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This Week's Citation Classic®

Nelson D H, Meakin J W & Thorn G W. ACTH-producing pituitary tumors following adrenalectomy for Cushing's syndrome.
Ann. Intern. Med. 52:560-9, 1960.
[Department of Medicine, Harvard Medical School, and Peter Bent Brigham Hospital, Boston, MA]

This paper describes patients who, following adrenalectomy for Cushing's syndrome, were found to have pituitary tumors that produced large quantities of ACTH. The increased ACTH production was accompanied by melanocyte-stimulating activity, and thus, the skin of the patients was highly pigmented. [The *SCI*® indicates that this paper has been cited in over 230 publications since 1960.]

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The publication of this paper, and the single case report that preceded it, was the result of fortunate collaborations. During the Korean War, many physicians were called to active duty, and a few of us with research experience were assigned to military research facilities. I had previously worked with Leo T. Samuels in the development of a method for the measurement of corticosteroids in blood.[1]

I was assigned to the Naval Medical School and Naval Medical Research Institute at Bethesda, Maryland, where I was able to collaborate with David Hume in the development of a bioassay for the estimation of ACTH in blood.[2] This assay consisted of injecting whole plasma into the circulation of hypophysectomized dogs and then measuring the cortisol output in the adrenal venous effluent from that animal. This required the surgical skills of Hume and a method for assaying cortisol in blood, which was now available. Using this bioassay, we were able to measure elevated levels of ACTH in plasma in a number of conditions including some patients with pituitary-dependent Cushing's syndrome.

It was natural, therefore, that when a deeply pigmented patient with a pituitary tumor that had appeared since adrenalectomy for Cushing's syndrome came to George W. Thorn's unit at the Peter Bent Brigham Hospital (where I was later working), we should carry out an ACTH assay on that patient's plasma. Meakin, who was a research fellow with us at that time, had become expert at carrying out these assays and was elated to find extremely high levels of ACTH in the plasma of this patient.[3] Following the initial observation, we were quickly able to find a number of patients of a similar type, which resulted in the publication of this study. Grant Liddle, who used the ACTH bioassay for his studies of adrenal pituitary function, first used the term "Nelson's syndrome" to describe these patients.[4] More recently, work has been done on these patients at the Academy of Medicine, Warsaw, Poland.[5] At the time of this study, there was still some question whether hypersecretion of ACTH was an important factor in the development of Cushing's syndrome associated with adrenal hyperplasia when no pituitary tumor was evident. The demonstration of the pathophysiology of these patients was one of the findings that led to the recognition of microadenomas being etiologic factors in the production of Cushing's disease.

1. **Nelson D H & Samuels L T.** A method for the determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in the peripheral circulation. *J. Clin. Endocrinol. Metab.* 12:519-26, 1952.
[See also: **Nelson D H.** Citation Classic. *Current Contents/Clinical Practice* 9(1):16, 5 January 1981.]
2. **Nelson D H & Hume D M.** Corticosteroid secretion in the adrenal venous blood of the hypophysectomized dog as an assay for ACTH. *Endocrinology* 57:184-92, 1955. (Cited 105 times.)
3. **Nelson D H, Meakin J W, Dealy J B, Jr., Matson D D, Emerson K, Jr. & Thorn G W.** ACTH-producing tumor of the pituitary gland. *N. Engl. J. Med.* 259:161-4, 1958. (Cited 185 times.)
4. **Liddle G W, Island D & Meador C K.** Normal and abnormal regulation of corticotropin secretion in man. *Recent Prog. Hormone Res.* 18:125-66, 1962. (Cited 305 times.)
5. **Kasperlik-Zaluska A A, Nielubowicz J, Wislawski J, Hartwig W, Zaluska J, Jeske W & Migdalska B.** Nelson syndrome: incidence and prognosis. *Clin. Endocrinol.* 19:693-8, 1983.

