitary-adrenocortical abnormality similar in quality, and in some instances in degree, to that seen in Cushing's disease. Once again this abnormality is in the hands of a small group of researchers. Corticotropin-releasing factor and the hippocampus are among the topics of current interest. And observations continue to accrue, suggesting that the DST may help identify depressed patients who require somatic treatment, who are likely to relapse, and who are prone to suicide.⁵

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