

Carroll B J, Feinberg M, Greden J F, Tarika J, Alcala A A, Haskett R F, James N M, Kronfol Z, Lohr N, Steiner M, de Vigne J P & Young E. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. *Arch. Gen. Psychiat.* 38:15-22, 1981.

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Data are presented to validate the overnight dexamethasone suppression test for the diagnosis of melancholia. Abnormal plasma cortisol concentrations occurred within 24 hours for melancholic patients. [The *SC\** and *SSC\** indicate that this paper has been cited in over 1,225 publications.]

## Combining Laboratory and Clinical Criteria for Depression

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June 17, 1989

This work began when I was a psychiatry resident in Melbourne in 1967. I wanted to study in humans the mode of action of the then-new tricyclic antidepressant drugs. A neuroendocrine strategy was conceived in collaboration with F.I.R. Martin and Brian M. Davies, my mentors in endocrinology and psychiatry. We planned to perform hypothalamo-pituitary function tests in depressed patients before and then during tricyclic drug treatment. We soon found that many patients did not suppress plasma cortisol levels normally in response to dexamethasone, even before treatment.<sup>1</sup> For the last 21 years, I have explored the significance and mechanism of that observation.

By 1976 the time course of the escape from dexamethasone suppression was established,<sup>2</sup> and we knew that most nondepressed psychiatric patients had normal suppression when a 2 mg dose of dexamethasone was used.<sup>3</sup> It remained to explore with many colleagues in Ann Arbor the optimal dose for the procedure. The results reported in 1981 suggested that a 1 mg dose improved the sensitivity without lowering the specificity of the psychiatric dexamethasone suppression test (DST).

Many clinicians adopted the DST enthusiastically, some perhaps uncritically, while many research groups appropriately set about questioning the re-

port. The high rate of citation is related to the DST's practicality, as well as its clinical potential and its theoretical importance in revealing dysfunction in the limbic system of the brain, mediated by disturbed neurotransmitter function.<sup>4</sup>

Much controversy arose when the absolute specificity of the DST, rather than the value of the test in subtyping depression, became the focus of attention. I have repeatedly cautioned against using the DST as a screening test.<sup>5</sup> Another source of the controversy was the arbitrary, data-free change in the clinical diagnostic criteria for depression and melancholia introduced by the American Psychiatric Association in 1980 with the *Diagnostic and Statistical Manual, Third Edition (DSM III)*. This change had the effect of creating a nonvalidated "gold standard" against which the DST inevitably was compared, whereas the procedure was developed with the *International Classification of Diseases 9 (ICD)* clinical diagnostic system. We now know that the *ICD*-derived diagnoses agree with DST results much better than do *DSM III* diagnoses when both systems are compared in the same depressed patients.<sup>6</sup>

Over time, the controversy has subsided. The *DSM III* criteria already are obsolete, and psychiatrists have stopped expecting the DST to do more than we described or intended. Its value has been in teaching psychiatrists how to use laboratory tests judiciously; in promoting an era of clinical psychoendocrine research, out of which better tests should emerge; and in demonstrating a new dimension of biological heterogeneity in depressed patients.

Current research reports confirm and expand on the early intuitions about the DST in depression. The subgroup of depressed patients with abnormal DST results resembles the classical melancholic clinical profile, has a high rate of recurrence and a strong family history, has a poor prognosis if the test does not normalize with drug treatment, and has the highest rate of specific response to antidepressant drugs. Abnormal DST results are strongly associated with suicide or violent suicide attempts. The clinically relevant "bottom line" that seems to be emerging is the suggestion that this group of patients will fail to respond to psychosocial treatment of their depressions and that drug treatment for them will become a mandate of quality assurance. We await the data.

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