Nagoya J. Med. Sci. 45. 61 ~ 70, 1983

TRANSSPHENOIDAL MICROADENOMECTOMY IN CASES OF CUSHING'S DISEASE

NAOKI, KAGEYAMA, M.D., AKIO, KUWAYAMA, M.D.,
MASAO, WATANABE, M.D., TOSHICHI, NAKANE, M.D.,
TATSUO, TAKAHASHI, M.D. and NORIO, KANIE, M.D.

Department of Neurosurgery, Nagoya University School of Medicine

Abstract. Hypothalamo-pituitary functions in 60 cases of Cushing's disease have been followed up after transsphenoidal selective adenomectomy. The adenoma was found and selectively removed in 56 cases.

Remarkable clinical improvement followed within several months after selective adenomectomy in the successful cases, paralleled with endocrine results. Long follow-up studies demonstrated a recovery of the ACTH-cortisol system with restarting of the circadian rhythm and normal suppressibility to low-dose dexamethasone. The functions of the other anterior pituitary hormones such as GH, TSH, and gonadotropins also returned to normal after selective adenomectomy in the majority of the clinically cured cases.

These results strongly suggest that transsphenoidal pituitary exploration should be accepted as an initial treatment of Cushing's disease because of its high clinical remission rate in association with fair chance of radical cure and return to normal endocrine function.

Key Words: Cushing's disease · transsphenoidal operation · adenomectomy · pituitary adenoma.

Endocrinological studies by Orth and Liddle (1971) demonstrated that most cases of Cushing's syndrome were caused by hypersecretion of ACTH from the pituitary gland and approximately 25% caused by adrenal tumors and 16% by ectopic ACTH-producing tumors. Pathological changes of the sella turcica were, however, rarely found among the cases with apparent ACTH hypersecretion. Therefore, it had been generally believed that the true pathogenesis of Cushing's disease exists in the hypothalamus rather than in the pituitary itself.

Contemporary operative results by transsphenoidal microsurgery have shown that a small adenoma does exist in many cases of ACTH-dependent Cushing's disease and clinical symptoms improved markedly by excision of an adenoma[6),7),10),26),29),32)]. It sometimes happens, however, that an adenoma is not found through entire surgical procedures. In addition, there are some reports demonstrationg the presence of ACTH-cell hyperplasia in surgically excised specimens of the pituitary gland in Cushing's disease[20),25),27)]. Therefore, some scholars still support the theory that the functional changes of hypothalamus or limbic system is the primary etiology.

We have experienced transsphenoidal microsurgery in 60 patients with Cushing's disease. The following are the results of our experience.

景山直樹，桑山明夫，渡辺正男，中根藤七，高橋立夫，蟹江規雄
Received for Publication April, 25, 1983

SUMMARY OF CASES

Clinical Materials

This series consists of 60 patients (16 men and 44 women) with Cushing's disease who were subjected to transsphenoidal selective adenomectomy at the Neurosurgical Department of the Nagoya University School of Medicine between January, 1977 and December, 1981. Their mean age was 34 years, with the age range from 8 to 55 years. Forty-two (42) cases were previously untreated and 5 cases underwent sub-total or unilateral adrenalectomy. Pituitary irradiation was performed in 7 cases with or without medical treatment such as reserpine and resulted in temporary remission. The clinical symptoms of these cases are summarized in Table 1. Typical signs such as moon face and central obesity were lacking in some of the previously treated cases. Pituitary dwarfism was associated in one prepubertal boy. Mental changes were characterized in some cases.

Preoperative Endocrine Findings

Plasma ACTH and cortisol as well as other pituitary hormones were measured by radioimmunoassay (RI) using commercially available kits (CIS, France and Daiichi RI, Japan). The basal levels of plasma ACTH and cortisol in normal subjects were < 40 pg/ml and < 20 μg/dl, respectively. The preoperative basal levels in our 60 patients were repeatedly measured at least more than 2 times and their mean values are expressed in Fig. 1. In some cases they were within normal limits, although their diurnal rhythmicity was blunted in all cases with increased urinary excretion of 17-OHCS. Plasma ACTH and cortisol responsiveness to insulin hypoglycemia (regular insulin 0.1-0.2U/kg, i.v.) and 8-lysine vasopressin (10U, i.m.) was examined in the majority of cases before and after surgery. Although conspicuous responses of plasma ACTH to lysine vasopressin were obtained before surgery except in rare cases, ACTH responses to hypoglycemic stimuli were significant only in a few cases, as shown in Figures 2 and 3.

Metyrapone test (4.5 g, p.o. divided in 4 times) was examined in 47 cases (Fig. 4). Thirty-nine cases showed over 100% increase of urinary 17-OHCS. Incomplete responses with the increment of less than 100% were observed in 7 cases and paradoxical decrease in 1. Dexamethasone suppression tests using lower (2 mg) and higher (8 mg) doses were attempted according Liddle's method in 51 cases (Fig. 5). Lower doses did not suppress urinary 17-OHCS in most cases, but did suppress it in 3 cases. Conversely, higher doses of 8 mg suppressed urinary 17-OHCS to more than 50% of its basal secretion in most cases but failed to suppress it in 7 cases.

Pituitary reserves of other hormones were examined by appropriate provocative tests, namely, GH by insulin hypoglycemia, TSH by TRH (500 μg, i.v.) and gonadotropins by LH-RH (100 μg, i.v.). GH and TSH functions were frequently impaired with or without impaired gonadal functions as already reported[15].

Bilateral adrenal hyperplasia was confirmed by adrenal isotope scan and/or adrenal venography in the previously untreated cases.

Radiological Findings

Apparent enlargement of the sella turcica was found only in 2 cases and other 6 cases showed mild ballooning with slightly increased sella volume. Minimal suprasellar expansion of the diaphragma sella was observed in 2 cases on pneumotomography. All the others had grossly normal sella, but hypocycloidal tomography of the sella at 2 mm intervals disclosed localized changes or asymmetry of the sella floor in 21 cases (35.0%) suggesting the existence of microadenoma. In the remaining 31 cases (51.7%) no abnormality was found radiologically. Ordinary CT scan examination was of no help in finding an adenoma except in one case.

RESULTS

Operative Findings

The pituitary fossa was explored through the sublabial rhinoseptal transsphenoidal approach. The adenoma was confirmed by peroperative histological examination and was selectively removed in 56 out of 60 cases. Nine were macroadenomas and the other 38 were microadenomas with a diameter of less than 10 mm. Systematical intraglandular survey of the adenoma with vertical and/or horizontal incision of the pituitary gland was necessary in most cases of microadenoma. All suspected areas were biopsied and immediately examined with frozen section. The dead space of the adenoma was soaked with absolute alcohol for 5 to 10 minutes in the earlier cases, which was replaced by the section of the pituitary-tumor interface in the later cases.

The diameter of the microadenoma was measured as 5-10 mm in 23 cases and 2-5 mm in 24 cases. The location of the microadenoma was non-specific. Only 20 adenomas were situated on the midline, with unilateral extension into either of the lateral wings in 12 cases. Twenty-seven adenomas were buried in the lateral wing, completely apart from the midline. Posterior lobe invasion of the adenoma was seen in one case. No adenoma was found in 4 cases and partial or subtotal rather than total hypophysectomy was conducted considering the relatively younger ages of these cases.

Histological Findings

Among 54 adenomas histologically confirmed, 52 were of basophilic or mixed type and only 2 were chromophobic. The majority were diffuse adenomas and 4 showed a sinusoidal or papillary pattern. In 2 cases with tiny microadenoma, conspicuous adenomatous tissue was erroneously sucked out during operations, resulting in no histological confirmation. ACTH-positive granules in the cytoplasma were confirmed in most of the adenoma cells by immunohistochemical stains. Crooke's cells frequently predominated in the adjacent residual pituitary gland. ACTH-positive cells in the residual tissue were usually limited to these Crooke's cells in most cases. Crooke's cells in the anterior lobe tissue were also confirmed histologically in all 4 cases with no adenoma, suggesting reasonable preoperative diagnosis.

Table I

CLINICAL MANIFESTATIONS

	No. of cases
Moon face	54
Obesity	53
Red face	42
Buffalo hump	40
Purple striae	40
Hypertension	38
Acne	34
Hirsutism	34
Muscle weakness	31
Skin pigmentation	27
Amenorrhea	26
Mental change	10

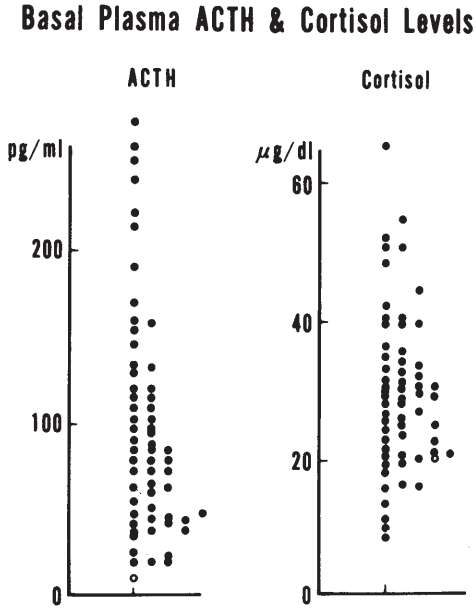

Fig. 1

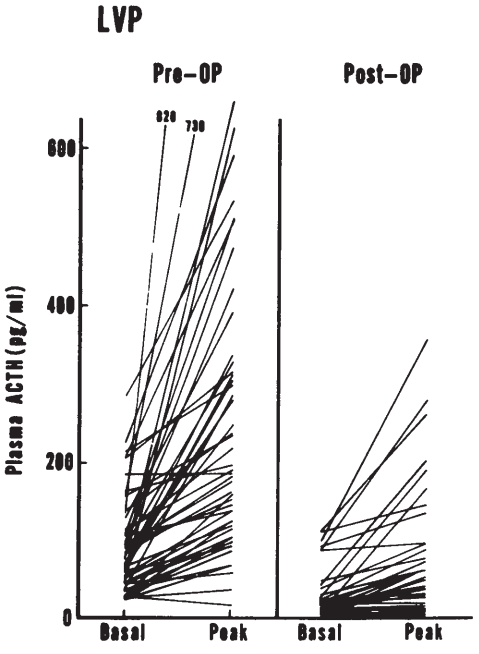

Fig. 2 Preoperative and Postoperative Lysin-Vasopressin Test

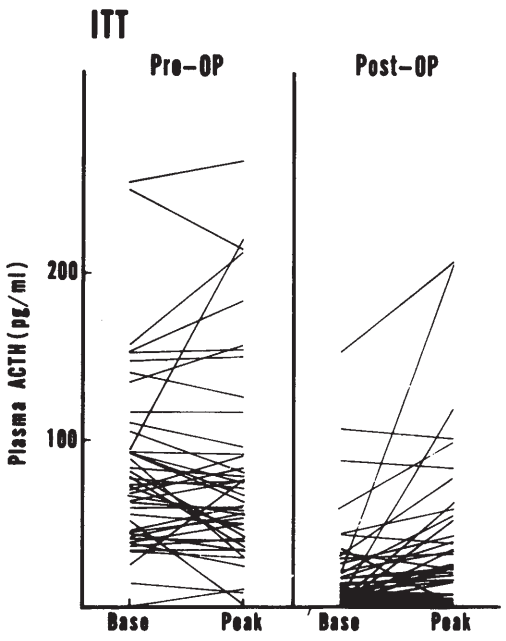

Fig. 3 Preoperative and Postoperative ACTH Response to Insulin Hypoglycemia

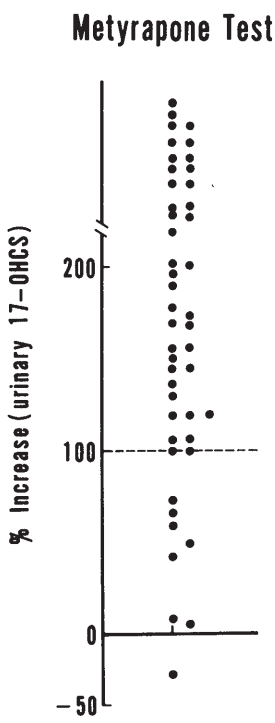

Fig. 4 Preoperative Metyrapone Test

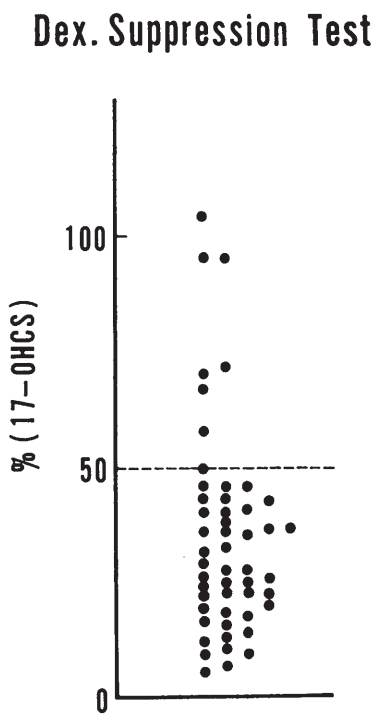

Fig. 5 Preoperative Dexamethasone Suppression Test Using 8 mg.

Operative Results

Selective adenomectomy resulted in dramatic improvement of clinical symptoms in most cases. Body weight began to decrease and acne or pigmentation disappeared within the first postoperative month. Several months were necessary before the disappearance of moon face, central obesity and hirsutism occurred. Regular menstrual cycle was restored in all premenopausal patients after surgery.

Steroid was not given at any stage before or during surgery. Complimentary steroid therapy for postoperative hypocortisol syndrome was begun when general fatigue and appetite loss of high degree were recognized. In 23 cases which could be followed up for more than one year, the steroid administration was successfully terminated in 7 cases in 6 months, 6 cases in between a half and one year, and 10 cases in over a year.

Poor clinical remission was associated with selective adenomectomy in 2 out of 56 cases with adenoma. Until now, clinical recurrence has happened in 2 out of 54 cases with remission. These 4 cases with poor clinical results necessitated no or transient replacement of glucocorticoid. No clinical changes occurred after surgery in the 4 cases with no adenoma. Pancreatic carcinoid with ectopic ACTH production was diagnosed in one case after surgery.

Operative death was experienced in one advanced case due to cardiac failure. This patient was already in serious condition preoperatively. However, no other means except transsphenoidal operation seemed effective to prevent further progress of the disease. In all other cases morbidity was minimal except for the occurrence of transient diabetes insipidus in 23 cases.

Endocrinological Evaluations

The earliest postoperative endocrinological evaluations were performed during the 3rd to the 6th weeks after surgery. Although substitution of glucocorticoid was necessary in most cases, it was interrupted at least 24 hours before tests to avoid its influence on the results. When limited to the cases with selective adenomectomy, marked decrease of plasma ACTH and cortisol was followed by obvious clinical improvements. The basal levels of plasma ACTH and cortisol decreased on the average (M ± S.D.) from 98.7 ± 59.3 pg/ml and 28.2 ± 9.3 μg/dl to 21.7 ± 23.3 pg/ml and 6.4 ± 7.7 μg/dl, respectively.

The basal levels of plasma ACTH in 22 out of 56 cases and the basal levels of cortisol in 12 cases became undetectable (< 10 pg/ml, < 1.25 μg/dl, respectively) (Fig. 6). ACTH responsiveness to insulin hypoglycemia became positive in about half of the cases after surgery, compared with almost non-significant preoperative responses (Fig. 3). Contrarily, conspicuous preoperative ACTH responses to lysine vasopressin became blunted in most cases and became completely negative in some (Fig. 2). Normal circadian rhythms of plasma ACTH and cortisol were not demonstrated yet at this acute postoperative stage with sustained low levels of them in plasma.

Long term follow-up studies over 6 months after surgery were obtainable in 12 cases. Normal diurnal rhythms of plasma ACTH and cortisol became apparent in 9 cases with normal suppresibility to low dose dexamethasone (1 mg). Other pituitary functions such as GH and TSH systems, which were highly suppressed preoperatively, showed definite functional recovery already in the acute postoperative stage (Fig. 7). Although the recovery of LH function was not clearly demonstrated, all the patients with impaired preoperative gonadal function showed apparent recovery and restoration of regular menstrual cycle. This functional recovery of pituitary hormones became much more prominent in most cases within several months after surgery (Fig. 8). The changes of FSH and PRL were minimal.

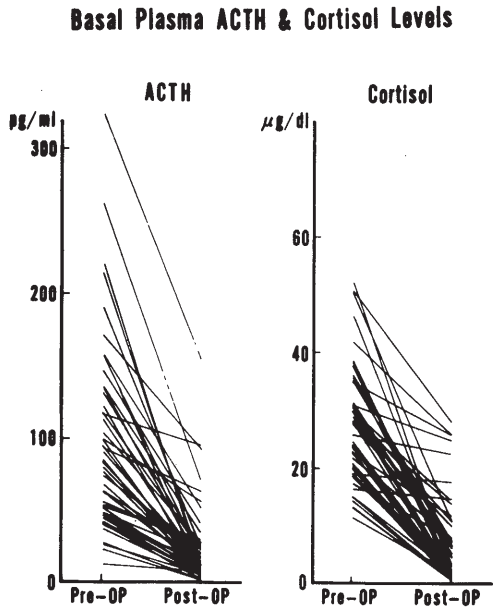

Fig. 6 Surgical Results on Basal Levels of Plasma ACTH and Cortisol

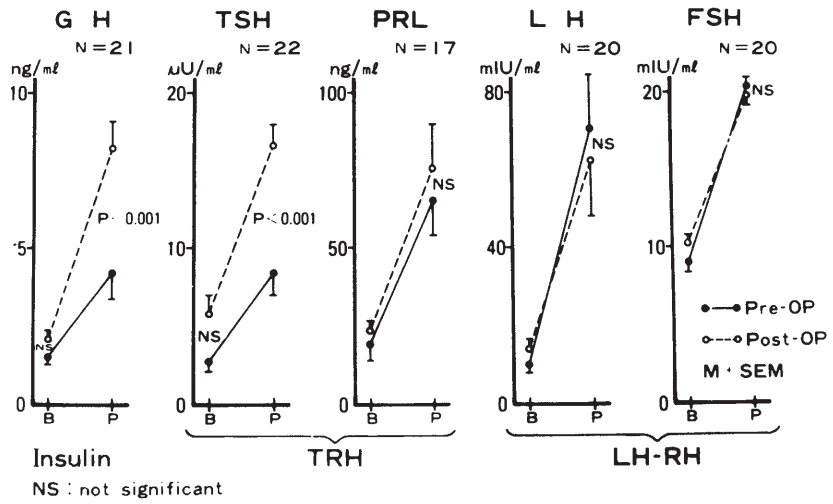

Fig. 7 Pre- and Postoperative Responses of Pituitary Hormones Other than ACTH B: Base P: Peak

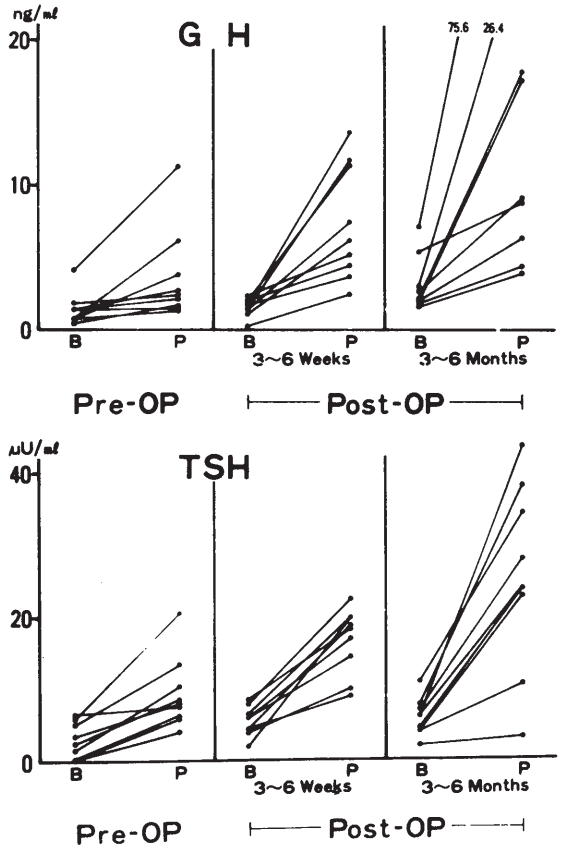

Fig. 8 Postoperative Follow-up of GH Response to Insulin and TSH Response to TRH

DISCUSSION

Surgical results of our series after selective adenomectomy correspond well to those reported by Hardy,[6] Tyrrell,[29] Salassa[26] and others. Microsurgical selective adenomectomy in Cushing's diseases is the outstanding method because of its high cure rate, good selectivity between normal and pathological tissues, and low mortalities and morbidities. Aside from the technical problems in detecting microadenomas, it is of great merit that a moderate amount of residual tissue can be preserved by selective adenomectomy and its functional recovery of not only ACTH but also GH, TSH, LH and FSH systems positively supports this treatment of Cushing's disease.

As far as medical treatment is concerned, no matter what medication is to be applied, the cure rate or remission rate of such is definitely inferior to surgical results. Moreover, patients are frequently annoyed with various side-effects. OP-DD, metyrapone, reserpine, cyproheptadine, L-DOPA and bromocriptine are the drugs used nowadays, but none of these is satisfactory.[4),8),12),13),22),24),31)]

Radiation therapy for the pituitary body is reported to be quite effective for children,[9] but this is not always true with adults.[1] Stereotactic cryosurgery or radiosurgery are also inferior to microadenomectomy in the sense of their remission rate and side-effects. Pituitary destruction by heavy particles is highly evaluated because of its high effective rate,[11),17),19)] but this method may involve healthy parts of the pituitary body and its surrounding tissues.

As far as the diagnostic method is concerned, it is hardly possible in the majority of the cases to secure decisive evidence of intrasellar microadenoma before surgery, even with fine neuroradiological techniques such as sellar polytomography and metrizamide cisternography. From our own experiences, abnormality was demonstrated only in half of the total number of cases. Today, high resolution CT has the greatest prospect for the diagnosis of microadenoma. However, our preliminary study teaches us that CT's diagnostic value is still limited to some of the cases with relatively large adenomas. Consequently, any positive radiological findings may actually give us great prospection of the size and location of the adenoma, but negative results do not necessarily mean contraindication of transsphenoidal pituitary exploration.

Therefore, endocrinological examinations are very important to decide whether Cushing's disease is of pituitary origin or not. Measuring the ACTH level alone is not sufficient. In most cases the ACTH level is elevated only slightly or even remains within normal limits. Consequently, additional endocrinological examinations such as metopyrone test, dexamethasone suppression test, lysine-vasopressin test, insulin-induced hypoglycemic test, circadian rhythm and so forth are necessary for the diagnosis of Cushing's disease.

In spite of careful preoperative endocrinological and radiological study, we could not find any adenoma in 4 cases. One case was finally diagnosed as Cushing's syndrome due to an ectopic ACTH-producing tumor. Ectopic ACTH-producing tumors may be misdiagnosed, although rarely, as we did in this case. Therefore, we now believe that selective venous sampling for the confirmation of pituitary ACTH-hypersecretion should be performed when clinical and endocrinological findings are suggestive of ectopic ACTH-production.

As for the other 3 cases with no adenoma, the true pathogenesis was not obvious. Histological examinations of biopsy specimens of the pituitary in these cases revealed that Crooke's changes were noted in the anterior pituitary tissue in all cases and no hyperplasia was observed anywhere. This fact suggests that the possibility of some ACTH-producing tissue existing in the pituitary body or in other parts of the body is much higher than the possibility of it being the results of hyperfunctions of either the hypothalamus or limbic

system. Postoperative observations over a year resulted in no change of clinical signs in all cases, leaving little possibility of it being a malignant tumor with ectopic ACTH-production. Therefore, the most reasonable explanation of surgical failure in these cases would seem to be due to an inadequate intraparenchymal survey of the pituitary gland. Only partial or subtotal hypophysectomy was done considering the relatively young ages of the patients. Such a very small microadenoma with a diameter of less than 2 mm, as reported by Wilson and Dempsey,[32] might have existed in the remaining tissue. These bitter experiences are teaching us the importance of systematic intraparenchymal survey of the pituitary gland for better surgical results.

So-called diffuse hyperplasia of ACTH-cells, a case which was recently reported by Schnall et al,[27] would be another explanation of the cases with no adenoma in Cushing's disease. However, we do not yet have enough data about this pathology. The immunohistochemical studies using anti-ACTH serum were done in the above-mentioned 3 cases but failed to demonstrate hyperplasia of ACTH-cells.

Theoretically, it is most important to measure the corticotrophine releasing factor (CRF) as a direct index, but unfortunatly this method has not yet been established technically. Further analysis and knowledge are necessary to reach a conclusion.

Conclusion

We have performed transsphenoidal microadenomectomy on 60 cases of ACTH-dependent Cushging's disease. In 56 cases adenoma was found in the pituitary body and clinical remission was assured with most of the patients. Careful clinical follow-up observation over a long period of time proved the satisfactory recovery of the pituitary functions. Therefore, microsurgical selective adenomectomy seems to be the best treatment and should be taken as the first choice.

Acknowledgement: This work was supported by the Research Grant for Intractable Diseases from the Ministry of Health and Welfare and Grant 457351 from the Ministry of Education, Science, and Culture of Japan.

REFERENCES

1) Aristizabal, S., Caldwell, W. L. and Avila, J. et al: Relationship of time dose factors to tumor control and complications in the treatment of Cushign's disease by irradiation. *Int. J. Radiat. Oncol. Biol. Phys.*, **2**, 47-54, 1977.
2) Bigos, S. T., Robert, F. and Pelletier, G. et al: Cure of Cushing's disease by transsphenoidal removal of a microadenoma from pituitary gland despite a radiographically normal sella turcia. *J. Clin. Endocrinol. Metab.*, **45**, 1251-1260, 1977.
3) Cassar, J., Doyle, F. H. and Mashiter, K. et al: Treatment of Cushing's disease in juveniles with interstitial pituitary irradiation. *Clin. Endocrinol.*, **11**, 313-321, 1979.
4) E'Ercole, A. J., Morris, M. A. and Underwood, L. E. et al: Treatment of Cushing's disease in childhood with cyproheptadine. *J. Pediatr.* **90**, 834-835, 1977.
5) Feldman, J. M.: Cushing's disease: A hypothalamic flush. *N. Engl. J. Med.*, **293**, 930-931, 1975.
6) Hardy, J.: Transsphenoidal surgery of hypersecreting pituitary tumors. In Pituitary Tumors, pp. 179-194. Ed. by P. O. Kohler. and G. T. Ross., Exc. Med. Am. Elsv., New York, 1973.
7) Hardy, J.: Transsphenoidal microsurgical removal of pituitary adenoma. In Recent Progress in Neurological Surgery, pp. 86-91, Ed. by K. Sano and S. Ishii, Exc. Med. Am. Elsv., New York, 1974.

8) Jeffcoate, W. J., Rees, L. H. and Tomlin, S. et al: Metyrapone in long-term management of Cushign's disease. *Brit. Med. J.*, **2**, 215-217, 1977.
9) Jennings, A. S., Liddle, G. W. and Orth, D. N. et al: Results of treating childhood Cushing's disease with pituitary irradiation. *N. Engl. J. Med.*, **297**, 957-962, 1977.
10) Kageyama, N., Kuwayama, A. and Yoshida, J. et al: The results of transsphenoidal microsurgery in cases of functioning pituitary adenomas. *Sera Med. Neurochir.*, **7**, 231-248, 1978.
11) Kjellberg, R. N., Kliman, B. and Swisher, B. J. et al: Radiosurgery for pituitary adenoma with bragg peak proton beam. In Pituitary Adenomas, pp. 209-217. Ed. by P. J. Derome, C. P. Jedynak and F. Peillon. France, Asclipios Pub. 1980.
12) Krieger, D. T., Amorosa, L. and Linick, F. et al: Cyproheptadine-induced remission of Cushing's disease. *N. Engl. J. Med.*, **293**, 893-896, 1975.
13) Krieger, D. T.: Lack of responsiveness to l-dopa in Cushing's disease. *J. Clin. Endocrinol. Metab.*, **36**, 277-284, 1973.
14) Krieger, D. T. and Luria, M.: Effectiveness of cyproheptadine in decreasing plasma ACTH concentrations in Nelson's syndrome. *J. Clin. Endocrinol. Metab.*, **43**, 1179-1182, 1976.
15) Kuwayama, A., Kageyama, N. and Nakane, T. et al: Anterior pituitary funciton after transsphenoidal selective adenomectomy in patients with Cushing's disease. *J Clin. Endocrinol. Metab.*, **53**, 165-173, 1981.
16) Lagerquist, L. G., Meikle, A. W. and West, C. D. et al: Cushing's disease with cure by resection of a pituitary adenoma. *Am. J. Med.*, **57**, 826-830, 1974.
17) Lawrence, J. H., Tobias, C. A. and Linfoot J. A. et al: Heavy-particle therapy in acromegaly and Cushing's disease. *J. A. M. A.*, **235**, 2307-2310, 1976.
18) Liddle, G. W.: Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. J. Clin. Endocrinol. Metab., **20**, 1539-1560, 1960.
19) Linfoot, J. A.: Alpha particle irradiation in the primary and postsurgical management of pituitary microadenomas. In Pituitary Microadenomas, pp. 515-530. Ed by G. Faglia, M. A. Giovanelli, London, Academic Press, 1980.
20) Lüdecke, D., Kautzky, R. and Saeger, W. et al: Selective removal of hypersecreting pituitary adenomas. *Acta Neurochir.*, **35**, 27-42, 1976.
21) MacEerlean, D. P. and Doyle, F. H.: The pituitary fossa in Cushing's syndrome; A retrospective analysis of 93 patients. *Brit. J. Radiol.*, **49**, 820-826, 1976.
22) Miura, K., Aida, M. and Kihara, A. et al: Treatment of Cushing's disease with reserpine and pituitary irradiation. *J. Clin. Endocrinol. Metab.*, **41**, 511-526, 1975.
23) Orth D. N. and Liddle, G. W.: Results of treatment in 108 patients with Cusing's disease. *N. Engl. J. Med.*, **285**, 243-247, 1971.
24) Orth D. N. Metyrapone is useful only as adjunctive therapy in Cusing's disease. *Ann. Int. Med.*, **89**, 129-130, 1978.
25) Saeger, W.: Morphologische Klassifikation der Hypophysenadenom und ihre Bedeutung für die Klinische Diagnostik. *Endokrinologie.*, **72**, 45-59, 1978.
26) Salassa, R. M., Laws, E. R. Jr. and Carpenter, R. C. et al: Transsphenoidal removal of pituitary microadenoma in Cushing's disease. *Mayo Clin. Proc.*, **53**, 25-28, 1978.
27) Schnall, A. M., Kovacs, K. and Brodkey, J. S. et al: Pituitary Cushing's disease without adenoma. *Acta Endocrinol.*, **94**, 297-303, 1980.
28) Thoren, M., Rahn, T. and Hall, K. et al: Stereotactic radiosurgery as treatment in pituitary-dependent Cushing's syndrome. In Faglia, pp. 507-514. Academic Press, London, 1980.
29) Tyrrell, J. B., Brooks, R. M. and Fitzgerald, P. A. et al: Cushing's disease. *N. Engl. J. Med.*, **298**, 753-758, 1978.
30) Wajchenberg, B. K., Silveira, A. A. and Goldman, J. et al: Evaluation of resection of pituitary microadenoma for the treatment of Cushing's disease in patients with radiologically normal sella turcica, *Clin. Endocrinol.*, **11**, 323-331, 1979.
31) Werder, K., Brendel, C. and Eversmann, T. et al: Medical therapy of hyperprolactinemia and Cushing's disease associated with pituitary adenomas. In Pituitary Microadenomas, pp. 383-397, ed. by G. Faglia, M. A. Giovanelli and R. M. MacLeod., Academic Press, London, 1980.
32) Wilson, C. B. and Dempsey, L. C.: Transsphenoidal microsurgical removal of 250 pituitary adenomas. *J. Neurosurg.*, **48**, 13-22, 1978.