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The Nelson's syndrome. . . revisited

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Abstract. **Adrenalectomy is a radical therapeutic approach to control hypercortisolism in some patients with Cushing's disease. However it may be complicated by the Nelson's syndrome, defined by the association of a pituitary macroadenoma and high ACTH secretion after adrenalectomy. This definition has not changed since the end of the fifties. Today the Nelson's syndrome must be revisited with new to criteria using more sensitive diagnostic tools, especially the pituitary magnetic resonance imaging.**

In this paper we will review the pathophysiological aspects of corticotroph tumor growth, with reference to the impact of adrenalectomy. The main epidemiological data on the Nelson's syndrome will be presented.

More importantly, we will propose a new pathophysiological and practical approach to this question which attempts to evaluate the Corticotroph Tumor Progression after adrenalectomy, rather than to diagnose the Nelson's syndrome. We will discuss the consequences for the management of Cushing's disease patients after adrenalectomy, and will also draw some perspectives.

The Nelson's syndrome was first identified at a time when radioimmunoassay (RIAs), the corticotrophin releasing hormone (CRH), magnetic resonance imaging (MRI), transsphenoidal surgery . . . were unknown!

The description of this syndrome, however, came as an illuminating clue to elucidate the pathogenesis of Cushing's disease.

The remarkable progresses of the last decades have provided us with new pathophysiological knowledge and investigative tools that allow us to revisit this syndrome and propose a new approach: how to predict, assess, and manage possible Corticotroph Tumor Progression (CTP) after adrenalectomy ?

History

In 1958 Nelson et al. [1] first described a 33 year old woman who developed marked skin hyperpigmentation, and evidence of pituitary tumor (enlarged sella on skull X-Ray and visual field defects), three years after she had been subjected to bilateral adrenalectomy for Cushing's syndrome. ACTH plasma levels were high enough to be measured by a bioassay in the hypophysectomized dog. . . Other authors independently reported similar cases [2–5].

These observations were taken as evidence for a role of the pituitary in the pathogenesis of "Cushing's disease", as had been anticipated by Harvey Cushing [6].

Pathophysiological aspects

The biology of the corticotroph adenoma of the Nelson's syndrome

Close MRI follow-up of adrenalectomized patients have shown that "Nelson's syndrome", as previously diagnosed, was not due to the "appearance" of a pituitary tumor, rather it was associated with its progression. In other words, the day after adrenalectomy, it is the same tumor, the corticotroph adenoma, that will eventually grow (Fig. 1).

Therefore, pituitary tissues obtained in patients with "the Nelson's syndrome" essentially show molecular features identical to that observed in corticotroph adenomas of "the Cushing's disease" [7] :

– *POMC* gene transcription is qualitatively unaltered, generating the normal 1200 nt POMC mRNA [8]
– POMC is normally processed, generating intact ACTH, with no unanticipated POMC product [9]
– Most tumors are loaded with CRH-R1 and vasopressin V3 receptors, and remain highly responsive to their ligands [7–11].
– They express a variety of nuclear factors that are associated with the corticotroph phenotype: Ptx1, Tpit, Neuro D, Nurr 77, Nur 1, the gluccorticoid receptor type II, . . . [10]
– They are monoclonal tumors [12,13]

Yet these tumors, like corticotroph adenomas in general, show a set-point defect or partial resistance to glucocorticoids. This is best shown by *in vivo* studies showing that ACTH plasma levels are not normally suppressed by glucocorticoid administration in patients with Nelson's syndrome [14]. Confirmation of this feature *in vitro* is difficult because the direct comparison

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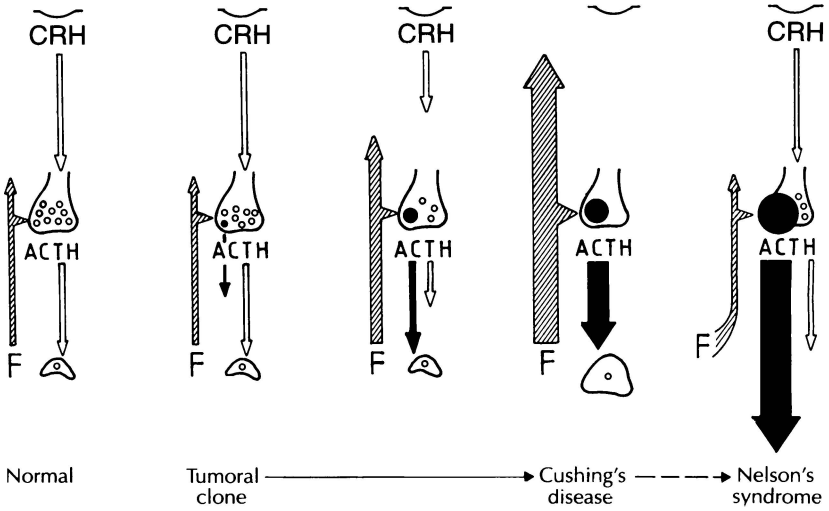

Fig. 1. *A schematic view of the pathogenesis of Cushing's disease and the consequences of adrenalectomy (from Ref. 7).*

with normal corticotroph cells is absent in most studies [15].

Does adrenalectomy boost corticotroph tumor progression?

Many studies have been done on the pathogenesis of corticotroph tumors, yet with very little success [10]. Among the many questions that still have no clear answer, is whether adrenalectomy is responsible for increasing the growth rate of a previously existing corticotroph tumor?

Adrenalectomy abrogates the chronic cortisol excess, and should consequently restore a normal hypothalamic CRH drive, as suspected on the normal circadian rhythm of cortisol secretion observed in patients with Cushing's disease who have been cured by transsphenoidal surgery [7]. It may also have other consequences with potential influence on corticotroph tumor growth.

Corticotroph adenoma cells express the ubiquitous glucocorticoid receptor (GR), with no evidence for imbalance between its two isoforms [16,17]. Cortisol lowers the proliferation rate of human corticotroph adenoma cells in primary culture [16]. In rats, dexamethasone induces apoptosis of a subpopulation of anterior pituitary cells that is expanded by adrenalectomy [18]. Whether these cells are corticotroph cells remains to be established. One case of somatic mutation in an aggressive corticotroph tumor in a patient with the Nelson's syndrome has been reported, but seems to be uncommon [19]. Furthermore, LOH at the GR locus was found in 6 of 22 corticotroph adenomas [20], but haploinsufficiency was not established. Whether these abnormalities are more frequent in aggressive tumors of the Nelson's syndrome is not known. These data would plead for a direct glucocorticoid inhibition of the corticotroph tumor growth, but such an evidence in Cushing's disease is not demonstrable, as glucocorticoids have undissociable pleitrophic effects such as CRH down-regulation. Thus we cannot definitely conclude that abrogation of chronic glucocorticoid-excess after adrenalectomy would boost the corticotroph tumor growth.

After adrenalectomy it is believed that the hypothalamic CRH drive is restored (Fig. 1). More importantly, in most patients, the glucocorticoid replacement is discontinued during all the night period. In such patients it is conceivable that the restored hypothalamic CRH drive exerts its effects in the absence of any glucocorticoid counteraction. CRH excess induces an increase of corticotroph cells number, as seen in tumors with ectopic CRH secretion [21], in rats with chronic CRH infusion [22] and in transgenic mouse overexpressing CRH-R1[23]. CRH receptor 1 (CRH-R1) is abundantly expressed in corticotroph adenomas [24,25]. However no mutation of CRH-R1was found in corticotroph adenomas [25]. Adrenalectomy in rats increases hypothalamic CRH transcription, and is followed by a moderate increase of corticotroph cell number [26], and by a down-regulation of CRH-R1 expression [27,28]. To our knowledge no data are available on the kinetics of CRH-R1 expression in human corticotroph adenomas after adrenalectomy. Moreover, evaluating the CRH tone in humans after adrenalectomy is challenging, so that the role for CRH in stimulating the proliferation of corticotroph adenoma after adrenalectomy, although attractive, remains speculative.

Other factors may interfere with corticotroph adenoma growth after adrenalectomy. For instance hypothalamic expression of arginine vasopressin (AVP) is increased after adrenalectomy in rats [26], AVP receptor V3 is abundantly expressed in corticotroph

adenoma [24], and AVP induces pituitary cell proliferation *in vitro* [29].

In patients, a single retrospective study reported a higher incidence of Nelson's syndrome when glucocorticoid substitution was insufficient [30], but two other studies did not confirm these results [31,32]. One other study suggested that a extra glucorticoid replacement dose at 6 pm would reduce the incidence of Nelson's syndrome [33].

Are there specific molecular features in rapidly growing tumors?

The search for the molecular mechanisms(s?) responsible for the pathogenesis of corticotroph adenomas has been extensive and recently reviewed [10].

A fairly good number of more or less obvious candidates have been examined: oncogenes, tumor suppressor genes, growth factors, transcription factors, various signalling pathways, some of them rather specific to the corticotroph phenotype, cell-cycle associated genes, angiogenic factors, genes responsible for genetic syndromes that may be associated with Cushing's disease (*menin*), genes the manipulation of which in experimental models unexpectedly generated POMC producing pituitary tumors (most often in the intermediate lobe of the mice, which may have no relevance to the human disease !), ...It is fair to say that no clear information is available to day on the molecular pathogenesis of corticotroph adenomas.

We do not even know if corticotroph adenoma formation is the result of a unique molecular mechanism, a predominant one (as observed in other types of endocrine tumors, for example in GH secreting pituitary adenomas), or a constellation of many different possibilities; depending on the responsible mechanism one can imagine that glucocorticoids — and therefore glucocorticoid deprivation and its consequences — might have highly variable effects on tumor growth.

It emphasizes the concept that assessing the potential growth rate of the corticotroph tumor is the real question. The pathophysiology of an accelerated tumor growth is poorly understood. We can underline that the reported case of glucocorticoid mutation [19] was associated to a very fast growing tumor. Other molecular features associated to this phenotype are not known. Comparing molecular features between rapidly growing and slowly growing corticotroph adenomas after adrenalectomy might bring some answer. A study, yet to be done ...!

Epidemiology of the classical Nelson's Syndrome

Prevalence

About fifty series reported on the so-called Nelson's syndrome, grossly defined by the association of an expanding pituitary tumor and a "high" ACTH secretion after adrenalectomy in Cushing's disease. The prevalence of Nelson's syndrome ranges from 8 to 29% in the largest series with more than 40 patients [2,30,34–43], with a time interval between adrenalectomy and the diagnosis of Nelson's syndrome ranging from 0.5 to 24 years. Patients were included between the middle of the fifties until the end of the nineties, with an inclusion time ranging from 9 to 36 years.

Predictive factors

These Nelson's syndrome studies provided also predictive factors.

A high basal ACTH after adrenalectomy is the best validated predictive factor [30–32, 35,44–46], but no unique threshold value can be defined. Other predictive factors have been described, such as the young age at adrenalectomy in some studies [36,38,47,48] but not all [30,40], with an apparent increase of incidence in children [47], the surgical or morphological documentation of a pituitary adenoma before adrenalectomy [40,45,46], the existence of an adrenal remnant after adrenalectomy in some studies [37,46] but not all [30], the duration of the Cushing's disease in some studies [32] but not all [30,36,38,44], free urinary cortisol before adrenalectomy in some studies [30,40] but not all [31,32,46]. Pituitary irradiation prior to adrenalectomy was found protective in some studies [45] but not all [37,38,40,46,49]. Finally some factors have never been demonstrated as predictive, such as the sex [30,36,38, 40], baseline ACTH in the morning before adrenalectomy [31,36,38,46], the level of glucocorticoid substitution after adrenalectomy [30–32], the pregnancy [35].

Complications

The complications related to the Nelson's syndrome are essentially due to the tumoral volume: chiasmatic compression with visual field loss, either transitory or definitive is the most frequent complication described, with a prevalence ranging from 1/10 to 4/9 [24,30,32,35, 37,38,45,47,49–52]. Occulomotor nerve palsy has also been described [49], as well as tumor necrosis with sudden intracranial hypertension [35,51]. Cases of diabetes insipidus [5] and hypopituitarism are exceptional. Cases of pituitary tumor with distant metastases have also been described [35,38].

Finally, complications related to the high ACTH levels have been reported with exceptional occurrence. Paratesticular and paraovarian tumors producing cortisol or androgens in an ACTH-dependent manner have been described [53–55], as well as testicular adrenal rests with hyperplasia provoked bilateral testicular tumors [56,37].

Revisiting the Nelson Syndrome

An ill-defined condition

The definition of "the Nelson's syndrome" is ...highly variable ! and it is difficult to draw a general consensus from a vast analysis of the litteraure on the subject:

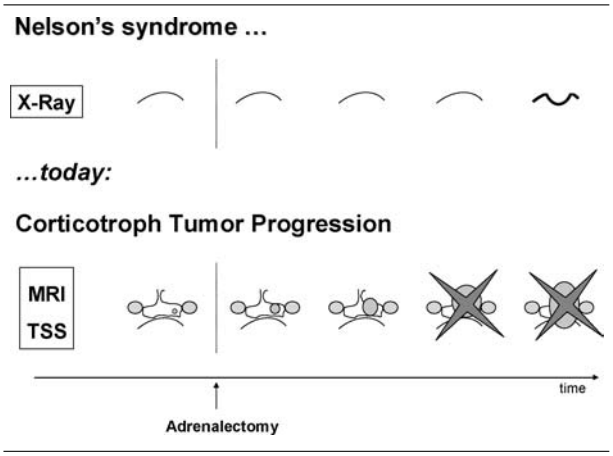

Fig. 2. *Opposing Nelson's syndrome as it was historically diagnosed (upper part), and the CTP concept which can be closely followed by MRI (lower part).*

- evidence of pituitary tumor (or pituitary tumor growth) relies on sellar X-Ray, visual field defect, rarely CT-scan. . .
- evidence for "high" ACTH secretion relies on the presence of cutaneous hyperpigmentation, ACTH measured by bioassay, ACTH measured by immunoassays with highly variable sensitivities and cut-offs.
- Most series are composed of heterogeneous patient populations, some of them having received interfering treatment such as pituitary radiotherapy.

To day it is quite clear that there cannot be a definition of "the Nelson's syndrome"!

As examplified in the scheme of Figure 2, our current pathophysiological knowledge, and our sensitive means to image pituitary tumors have radically changed our vision of Cushing's disease, and its potential evolution after adrenalectomy:

- In a patient with Cushing's disease, we are no longer asking ourselves whether a pituitary tumor is present, we are asking whether the responsible pituitary tumor will grow, will grow faster after adrenalectomy, will grow to a point that might create further threats to the patient.

Rather than diagnose Nelson's syndrome, at a late stage, with non sensitive means (sellar X-Ray), the challenge is now to screen for early evidence of tumor growth with the most sensitive imaging and/or biological means. For this we have to generate data on the natural history of Corticotroph Tumor Progression (CTP) after adrenalectomy.

Corticotroph tumor progression (CTP) after adrenalectomy

In the last years, we have undertaken a vast study the aim of which was to assess CTP in a homogeneous series of 53 patients followed in a single Center (Endocrine Department, hôpital Cochin, Paris), and who had all been subjected to adrenalectomy for Cushing's disease. None had pituitary radiation. All had pituitary MRI before adrenal surgery, and all were closely followed with yearly pituitary MRI and ACTH measurements. The median follow-up after adrenalectomy was 4.6 years (range 0.5–13.5).

CTP was defined either by the occurrence of an adenoma at MRI, or the growth of a pre-existing adenoma on pituitary MRI.

The prevalence of CTP reaches 38% at three years, and 47% at seven years, and plateaus thereafter.

Factors that were found to be significantly associated with a higher risk to develop CTP were: duration of Cushing's disease, baseline ACTH plasma level in the year following adrenalectomy, the rate of increase in ACTH plasma levels after adrenalectomy.

Among the 10 patients who developed CTP, a single complication was observed in a case where spontaneous tumor necrosis induced transient ocular nerve palsy. Four patients were subsequently subjected to conventional pituitary radiotherapy.

Management of CTP

The historical cases of Nelson's syndrome were characterized by large invasive pituitary macroadenomas presenting a major therapeutic challenge. Today with pituitary MRI the tumor could have been detected much earlier at a smaller size, and the surgical procedures have improved, as well as the radiotherapeutic protocols [58].

After adrenalectomy, the goal is not to cure the pituitary adenoma, but rather to manage CTP so that no complication related to the tumor burden occurs. Indeed, a microadenoma appeared on MRI after adrenalectomy may not be removed as far as it does not grow, especially in patients with high risk pituitary surgery. A close pituitary MRI follow-up is necessary for an early CTP diagnosis.

The identification of clinical and molecular factors predicting aggressive CTP are needed. With such factors, we could adapt the pituitary MRI follow-up schedule, we could propose pituitary irradiation in high risk patients, and we could better choose the right time for pituitary surgery in face of a growing pituitary adenoma.

Perspectives

Indication for adrenalectomy in Cushing's disease

There is no discussion that pituitary surgery should be the first line treatment in most patients with Cushing's disease [7]. It is the sole therapeutic option that offers a possibility of authentic cure, with a *restitutio ad integrum* of the entire hypothalamic-pituitary-adrenal axis. Yet there is no discussion also that it does not always work. . .

Unfortunately, at this stage, all other therapeutic options (radiotherapy, anticortisolic drugs, adrenalectomy) have important and inescapable side effects, or questionable success. Among them, adrenalectomy, performed today by videoscopic surgery, with low morbidity and mortality, in experienced teams, is the only one that offers an immediate control of hypercortisolism with 100% certainty [59].

The recent description of CTP with sensitive means—i.e. pituitary MRI and ACTH plasma levels–offers new bases for a better evaluation of the risks of such an approach. Even though a reliable predictive factor for CTP still remains to be found, its occurrence is not inevitable, and its—potential—complications are preventable by a close surveillance.

The need for drugs acting at the corticotroph tumor

Much progress has been done in the recent years in the pharmacological control of pituitary tumors. Highly successful treatment of prolactinomas, GH secreting adenomas, and TSH secreting adenomas have been obtained with dopaminergic- or somatostatinergic drugs.

The corticotroph adenoma remains an "orphan" pituitary tumor that has yet to find its therapeutic counterpart.

Hopes have recently emerged with studies in experimental models and in man with new and more selective somatostatin analogs, retinoids, and PPAR-γ agonists, that seem to directly suppress ACTH secretion by corticotroph tumors [60–62]. New molecules, with selective glucocorticoid activity, SEGRA, might prove able to suppress tumor ACTH secretion with little peripheral effects [63]. Such medications would of course be highly useful in the treatment of Cushing's disease, and potentially, also, to prevent or treat CTP after adrenalectomy.

Assessment of pituitary tumor growth

There is a definite need to improve the accuracy of our means to assess pituitary tumor growth by imaging. Pituitary MRI has brought a real revolution in the field [64–66], yet little data are available that provide us with clear tools to evaluate subtle morphological changes. Progresses are needed to obtain higher reproducibility in measuring pituitary tumor dimensions or volumes. They will be useful not only to follow CTP after adrenalectomy in Cushing's disease, but also in other circumstances, when other types of adenomas are subjected to direct – medical or radiotherapeutic – treatments, or, when patients with acromegaly are treated with GH – antagonists.

Biological markers of CTP are still to be found as well. There is good evidence that ACTH plasma levels are indicators of such progression...but only after the adrenalectomy has been performed! Even at this time it will be important to set the best conditions where ACTH plasma levels can be measured with good reproducibility: under appropriate "substitutive treatment", using repeat baseline levels or dynamic tests?

Since transsphenoidal surgery is usually performed as a first-line treatment in these patients, tumor tissue should be available for the search of markers of progression *in situ*. Classical histological approaches (mitoses, KI-67), have not provided the solution yet. Other molecular markers will have to be found, based on our growing knowledge on the pathogenesis of endocrine and pituitary tumorigenesis [67,68], and on the availability of new technical approaches such as transcriptome analysis by microarrays [69]. This aspect emphasizes the importance of transsphenoidal surgery and the careful collection of the adenomatous tissue for all patients: years after the pituitary surgery, they might provide the therapeutist with important informations in case of recurrent hypercortisolism and if adrenalectomy is discussed as a possible therapeutic option.

References

1. Nelson DH, Meakin JW, Dealy JB Jr, Matson DD, Emerson K Jr, Thorn GW. ACTH-producing tumor of the pituitary gland. *N Engl J Med* 1958;259(4):161–164.
2. Salassa RM, Kearns TP, Kernohan JW, Sprague RG, Maccarty CS. Pituitary tumors in patients with Cushing's syndrome. *J Clin Endocrinol Metab* 1959;19:1523–1539.
3. Montgomery DA, Welbourn RB, McCaughey WT, Gleadhill CA. Pituitary tumours manifested after adrenalectomy for Cushing's syndrome. *Lancet* 1959;2:707–710.
4. Glenn F, Karl RC, Horwith M. The surgical treatment of Cushing's syndrome. *Ann Surg* 1958;148(3):365–374.
5. Rees JR, Zilva JF. Diabetes insipidus complicating total adrenalectomy. *J Clin Pathol*. 1959;12:530–534.
6. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Bull John Hopkins Hosp* 1932;50:137–195.
7. Bertagna X, Raux-Demay MC, Guilhaume B et al. Cushing's Disease. In *The Pituitary*, S. Melmed, ed, 2nd ed. Blackwell 2002: pp 496–560.
8. de Keyzer, Bertagna X, Lenne F, et al. Proopiomelanocortin gene expression in ACTH secreting non-pituitary tumors. *J Clin Invest* 1985;76:1892–1898.
9. Raffin-Sanson ML, de Keyzer Y, Bertagna X. Proopiomelanocortin, a polypeptide precursor with multiple functions: From physiology to pathological conditions. *Eur J Endocrinol* 2003;149(2):79–90. Review
10. Dahia PL, Grossman AB. The molecular pathogenesis of corticotroph tumors. *Endocr Rev* 1999;20(2):136–155.
11. de Keyzer Y, Rene P, Lenne F, Auzan C, Clauser E, Bertagna X. V3 vasopressin receptor and corticotropic phenotype in pituitary and nonpituitary tumors.*Horm Res* 1997;47(4–6):259–262. Review
12. Herman V, Fagin J, Gonsky R, Kovacs K, Melmed S. Clonal origin of pituitary adenomas. *J Clin Endocrinol Metab* 1990;71(6):1427–1433.
13. Gicquel C, Le Bouc Y, Luton JP, Girard F, Bertagna X. Monoclonality of corticotroph macroadenomas in Cushing's disease. *J Clin Endocrinol Metab* 1992;75(2):472–475.
14. Wolfsen AR, Odell WD. The dose-response relationship of ACTH and cortisol in Cushing's disease. *Clin Endocrinol (Oxf)* 1980;12(6):557–568.

15. Suda T, Tozawa F, Dobashi I, Horiba N, Ohmori N, Yamakado M, Yamada M, Demura H. Corticotropin-releasing hormone, proopiomelanocortin, and glucocorticoid receptor gene expression in adrenocorticotropin-producing tumors in vitro. *J Clin Invest* 1993;92(6):2790–2795.
16. Resetic J, Reiner Z, Ludecke D, Riznar-Resetic V, Sekso M. The effects of cortisol, 11-epicortisol, and lysine vasopressin on DNA and RNA synthesis in isolated human adrenocorticotropic hormone-secreting pituitary tumor cells. *Steroids* 1990;55(3):98–100.
17. Dahia PL, Honegger J, Reincke M, et al. Expression of glucocorticoid receptor gene isoforms in corticotropin-secreting tumors. *J Clin Endocrinol Metab* 1997;82(4):1088–1093.
18. Nolan LA, Levy A. Temporally sensitive trophic responsiveness of the adrenalectomized rat anterior pituitary to dexamethasone challenge: Relationship between mitotic activity and apoptotic sensitivity. *Endocrinology* 2003;144(1):212–219.
19. Karl M, Von Wichert G, Kempter E, et al. Nelson's syndrome associated with a somatic frame shift mutation in the glucocorticoid receptor gene. *J Clin Endocrinol Metab* 1996;81(1):124–129.
20. Huizenga NA, de Lange P, Koper JW, et al. Human adrenocorticotropin-secreting pituitary adenomas show frequent loss of heterozygosity at the glucocorticoid receptor gene locus. *J Clin Endocrinol Metab* 1998;83(3):917–921.
21. Carey RM, Varma SK, Drake CR Jr., et al. Ectopic secretion of corticotropin-releasing factor as a cause of Cushing's syndrome. A clinical, morphologic, and biochemical study. *N Engl J Med* 1984;311(1):13–20.
22. Gertz BJ, Contreras LN, McComb DJ, Kovacs K, Tyrrell JB, Dallman MF. Chronic administration of corticotropin-releasing factor increases pituitary corticotroph number. *Endocrinology* 1987;120(1):381–388.
23. Stenzel-Poore MP, Cameron VA, Vaughan J, Sawchenko PE, Vale W. Development of Cushing's syndrome in corticotropin-releasing factor transgenic mice. *Endocrinology* 1992;130(6):3378–3386.
24. de Keyzer Y, Rene P, Beldjord C, Lenne F, Bertagna X. Overexpression of vasopressin (V3) and corticotrophin-releasing hormone receptor genes in corticotroph tumours. *Clin Endocrinol (Oxf)* 1998;49(4):475–482.
25. Dieterich KD, Gundelfinger ED, Ludecke DK, Lehnert H. Mutation and expression analysis of corticotropin-releasing factor 1 receptor in adrenocorticotropin-secreting pituitary adenomas. *J Clin Endocrinol Metab* 1998;83(9):3327-3331.
26. McNicol AM, Carbajo-Perez E. Aspects of anterior pituitary growth, with special reference to corticotrophs. *Pituitary* 1999;1(34):257–268.
27. Wynn PC, Harwood JP, Catt KJ, Aguilera G. Regulation of corticotropin-releasing factor (CRF) receptors in the rat pituitary gland: Effects of adrenalectomy on CRF receptors and corticotroph responses. *Endocrinology* 1985;116(4):1653–1659.
28. Sakai K, Horiba N, Sakai Y, Tozawa F, Demura H, Suda T. Regulation of corticotropin-releasing factor receptor messenger ribonucleic acid in rat anterior pituitary. *Endocrinology* 1996;137(5):1758–1763.
29. van Wijk PA, van Neck JW, Rijnberk A, Croughs RJ, Mol JA. Proliferation of the murine corticotropic tumour cell line AtT20 is affected by hypophysiotrophic hormones, growth factors and glucocorticoids. *Mol Cell Endocrinol* 1995;111(1):13–19.
30. Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM, van de Velde CJ. Long-term results of total adrenalectomy for Cushing's disease. *World J Surg* 2000;24(1):108–113.
31. Barnett AH, Livesey JH, Friday K, Donald RA, Espiner EA. Comparison of preoperative and postoperative ACTH concentrations after bilateral adrenalectomy in Cushing's disease. *Clin Endocrinol (Oxf)* 1983;18(3):301–305.
32. Kelly WF, MacFarlane IA, Longson D, Davies D, Sutcliffe H. Cushing's disease treated by total adrenalectomy: Long-term observations of 43 patients. *Q J Med* 1983;52(206):224–231.
33. Streeten DH, Anderson GHJ. *Endocrine Society Meeting* 1994:abstract 44c.
34. Chapuis Y, Pitre J, Conti F, Abboud B, Pras-Jude N, Luton JP. Role and operative risk of bilateral adrenalectomy in hypercortisolism. *World J Surg* 1996;20(7):775–779; discussion 779–780.
35. Kasperlik-Zaluska AA, Nielubowicz J, Wislawski J, et al. Nelson's syndrome: Incidence and prognosis. *Clin Endocrinol (Oxf)* 1983;19(6):693–698.
36. Kemink L, Pieters G, Hermus A, Smals A, Kloppenborg P. Patient's age is a simple predictive factor for the development of Nelson's syndrome after total adrenalectomy for Cushing's disease. *J Clin Endocrinol Metab* 1994;79(3):887–889.
37. Manolas KJ, Farmer HM, Wilson HK, et al. The pituitary before and after adrenalectomy for Cushing's syndrome. *World J Surg* 1984;8(3):374–387.
38. Moore TJ, Dluhy RG, Williams GH, Cain JP. Nelson's syndrome: Frequency, prognosis, and effect of prior pituitary irradiation. *Ann Intern Med* 1976;85(6):731–734.
39. Watson RG, van Heerden JA, Northcutt RC, Grant CS, Ilstrup DM. Results of adrenal surgery for Cushing's syndrome: 10 years' experience. *World J Surg* 1986;10(4):531–538.
40. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. *J Clin Endocrinol Metab* 1996;81(7):2647–2652.
41. Welbourn RB, Montgomery DA, Kennedy TL. The natural history of treated Cushing's syndrome. *Br J Surg* 1971;58(1):1–16.
42. Grabner P, Hauer-Jensen M, Jervell J, Flatmark A. Long-term results of treatment of Cushing's disease by adrenalectomy. *Eur J Surg* 1991;157(8):461–464.
43. Bennett AH, Cain JP, Dluhy RG, Tynes WV, Harrison JH, Thorn GW. Surgical treatment of adrenocortical hyperplasia: 20-year experience. *J Urol* 1973;109(3):321–324.
44. Moreira AC, Castro M, Machado HR. Longitudinal evaluation of adrenocorticotrophin and beta-lipotrophin plasma levels following bilateral adrenalectomy in patients with Cushing's disease. *Clin Endocrinol (Oxf)* 1993;39(1):91–96.
45. Jenkins PJ, Trainer PJ, Plowman PN, et al. The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 1995;80(1):165–171.
46. Pereira MA, Halpern A, Salgado LR, et al. A study of patients with Nelson's syndrome. *Clin Endocrinol (Oxf)* 1998;49(4):533–539.
47. Thomas CG, Jr., Smith AT, Benson M, Griffith J. Nelson's syndrome after Cushing's disease in childhood: A continuing problem. *Surgery* 1984;96(6):1067–1077.
48. Imai T, Funahashi H, Tanaka Y, et al. Adrenalectomy for treatment of Cushing syndrome: Results in 122 patients and long-term follow-up studies. *World J Surg* 1996;20(7):781–786; discussion 786–787.
49. McCance DR, Russell CF, Kennedy TL, Hadden DR, Kennedy L, Atkinson AB. Bilateral adrenalectomy: Low mortality

and morbidity in Cushing's disease. *Clin Endocrinol (Oxf)* 1993;39(3):315–321.
50. Cohen KL, Noth RH, Pechinski T. Incidence of pituitary tumors following adrenalectomy. A long-term follow-up study of patients treated for Cushing's disease. *Arch Intern Med* 1978;138(4):575–579.
51. Ernest I, Ekman H. Adrenalectomy in Cushing's disease. A long-term follow-up. *Acta Endocrinol Suppl (Copenh)* 1972;160:3–41.
52. Hopwood NJ, Kenny FM. Incidence of Nelson's syndrome after adrenalectomy for Cushing's disease in children: Results of a nationwide survey. *Am J Dis Child* 1977;131(12):1353–1356.
53. Krieger DT, Samojlik E, Bardin CW. Cortisol and androgen secretion in a case of Nelson's syndrome with paratesticular tumors: Response to cyproheptadine therapy. *J Clin Endocrinol Metab* 1978;47(4):837–844.
54. Baranetsky NG, Zipser RD, Goebelsmann U, et al. Adrenocorticotropin-dependent virilizing paraovarian tumors in Nelson's syndrome. *J Clin Endocrinol Metab* 1979;49(3):381–386.
55. Ntalles K, Kostoglou-Athanassiou I, Georgiou E, Ikkos D. Paratesticular tumours in a patient with Nelson's syndrome. *Horm Res* 1996;45(6):291–294.
56. Shekarriz M, Schneider C, Sabanegh E, Kempter F, Waldherr R. Excessive testosterone production in a patient with Nelson syndrome and bilateral testicular tumors. *Urol Int* 1996;56(3):200–203.
57. Johnson RE, Scheithauer B. Massive hyperplasia of testicular adrenal rests in a patient with Nelson's syndrome. *Am J Clin Pathol* 1982;77(4):501–507.
58. Mahmoud-Ahmed AS, Suh JH. Radiation therapy for Cushing's disease: A review. *Pituitary* 2002;5(3):175–180.
59. Vella A, Thompson GB, Grant CS, van Heerden JA, Farley DR, Young WF Jr. Laparoscopic adrenalectomy for adrenocorticotropin-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 2001;86(4):1596–1599.
60. van der Hoek J, Waaijers M, van Koetsveld PM, Sprij-Mooij D, Feelders RA, Schmid HA, Schoeffter P, Hoyer D, Cervia D, Taylor JE, Culler MD, Lamberts SW, Hofland LJ. Distinct functional properties of native somatostatin receptor subtype 5 compared with subtype 2 in the regulation of ACTH release by corticotroph tumor cells. *Am J Physiol Endocrinol Metab* 2005 March 15
61. Paez-Pereda M, Kovalovsky D, Hopfner U, Theodoropoulou M, Pagotto U, Uhl E, Losa M, Stalla J, Grubler Y, Missale C, Arzt E, Stalla GK. Retinoic acid prevents experimental Cushing syndrome. *J Clin Invest* 2001;108(8):1123–1131.
62. Heaney AP, Fernando M, Yong WH, Melmed S. Functional PPAR-gamma receptor is a novel therapeutic target for ACTH-secreting pituitary adenomas.*Nat Med* 2002;8(11):1281–1287. Epub 2002 Oct 15.
63. Schacke H, Schottelius A, Docke WD, Strehlke P, Jaroch S, Schmees N, Rehwinkel H, Hennekes H, Asadullah K. Dissociation of transactivation from transrepression by a selective glucocorticoid receptor agonist leads to separation of therapeutic effects from side effects. *Proc Natl Acad Sci USA* 2004; 101(1):227–232. Epub 2003 Dec 23.
64. Juliani G, Avataneo T, Potenzoni F, Sorrentino T. [CT and MR compared in the study of hypophysis]. *Radiol Med (Torino)* 1989;77(1-2):51–64.
65. Johnson MR, Hoare RD, Cox T, et al. The evaluation of patients with a suspected pituitary microadenoma: Computer tomography compared to magnetic resonance imaging. *Clin Endocrinol (Oxf)* 1992;36(4):335–338.
66. Vest-Courtalon C, Ravel A, Perez N, et al. Pituitary gland MRI and Cushing disease: Report of 14 operated patients. *J Radiol* 2000;81(7):781–786.
67. Melmed S. Mechanisms for pituitary tumorigenesis: The plastic pituitary. *J Clin Invest* 2003;112(11):1603–1618. Review.
68. Heaney AP, Melmed SR. Molecular targets in pituitary tumours. *Nat Rev Cancer* 2004;4(4):285–295. Review.
69. Evans CO, Young AN, Brown MR, Brat DJ, Parks JS, Neish AS, Oyesiku NM. Novel patterns of gene expression in pituitary adenomas identified by complementary deoxyribonucleic acid microarrays and quantitative reverse transcription-polymerase chain reaction. *J Clin Endocrinol Metab* 2001;86(7):3097–3107.