

Providing state-of-the-art treatment and world-class care

California Center for Pituitary Disorders at UCSF

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The California Center for Pituitary Disorders at the University of California, San Francisco (UCSF) is a multidisciplinary center designed to provide comprehensive care to all patients with newly diagnosed and pre-existing pituitary disorders. The Center was formed in May 2007, and is built upon decades of recognized excellence in neurosurgical and neuroendocrine care and research at UCSF.

In 1922, Howard Naffziger, the first Chair of Neurological Surgery at UCSF, performed one of the first surgeries for acromegaly. In 1933, he conducted a craniotomy to achieve partial hypophysectomy for what we now recognize as Cushing's disease. By 1962, the pituitary surgery case load was approximately 15 cases annually. In 1965, cryohypophysectomy was proposed as a treatment for acromegaly, and by 1970, about 70 procedures had been performed for acromegaly and 15 for treatment of malignancy and diabetic retinopathy. The landscape of pituitary surgery was changed forever, however,

with the advent of the transsphenoidal microsurgical approach in the early 1970s. Charles Wilson, a visionary in the field of pituitary surgery, is recognized as one of the few neurosurgeons who perfected this technique, which permits tumor resection and preservation of pituitary function. By the time of his retirement, Dr. Wilson had performed well over 3000 of these procedures for patients with pituitary disorders.

Today, the tradition of excellence in pituitary surgery is being carried on by the Surgical Director of the California Center for Pituitary Disorders at UCSF, Sandeep Kunwar MD. In 2000, he improved transsphenoidal surgery by developing the direct endonasal approach. This minimally invasive procedure provides the excellent results that referring physicians come to expect from UCSF and greatly reduces surgical complications. Times have certainly changed since 1962. The annual number of surgical procedures performed for pituitary disease at UCSF has increased by more than ten-fold and we now treat over 150 patients annually.

In January 2008, we were joined by rising neurosurgeon Manish Aghi MD, PhD, who was recently an instructor at Massachusetts General Hospital and Harvard Medical School and has a special interest in endoscopic-based neurosurgery. Lewis Blevins Jr. MD, Medical Director of the California Center for Pituitary Disorders at UCSF, has 17 years experience in the evaluation and management of patients with various pituitary disorders, including residual and recurrent hormonally active pituitary tumors, hypopituitarism, and diabetes insipidus. Under the leadership of Drs. Blevins and Kunwar, our program is becoming one of the busiest and most successful pituitary centers in the world. Through this newsletter we hope to continue advancing knowledge of pituitary disease by providing updates on notable developments in our field and at our Center.

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Focus on Pituitary Surgery

In the last decade, several major advances have enhanced the safety, efficacy, and tolerability of surgery for pituitary adenomas. In almost all cases, small and large tumors can be removed using a transsphenoidal approach, eliminating the need to perform a craniotomy.

In 1910, Harvey Cushing performed the first successful removal of a pituitary tumor using a sublabial (incision under the lip) transsphenoidal approach. Neurosurgeons Norman Dott, Gerard Guiot, and Jules Hardy

continued to advance the operation adding the use of a speculum, fluoroscopy, and the operating microscope. Charles Wilson further improved the surgery, perfecting complete tumor removal with preservation, and sometimes improvement, of normal gland function. In many cases, curative removal of the tumor is performed even for larger tumors.

Since 2000, the endonasal transsphenoidal approach has been developed, which eliminates the need for any sublabial or intranasal incision, as well as post-

operative nasal packing, and improves overall recovery. This less-invasive approach improves complications and allows complete tumor removal of small and large tumors in most cases. Sandeep Kunwar MD has performed over 1000 endonasal transsphenoidal operations at UCSF, which continues to lead in innovation to improve the lives of patients with pituitary pathology. The use of this operation is now being expanded to other brain tumors, including meningiomas, optic nerve tumors, hypothalamic masses, and clival lesions.

What's New in Pituitary Disorders

- **Lanreotide depot, an injectable somatostatin analogue, has been approved by the US Food and Drug Administration for the management of acromegaly. The formulation provides opportunity for convenient monthly, self-administered injections. Insulin-like growth factor I (IGF-I) normalization can be expected in nearly one-half of treated patients. Physicians at the California Center for Pituitary Disorders have experience using this drug and other pharmacologic agents for the medical management of residual and recurrent acromegaly.**

- **Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency have been revised and published (Ho, KK. *Eur J Endocrinol* 2007;157:695-700). Workshop participants recommend that testing for growth hormone deficiency should include those patients with a history of traumatic brain injury, in addition to those with classic forms of hypothalamic and pituitary disease and others at risk for hypopituitarism. They consider the insulin tolerance**

test; a combination of growth hormone releasing hormone and arginine; and glucagon to be valid stimulation tests in adult patients. They recognize that a normal level of IGF-I does not exclude a potential diagnosis of growth hormone deficiency and that a low level of IGF-I in the setting of multiple pituitary hormone deficiencies is a reliable diagnostic indicator of growth hormone deficiency. They also recommend evaluating patients with childhood growth hormone deficiency as they transition to adulthood. They proposed monitoring IGF-I levels, body composition, and quality-of-life to assess the efficacy of ongoing therapy.

- **Dopamine agonist drugs employed in high doses have been implicated in the development of valvular heart disease. Clinically important valvular regurgitation was seen in 28.6% of patients taking high doses of cabergoline (Zanettini R, et al. *N Engl J Med* 2007;356:39-46). Similar observations were not apparent in control subjects (5%) or in patients taking non-ergot derived dopamine agonists.**

It remains to be determined whether high doses given to patients taking cabergoline for pituitary disorders will result in cardiac valvular abnormalities. A study evaluating nearly 50 patients treated with dopamine agonist drugs for pituitary disorders at Vanderbilt University detected asymptomatic and probably clinically insignificant cardiac valvular abnormalities in 7% of patients (data not yet published). Until the issue is further resolved, we recommend echocardiography on an annual basis in patients treated with cabergoline. Detection of cardiac valvular abnormalities during treatment should prompt discussion with the patient regarding the findings, pathophysiology of disease, and perhaps alterations in therapy.



Recent Publications

from the California Center for Pituitary Disorders at UCSF

Devin JK, Blevins LS Jr, Verity DK, Chen Q, Bloodworth JR Jr, Covington J, Vaughan DE. Markedly impaired fibrinolytic balance contributes to cardiovascular risk in adults with growth hormone deficiency. *J Clin Endocrinol Metab* 2007;92(9):3633-3639.

Devin JK, Vaughan DE, Blevins LS Jr, Chen Q, Covington J, Verity DK, Young PP. Low-dose growth hormone administration mobilizes endothelial progenitor cells in healthy adults [published online ahead of print December 29, 2007]. *Growth Horm IGF Res*. doi:10.1016/j.ghir.2007.11.001.

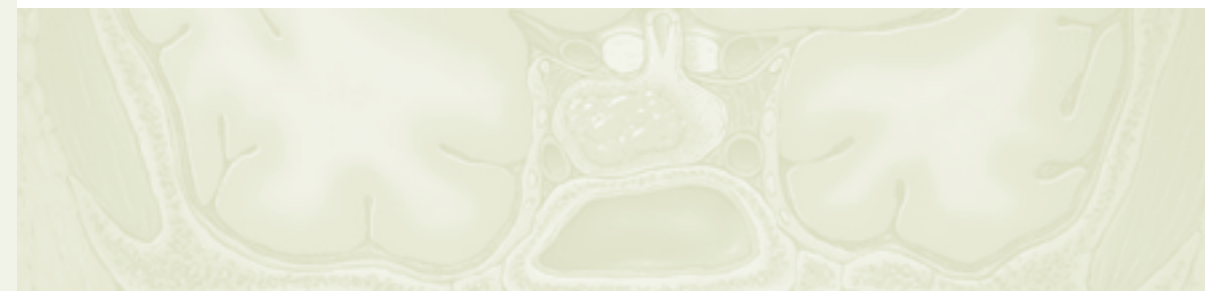
Sanai N, Quiñones-Hinojosa A, Narvid J, Kunwar S. Safety and efficacy of the direct endonasal transsphenoidal approach for challenging sellar tumors [published online ahead of print December 19, 2007]. *J Neurooncol*. doi: 10.1007/s11060-007-9512-2.

Comment: Epidemiologic studies have shown that mortality in patients with hypopituitarism is nearly double that of an age-matched, normal population. In addition, the survival rate of patients with genetic disorders causing isolated growth hormone deficiency is markedly lower than that of unaffected relatives.

These observations have led to speculation that growth hormone deficiency itself may play a major role in the increased mortality of patients with hypopituitarism. Studies have demonstrated that adults with deficient levels of growth hormone have a greater prevalence of hypercholesterolemia, an abnormal LDL to HDL ratio, and a thickened carotid intima. The publications listed at left by Devin et al. illustrate that adults with growth hormone deficiency demonstrate altera-

tions in plasma fibrinolytic balance, including elevated levels of plasminogen activator inhibitor-1 antigen and decreased activity of tissue plasminogen activator. We speculate that these changes may contribute to the increased cardiovascular morbidity within this population. Based on observations in healthy adults, growth hormone administration in the setting of growth hormone deficiency may have a role in maintaining vascular integrity.

Further studies are necessary to define the pathophysiologic mechanisms of cardiovascular disease in patients with hypopituitarism and the precise benefits afforded by growth hormone replacement in adults with growth hormone deficiency.





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Have a question about one of your patients? Write directly to Lewis Blevins Jr. MD at blevinsl@neurosurg.ucsf.edu or to Sandeep Kunwar MD at kunwars@neurosurg.ucsf.edu

Center physicians are available for either consultation or assumption of care regarding diagnostic and management strategies for patients with pituitary tumors and other disorders of the hypothalamic-pituitary unit. We are committed to excellence in patient care and the education and involvement of referring physicians in the care of their patients referred to our center.

To schedule an appointment call 1866-559-5543 or (415) 353-2948

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