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Acta Medica Okayama

Volume 44, *Issue* 3 1990 *Article* 6

JUNE 1990

Combined anterior pituitary function test using CRH, GRH, LH-RH, TRH and vasopressin in patients with non-functioning pituitary tumors.

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Abstract

We examined 8 normal subjects and 16 patients with non-functioning pituitary tumors with a combined anterior pituitary test to evaluate the clinical usefulness of the test. Diagnoses included 9 of chromophobe adenoma, 3 of craniopharyngioma, 2 of Rathke's cleft cyst, and 1 each of intrasellar cyst and tuberculum sella meningioma. All subjects received hypothalamic releasing hormones: 1 micrograms/kg corticotropin releasing hormone (CRH), 1 micrograms/kg growth hormone releasing hormone (GRH), 500 micrograms thyrotropin-releasing hormone (TRH), 100 micrograms luteinizing hormone releasing hormone (LH-RH), and a relatively small dose (5 mU/kg) of lysine vasopressin (LVP). In the normal subjects, the addition of LVP potentiated the secretion of adenocorticotropic hormone (ACTH) induced by CRH, but had no significant effect on the secretion of other anterior pituitary hormones. In the combined test with 5 releasing hormones, the plasma ACTH and cortisol responses were not impaired in the majority of the patients before pituitary surgery. Serum thyroid-stimulating hormone (TSH), prolactin (PRL) and follicle-stimulating hormone (FSH) responses were not impaired in 82%, 70% and 67% of the patients, respectively, while the serum LH and GH responses were impaired in 67% and 73% of the patients, respectively. Following pituitary surgery, responses of these hormones to combined testing were similarly impaired in more than 75% of the patients. These results indicate that plasma ACTH, cortisol and serum TSH responses are fairly good before pituitary surgery but are impaired significantly after surgery. No subjects experienced any serious adverse effects related to the testing. These results suggest that combined testing with hypothalamic hormones is a convenient and useful method for evaluating pituitary function.

KEYWORDS: anterior pituitary function test, pituitary tumors, corticotropin releasing hormone, growth hormone releasing hormone, luteinzing hormone releasing hormone, thyrotropin releasing hormone

*PMID: 2200236 [PubMed - indexed for MEDLINE]
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Acta Med Okayama 44 (3) 141-147 (1990)

Combined Anterior Pituitary Function Test Using CRH,GRH, LH-RH, TRH and Vasopressin in Patients with Non-Functioning Pituitary Tumors

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We examined 8 normal subjects and 16 patients with non-functioning pituitary tumors with a combined anterior pituitary test to evaluate the clinical usefulness of the test. Diagnoses included 9 of chromophobe adenoma, 3 of craniopharyngioma, 2 of Rathke's cleft cyst, and 1 each of intrasellar cyst and tuberculum sella meningioma. All subjects received hypothalamic releasing hormones: 1 μg/kg corticotropin releasing hormone (CRH), 1 μg/kg growth hormone releasing hormone (GRH), 500 μg thyrotropin-releasing hormone (TRH), 100 μg luteinizing hormone releasing hormone (LH-RH), and a relatively small dose (5 mU/kg) of lysine vasopressin (LVP). In the normal subjects, the addition of LVP potentiated the secretion of adenocorticotropic hormone (ACTH) induced by CRH, but had no significant effect on the secretion of other anterior pituitary hormones. In the combined test with 5 releasing hormones, the plasma ACTH and cortisol responses were not impaired in the majority of the patients before pituitary surgery. Serum thyroid-stimulating hormone (TSH), prolactin (PRL) and follicle-stimulating hormone (FSH) responses were not impaired in 82%, 70% and 67% of the patients, respectively, while the serum LH and GH responses were impaired in 67% and 73% of the patients, respectively. Following pituitary surgery, responses of these hormones to combined testing were similarly impaired in more than 75% of the patients. These results indicate that plasma ACTH, cortisol and serum TSH responses are fairly good before pituitary surgery but are impaired significantly after surgery. No subjects experienced any serious adverse effects related to the testing. These results suggest that combined testing with hypothalamic hormones is a convenient and useful method for evaluating pituitary function.

Key words : **anterior pituitary function test, pituitary tumors, corticotropin releasing hormone, growth hormone releasing hormone, luteinizing hormone releasing hormone, thyrotropin releasing hormone**

Vasopressin acts synergistically with corticotropin-releasing hormone (CRH) to release adrenocorticotropic hormone (ACTH) from corticotrophs (1-4). Therefore, the simultaneous

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Produced by The Berkeley Electronic Press, 1990

administration of CRH and vasopressin would be expected to be more effective in stimulating corticotrophin release than CRH alone. In a previous study, we reported that plasma ACTH showed a more rapid and marked response to the combined administration of CRH (1 μg/kg body weight) and a relatively small dose (5 mU/kg body weight) of lysine vasopressin (LVP) than to CRH alone, and recommended combined testing as a useful method for examining pituitary-adrenocortical reserve function (5). In this study we examined the feasibility and usefulness of a combined anterior pituitary test using the intravenous (iv) administration of CRH, LVP, growth hormone releasing hormone (GRH), luteinizing hormone releasing hormone (LH-RH) and thyrotropin-releasing hormone (TRH) in normal persons and in patients with non-functioning pituitary tumors.

Materials and Methods

Experiment 1. Three methods of combined hormone administration were evaluated in 5 normal subjects aged 28–45 years: a) the combined administration of human CRH (1 μg/kg body weight) and LVP (5 mU/kg body weight) as previously reported (CRH-LVP test, Hashimoto *et al.* 1988); b) the combined administration of GRH (1 μg/kg body weight), TRH (500 μg) and LH-RH (100 μg) (GRH, TRH and LH-RH test); c) the combined administration of CRH, LVP, GRH, TRH and LH-RH (CRH, LVP, GRH, TRH and LH-RH test). In these tests, releasing hormones were mixed with 0.9% saline shortly before injection. They were injected intravenously after a 15 min rest period. Blood samples were collected just before the injection and 15, 30, 60 and 90 min afterwards. Two ml of each 8 ml blood sample was collected into a chilled plastic tube containing EDTA for assay of ACTH and cortisol. The remainder of each sample was collected into a glass tube and centrifuged at 4°C for 10 min. Plasma and serum were then stored at −20°C. In the CRH-LVP test, plasma levels of ACTH and cortisol were measured. In the other combined tests, serum GH, LH, FSH, TSH and prolactin (PRL) were measured in addition to ACTH and cortisol. TRH and LH-RH were provided by Tanabe Pharmaceutical Company (Osaka, Japan). LVP was provided by Sandoz Ltd. (Basel, Switzerland). CRH and GRH were purchased from Peptide Institute, Inc. (Osaka, Japan) and prepared as reported previously (5).

Experiment 2. The combined administration of CRH, LVP, GRH, TRH and LH-RH was carried out in 16 patients aged 23–67 years, 8 men and 8 women, with non-functioning pituitary tumors: 9 chromophobe adenomas, 3 craniopharyngiomas, 2 Rathke's cleft cysts, 1 intrasellar cyst and 1 tuberculum sella meningioma. A total of 12 tests were performed before pituitary surgery and 9 tests were performed 3–6 weeks following pituitary surgery. Five of the 9 patients tested after surgery were receiving replacement therapy with hydrocortisone (10–20 mg/day) and desiccated thyroid extracts (30–40 mg/day). Such replacement therapy was stopped after giving the last dose on the morning preceding testing. These supplemental doses of hydrocortisone and thyroid hormone had been decided according to baseline levels of plasma cortisol and thyroid hormones. These supplemental doses did not affect pituitary hormonal response to the releasing hormones. A combined test was performed in 8 control subjects aged 27–57 years, 6 men and 2 women, including the 5 subjects who participated in experiment 1. Consent for testing was obtained from each subject.

Hormone assays. Plasma ACTH was measured using a radio-immunoassay (RIA) kit (CEA-IRE-Sorin, Gif-sur-Yvette, France). Plasma cortisol, serum LH, FSH and PRL were measured using RIA kits (Daiichi Radioisotope Laboratories, Ltd, Tokyo, Japan). Serum GH and TSH were each measured with RIA kits (Dainabot Co., Tokyo, Japan).

Statistical analysis. Statistical analysis was conducted by Student's t test.

Results

Combined testing in control subjects. Responses of plasma ACTH and cortisol to the administration of CRH-LVP were similar to those obtained with the combined administration of CRH, LVP, GRH, TRH and LH-RH (Fig. 1). The administration of GRH, TRH and LH-RH did not stimulate the secretion of ACTH or cortisol.

The administration of CRH-LVP did not

affect the peak serum levels of GH, PRL, TSH, LH and FSH evoked by the combined administration of GRH, TRH and LH-RH (Figs. 2 and 3). However, peak serum GH levels appeared earlier following the CRH, LVP, GRH, TRH and LH-RH test than in the GRH, TRH and LH-RH test. ACTH, GH and PRL reached peak levels 15 min after injection, while peak levels of cortisol, TSH, LH and FSH were seen at 30–60 min in the CRH, LVP, GRH, TRH and LH-RH test.

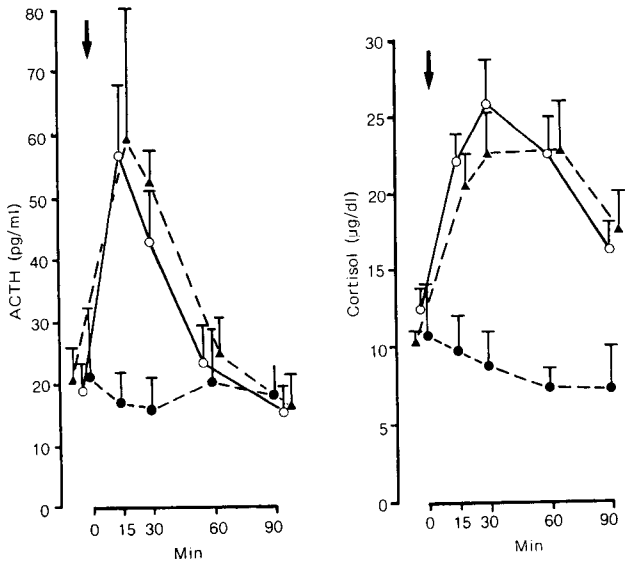

Fig. 1 Plasma ACTH and cortisol responses to three kinds of combined administrations in 5 normal subjects. 1) CRH (1 μg/kg) plus LVP (5 mU/kg) (CRH-LVP test) (▲----▲), 2) CRH, LVP, GRH (1 μg/kg), TRH (500 μg) plus LH-RH (100 μg) (CRH, LVP, GRH, TRH plus LH-RH test) (○——○), and 3) GRH, TRH plus LH-RH (GRH, TRH plus LH-RH test) (●----●). Points and vertical lines represent means+SEM.

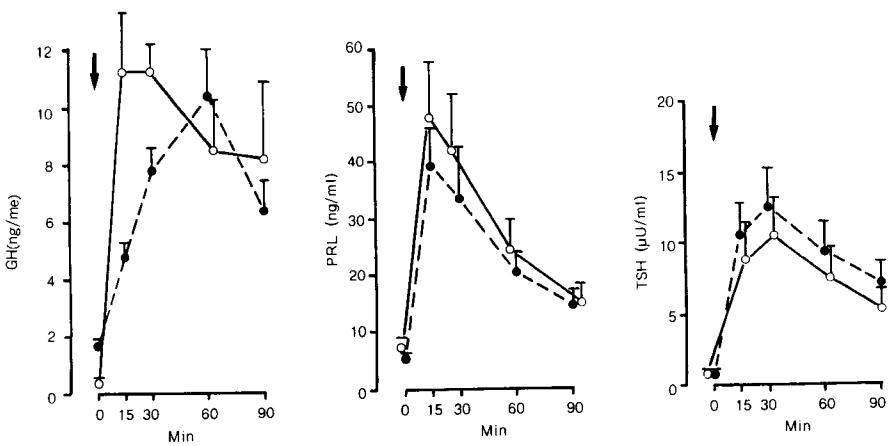

Fig. 2 Serum GH, Prolactin and TSH responses to the CRH, LVP, GRH, TRH plus LH-RH test (○——○) and the GRH, TRH plus LH-RH test (●----●). Points and vertical lines represent means+SEM.

Responses to combined testing in patients with pituitary tumors. Plasma ACTH and cortisol responses were not impaired in the majority of the patients (11/12 and 12/12, respectively) before undergoing pituitary surgery (Fig. 4), but their ACTH and cortisol responses were

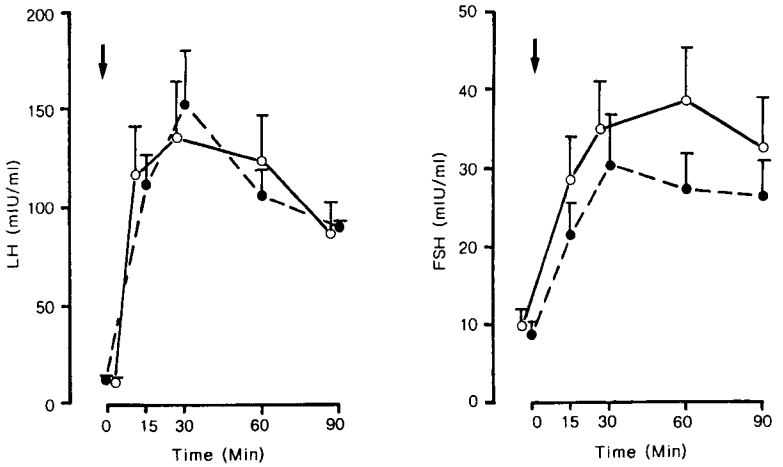

Fig. 3 Serum LH and FSH responses to the CRH, LVP, GRH, TRH and LH-RH test (○——○) and the GRH, TRH and LH-RH test (●----●). Points and vertical lines represent means+SEM.

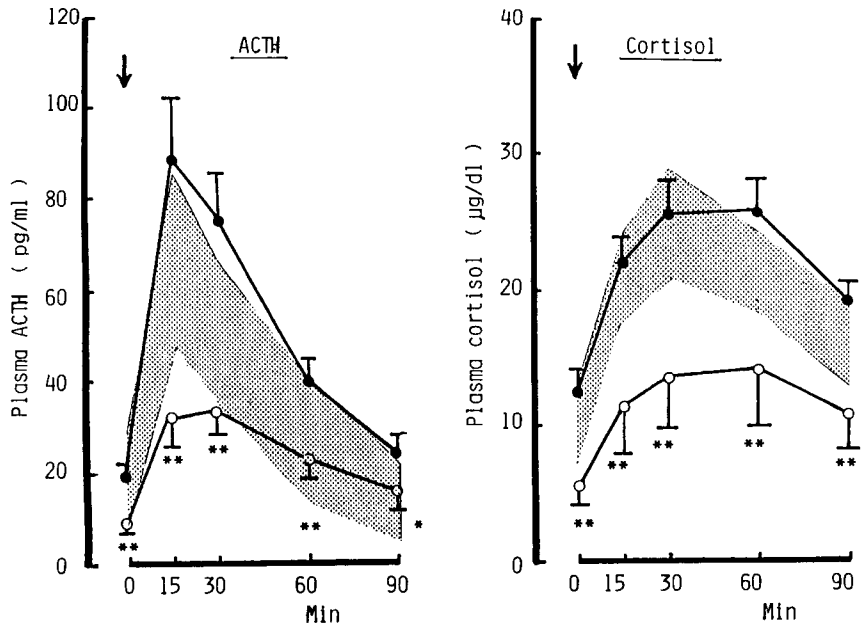

Fig. 4 Plasma ACTH and cortisol responses to the CRH, to the CRH, LVP, GRH and TRH plus LH-RH test before (●——●, n = 12) and after (○——○, n = 9) pituitary surgery in patients with non-functioning pituitary tumors. The points and vertical lines represent means+or−SEM. The shaded area shows the range of responses (mean ± SD) of 8 normal subjects. ＊＊P < 0.01, ＊P < 0.05 vs before surgery.

significantly lower after surgery. In 7 of 9 patients, both the peak serum levels and increases in plasma ACTH and cortisol were below the mean − 1 SD of the average peak level and increase in normal responses (impaired response). The shaded area shows the range of responses (mean ± SD) of 8 normal subjects. More than 70 % of the patients showed an impaired serum GH response both before (8/11) and after (7/9) surgery (Fig. 5). The majority of the patients (9/11) showed a normal serum TSH response before surgery, whereas after surgery, both the

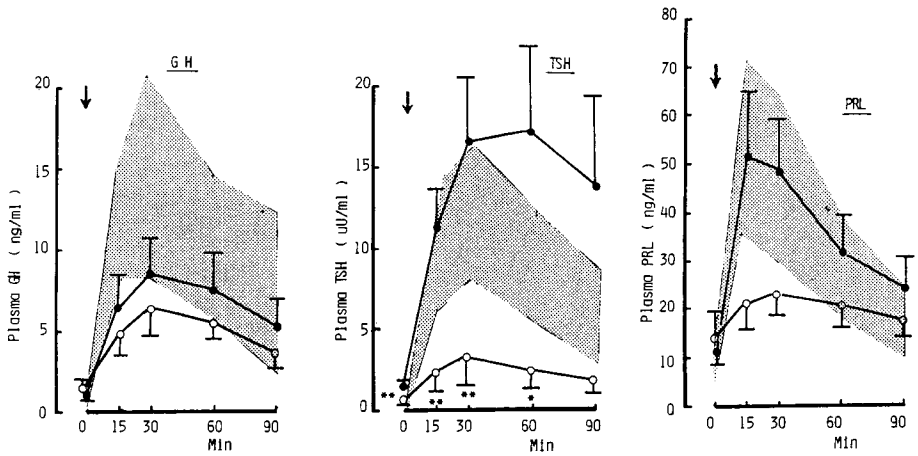

Fig. 5 Serum GH, TSH and prolactin responses to the CRH, LVP, GRH plus LH-RH test before (●—●, n = 11) and after (○—○, n = 9) pituitary surgery in patients with non-functioning pituitary tumors. Points and vertical lines represent means + or − SEM. The shaded area shows the range of responses (mean ± SD) of 8 normal subjects. ＊＊P < 0.01, ＊P < 0.05 vs before surgery.

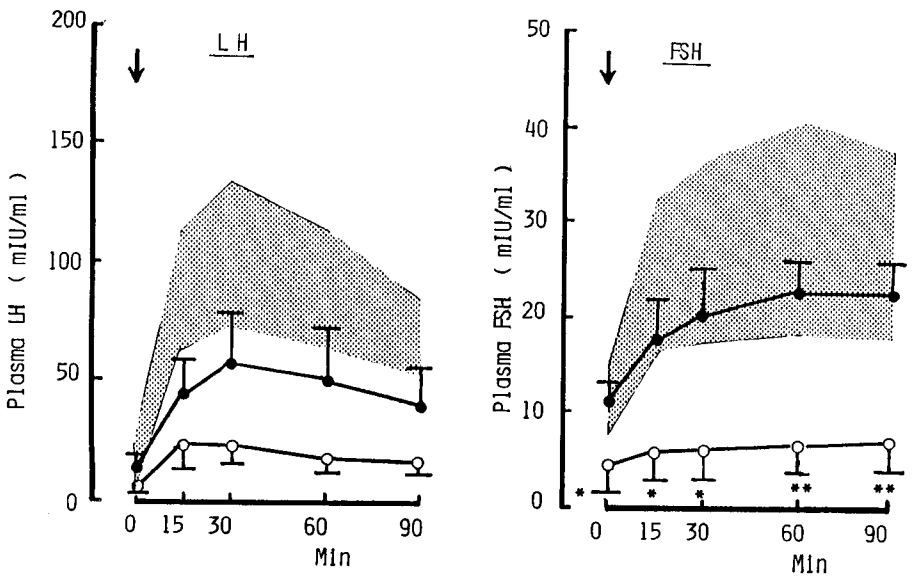

Fig. 6 Serum LH and FSH responses to the CRH, LVP, GRH, TRH plus LH-RH test before (●—●, n = 9) and after (○—○, n = 8) pituitary surgery in patients with non-functioning pituitary tumors. Points and vertical lines represent means + or − SEM. The shaded area indicates the range of responses (mean ± SD) of 8 normal subjects. ＊＊P < 0.01, ＊P < 0.05 vs before surgery.

peak level and increase in TSH were below mean − 1 SD of the normal response in 7 of the 9 patients. Seven of 10 patients showed a normal serum PRL response before surgery, whereas 6 of 8 patients showed an impaired response afterwards. Fig. 6 shows LH and FSH responses in normal subjects and patients under the age of 50. More than two-thirds of these patients showed an impaired serum LH response both before (6/9) and after (6/8) surgery. Six of 9 patients showed a normal serum FSH response before surgery, but 7 of 8 patients showed an impaired FSH response after surgery.

Adverse effects. No subjects experienced any serious adverse effects during these studies. In the CRH-LVP test, approximately 50% showed facial pallor lasting several min. Blood pressure elevation observed in 50% of the patients was both minor and transient. In the GRH, TRH and LH-RH test, more than half the subjects complained of a transient hot facial flush and mild tightness of the chest. These side effects were similar or milder in the CRH, LVP, GRH, TRH and LH-RH test. An occasional patient reported mild urinary urgency.

Discussion

We previously reported that the simultaneous administration of CRH and vasopressin was more effective than CRH alone for stimulating ACTH, as vasopressin acts synergistically with CRH to stimulate ACTH release (5). Results of this study show that the combined administration of CRH, LVP, GRH, TRH and LH-RH evokes responses of ACTH and cortisol similar to those observed with the administration of CRH-LVP, and evokes response of GH, TSH, PRL, LH and FSH similar to those observed with the administration of GRH, TRH and LH-RH. However, serum GH peaked earlier when CRH and LVP were injected simultaneously with GRH, TRH and LH-RH. LVP evoked earlier ACTH secretion when it was administered with CRH (5). Therefore, LVP may also induce earlier GH secretion when it is combined with GRH. Sheldon *et al.* (6) reported that the combined administration of four hypothalamic releasing hormones (ovine CRH, GRH TRH and LH-RH) caused no apparent inhibition or synergism with respect to the individual hormone responses compared to their individual administration. Cohen *et al.* (7) also examined the combined administration of those four releasing hormones and observed no significant differences in the response to the separate and combined tests for ACTH, cortisol, GH, LH and FSH. However, the responses of plasma TSH and PRL were significantly higher with combined testing. We did not find increased PRL and TSH responses in the combined testing. The reason for the discrepancy is difficult to explain. Cohen *et al.* assumed that the increased PRL and TSH responses might be due to a change in the metabolic clearance rates of TSH and PRL brought about by multihormone hypersecretion, or to slower degradation of the TRH when administered in combination with the other peptides.

There are several advantages to combined testing. It can save time, as the responses of all six anterior pituitary hormones can be examined within 2 h. It can be safely performed on an outpatient basis. CRH, GRH and TRH cause facial flushing, and LVP causes facial pallor. However, these side effects appear to be milder in combination testing probably because they cancel each other. In the TRH test the subjects sometimes experience facial flushing, mild tightness of the chest, urinary urgency and slight nausea. In combination testing the subjects occasionally experienced similar side effects, but they were no more severe than those seen with TRH given alone. However, combination testing may present a problem in patients with Cushing's disease (8, 9) or acromegaly (10, 11) whose pituitary hormones often show paradoxical responses to hypothalamic releasing hormones. We cannot be certain which releasing hormone induces the pituitary hormone responses during combined testing.

Kumahara *et al.* (12) tested pituitary GH, ACTH, TSH, PRL, LH and FSH reserves in patients with hypothalamic and pituitary tumors by the insulin tolerance test, metyrapone test, LH-RH test and TRH test. In their study, 95 % of the patients with craniopharyngioma and chromophobe adenoma showed an impaired GH response. LH and FSH responses were impaired in approximately 70 and 50 % of the patients, respectively, and TSH, PRL and ACTH responses were impaired in 46, 23 and 21 % of the patients, respectively. In our study, GH responses were also impaired in the majority of patients with non-functioning pituitary tumors before the pituitary operation. The LH response was impaired in more than one-half the patients, and FSH and PRL responses were impaired in one-third. TSH and ACTH responses were impaired in less than 20 %, which is fortunate since thyroid hormones and adrenocortical hormones are vital. Following pituitary surgery, responses of these pituitary hormones were impaired similarly in many patients. These results suggest that many patients require supplemental therapy with hydrocortisone and/or thyroid hormones after surgery for a nonfunctioning pituitary tumor. Combined testing can provide important informatin for choosing supplemental therapy.

In the present investigation, the responses of the anterior pituitary hormones in patients with pituitary tumors were compared with those of normal subjects aged 27–57. LH and FSH responses were compared in subjects under 50 years of age. It is well known that pituitary hormone responses to GRH, TRH or LH-RH vary with age and sex. Thus, normal ranges according to sex and age of these pituitary hormone responses to the combined testing should be established.

The findings of this study suggest that combined testing with 5 hypothalamic releasing hormones is a convenient and useful method for evaluating pituitary function and for administering supplemental hormone therapy in patients with pituitary tumors.

Acknowledgments. We thank the Department of Neurosurgery for providing us the opportunity to examine the patients with pituitary tumors. This work was supported in part by a grant from the Japanese Ministry of Public Welfare.

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Received January 5, 1990; accepted April 3 1990.