Nelson syndrome: historical perspectives and current concepts

MARK HORNVAK, M.D.,1 MARTIN H. WEISS, M.D.,2 DON H. NELSON, M.D.,3 AND WILLIAM T. COULDWELL, M.D., PH.D.1

Departments of 1Neurosurgery and 1Medicine, University of Utah, Salt Lake City, Utah; and 2Department of Neurological Surgery, University of Southern California, Los Angeles, California

The appearance of an adrenocorticotropic hormone (ACTH)-producing tumor after bilateral adrenalectomy for Cushing disease was first described by Nelson in 1958. The syndrome that now bears his name was characterized by hyperpigmentation, a sellar mass, and increased plasma ACTH levels. The treatment of Cushing disease has changed drastically since the 1950s, when the choice was adrenalectomy. Thus, the occurrence, diagnosis, and treatment of Nelson syndrome have changed as well. In the modern era of high-resolution neuroimaging, transsphenoidal microneurosurgery, and stereotactic radiosurgery, Nelson syndrome has become a rare entity. The authors describe the history of the diagnosis and treatment of Nelson syndrome. In light of the changes described, the authors believe this disease must be reevaluated in the contemporary era and a modern paradigm adopted. (DOI: 10.3171/FOC-07/09/E12)

KEY WORDS • Cushing disease • Cushing syndrome • Nelson syndrome • neurosurgery history

History of Cushing Disease

In 1958, Nelson et al.72 first described the appearance of an ACTH-producing tumor after bilateral adrenalectomy for Cushing disease. Dr. Don H. Nelson (Fig. 1) was a fellow in endocrinology and had already done considerable basic research in adrenal physiology when he initially reported the syndrome that now bears his name. In the original paper, the authors indicated that the syndrome was characterized by hyperpigmentation, sellar mass demonstrated by an enlarged sella turcica on skull radiographs, and increased plasma ACTH levels.72 Two years later, Nelson and colleagues73 had compiled the information obtained in nine additional patients with the same characteristics and findings as the patient in the initial case description. This clinical syndrome was initially known as postadrenalectomy syndrome but by 1962 became known as Nelson syndrome.96 Although the early definitions of this syndrome are paramount in the history of Nelson syndrome, the complete story involves the history of the treatment and diagnosis of Cushing disease and Dr. Nelson’s contributions to the fields of endocrinology and neurosurgery.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; MR = magnetic resonance.
Because of the controversy and limited understanding of pituitary physiology and disease, adrenalectomy was most often the primary treatment of Cushing syndrome at the time Nelson and colleagues initially described the syndrome of ACTH hypersecretion. Pituitary surgery was usually reserved for cases involving visual loss and was performed almost exclusively with craniotomy. At that time, it was known that Cushing syndrome was attributable to excess adrenal steroids in the blood,47 that this excess was unhealthy, and that adrenalectomy improved the clinical syndrome and extended the life expectancy of patients with this disease. Although there are scattered reports of cases of Cushing disease that were successfully treated with pituitary surgery (the earliest in 1933 by Dr. Naffziger48), pituitary surgery undertaken to treat endocrinological disorders was not truly accepted until after transsphenoidal microsurgery was reintroduced to the neurosurgical community by Jules Hardy in 1971,31 and Tyrrell et al.90 and Salassa et al.44 reported the cure of hypercortisolemia with the removal of microadenomas in their respective surgical series of 1978.

History of Nelson Syndrome

Until the 1950s, only rather primitive mechanisms were available for evaluating adrenal cortical function. Despite the fact that Dr. Thomas Addison1 had described the syndrome of adrenal insufficiency in 1855, little was known about the hormones involved. While he was a research fellow, and later as a postdoctoral fellow at the University of Utah in the 1940s, Nelson and his colleagues working in Leo Samuels’s laboratory endeavored to discover and quantify the adrenal steroids in human blood and serum.89 The specific steroid to be measured remained unknown until 1953.44 In 1950, Nelson and Samuels (Fig. 2) published a paper in which they described the process for isolating a steroid hormone from the blood of dogs.74 The availability of the “Nelson–Samuels” method allowed the accelerated pursuit of the physiology of adrenocortical secretions,10,11,33,75 including the ability to measure corticosteroids in human blood.79 Nelson was drafted into military service in 1952 and continued his research at the Naval Medical Research Institute in Bethesda. He continued to study adrenal physiology, and in 1955 he, along with his colleague David Hume, reported a method they had developed to determine the concentration of ACTH in human serum.71 This test was a bioassay in which they used hypophysectomized dogs. It was rather crude by modern standards, but significantly elevated levels of ACTH could be determined. Nelson then used this assay while serving as a house officer and research fellow at the Peter Bent Brigham Hospital in Boston to study the physiology in Cushing syndrome, especially in cases in which no pituitary or adrenal tumor could be found. This was the only assay available to measure ACTH, and it was used in the first reported case of hyperpigmentation, elevated serum ACTH level, and pituitary tumor as well as visual loss in a patient who had undergone adrenalectomy for Cushing syndrome. It was this postadrenalectomy syndrome that later became known as Nelson syndrome (the pituitary tumor was often called a Nelson tumor).

In 1958, Nelson and colleagues32 reported in the New

![Fig. 1. Recent photograph of Dr. Don H. Nelson, M.D.](image-url)
England Journal of Medicine (Fig. 3) the case of their 33-
year-old woman, “C.R.” She had initially presented in 1954
with a 1-year history of nervousness, weakness, leg cramps,
amenorrhea, acne, hirsutism, deepened voice, abdominal
striae, polydipsia, and polyuria. On physical examination,
she was observed to be obese, with a moon face, acne, mild
hirsutism, and multiple ecchymoses and abdominal striae.
She was hypertensive, her visual fields were normal, and
her pituitary fossa size was “at the upper limits of normal”
on a skull x-ray film. Laboratory studies revealed that she
had glycosuria and hyperglycemia as well as an elevated
level of 17-hydroxycorticosteroids in her urine. One month
after her initial presentation, the patient underwent bilat-
eral adrenalectomy. Her adrenal glands were normal in
weight, but hyperplasia was demonstrated histologically.
Postoperatively, she was placed on a daily regimen of 50
mg of cortisol. After 2 months, her symptoms had re-
solved, her endocrinological levels were normal, and she
began to menstruate normally. Two years later, she com-
plained of menorrhagia and cutaneous pigmentation, but no
other abnormalities were found, and her serum glucose
level remained normal.

In 1957, 3 years after her initial presentation, the patient
began to suffer renewed amenorrhea and progressive loss
of vision in her left eye. On examination, her skin was
found to be deeply pigmented (Fig. 4), and she had a near-
ly complete bitemporal hemianopsia. Examination of lab-
oratory studies showed that the level of 17-hydroxycortico-
steroids was normal, but the level of ACTH exceeded 200
mU/100 ml (normal levels were undetectable using the
Nelson–Hume method). A radiographic workup, including
skull radiographs, laminagrams, and a fractional air study,
now demonstrated expansion of the sella turcica with
destruction of the dorsum sellae and the presence of a
suprasellar tumor. Radiotherapy was initiated, but after 24
treatments hemorrhage into the tumor suddenly occurred.
Because of the apoplexy, the patient was taken to the oper-
ating room where she underwent urgent decompression via
craniotomy. A soft, hemorrhagic tumor was resected with-
out complication, and she recovered well. Her vision im-
proved, and her ACTH level became undetectable. She
underwent monitoring for an additional 18 weeks. During
this time, her cutaneous pigmentation subsided (Fig. 4) and
her ACTH remained low, similar to that of other patients
with hypoadrenocorticism.

In discussing this case, Nelson first debated the possibil-
ity of two causes of Cushing syndrome: one of adrenal and
one of pituitary origin. He stated that a pituitary tumor
should elevate the serum ACTH level but admitted that his
“methods for the determination of ACTH in plasma are
generally not sensitive enough” to determine moderately
increased levels. He also surmised that the patient might
have had an ACTH-secreting pituitary tumor and that “the
removal of the adrenal glands may have acted as a stimulus
to the pituitary gland, with growth of the tumor and
increased secretion of ACTH resulting.” Finally, he con-
cluded that “development of a pituitary tumor is a possible
sequela of bilateral adrenalectomy for Cushing’s syn-
drome.”

Because many adrenalectomies were being performed, it
came increasingly evident that, in a certain population of
patients, adrenalectomy caused the clinical syndrome of
hyperpigmentation and pituitary tumor (Nelson syndrome). It was believed by many that the removal of the adrenal glands caused the de novo formation of a pituitary tumor. When testing for serum ACTH levels became available,71,79 Nelson was able to report the abnormally high levels of this hormone after adrenalectomy.77 By 1960, he had identified 10 patients with this “post-adrenalectomy” syndrome.73 In this second paper on the syndrome (Fig. 5), Nelson made three notable observations. First, he discovered the suppressibility of ACTH secretion in patients with pituitary tumors after they were given hydrocortisone therapy. Second, he described a patient who suffered from Cushing syndrome and was found to have an elevated ACTH level but no evidence of a pituitary tumor. This patient underwent a partial adrenalectomy, which led to a remission of the Cushing syndrome, but later suffered recurrence of the Cushing syndrome, an increased ACTH level, and a sellar tumor but no hyperpigmentation. Nelson himself remarked, "It has not been possible with the present technic to detect normal circulating levels of plasma-ACTH, and therefore a slight elevation of ACTH above ‘normal’ would presumably not be detected by the assay procedure used." Six years later he reported the elevation of ACTH in a patient with Cushing syndrome and a pituitary tumor before any treatment, foreshadowing the importance of this test in the determination of a pituitary source of Cushing syndrome.

Nelson and Cushing Syndromes in the Modern Era

The development of Nelson syndrome after adrenalectomy for Cushing syndrome has been reported in between 8 and 47% of cases.4,15,16,19,26,30,45,48–50,62,65,68,80,87,95 These numbers vary depending on the extent of adrenalectomy, the causes of the hypercortisolemia in the treated patients, and the year the surgery was performed. As endocrinological, radiological/imaging, and neurosurgical advances were made in the understanding of and ability to diagnose the causes of Cushing syndrome and the modes of therapy, management of both Cushing and Nelson syndromes moved into the modern era.

The advances in endocrinology led to a better ability to diagnose Cushing disease and differentiate its various causes. The first development, as described above, was the ability to measure corticosteroid and ACTH levels in human blood samples. In part because of the observations made by Nelson in 1960, the low- and high-dose dexamethasone suppression tests became available to differentiate adrenal and pituitary-dependent hypercortisolemia. Liddle reported that the abnormally elevated levels of urinary corticosteroids were suppressed in all patients with a known pituitary tumor by high doses of dexamethasone (2 mg every 6 hours) but not with low doses (0.5 mg every 6 hours). Individuals with a known adrenal tumor were completely resistant to high and low doses of the drug. This was the first reliable test to differentiate among the causes of Cushing syndrome. Although this test offered improved
History of Nelson syndrome

Fig. 4. Photographs of Patient C.R., the first reported case of Nelson syndrome, before (left) and after (right) adrenalectomy for Cushing disease. Note the features of Cushing disease preoperatively and the skin pigmentation after. Adapted with permission from Nelson DH, The Adrenal Cortex, W. B. Saunders, 1980.

ability for differentiation because it was somewhat specific, it was not very sensitive, as many patients tested equivocally. Therefore, again following the lead of Nelson, the assay for the determination of ACTH in plasma was refined. With the production of specific antibodies, a radioimmunoassay could be performed. In 1964, Yalow et al. reported the results of an assay for ACTH that required less than 0.2 ml of serum and had a sensitivity as low as 0.06 mU/100 ml, approximately 100-fold more sensitive than Nelson’s bioassay. This allowed the detection of mildly elevated ACTH levels that could be caused by a pituitary microadenoma. With the advent of stimulation testing with corticotropin-releasing factor, the ability to distinguish the different causes of Cushing syndrome became even more widely available.

Several advances in radiography and neuroimaging also led to a change in the differential diagnosis of Cushing syndrome. A patient with Cushing syndrome or hyperpigmentation after adrenalectomy was typically screened with skull radiography, but current MR imaging findings correlated with surgical findings can be identified after adrenalectomy, and further investigations can be performed. Serial imaging after treatment for Cushing disease is now routine. Initially, the sella was imaged only with skull radiography, but current MR imaging systems can detect small-size tumors. Similarly, the surgical treatment of Nelson tumors has evolved. The earliest report of pituitary surgery for Nelson syndrome was published by Espinoza et al. in 1973, who performed surgery in three patients via a transsphenoidal approach and were able to normalize the ACTH in two and reduce the level in the third patient postoperatively; no more than immediate results were reported.

Although the authors of early series found only limited success after transphenoidal pituitary surgery for Nelson syndrome (27% success), the authors of later reports showed somewhat better outcomes (success rate range 46–80%). As with other tumors of the pituitary, residual or recurrent tumors can be treated with stereotactic radiosurgery.

The current treatment paradigm for Cushing disease includes aggressive treatment with therapies directed at the pituitary tumor. Resection is the primary treatment modal-

microadenomas, respectively. High field strength MR imagers and dynamic imaging techniques have improved the sensitivity in recent years. Last, the invasive endovascular technique of inferior petrosal sinus sampling was developed, yielding very high sensitivity and specificity in cases of pituitary-dependent Cushing disease.

The last advances to consider in the recent developments in management of Cushing disease are the contributions of neurosurgeons. Pituitary surgery was initially attempted in 1893 by Caton and Paul in a patient with acromegaly. It soon became apparent to the neurosurgical community, however, that pituitary surgery was a morbid endeavor and therefore its use was largely abandoned, except in the most extreme cases, which were treated with transcranial operations.

The earliest reported successful pituitary surgery for microadenoma-related Cushing disease was conducted in 1933 (but not published until 1944), yet most patients with Cushing syndrome and a pituitary tumor underwent sellar radiotherapy and adrenalectomy; the adrenalectomy treated the hypercortisolism and the radiotherapy successfully controlled the growth of most of these tumors. With improvements in antibiotic therapy and intraoperative technology (including instrumentation, operative microscopy and microsurgery, and fluoroscopy), transphenoidal pituitary surgery slowly gained acceptance, largely because of the work of Jules Hardy. As pituitary surgery became more widely accepted, it was used successfully to treat Cushing disease but was still not considered the standard of care into the 1980s. For instance, there was debate over the effectiveness of prophylactic sellar irradiation in the prevention of Nelson syndrome. In 1980, Nelson wrote in an editorial, “...in those patients who fail to be cured adequately by the transphenoidal approach, irradiation should be considered.”

These advancements associated with improved management of Cushing syndrome also apply to the diagnosis and treatment of Nelson syndrome. Currently, measurement of ACTH is a reliable and routine laboratory investigation that is widely available. Even minor elevations in ACTH levels can be identified after adrenalectomy, and further investigations can be performed. Serial imaging after treatment for Cushing disease is now routine. Initially, the sella was imaged only with skull radiography, but current MR imaging systems can detect small-size tumors. Similarly, the surgical treatment of Nelson tumors has evolved. The earliest report of pituitary surgery for Nelson syndrome was published by Espinoza et al. in 1973, who performed surgery in three patients via a transphenoidal approach and were able to normalize the ACTH in two and reduce the level in the third patient postoperatively; no more than immediate results were reported.
A METHOD FOR THE DETERMINATION OF 17-HYDROXYCORTICOSTEROIDS IN BLOOD: 17-HYDROXYCORTICOSTERONE IN THE PERIPHERAL CIRCULATION*

DON H. NELSON, M.D.† AND LEO T. SAMUELS, PH.D.
From the Department of Biochemistry, University of Utah College of Medicine, Salt Lake City, Utah

ADRENAL steroid activity has been demonstrated in adrenal venous blood by means of biologic assay (1, 2). The biologic techniques, although successful in demonstrating the presence of adrenal steroids, have been unsatisfactory from a quantitative standpoint and have given little information regarding the specific compound being measured. Chemical methods for the determination of adrenal steroids in blood have been proposed by Coreoran and Page (3), and by Porter and Silber (4).

The method of Coreoran and Page was found to give high values due to the formation of formaldehyde from phospholipids, traces of which could not be eliminated even by repeated precipitation with acetone. The color reaction of Porter and Silber depends on the formation of phenylhydrazones in acid solution. Under the conditions given, the 17,21-dihydroxy-20-ketosteroids showed a strong maximum absorption at 410 mμ when several steroid ketones were tested. The purification procedure used with plasma, however, was so nonspecific as to raise the question of the influence of other compounds on the reaction.

The present communication deals with the development of a method for the quantitative estimation of 17-hydroxy corticosteroids in peripheral blood, using the color reaction described by Porter and Silber. The chief compound measured is apparently 17-hydroxycorticosterone1 (5).

Conclusions

Thus, all the pieces came together to bring Cushing syndrome into the contemporary era. The different causes of this syndrome can be diagnosed with great accuracy, and microsurgical treatment directed at the pituitary gland has failed. After adrenalectomy, patients must be carefully observed with serial MR imaging and laboratory investigations. The use of prophylactic sellar irradiation in the cases of persistent hypercortisolemia and without the demonstration of pituitary adenoma is controversial.34

Cortisolemia and tests became available to diagnose the cause, the number of patients undergoing adrenalectomy in the modern era decreased, and even fewer are developing Nelson syndrome. In light of these considerations, we believe that Nelson syndrome should be reevaluated to determine the roles of surgery, radiotherapy, and radiosurgery in the modern era.

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History of Nelson syndrome

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Appendix: Biography of Dr. Don H. Nelson

Don Nelson was born in Salt Lake City, Utah, in 1925. He attended the University of Utah where he received his B.A. It was while at the University of Utah Medical School that he first became interested in endocrinology research. Dr. Leo Samuels was the chairman of the Department of Biochemistry and had already established himself as an expert in steroid biochemistry. Nelson joined Samuels’s laboratory after his internship, and there made substantial contributions to clinical adrenal biochemistry and physiology. He graduated from medical school in 1947 and completed an internship at Milwaukee County Hospital the following year. He then returned to the University of Utah and Dr. Samuels’s laboratory as a research fellow and, later, became a research assistant professor of biochemistry. Nelson was drafted into the Navy in 1952. He was stationed in Bethesda, Maryland, where he continued his research at the Naval Medical Research Institute.

While in Bethesda, Nelson and Hume developed a method for measuring ACTH levels in blood. In 1954, Nelson was discharged from the military and moved to Boston to start his residency in internal medicine. While at Harvard, he also completed a fellowship in endocrinology under Dr. George Thorn, and he was one of the first fellows of the Howard Hughes Medical Institute, where he used his ACTH assay to study the possible causes of Cushing syndrome. Using this assay, Nelson and his colleagues reported the case of “C. R.,” and the postadrenalectomy syndrome that eventually became known as Nelson syndrome. This case report was widely read and well received. After completing his training, he joined the faculty of the Peter Bent Brigham Hospital and became the director of its Clinical Research Center. In 1959 he moved to Los Angeles to become the chief of endocrinology at the University of Southern California, where he established a new clinical research center, maintaining his ties to the Howard Hughes Medical Institute. In 1959, with the support and urging of Dr. Wintrobe, the head of the Department of Medicine at the University of Utah, he moved back to his hometown of Salt Lake City to head the newly founded Department of Medicine at LDS Hospital. He created a strong department based on clinical and basic research. He also established an affiliation with the University of Utah, training successive generations of medical students, resident physicians, and research fellows. In 1980 he became the head of the Division of Endocrinology at the University of Utah. Dr. Nelson’s bibliography speaks for itself. He was a leading scientist and clinician in endocrinology. He is now retired from the clinical practice of medicine and still lives in Salt Lake City. He continues to follow his interests in endocrinology and contribute to the body of medical knowledge. He maintains an active affiliation with the Division of Endocrinology at “the U” and continues to publish in his field. His chief contribution in recent years has been the discovery that sphingolipids mediate the biochemical effects of corticosteroids and the harmful effects that we associate with Cushing syndrome.

[Dr. Nelson reviewed the historical aspects of this paper.]

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Address reprint requests to: William T. Couldwell, M.D., Ph.D., Department of Neurosurgery, University of Utah, 175 North Medical Drive East, Salt Lake City, Utah 84132. email: neuropub@hsc.utah.edu.