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Brown W A & Qualls C B. Pituitary-adrenal disinhibition in depression: marker of a subtype with characteristic clinical features and response to treatment? *Psychiat. Res.* 4:115-28, 1981.

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Among depressed patients, resistance to dexamethasone suppression appeared to be associated with primary—as opposed to secondary—depression, older age, frequent depressive episodes, cognitive impairment, good improvement with hospitalization, and response to specific antidepressants. Thus, enhanced pituitary-adrenocortical activity may characterize a depressive subtype with a distinct pathophysiology, clinical course, and treatment response. [The *SCI*® and *SSCI*® indicate that this paper has been cited in over 80 publications.]

Can Hormones Subtype Depression?

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In 1974, fortified with a residency in psychiatry and a fellowship in neuroendocrinology, I took a job at Brown University's new medical school, set up shop at the Providence Veterans Administration (VA) Medical Center, and was ready to take on the mind-brain problem. For two years I scrutinized the relationship between hormones and psychological state in healthy young men—in retrospect a maneuver designed to stave off the booby traps of clinical research. But my innocence was short-lived. In 1976 Bernard J. Carroll and his associates reported that 48 percent of depressed patients, but only 2 percent of those with other psychiatric diagnoses, show early escape from dexamethasone suppression.[1] A biological abnormality specific to depressive illness? As my first clinical study I tried to replicate Carroll's study.

Our psychiatric ward until then had been untainted by research, and the prospect of adding a research protocol to ongoing clinical matters was greeted by the ward staff with something less than unbridled enthusiasm. Nonetheless, owing to the unwavering support of my chief, Demmie Mayfield, and the collaboration and good humor of the nurses and other clinical staff, we carried off a reasonably good study.[2] The results confirmed Carroll's findings. Later, when thousands of psychiatric patients had been given the dexamethasone suppression test (DST), the specificity for depressive illness of early escape from dexamethasone suppression appeared less absolute; but the existence of pituitary-adrenocortical dysfunction in a substantial proportion of depressed patients remains indisputable.

From my first foray into the endocrine features of depression, I was intrigued by the fact that, however precisely and narrowly one defines depression, pituitary-adrenocortical dysfunction occurs in only about half the patients. I wondered if depressed patients with and without this endocrine dysfunction had different illnesses with dissimilar pathophysiologies and treatment requirements. This question has organized my research for the past 13 years.

In 1978 Iris Shuey, a psychiatric resident; C. Brandon Qualls and Richard Haier, collaborators at Providence's Butler Hospital; and I began to look for features of depression—symptoms, illness course, cognitive function, age, treatment response—associated with normal and abnormal pituitary-adrenocortical activity. When three separate studies had been completed, Brandon and I decided to summarize our observations in light of the possibility that pituitary-adrenocortical abnormality characterizes a pathophysiologically discrete depressive subtype. So we wrote this paper.

I was surprised to hear that, by whatever circuitous route, our paper has achieved *Citation Classic* status. Surprised and gratified. I was pleased with this paper when we wrote it and I still am. It provided an opportunity to present evidence in support of a fundamental proposition. I fear, however, that our paper is cited not because of its weighty implications, but because it appeared before the outpour of DST reports and offered data on a number of DST matters—age, treatment response, severity—that were and continue to be under investigation.

The informal collaborations that brought off the studies reported in this paper have evolved into an affective disorders research group. Now a greater range of projects—ECT, psychosocial treatment, "biology" of suicide, family dynamics—are on the table, we're a bit larger, and we meet regularly. But there's no written agenda and in most other ways we're as untidy as ever. The VA Medical Center's psychiatric ward has become a center for clinical psychiatric research.

The possibility that measures of pituitary-adrenocortical function identify meaningful subtypes of depressive illness continues to be explored.[3] In 1984, in the context of an antidepressant study, Mihaly Arato, a visiting professor from Hungary; Ram K. Shrivastava, a collaborator from New York; and I noticed quite unexpectedly that 50 percent of the DST suppressors but none of the nonsuppressors responded to placebo. Since then, we and others have replicated this observation.[4] It suggests that depressed patients with pituitary-adrenocortical disinhibition have a relatively tenacious illness likely to require antidepressant treatment.

1. **Carroll B J, Curtis G C & Mendels J.** Neuroendocrine regulation in depression: II. Discrimination of depressed from nondepressed patients. *Arch. Gen. Psychiat.* 33:1051-8, 1976. (Cited 450 times.)
2. **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. (Cited 265 times.)
3. **Garvey M J, Schaffer C, Schaffer L & Perry P J.** Is DST status associated with depression characteristics? *J. Affect. Disorders* 16:159-65, 1989.
4. **Brown W A, Shrivastava R K & Arato M.** Pre-treatment pituitary-adrenocortical status and placebo response in depression. *Psychopharmacol. Bull.* 23:155-9, 1987.

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