

## Update in Pituitary Disease

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**The pituitary gland secretes vital trophic hormones that maintain homeostatic regulation of the metabolic milieu. Not surprisingly, several thousand papers relevant to the pituitary gland were published this past year, including publication of important transforming advances in our understanding of the pathogenesis, diagnosis, and treatment of pituitary disorders. In an attempt to focus on outstanding key articles reporting highlights of the year, quality inclusion criteria were applied. High-quality articles were selected for their translational impact, scientific advances, enrichment of new knowledge, influence on how we understand pituitary disorders, transformation of therapeutic principles, and opening up new research vistas. Using these selection criteria, highlighted papers within the following categorical topics were further selected for analysis and review: advances in understanding subcellular mechanisms subserving the pathogenesis of pituitary disorders including pituitary tumors and pituitary failure; new challenges facing the physician treating patients harboring prolactinomas with dopamine agonists; and the appearance of new publications reporting the efficacy of long-term prospective medical treatment of acromegaly that now provide more rigorous patient outcome information.**

**Selected papers categorized by these topics all serve to significantly impact how the endocrinologist views disease pathogenesis, diagnosis, and treatment outcomes of patients with pituitary disease in 2007. The results of these publications have transformed our understanding of important principles underlying normal and abnormal pituitary function, as well as our approach to the management of pituitary disorders. Notably, they open up new vistas for creative scholarship in unraveling the challenges of pituitary medicine. (*J Clin Endocrinol Metab* 93: 331–338, 2008)**

**P**apers relating to translational and clinical discovery in pituitary medicine and published in 2006–2007 were reviewed. Several selection criteria were applied for inclusion in the Year in Pituitary at the 89th Annual Meeting of The Endocrine Society, Toronto, Canada, June 2007. Notably, papers were chosen if they influence the understanding and treatment of pituitary disease by asking defined, important questions. Scores of descriptive papers were excluded. Those selected for presentation are of the highest impact, as defined by clearly advancing clinical science, transforming therapeutic principles, opening new research vistas, and most importantly lead to creation of new knowledge in pituitary medicine (Table 1). Selected papers in each of these areas are discussed and put into perspective as to how they shed light and add new knowledge to the context of translational science in pituitary medicine.

### Pituitary Tumor Pathogenesis

Several papers were published this past year which redefine our thinking on the pathogenesis of pituitary adenomas. Canibano *et al.* (1) reported the discovery that pituitary transcription factor-1, the pituitary-specific transcription factor regulating cell differentiation and GH, prolactin, and TSH expression, also acts as a cell cycle suppressor within the anterior pituitary. These authors defined a novel intrinsic mechanism whereby somatotrophs mediate apoptosis/cell survival through the Ret receptor. This pathway is potentially a target for treating GH-cell adenomas. Bone morphogenic protein-4 was shown to inhibit corticotroph tumor cell growth and is involved in the retinoic acid inhibitory action on ACTH-secreting tumor proliferation. Thus, a novel subcellular target for Cushing's disease therapy has

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Abbreviations: AIP, Aryl hydrocarbon receptor interacting protein; HDAC, histone deacetylase; 5-HT<sub>2B</sub>, 5-hydroxytryptamine receptor 2B; LAR, long-acting release; SNP, single nucleotide polymorphism.

**Table 1.** Criteria for article selection

**Inclusion Criterion:**

→ Influence how we understand and treat pituitary disease by asking defined important questions

**Impact:**

- Advance clinical science
- Transform therapeutic principles
- Open new research vistas
- Creates new knowledge

been proposed (2). Drouin and colleagues (3) discovered that glucocorticoid resistance of ACTH-secreting tumors can be attributed to loss of Brg1 or histone deacetylase (HDAC)-2 nuclear expression. This transrepression of the POMC gene in corticotrophs could therefore be a mechanism underlying the formation of ACTH-secreting tumors (3).

Fedele *et al.* (4) showed that HMGA2 induces pituitary tumorigenesis by enhancing E<sub>2</sub>F activity. The paper was based on prior findings of this group that transgenic mice overexpressing HMGA2, a nuclear architectural protein, exhibit a high prevalence of pituitary tumors. These workers now show a mechanism for pituitary tumor formation in human pituitary tumors whereby HMGA2 displaces HDAC, the histone deacetylase from the pRB complex. Displacement of HDAC by HMGA2 leads to acetylation of start sites, acetylation of E<sub>2</sub>F<sub>1</sub>, liberation of the pRB complex from E<sub>2</sub>F<sub>1</sub>, and the cell consequently driven into S phase. This is an elegant mechanistic demonstration of cell cycle initiation in human pituitary tumor cells. HMGA2 was also shown to be abundantly expressed in tumor cells derived from patients with prolactinomas (5).

A large body of work was published relating to the genetic analysis of pituitary tumors. A comprehensive study from Belgium (6) characterized familial isolated pituitary adenomas. These very rarely encountered index families comprised patients with heterogenous features of acromegaly, prolactinoma, and Cushing's disease. Significantly affected individuals were younger, some were giants, and some harbored more invasive tumors than sporadic patients. The challenge in these rarely encountered and similar families (7) has been that they appear to harbor a mutation in the 11q region, distinct from multiple endocrine neoplasia-1 or any other related tumor suppressor gene. The challenging question in these families has been that the identity of the gene on 11q that predisposes to these traits has remained elusive.

A recent paper (8), for the first time, proposed the aryl hydrocarbon receptor interacting protein (AIP) gene as predisposing to pituitary adenoma. The authors describe pituitary adenoma predisposition caused by germ line mutations in the gene encoding AIP. AIP functions as a chaperone protein and complexes with aryl hydrocarbons, heat shock proteins, and the aryl hydrocarbon receptor (9). The aryl hydrocarbon receptor also binds carcinogenic hydrocarbons including dioxin (10) and inactivates phosphodiesterase, hydrolyzing cAMP (11). There

have been a number of subsequent papers testing the relevance of this finding for both familial and sporadic pituitary adenomas. Iwata *et al.* (12) detected an AIP germline mutation (deletion of IGT) in three patients, all of whom had familial acromegaly. Overall, 15% of families with familial predisposition to pituitary tumors harbor at least 10 different germline AIP mutations. In the subsequent months, six reports appeared testing or extending this finding for patients harboring sporadic pituitary tumors. The original Finnish group in a subsequent paper (13) sought mutations in a heterogenous group of pituitary adenoma patients, including young acromegalic patients from Germany and Finland; unselected tumors from Italy, the United States, and Poland; and multiple endocrine neoplasia-1-negative familial pituitary tumors obtained from Spain and The Netherlands. Mutations were detected at an extremely low prevalence (13). At least 565 patients have now been reported in the past 12 months (6, 14-16). AIP mutations were detected in two of 113 (United States), one (Poland), two (Germany), and four of 10 patients with sporadic tumors from Finland (13). No mutations were detected in western Europe, Japan, and the United States embodying published studies (6, 12, 14-17) (Fig. 1). The question arises as to how many unselected sporadic tumors are in fact components of undiagnosed familial syndromes? For example, a reported sporadic tumor was present in an 8-yr-old patient (13). Whether these patients comprise a familial adenoma syndrome should be rigorously excluded. Early evidence has been presented that the AIP protein could act as a tumor suppressor gene. For example, AIP immunostaining was abundant in a normal pituitary gland and a pituitary adenoma without the mutation. In contrast, a pituitary adenoma derived from a patient harboring an AIP germline mutation was almost devoid of AIP (13).

How do we interpret these new findings and where does the field go from here based on published AIP findings? Several important postulates are yet to be satisfied to confirm whether this mutation directly leads to pituitary tumors. We require information regarding systematic AIP mRNA and protein expression profiles in both truly sporadic and familial tumors. The next step will be to reintroduce a mutated AIP gene into pituitary cells and test resultant tumor growth and hormone secretion. This will be a challenging experiment because no functional human pituitary cell lines are available for this experiment. Because abundant wild-type AIP is likely present in the overwhelming majority of



**FIG. 1.** AIP mutations in 565 sporadic pituitary tumors (13-17).

pituitary tumors, allelic deletion will be required to understand mechanisms of AIP action. The ultimate proof will be to test whether a mutant AIP transgene will or will not result in murine pituitary tumor formation.

The Finnish group has proposed population screening using AIP germline mutations for pituitary tumors, which I believe is premature, based on the extreme rarity of the finding. The challenges for recommending AIP screening are that these patients with pituitary tumors will likely also have hypogonadism because of the large macroadenomas. Disease transmission will therefore be difficult to map because many patients will in fact be infertile. There is also an extremely low frequency of familial pituitary adenomas in the general population, and of these, only 15% appear to harbor the germline mutation. Magnetic resonance imaging screening of afflicted families for pituitary tumors is far easier and less costly but is quite nonspecific with at least a 15% false-positive rate. Biochemical screening, which is not expensive and universally available, remains the standard screening tool for clinicians. Biochemical screening is easier, reasonably priced, and will yield accurate information for understanding whether a patient, or the family, harbors a clinically significant occult pituitary tumor (18).

Nelson's syndrome develops when the adrenal glands are resected and the pituitary gland responds to loss of glucocorticoid feedback inhibition by secreting excess ACTH. The gland expands, leading to hypertrophy, hyperplasia, and ultimately corticotroph tumor formation. The condition is difficult to treat, and patients may be resistant to surgery and radiation. Bertagna and colleagues (19) have now demonstrated that the pathogenesis of Nelson's syndrome is in fact a reflection of progression of an underlying corticotroph adenoma already present before adrenalectomy. In following 53 patients without corticotroph tumor progression after bilateral adrenalectomy, pituitary hyperplasia or tumor formation developed at a relatively high frequency for the first 6 yr. Thereafter no more patients appear to develop these corticotroph tumors as observed for up to 14 yr. The authors provided evidence that in fact what was termed Nelson's syndrome in earlier years was revealed by insensitive pituitary sella x-ray. In contrast, by using available sensitive magnetic resonance imaging, the early underlying tumor can be visualized *a priori* before adrenalectomy. Thus, the natural history of Nelson's after adrenalectomy is in reality a reflection of continued tumor growth. The authors, by their analysis, proposed predictors for which patients will in fact develop pituitary hyperplasia and tumors after adrenalectomy and therefore should likely not undergo adrenalectomy. Based on their analysis, these predictors, including early ACTH elevation, an adenoma already visible before adrenalectomy, high ACTH levels after 1,1-dichlorodiphenildichloroethane suppression or adrenalectomy, and most importantly, the mitotic activity of the original pituitary adenoma if the patient initially underwent surgery for corticotroph adenoma resection before planned adrenalectomy determined the diagnosis.

Interestingly, a case report by Kovacs *et al.* (20) actually demonstrated the presence of true corticotroph hyperplasia preceding adenoma formation in a patient with well-defined Nelson's syndrome.

## Prolactin Disorders

A pituitary mass arising from any cause (neoplastic, inflammatory, vascular, or other) results in hyperprolactinemia secondarily to the pressure of the mass on pituitary dopamine pathways (stalk section phenomenon). The differential diagnosis challenge is whether observed high prolactin levels are due to direct prolactinoma hypersecretion, which requires one set of treatments, or whether a nonfunctioning mass is causing the prolactin to rise. Wass and colleagues (21) rigorously verified the presence of nonfunctioning pituitary macroadenomas in 226 patients. The authors measured prolactin levels in patients harboring null cell or gonadotroph cell tumors and not receiving drugs known to elevate prolactin levels. Two hundred twenty-two of 223 patients with nonfunctioning adenomas had a prolactin level less than 100 ng/ml. Prolactin levels of greater than 2000 mU/liter (<100 ng/ml) in the face of a nonfunctioning mass implies that that patient harbors a prolactinoma and not a nonfunctioning macroadenoma. This rigorous, well-defined cutoff value will be of great help in clinical management of patients with elevated prolactin levels and a large pituitary mass.

Cabergoline has been the mainstay of prolactinoma treatment for almost a decade. This long-acting dopamine agonist has been used as a safe and efficacious drug. A set of papers in the *New England Journal of Medicine* had arguably the single most important impact on pituitary disease management in the past 12 months. These were reports of the risk for cardiac valve regurgitation by long-acting dopamine agonists. Schade (22), studied 12,794 patients receiving anti-Parkinsonian prescriptions, excluding those with preexisting heart disease or those receiving drugs known to be associated with heart valvulopathy. They were left ultimately with 11,400 patients, of whom new cardiac valve regurgitation was discovered in 81. All patients were receiving anti-Parkinsonian treatment including a dopamine agonist, cabergoline, pergolide, or a non-ergot dopamine agonist. Of these 81 patients, 50 were further excluded for myocardial infarction or known valve disease, and 31 case patients were validated. A nested control analysis was performed with approximately 25 controls for each patient. Of six patients receiving cabergoline, all had some degree of valvular regurgitation, and two patients had involvement of three valves. The reported adjusted incidence rate ratio for valvular regurgitation in a patient taking cabergoline was 4.9, and the risk of valve regurgitation in all 31 patients was dose dependent. Less than 3 mg daily dose of cabergoline has a 3-fold adjusted incidence rate ratio, but more than 3 mg daily dose led to a 50-fold adjusted incidence rate ratio for valve regurgitation.

To put these results into perspective, the average endocrine dose for patients harboring prolactinomas is 1 or 2 mg/wk. Another study in the same issue of the *New England Journal of Medicine* (23) showed similar results. They undertook an echocardiographic valvulopathy prevalence study in 155 patients receiving anti-Parkinsonian treatments. These patients had known echocardiographic valvulopathy and 29% of the cohort were receiving cabergoline, of whom 29% had valvulopathy, with elevated valve regurgitation risk ratios, ranging from 4 to 7. These authors also observed dose dependency of

valve regurgitation grade with cabergoline. Regurgitation grade of 0–2 was associated with a cumulative cabergoline dose of 2321 mg and a grade of 3–4 with a dose of 4000 mg. A summary of the two paper shows no differences in diabetes, or cardiovascular disease, between controls, pergolide, cabergoline, or dopamine agonist groups. Average daily doses of cabergoline in the study was 3.6 mg, which is approximately 7 times higher than the maximal dose used for patients with prolactinomas. The cumulative dose of cabergoline was 2800 g for those patients.

To put these findings into perspective, the daily cabergoline dose for treatment of prolactinoma, is 70–300  $\mu\text{g}$ . Should patients continue taking this highly effective drug, which cures patients with prolactinoma, reverses hypogonadism, and shrinks the adenoma mass, or should we be concerned that this dose is cardiotoxic? The answer will likely derive from understanding the pathogenesis of valvulopathy (Fig. 2). Ergotamine, methysergide, amphetamine derivatives, ecstasy, pergolide, and cabergoline are 5-hydroxytryptamine receptor 2B (5-HT<sub>2B</sub>) agonists. Their mechanism of action is mediated by binding to the 5-HT<sub>2B</sub> G protein-coupled receptor and signal through ERK and Src pathways and also via protein kinase C to phosphorylate RB (24). RB phosphorylation, uniquely and in a tissue-specific fashion, causes mitogenesis of previously quiescent valve cells, with resultant regurgitation because of structural tricuspid, mitral, and aortic valve damage. Leaflets and chordae are thickened, with refractory surface plaques. This pathogenesis is reminiscent of carcinoid heart disease, *i.e.* high doses of cabergoline appear to induce a carcinoid-like heart disease by interacting with the cardiac 5-HT<sub>2B</sub> receptor.

A prospective controlled study is required to assess the true prevalence of valvulopathy using cabergoline doses commonly used in treating patients harboring prolactinomas. Nevertheless, the available data indicate that valvulopathic effects of cabergoline are dose dependent.

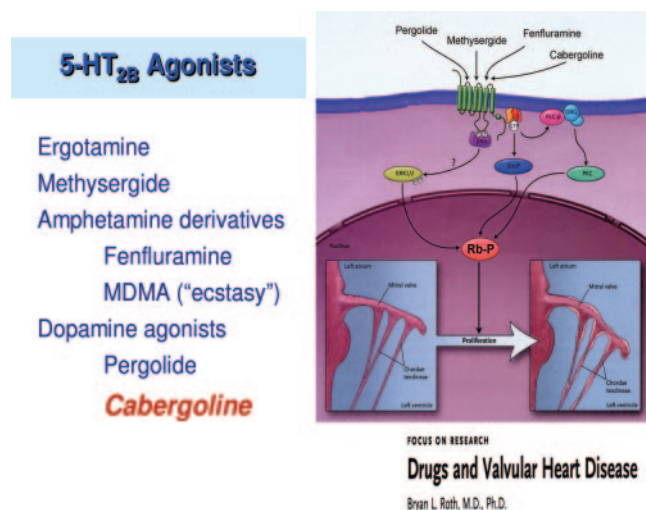


FIG. 2. 5-HT<sub>2B</sub> agonists (24). PLC, Phospholipase; DAG, diacylglycerol; PKC, phosphokinase C; Rb-P, phosphorylated Rb protein; MDMA, methylenedioxy metamphetamine.

## GH

GH secretion by the pituitary is controlled by hypothalamic GHRH and somatostatin and stimulates IGF-I production (mainly in the liver and muscle), and both IGF-I and GH mediate physiologic growth. Somatic muscle and bone development are under GH and IGF-I control. Deficient GH or IGF-I secretion or action leads to short stature or adult GH deficiency. Excess of these hormones results in features of growth and metabolic dysfunction unique for acromegaly. Studies this past year have impacted our understanding of GH action, assays, body growth, and inappropriate GH use in the elderly.

A key paper published in *Science* this year (25) studied dog growth and effectively changed the paradigm of how we view growth and growth disorders. These investigators questioned why some dog breeds are small and others large. They undertook a survey of genetic variation for 116 single-nucleotide polymorphisms (SNPs) in 526 dogs. Twenty-three small dog breeds were found to harbor a single IGF-I allele, and the presence of this SNP 5A allele was the determinant of small size. Small dogs are small because they carry this noncoding SNP in the gene encoding IGF-I, which is absent in 20 giant dog breeds. When dog size was plotted *vs.* the presence of the IGF-I gene 5A allele (Fig. 3), all small dogs were shown to possess the allele, whereas none of the larger Great Danes or Mastiffs harbor the allele. The fascinating question to be tested is whether a human IGF-I gene SNP is associated with stature? Results of this study have now remodeled theories of growth to focus on noncoding genomic changes, in addition to our current focus on GH or IGF-I synthesis or biochemical action.

The International Olympic Committee has undertaken an ongoing initiative to overcome the challenge of diagnosing doping in sports. One of the challenges for athlete testing is the poor quality of surrogate marker assays for GH action. Ho and colleagues (26) studied 1100 athletes for GH and bone markers to determine demographic factors influencing test results. Results of IGF-I measurements were accurately assessed by age in a group of healthy volunteers up to the age of 60 yr. This elegant normal population study will enable clinicians to diagnose pathologic short stature, tall stature, acromegaly, or normal based on normal IGF-I values, which can now accurately be derived. Thus, this paper provides the clinician with demographically relevant reference ranges. The authors also assessed sporting type, ethnicity, body mass index, gender, and age as determinants of the GH axis, including IGF-I, IGF binding protein-3,

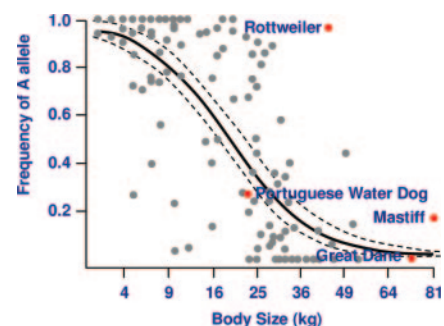


FIG. 3. Association of body size and frequency of the SNP 5A allele (25).

and acid-labile subunit, and bone markers. For growth or bone axis markers, age is the most important determinant of marker level. Interestingly, sport type contributes less than 5% to the variation of IGF-I levels or bone markers. IGF-I levels can change, depending on sport type participation. Confrontational endurance sports yield higher IGF-I levels than those in subjects performing simple walking or throwing a ball.

A disturbing but significant study evaluated GH and IGF-I assay reproducibility (27). The authors participated with 23 centers in the United Kingdom and sent the same 2 GH and IGF-I samples to each center. Nadir GH results after glucose loading ranged from close to zero to up to 3.5  $\mu$ U/ml, depending on which mass conversion unit was used. The same sample, derived from the same patient and measured in different laboratories (and even in the same center) yielded significantly different results. Measurements of GH therefore still require major assay refinements (28). The upper limits of normal for IGF-I levels in this study ranged from +60% to –60%, a 100% variation. In fact, 30% of the results were against the original diagnosis, and reference ranges exhibited a 50% variance. These results will inject a justifiable caution as we derive therapy and outcome decisions based on laboratory results.

Gotherstrom *et al.* (29) published the first long-term results of a 10-yr prospective study of GH replacement to GH-deficient adults. These patients had documented pituitary damage and GH deficiency and have now received GH replacement and been carefully followed up for 10 yr (Fig. 4). Male and female IGF-I levels and bioresponses differ significantly. IGF-I levels rise in the first year but then plateau. However, in males, total body fat drops dramatically while on GH (20%) and stays below 10% for 10 yr, whereas women do not appreciably change body fat mass. Lean body mass improvement is sustained for 10 yr. Interestingly, hemoglobin A1c levels are significantly attenuated and stay low for 10 yr. This is helpful information for managing these patients, who are often insulin resistant. The initial mean GH dose was 0.98 mg/d, and by 10 yr had been dropped by half. Less GH is required to sustain lowered hemoglobin A1c and improve lean body mass as the decade progresses. Thus, chronic dosing schedules for adult GH replacement will likely be lowered by practicing endocrinologists.

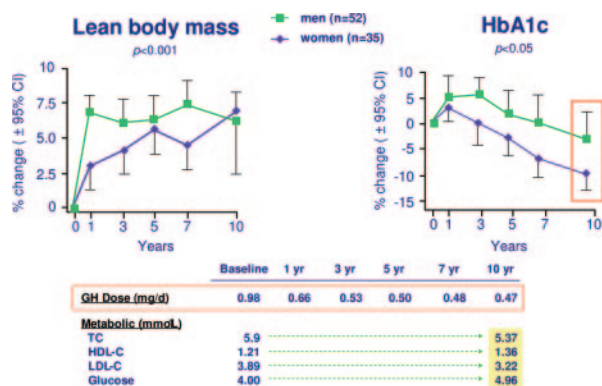


FIG. 4. Ten-year GH therapy in 87 GHD adults (29). GHD, GH deficiency; CI, confidence interval; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol.

There has been a flurry of lay interest in the use of GH to reverse the frailty of aging. In a well-controlled study, Giannoulis *et al.* (30) investigated four groups of healthy, elderly individuals, comprising 80 subjects aged 65–80 yr old and followed them for 26 wk. Cohorts received placebo, testosterone, GH, or GH plus testosterone. The question posed was whether the frailties of aging could be reversed in a controlled fashion by GH and or testosterone supplements. The answer provided by the authors is that the combined GH and testosterone regimen for 6 months resulted in significantly increased lean body mass and decreased fat mass. However, significant changes in muscle strength and cognitive function were not demonstrated. Further studies are required to assess more rigorous surrogate frailty end points for cotreatment of these subjects. Interestingly, blood sugar levels were not elevated by GH after 6 months.

A critical analysis of the published literature in healthy individuals receiving GH was undertaken (31). Conclusions were that GH is widely sold, had no effects on body composition, but administration leads to frequent adverse events. Clinical trials have usually been small and may not be sufficiently robust to detect important differences. The risks of GH far outweigh the benefits when used as an antiaging treatment in healthy older adults. Fifty percent of reported patients in the literature developed fluid retention and edema, 20% had carpal tunnel syndrome, 6% had gynecomastia, but most intriguingly, 27% developed diabetes or glucose intolerance when receiving GH unnecessarily. We do not yet know whether an increased propensity for development of cancer exists in these patients.

### Acromegaly

Octreotide long-acting release (LAR) has been used as a safe and effective drug for controlling GH and IGF-I levels, tumor growth, and comorbidities in patients with acromegaly. Cozzi *et al.* (32) now reports an open consecutive trial of 67 patients receiving octreotide LAR as primary treatment for up to 9 yr. For those patients not switched to other treatment modalities, GH and IGF-I levels are controlled in more than 80% of patients (Fig. 5). Sixty-two percent mean pituitary tumor volume reduction was observed, and 11 of 55 patients had reduction to an empty sella or cavernous sinus mass resolution, or the tumor was no longer visible. In this 9-yr study of primary medical treatment, the longest in the published literature, tumor shrinkage was progressive and occurred more frequently in younger patients. Forty-five percent of patients exhibited tumor shrinkage before GH and IGF-I levels are normalized; however, 35% have tumor shrinkage without GH control and 3% of patients showed no shrinkage despite GH control. Although they report a spectrum of responses, most patients experience tumor shrinkage on medical treatment and may not require neurosurgical tumor resection.

Colao *et al.* (33) showed that decreased tumor volume during primary somatostatin receptor ligand treatment correlates with IGF-I levels, and if IGF-I normalizes with somatostatin treatment, the patient will likely experience tumor shrinkage and not require neurosurgery. Overall, approximately 75% of patients

	<b>%</b>
Safe GH (<2.5 ug/L)	69
Normal IGF-I	70
Tumor Shrinkage	82
Unsafe GH and no tumor change	15

Glucose (g/L)	Basal	Rx	P
Fasting	1.13 ± 0.36	1.13 ± 0.26	ns
OGTT peak	1.54 ± 0.55	1.71 ± 0.57	ns
HbA1c (%)	6.2 ± 1.3	6.3 ± 1	ns
Cholesterol (g/L)	2.12 ± 0.49	2.15 ± 0.49	ns
Triglycerides (g/L)	1.42 ± 0.54	1.11 ± 0.37	0.01

FIG. 5. Primary octreotide treatment in 67 consecutive patients (32). OGTT, Oral glucose tolerance test; HbA1c, hemoglobin A1c; Rx, treatment regimen; ns, not significant.

will exhibit more than 25% tumor mass shrinkage as long as they receive long-acting somatostatin receptor ligand. These two studies provide new evidence that supports the hypothesis that patients who are not destined for surgical cure, are too frail for anesthesia, and undertake an informed choice may not require neurosurgical intervention and will benefit from primary medical treatment. Nevertheless, based on a well-controlled study (34), evidence is shown that partial resection of GH-secreting tumors enhances octreotide LAR responsiveness.

### Nonfunctioning Pituitary Macroadenomas

Dekkers *et al.* (35) studied 109 patients with pituitary macroadenoma. Patients were prospectively observed, and preoperatively these patients had a high degree of pituitary failure. After surgery they exhibited no overall improvement in pituitary deficiency; in fact, postoperative pituitary failure was somewhat exacerbated, compared with preoperative status, suggesting aggressive surgical resection. Likely, normal pituitary tissue was not spared and patients required postoperative pituitary hormone replacement. The clinical question raised for these patients was whether they required prophylactic postoperative irradiation. There have been several uncontrolled studies suggesting to either irradiate or not irradiate these patients prophylactically. This prospective study concluded that prophylactic irradiation was not warranted. In fact, if residual tumor was not observed after surgery, there was a 100% regrowth-free survival for 10 yr. If residual tumor or tissue was present after surgery, there was a 75% regrowth-free survival over 10 yr. Factors not determining tumor recurrence included radiation therapy, ACTH positivity (for diagnosing silent corticotroph adenoma), tumor size, or the presence of a residual tumor. However, duration of follow-up was the most significant factor determining recurrence (Fig. 6). If, in fact, the patient develops a recurrent tumor, then at that point irradiation or second surgery could be indicated. These observations are important for justifying expectant observation in management of patients with nonfunctioning pituitary tumors.

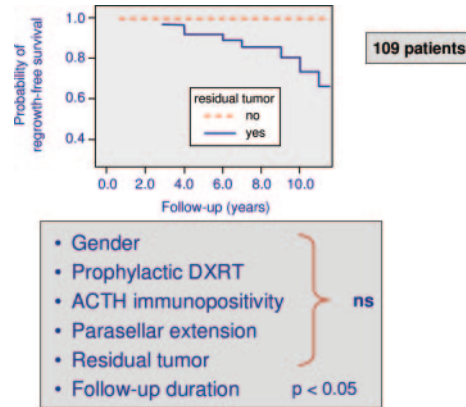


FIG. 6. Growth-free survival rates of non-functioning pituitary adenomas (35). DXRT, Radiation therapy; ns, not significant.

### Miscellaneous

There was a set of papers defining both the validation and use of pituitary antibodies as peripheral serum diagnostic tools (36, 37). These studies show that autoimmune polyendocrine failure or isolated childhood GH deficiency can be diagnosed by measuring circulating pituitary autoantibodies, thus offering new tools for identifying patients prone to develop pituitary failure.

In a paper that impacts our understanding of aging, a new progeroid syndrome was described (38), suggesting that the genotoxic stress of premature aging is at least in part mediated by the GH-IGF-I system. Results of this study showed that aging is determined by both stochastic DNA damage and genetic factors determining the rates of such damage. Given the intense interest in using GH for treating the frailties of aging, this study provides a scientific foundation for further exploration of the role of GH and IGF-I in the aging process.

Papers on understanding pituitary function provided new insights for known clinical conundrums. A prospective study rigorously defined the predictive accuracy of the Cortrosyn stimulation test (39). This information will allow appropriate use and interpretation of testing for secondary adrenal insufficiency. The risk of pituitary failure was further delineated in patients with traumatic brain injury (40). This paper contributes to the increased awareness of testing pituitary function in patients both immediately after and during long-term follow-up after brain injury. This paper heightens awareness for this previously neglected cause of long-term hypopituitarism.

I end by citing Ho (41), who wrote a futuristic vision of endocrinology during the next 60 yr. After enunciating the major benefits and forthcoming exciting contributions of endocrinology to human disease and well-being, Ho pleaded for caution in understanding the danger of cosmetic endocrinology, which flourishes under the guise of improving health. This is a major problem in the United States where more than 100,000 illegitimate prescriptions for GH are issued each year (42). Many billions of dollars are therefore being spent on patient care for cosmetic endocrinology including inappropriate use of GH, testosterone, and other steroids. We are in an era when unscrupulous gene profiling and gene modifications have been promised to lead to longevity, increased life satisfaction, and slowing of the

genetic clock. Daily TV and newspaper advertisements assure the public that endocrinologists can reverse short stature, flabbiness, hirsutism, baldness, hyposexuality, and promise to “retune our glands in the search of elusive health” (41). These are slippery cocktails of myth and fact, and I urge us not to fall on this very prevalent slippery slope. Our mandate to society is to maintain focus on rigorous, scientifically sound, peer-reviewed research advances.

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## References

- Canibano C, Rodriguez NL, Saez C, Tovar S, Garcia-Lavandeira M, Borrello MG, Vidal A, Costantini F, Japon M, Dieguez C, Alvarez CV 2007 The dependence receptor Ret induces apoptosis in somatotrophs through a Pit-1/p53 pathway, preventing tumor growth. *EMBO J* 26:2015–2028
- Giacomini D, Paez-Pereda M, Theodoropoulou M, Labeur M, Refojo D, Gerez J, Chervin A, Berner S, Losa M, Buchfelder M, Renner U, Stalla GK, Arzt E 2006 Bone morphogenetic protein-4 inhibits corticotroph tumor cells: involvement in the retinoic acid inhibitory action. *Endocrinology* 147:247–256
- Bilodeau S, Vallette-Kasic S, Gauthier Y, Figarella-Branger D, Brue T, Berthelet F, Lacroix A, Batista D, Stratakis C, Hanson J, Meij B, Drouin J 2006 Role of Brg1 and HDAC2 in GR trans-repression of the pituitary POMC gene and misexpression in Cushing disease. *Genes Dev* 20:2871–2886
- Fedele M, Visone R, De Martino I, Troncone G, Palmieri D, Battista S, Ciarmiello A, Pallante P, Arra C, Melillo RM, Helin K, Croce CM, Fusco A 2006 HMGA2 induces pituitary tumorigenesis by enhancing E2F1 activity. *Cancer Cell* 9:459–471
- Fedele M, Pierantoni GM, Visone R, Fusco A 2006 Critical role of the HMGA2 gene in pituitary adenomas. *Cell Cycle* 5:2045–2048
- Daly AF, Jaffrain-Rea ML, Ciccarelli A, Valdes-Socin H, Rohmer V, Tamburrano G, Borson-Chazot C, Estour B, Ciccarelli E, Brue T, Ferolla P, Emy P, Colao A, De Menis E, Lecomte P, Penfornis F, Delemer B, Bertherat J, Wémeau JL, De Herder W, Archambeaud F, Stevenaert A, Calender A, Murat A, Cavagnini F, Beckers A 2006 Clinical characterization of familial isolated pituitary adenomas. *J Clin Endocrinol Metab* 91:3316–3323
- Gadelha MR, Une KN, Rohde K, Vaisman M, Kineman RD, Frohman LA 2000 Isolated familial somatotropinomas: establishment of linkage to chromosome 11q13.1–11q13.3 and evidence for a potential second locus at chromosome 2p16–12. *J Clin Endocrinol Metab* 85:707–714
- Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R, Gündogdu S, De Menis E, Mäkinen MJ, Launonen V, Karhu A, Aaltonen LA 2006 Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 312:1228–1230
- Bell DR, Poland A 2000 Binding of aryl hydrocarbon receptor (AhR) to AhR-interacting protein. The role of hsp90. *J Biol Chem* 275:36407–36414
- Ema M, Matsushita N, Sogawa K, Ariyama T, Inazawa J, Nemoto T, Ota M, Oshimura M, Fujii-Kuriyama Y 1994 Human arylhydrocarbon receptor: functional expression and chromosomal assignment to 7p21. *J Biochem (Tokyo)* 116:845–851
- McPhee I, Pooley L, Lobban M, Bolger G, Houslay MD 1995 Identification, characterization and regional distribution in brain of RPDE-6 (RNPDE4A5), a novel splice variant of the PDE4A cyclic AMP phosphodiesterase family. *Biochem J* 310(Pt 3):965–974
- Iwata T, Yamada S, Mizusawa N, Golam HM, Sano T, Yoshimoto K 2007 The aryl hydrocarbon receptor-interacting protein gene is rarely mutated in sporadic GH-secreting adenomas. *Clin Endocrinol (Oxf)* 66:499–502
- Georgitsi M, Raitila A, Karhu A, Tuppurainen K, Mäkinen MJ, Vierimaa O, Paschke R, Saeger W, van der Luitj RB, Sane T, Robledo M, De Menis E, Weil RJ, Wasik A, Zielinski G, Luczewicz O, Lubinski J, Launonen V, Vahteristo P, Aaltonen LA 2007 Molecular diagnosis of pituitary adenoma predisposition caused by aryl hydrocarbon receptor-interacting protein gene mutations. *Proc Natl Acad Sci USA* 104:4101–4105
- Barlier A, Vanbellinthen JF, Daly AF, Silvy M, Jaffrain-Rea ML, Trouillas J, Tamagno G, Cazabat L, Bours V, Brue T, Enjalbert A, Beckers A 2007 Mutations in the aryl hydrocarbon receptor interacting protein gene are not highly prevalent among subjects with sporadic pituitary adenomas. *J Clin Endocrinol Metab* 92:1952–1955
- Yu R, Bonert V, Saporta I, Raffel LJ, Melmed S 2006 Aryl hydrocarbon receptor interacting protein variants in sporadic pituitary adenomas. *J Clin Endocrinol Metab* 91:5126–5129
- Toledo RA, Lourenco Jr DM, Liberman B, Cunha-Neto MB, Cavalcanti MG, Moyses CB, Toledo SP, Dahia PL 2007 Germline mutation in the aryl hydrocarbon receptor interacting protein gene in familial somatotropinoma. *J Clin Endocrinol Metab* 92:1934–1937
- Daly AF, Vanbellinthen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA, Murat A, Emy P, Gimenez-Roqueplo AP, Tamburrano G, Raverot G, Barlier A, De Herder W, Penfornis A, Ciccarelli E, Estour B, Lecomte P, Gatta B, Chabre O, Sabaté MI, Bertagna X, Garcia Basavilbaso N, Stalldecker G, Colao A, Ferolla P, Wémeau JL, Caron P, Sadoul JL, Oneto A, Archambeaud F, Calender A, Similnikova O, Montañana CF, Cavagnini F, Hana V, Solano A, Delellieres D, Luccio-Camelo DC, Basso A, Rohmer V, Brue T, Bours V, Teh BT, Beckers A 2007 Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J Clin Endocrinol Metab* 92:1891–1896
- Melmed S 2007 Aryl hydrocarbon receptor interacting protein and pituitary tumorigenesis: another interesting protein. *J Clin Endocrinol Metab* 92:1617–1619
- Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugué MA, Karray F, Dousset B, Bertherat J, Legmann P, Bertagna X 2007 Corticotroph tumor progression after adrenalectomy in Cushing’s disease: a reappraisal of Nelson’s syndrome. *J Clin Endocrinol Metab* 92:172–179
- Kovacs K, Horvath E, Coire C, Cusimano M, Smyth H, Scheithauer BW, Lloyd RV 2006 Pituitary corticotroph hyperplasia preceding adenoma in a patient with Nelson’s syndrome. *Clin Neuropathol* 25:74–80
- Karavitiaki N, Thanabalasingham G, Shore HC, Shore HC, Trifanescu R, Ansoorge O, Meston N, Turner HE, Wass JA 2006 Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. *Clin Endocrinol (Oxf)* 65:524–529
- Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E 2007 Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med* 356:29–38
- Zanettini R, Antonini A, Gatto G, Gentile R, Tesi S, Pezzoli G 2007 Valvular heart disease and the use of dopamine agonists for Parkinson’s disease. *N Engl J Med* 356:39–46
- Roth BL 2007 Drugs and valvular heart disease. *N Engl J Med* 356:6–9
- Sutter NB, Bustamante CD, Chase K, Gray MM, Zhao K, Zhu L, Padhukasa-harasm B, Karlins E, Davis S, Jones PG, Quignon P, Johnson GS, Parker HG, Fretwell N, Mosher DS, Lawler DF, Satyaraj E, Nordborg M, Lark KG, Wayne RK, Ostrander EA 2007 A single IGF1 allele is a major determinant of small size in dogs. *Science* 316:112–115
- Nelson AE, Howe CJ, Nguyen TV, Leung KC, Trout GJ, Seibel MJ, Baxter RC, Handelsman DJ, Kazlauskas R, Ho KK 2006 Influence of demographic factors and sport type on growth hormone-responsive markers in elite athletes. *J Clin Endocrinol Metab* 91:4424–4432
- Pokrajac A, Wark G, Ellis AR, Wear J, Wieringa GE, Trainer PJ 2007 Variation in GH and IGF-I assays limits the applicability of international consensus criteria to local practice. *Clin Endocrinol (Oxf)* 67:65–70
- Strasburger CJ, Bidlingmaier M 2005 How robust are laboratory measures of growth hormone status? *Horm Res* 64(Suppl 2):1–5
- Gotherstrom G, Bengtsson BA, Bosaeus I, Johannsson G, Svensson J 2007 A 10-year, prospective study of the metabolic effects of growth hormone replacement in adults. *J Clin Endocrinol Metab* 92:1442–1445
- Giannoulis MG, Sonksen PH, Umpleby M, Breen L, Pentecost C, Whyte M, McMillan CV, Bradley C, Martin FC 2006 The effects of growth hormone and/or testosterone in healthy elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 91:477–484
- Liu H, Bravata DM, Olkin I, Nayak S, Roberts B, Garber AM, Hoffman AR 2007 Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 146:104–115
- Cozzi R, Montini M, Attanasio R, Albizzi M, Lasio G, Lodrini S, Doneda P, Cortesi L, Pagani G 2006 Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the

- control of disease activity and tumor shrinkage. *J Clin Endocrinol Metab* 91:1397–1403
33. Colao A, Pivonello R, Auriemma RS, Briganti F, Galdiero M, Tortora F, Caranci F, Cirillo S, Lombardi G 2006 Predictors of tumor shrinkage after primary therapy with somatostatin analogs in acromegaly: a prospective study in 99 patients. *J Clin Endocrinol Metab* 91:2112–2118
34. Jallad RS, Musolino NR, Kodaira S, Cescato VA, Bronstein MD 2007 Does partial surgical tumour removal influence the response to octreotide-LAR in acromegalic patients previously resistant to the somatostatin analogue? *Clin Endocrinol (Oxf)* 67:310–315
35. Dekkers OM, Pereira AM, Roelfsema F, Voormolen JH, Neelis KJ, Schroijen MA, Smit JW, Romijn JA 2006 Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab* 91:1796–1801
36. De Bellis A, Salerno M, Conte M, Coronella C, Tirelli G, Battaglia M, Esposito V, Ruocco G, Bellastella G, Bizzarro A, Bellastella A 2006 Antipituitary antibodies recognizing growth hormone (GH)-producing cells in children with idiopathic GH deficiency and in children with idiopathic short stature. *J Clin Endocrinol Metab* 91:2484–2489
37. Bensing S, Fetisov SO, Mulder J, Perheentupa J, Gustafsson J, Husebye ES, Oscarson M, Ekwall O, Crock PA, Hökfelt T, Hulting AL, Kämpe O 2007 Pituitary autoantibodies in autoimmune polyendocrine syndrome type 1. *Proc Natl Acad Sci USA* 104:949–954
38. Niedernhofer LJ, Garinis GA, Raams A, et al 2006 A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis. *Nature* 444:1038–1043
39. Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM 2006 The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. *J Clin Endocrinol Metab* 91:43–47
40. Tanriverdi F, Senyurek H, Unluhizarci K, Selcuklu A, Casanueva FF, Keleştimur F 2006 High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. *J Clin Endocrinol Metab* 91:2105–2111
41. Ho KK 2006 Endocrinology: the next 60 years. *J Endocrinol* 190:3–6
42. Perls TT, Reisman NR, Olshansky SJ 2005 Provision or distribution of growth hormone for “antiaging”: clinical and legal issues. *JAMA* 294:2086–2090