Endocrine Journal 1996, **43** (3), 307–312

Effects of Surgery on Testosterone Secretion in Male Patients with Pituitary Adenomas

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Abstract. The purpose of this study was to assess the effect of surgery on gonadal function in 42 male patients with pituitary adenomas. Gonadal functions were evaluated by measuring total serum testosterone concentrations pre- and postoperatively. The subjects of the study were 20 patients with GH secreting adenoma, 7 patients with prolactinoma and 15 patients with nonfunctioning (NF) adenoma. Their ages ranged from 18 to 60 years (mean ± SEM, 41 ± 1.9). The serum testosterone concentration was low at less than 300 ng/dl preoperatively in 14 of 20 patients (70%) with GH producing adenoma, 6 of 7 patients (86%) with prolactinoma, and 7 of 15 patients (47%) with NF adenoma. Postoperatively, the total serum testosterone concentration was normalized in 9 of 14 patients (64%) with GH producing adenoma, one of 6 patients (17%) with prolactinoma, and 5 of 7 patients (71%) with NF adenoma. The normalization of serum GH and prolactin concentrations is indispensable for the restoration of gonadal function. It is very important to preserve the normal preoperative gonadotropin secretion by means of gentle surgery.

Key words: Pituitary adenoma, Male, Gonadal function, Testosterone, Surgery

(*Endocrine Journal* **43**: 307–312, 1996)

SINCE pituitary adenomas are benign, postoperative deterioration of the pituitary function should be prevented, if possible. The preservation or restoration of anterior pituitary function, including gonadal function, is an important goal in these patients. Most male patients with pituitary adenomas have hypogonadism [1–10]. Hypogonadism is often detected in menstruating women because it can cause irregular menses, but it is difficult to recognize in men. Measurement of serum testosterone is useful for evaluating male gonadal function. We determined the pre- and postoperative total serum testosterone concentrations and evaluated the gonadal function of male patients with pituitary adenomas.

Received: July 13, 1995
Accepted: February 13, 1996
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Materials and Methods

Patients

Eighty adult men with pituitary adenomas were admitted to Hiroshima University Hospital between 1987 and 1994. The pre- and postoperative total serum testosterone values were measured in 42 of these patients. Twenty out of 42 patients had GH producing adenoma, 7 had prolactinoma and 15 had clinical non-functioning (NF) adenoma. Their ages ranged from 18 to 60 years (mean ± SEM, 41 ± 1.9).

Transsphenoidal adenomectomy was performed in all patients with GH producing adenoma, 5 patients with prolactinoma, and 11 patients with NF adenoma. Transcranial adenomectomy was performed in 2 patients with prolactinoma, and 3 patients with NF adenoma. Both transsphenoidal and transcranial adenomectomy were performed

in one patient with NF adenoma. To protect the normal pituitary gland and the hypothalamus from direct injury or impairment of blood circulation, we used the following surgical techniques: 1) soft and careful curettage, 2) not pulling down the suprasellar portion of the tumor capsule but rather waiting for it to fall into the sella by itself, 3) not peeling the normal pituitary gland from the dura mater.

Study protocol

Gonadal function was evaluated by using a LHRH loading test (LHRH 0.1 mg/body: iv) immediately before surgery and more than 3 months after surgery. Serum PRL and total testosterone values were measured before and more than 3 months after surgery in all patients. The serum GH concentration was measured before and more than 3 months after surgery in patients with GH producing adenoma.

The study protocol was approved by the Hospital Institutional Review Board.

Hormone measurements

Serum GH, PRL, LH, FSH and testosterone concentrations were measured with commercially available RIA or IRMA kits [Sensitive GH kit (Daiichi Radioisotope Lab., Tokyo, Japan); PROLACTIN DAIICHI II kit or SPAC-S PROLACTIN kit (Daiichi Radioisotope Lab., Tokyo, Japan); LH DAIICHI II kit or SPAC-S LH kit (Daiichi Radioisotope Lab., Tokyo, Japan); FSH DAIICHI II kit or SPAC-S FSH kit (Daiichi Radioisotope Lab., Tokyo, Japan); and TESTOSTERONE EIKEN kit (Eiken Chemical, Tokyo, Japan)]. The coefficient of variation of each assay was less than 10%. The values previously measured with the RIA kits were converted into those measured with the IRMA kits [11, 12]. Impaired LH and FSH secretion was defined as a low basal value and/or low response to the LHRH test. The revised criteria of the normal basal value and normal response to stimuli used in this study are shown in Table 1 [13, 14].

Statistical analysis

The results are expressed as the mean ± SEM. The Mann-Whitney U test or Wilcoxon signed rank test was used when appropriate. A P value <0.05 was considered significant.

Table 1. Normal serum hormone concentrations

Hormone		Base value	Peak value
GH	(ng/ml)	<5	
PRL	(ng/ml)	1.5–9.7	
LH	(mIU/ml)	1.8–5.2	>18 ┐ LHRH test
FSH	(mIU/ml)	2.9–8.2	>5 ┘ (0.1 mg/body)
Testosterone	(ng/dl)	>300	

Results

GH producing adenoma

The clinical data for all patients with GH producing adenoma are summarized in Table 2. In 14 out of 20 patients (70%), the serum testosterone concentration was low (less than 300 ng/dl) before the surgery. Pre-operatively, the serum GH concentration was greater than 20 ng/ml in 14 patients and the serum testosterone concentration was low in 12 of these patients. On the other hand, the serum GH concentration was less than 20 ng/ml in 6 patients, of whom two had a low serum testosterone concentration. There was a reverse correlation between serum GH and total serum testosterone concentrations (Fig. 1). Seven patients had hyperprolactinemia. The preoperative serum testosterone concentration in patients with normoprolactinemia was 349 ± 64.6 ng/dl and that in patients with hyperprolactinemia was 202 ± 36.1 ng/dl, which were not significantly different (P=0.23). Fifteen patients had a normal LH response to the administration of LHRH. Ten of these patients (67%) had a low serum testosterone concentration even though they had normal LH secretion. The serum GH concentration was normalized in 14 patients following surgery, while the total serum testosterone concentration was normalized in 11 patients (79%) postoperatively. Ten of these 11 patients had normal LH secretion pre-operatively. Six patients, who had normal serum testosterone concentrations pre-operatively, also had a normal serum testosterone concentration postoperatively. Patients who had normal gonadotropin secretion before the surgery regained their gonadal function with a decrease in the serum GH concentration.

Table 2. Summary of the patients with GH secreting adenomas (n=20)

Case No.	Age	Tumor size	Surgery	GH (ng/ml) pre	GH (ng/ml) post	PRL (ng/ml) pre	PRL (ng/ml) post	LH (mIU/ml) pre (B/P)	LH (mIU/ml) post (B/P)	FSH (mIU/ml) pre (B/P)	FSH (mIU/ml) post (B/P)	Testosterone (ng/dl) pre	Testosterone (ng/dl) post
1	45	14	TS	100	0.1	3.7	1.3	1.1/11	2.2/6.8	3.6/10	2.1/3.3	122	351
2	41	19	TS	93	5.7	22	2.0	1.8/19	1.8/6.5	2.9/8.2	5.3/9.9	80	380
3	24	18	TS	88	6.5	9.1	4.2	4.6/27	6.2/17	8.5/17	8.5/16	124	237
4	49	16	TS	86	6.5	102	18	4.0/22	5.0/24	3.8/8.0	5.5/10	120	400
5	31	39	TS	80	1.6	23	8.2	1.3/2.3	1.8/4.5	1.4/2.8	1.8/3.6	118	80
6	18	20	TS	76	10	1.6	1.0	0.5/0.7	0.5/0.5	0.2/4.1	0.5/2.9	70	120
7	35	22	TS	40	0.4	1.0	3.2	2.2/20	2.6/40	6.2/16	7.4/20	240	550
8	50	14	TS	37	0.1	14	2.0	3.7/26	9.0/38	8.0/28	12/18	240	890
9	41	27	TS	31	0.8	14	9.1	4.3/32	4.5/40	12/22	4.6/11	250	478
10	49	10	TS	27	2.2	28	1.7	2.1/19	2.1/19	13/29	9.4/20	270	486
11	46	12	TS	26	0.3	8.2	1.0	2.7/11	1.0/4.8	6.8/11	3.8/4.9	207	393
12	18	14	TS	24	14	23	12	1.6/10	2.1/12	4.7/7.9	3.9/6.6	335	517
13	39	15	TS	23	4.7	3.3	5.0	3.4/30	2.6/28	6.5/20	5.2/12	190	549
14	25	10	TS	22	2.3	4.4	2.8	6.6/28	3.2/29	7.5/14	4.8/8.5	440	757
15	43	15	TS	19	0.9	3.9	2.1	4.2/26	3.5/18	13/25	12/15	270	470
16	24	5	TS	14	5.2	5.5	3.9	2.3/19	2.3/20	4.3/4.8	2.6/5.8	677	659
17	51	8	TS	12	2.1	9.3	2.0	7.2/29	4.9/22	12/19	13/16	700	670
18	53	8	TS	11	0.8	4.4	2.1	1.6/24	3.5/19	4.3/8.0	7.0/11	570	640
19	47	13	TS	9.7	2.4	6.6	3.9	4.9/27	4.9/26	8.0/18	6.6/11	250	480
20	57	10	TS	6.1	0.9	3.1	2.4	5.7/30	2.6/22	10/22	7.8/12	680	1050

TS, transsphenoidal surgery; TC, transcranial surgery; pre, preoperation; post, postoperation; B/P, Base value/Peak value.

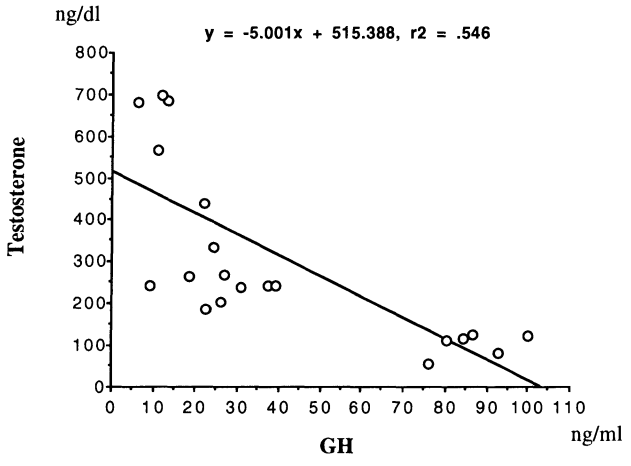

Fig. 1. The correlation between the preoperative serum GH concentration and serum testosterone concentration in 20 patients with GH producing adenoma. A reverse correlation was observed. (r= −0.737)

Prolactinoma

The clinical data for all patients with prolactinoma are summarized in Table 3. The serum testosterone concentration was low (less than 300 ng/dl) in 6 patients pre-operatively. Four of these patients had impaired LH secretion pre-operatively. The total serum testosterone concentration was normalized in only 1 of these patients (17%) following surgery. This patient had normal LH and FSH secretion both pre- and postoperatively. LH secretion was restored in one patient (case 21) after surgery, but his serum testosterone concentration did not increase.

NF adenoma

The clinical data for all patients with NF adenoma are summarized in Table 4. The preoperative total serum testosterone concentration was subnormal in 7 patients (47%) with NF adenoma. Four of these had mild hyperprolactinemia (less than 50 ng/ml) pre-operatively. Eight patients (53%) had impaired LH secretion pre-operatively. The total serum testosterone concentration was especially low in patients with hyperprolactinemia and a disorder of gonadotropin secretion. The total serum testosterone concentration was normalized in 5 of 7 patients (71%) postoperatively. The serum PRL concentration returned to normal in all patients. The pre-operative serum testosterone concentration was normal in 8 patients and it remained normal

Table 3. Summary of the patients with prolactinomas (n=7)

Case No.	Age	Tumor size	Surgery	PRL (ng/ml) pre	PRL (ng/ml) post	LH (mIU/ml) pre (B/P)	LH (mIU/ml) post (B/P)	FSH (mIU/ml) pre (B/P)	FSH (mIU/ml) post (B/P)	Testosterone (ng/dl) pre	Testosterone (ng/dl) post
21	56	41	TS	5990	56	2.3/5.3	3.0/18	4.3/5.7	6.5/7.3	110	140
22	36	23	TS	1200	239	2.1/14	2.1/8.2	2.6/5.1	2.9/4.4	155	244
23	42	24	TS	1100	358	0.6/6.0	0.5/5.5	2.8/7.7	1.6/2.6	49	184
24	33	8	TS	198	2.0	1.8/30	2.3/31	2.9/5.2	3.6/5.6	260	480
25	32	30	TC	156	29	4.3/33	4.5/28	4.6/8.8	4.5/6.8	350	480
26	18	45	TC	80	50	5.0/32	1.5/16	4.6/7.7	2.3/4.7	250	50
27	32	9	TS	40	15	1.3/3.4	3.5/9.7	1.7/4.1	2.5/4.8	30	40

TS, transsphenoidal surgery; TC, transcranial surgery; pre, preoperation; post, postoperation; B/P, Base value/Peak value.

Table 4. Summary of the patients with non-functioning adenomas (n=15)

Case No.	Age	Tumor size	Surgery	PRL (ng/ml) pre	PRL (ng/ml) post	LH (mIU/ml) pre (B/P)	LH (mIU/ml) post (B/P)	FSH (mIU/ml) pre (B/P)	FSH (mIU/ml) post (B/P)	Testosterone (ng/dl) pre	Testosterone (ng/dl) post
28	49	14	TS	6.0	2.6	0.8/6.1	3.3/13	2.7/5.1	3.4/3.5	390	260
29	22	19	TS	13	17	7.0/26	4.5/41	10/25	8.5/16	658	734
30	59	20	TC	1.3	3.0	1.8/16	3.6/18	2.4/4.6	4.4/4.6	25	369
31	44	21	TS	15	3.9	1.0/2.7	2.3/5.5	3.4/4.9	7.6/10	50	570
32	56	21	TS	22	5.0	2.1/13	4.9/21	5.4/9.7	8.1/13	110	679
33	39	22	TS	5.0	3.4	3.9/18	3.9/23	4.9/8.2	3.8/7.7	320	440
34	57	23	TS	4.4	2.6	1.8/3.8	2.2/5.6	6.7/8.1	6.8/9.1	232	578
35	41	28	TS	5.5	6.7	2.8/13	3.0/18	6.3/9.8	2.8/4.7	398	620
36	39	28	TS	13	6.6	2.1/7.2	4.5/20	3.2/7.1	5.6/8.3	100	448
37	57	32	TS	39	12	1.8/5.5	1.2/3.6	2.5/5.3	1.1/3.3	242	22
38	39	33	TS	12	2.3	2.8/18	1.9/5.8	5.1/7.5	4.5/4.9	500	348
39	60	35	TC	2.6	2.5	3.2/18	3.9/19	9.2/16	8.2/13	344	453
40	31	49	TC	7.7	3.6	1.4/4.9	1.6/6.9	3.9/4.7	4.3/4.6	360	350
41	40	50	TS, TC	3.1	1.0	4.8/29	1.3/6.3	4.8/8.5	1.8/3.1	677	87
42	50	57	TS	8.2	9.9	3.6/18	2.8/11	6.2/7.3	3.4/3.4	50	30

TS, transsphenoidal surgery; TC, transcranial surgery; pre, preoperation; post, postoperation; B/P, Base value/Peak value.

after surgery in 6. In patients with a tumor over 50 mm in size, the serum testosterone concentration did not increase following surgery, in fact in some patients with a tumor over 40 mm in size, the total serum testosterone concentration even decreased following surgery.

Discussion

The aim of this study was to clarify the percentage of male patients who recover their gonadal function following surgery and to determine the factors contributing to recovery.

Some authors have reported the effects of surgery or bromocriptine therapy in male patients with GH producing adenoma or prolactinoma [1–5]. Other authors have reported the effect of surgery for NF adenoma on anterior pituitary function, but they did not discuss male gonadal function in detail [6–9]. Ober *et al.* [10] have reported a patient who had restoration of his gonadal function postoperatively. Our study is the first compilation of gonadal function in male patients with NF adenomas.

Gonadal dysfunction is caused in male patients by hyperprolactinemia or a dysfunction of gonadotropin secretion, which is similar to that in females. In male patients, however, a prolactinoma tends to be detected after it causes visual deterioration, and usually is larger than in females. This may be the reason why male patients with prolactinoma have poor recovery of their gonadal function.

Many authors have suggested that hyperprolactinemia suppresses the secretion of gonadotropin via the hypothalamus [2–4, 15, 16]. On the other hand, Saitoh *et al.* [5] suggested that hyperprolactinemia suppresses testicular function.

It is thought that the LH burst amplitude is one of the most important factors in the total serum testosterone concentration [17]. An LHRH administration test is not useful for detecting hypothalamic dysfunction. Two patients (cases 33 and 39), in which serum LH responded normally to the LHRH test, had a low testosterone concentration before surgery. Their serum testosterone concentrations increased postoperatively. In these types of cases, hypothalamic dysfunction may be one of the factors causing gonadal dysfunction.

Increased serum GH concentrations decrease the total serum testosterone concentration in acromegalics. Hyperprolactinemia may contribute to the decreased serum testosterone concentration to some degree, but it is less important than GH in acromegalics. As for the mechanism of the negative correlation between the total serum testosterone and GH concentrations, several theories, such as the following have been proposed: a change in androgen metabolism [1, 18], gonadotropin suppression by increased somatostatin [19] or a decrease in the serum concentration of sex hormone binding globulin (SHBG) [20–23]. The SHBG theory raises the question of whether the free serum testosterone concentration is normal or not. No one has simultaneously measured total and free serum testosterone concentrations in patients with acromegaly. Since approximately 70% of serum testosterone is not bound to SHBG but rather to albumin or other proteins, a decrease in serum SHBG cannot be the sole cause of hypogonadism in those with acromegaly. The cause of hypogonadism in male acromegaly patients needs to be explored further.

In acromegalic patients, if there exists normal gonadotropin secretion prior to surgery, gonadal function can be restored with a decrease in the serum GH concentration. In male patients with prolactinomas, whose with a tumor over 20 mm in size do not regain gonadal function because of hyperprolactinemia.

Recently many studies, including immunochemicytochemistry, cell culture, Northern blot analysis and reverse hemolytic plaque assay, have suggested that many clinically non-functioning pituitary adenomas are potentially capable of hormone production [24–28]. But it is the compression of the normal pituitary gland by the tumor which brings about the endocrinological symptoms seen in patients with clinically nonfunctioning adenomas. We shall therefore discuss these tumors together. Patients with NF adenomas, who have a tumor under 40 mm in size or who have hyperprolactinemia preoperatively often get at least a partial restoration of gonadal function. In these patients, the normal pituitary gland is not destroyed and its ability to secrete gonadotropin is regained following decompression. In NF adenomas, hyperprolactinemia is caused by impairment of the prolactin inhibiting factor (PIF), and the serum prolactin concentration is normalized following surgery. In patients with a tumor over 40 mm in size, the serum testosterone concentration decreases following surgery. This fact reflects the difficulty in preserving or restoring anterior pituitary function in patients with large tumors.

Because pituitary adenomas are usually benign, the preservation and restoration of anterior pituitary function is an important goal of resection. In considering a patient's quality of life, the restoration of gonadal function is as important as the restoration of the ACTH or TSH axis. Recently, gonadotropin or sex steroid replacement therapy has been tried [29, 30]. This may involve some risks [31]. Gonadal function is said to be more difficult to restore than either the ACTH or TSH axis. We evaluated male gonadal function by measuring the serum testosterone concentration and found that surgical tumor resection brought restoration of gonadal function more often than anticipated.

References

1. Roelfsema F, Moolenaar AJ , Frolich M (1984) The influence of bromocriptine and transsphenoidal surgery on urinary androgen metabolite excretion in acromegaly. *Acta Endocrinol* 107: 302–311.
2. Carter JN, Tyson JE, Tolis G, Vliet SV, Faiman C, Friesen HG (1978) Prolactin-secreting tumors and hypogonadism in 22 men. *N Eng J Med* 299: 847–852.
3. Prescott RWG, Johnston DG, Taylor PK, Crombie

A, Hall K, Mcgregor A, Hall R (1982) Hyperprolactinaemia in men-response to bromocriptine therapy. *Lancet* 1: 245–248.
4. Murray FT, Cameron DF, Ketchum C (1984) Return of gonadal function in men with prolactin-secreting pituitary tumors. *J Clin Endocrinol Metab* 59: 79–85.
5. Saitoh Y, Arita T, Onishi T, Koga M, Mori S, Mogami H (1990) Hypogonadism of male prolactinomas: Relation to pulsatile secretion of LH. *Andrologia* 22: 519–524.
6. McLanahan CS, Christy JH, Tindall GT (1978) Anterior pituitary function before and after transsphenoidal microsurgical resection of pituitary tumors. *Neurosurgery* 3: 142–145.
7. Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986) Long-term results in transsphenoidal removal of nonfunctioning pituitary adenomas. *J Neurosurgery* 64: 713–719.
8. Arafah B, Brodkey J, Manni A, Velasco M, Kaufman B, Pearson H (1982) Recovery of pituitary function following surgical removal of large nonfunctioning pituitary adenomas. *Clin Endocrinol* 17: 213–222.
9. Arafah B (1986) Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab* 62: 1173–1179.
10. Ober KP, Kelly DL (1988) Return of gonadal function with resection of nonfunctioning pituitary adenoma. *Neurosurgery* 22: 386–387.
11. Aono T (1989) Multicentric basic and clinical studies on immunoradiometric assay (SPAC-S prolactin kit) for measurement of serum prolactin using WHO standard sample. *Hormone to Rinsho* 37: 441–455 (In Japanese).
12. Irahara M, Yasui T, K Higashi, Aono T (1988) Fundamental studies on immunoradiometric assays (SPAC-S LH, SPAC-S FSH) for measurement of serum LH and FSH using the pituitary gonadotropin standards. *Hormone to Rinsho* 36: 1223–1230 (In Japanese).
13. Uozumi T, Mori S, Watanabe M, Takimoto N, Mogami H, Hashimoto T, Onishi T, Miyai K, Kumahara Y (1976) Endocrinological evaluation of sellar and suprasellar tumor cases—The second report—on postoperative pituitary function. *No Shinkei Geka* 4: 73-78 (In Japanese).
14. Furuyama S, Mayes DM, Nugent CA (1970) A radioimmunoassay for plasma testosterone. *Steroids (United States)* 16: 415–428.
15. Nakano R, Yagi S, Nishiki T (1988) Pituitary and testicular response to luteinizing hormone releasing hormone in normal and sulpiride-induced hyperprolactinaemic men. *Exp Clin Endocrinol* 91: 191–196.
16. Heshmati H M, Turpin G, Nahoul K, Carayon A, Salmon D, Gueguen A, Gennes JL (1985) Testicular response to human chorionic gonadotrophin in chronic hyperprolactinaemia. *Acta Endocrinol* 108: 565–569.
17. Velrhuis JD, Urban RJ, Lizarralde G, Johnson ML, Iranmnesh A (1992) Attenuation of luteinizing hormone secretory burst amplitude as a proximate basis for the hypoandrogenism of healthy aging in man. *J Clin Endocrinol Metab* 75: 707–713.
18. Hellman I, Brandlaw HI, Zumoff B, Fukushima DK, Gallanger TF (1959) Thyroid-androgen interrelations and the hypocholesterolemic effect of androsterone. *J Clin Endocrinol Metab* 19: 936–948.
19. De Lange W, Verhoeff A, Sluiter W, Doorenbos H (1990) Hypogonadism in untreated male normoprolactinaemic acromegalics. *Neth J Med* 36: 191–195.
20. De moor P, Heyns W, Bouillon R (1972) Growth hormones and the steroid binding β globulin of human plasma. *J Steroid Biochem* 3: 593–600.
21. Zweirska-Korczala K, Ostrowska Z, Zych F, Buntner B (1991) The levels of pituitary-testicular axis hormones and SHBG in active acromegaly following bromocriptine treatment. *Endocrine Regulations* 25: 211–216.
22. Schwander J, Hauri C, Zapf J, Froesch E (1983) Synthesis and secretion of insulin-like growth factor and its binding protein by the perfused rat liver; dependence on growth hormone status. *Endocrinology* 113: 297–305.
23. Lindstedt G, Lindberg P, Hammond G, Vihko R (1985) Sex hormone binding globulin—still many questions. *Scand J Clin Lab Invest* 45: 1–6.
24. Black PM, Hsu, DW, Klibanski A, Kliman B, Jameson JL, Ridgway EC, Hedley Whyte ET, Zervas NT (1987) Hormone production in clinically nonfunctioning pituitary adenomas. *J Neurosurg* 1987; 66: 244–250.
25. Mashitar K, Adams E, Van Noorden S (1981) Secretion of LH, TSH, and PRL shown by cell culture and immunocytochemistry of human functionless pituitary adenoma. *Clin Endocrinol (Oxf)* 15: 103–112.
26. Asa SL, Gerrie BM, Singer W, Horvath E, Kovacs K, Smyth HS (1986) Gonadotropin secretion *in vitro* by human pituitary null cell adenomas and oncocytomas. *J Clin Endocrinol Metab* 62; 1011
27. Jameson JL, Klibanski A, Black PM, Zervas NT, Lindell CM, HsuDW, Ridgway EC, Habener JF (1987) Glycoprotein hormone genes are expressed in clinically nonfunctioning pituitary adenomas. *J Clin Invest* 80: 1472–1478.
28. Yamada S, Asa SL, Kovacs K, Muller P, Smyth HS (1989) Analysis of hormone secretion by clinically nonfunctioning human pituitary adenomas using the reverse hemolytic plaque assay. *J Clin Endocrinol Metab* 68: 73–80.
29. Carey PO, Howards SS, Vance ML (1988) Transdermal testosterone treatment of hypogonadal men. *J Urology* 140: 76–79.
30. McClure RD, Oses R, Ernest ML (1991) Hypogonadal impotence treated by transdermal testosterone. *Urology* 37: 224–228.
31. Farrel GC, Joshua DE, Uren RF, Baird PJ, Perkins KW, Kronenberg H (1975) Androgen-induced hepatoma. *Lancet* 1: 430.