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PITUITARY-ADRENOCORTICAL RESPONSE AFTER CRANIOTOMY FOR BRAIN TUMOR, AND ITS SUPPRESSION WITH ADMINISTERED GLUCOCORTICOID

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ABSTRACT

Nowadays large doses of glucocorticoids are administered to prevent cerebral edema during and after craniotomy for brain tumor. The influence of this glucocorticoids therapy on the hypothalamo-pituitary-adrenocortical response was studied clinically. Urinary total 17-hydroxycorticoids excretion (17-OH-CH) was estimated. Preoperative basal level of 17-OH-CS in brain tumor cases was lower than normal basal level except in some cases in which rapid increase in intracranial hypertension was the main sign. Adrenocortical response was more intense in brain tumor craniotomy than in other operations such as lumbar sympathectomy for Buerger's disease or craniotomy for various diseases of the brain and skull other than brain tumor.

Large doses of dexamethasone administered prophylactically to prevent cerebral edema, suppressed significantly this intense response to brain tumor craniotomy. It was reduced to a degree equal to adrenocortical response to operations of control cases. In most cases suppression with dexamethasone in craniotomy was correlated to preoperative suppression test with dexamethasone, suggesting that the same mechanism might play in both resting and stressful conditions.

More than four weeks after the operation, influence of this prophylactic dexamethasone therapy was tested; the suppression test was made and found to be within normal limit.

Glucocorticoids therapy to prevent cerebral edema is supported from this point of view, for the adrenocortical reserve may be maintained even during and after craniotomy.

PREFACE

Surgical stress is followed by a series of metabolic changes, among which functional changes in the adrenal cortex have been most thoroughly investigated[1)-10)]. Among the surgical operations, craniotomy causes an intense response by the adrenal cortex[11)-13)], Even head injury causes an intense response by the adrenal cortex[14)15)].

Studies on the influence of the central nervous system on the hypothalamo-

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pituitary-adrenocortical axis by the method of destruction, electrostimulation and corticosteroid implantation[16)17)], have revealed the importance of the limbic system (amygdala and hypocampus) and the reticular activating system. The results indicate that the most essential areas secreting the corticotrophin releasing factor (CRF) are the "median eminence" and "postoptic region" and other portions have only an indirect effect. However, these data are the results of animal studies. In man, Bauer[18)] reported that the initial symptom of hypothalamic disease was endocrine disorder. On the other hand Kahana *et al.*[19)] reported that intracranial extrasellar lesion might cause endocrine manifestations.

Concerning the problem of adrenocortical function in patients with brain tumor, Brilmayer[20)] reported a certain relationship to exist between adrenocortical function and duration of intracranial hypertension. Uozumi[12)] reported that the adrenocortical response to operative stress had a proportional relationship to the preoperative response to adrenocorticotropin (ACTH-Z). Adrenocortical hyperresponse to surgical stress has been observed in patients with brain tumor more frequently than in other diseases. Two reasons may be considered for the adrenal cortical hyperresponse in patients with brain tumor. One is that the operative stress involves the central nervous system, the center of the endocrine organs depending on the site of operation The second reason is that the operative stimulus is more intense than in other operations. In the latter, the more intense the operative stress becomes the stronger the resultant adrenal response. In man the maximum response of the adrenal cortex to surgical stress or exogenous ACTH has an upper limit estimated to be 400 mg/day as corticoid secretion level from the adrenal cortex[21)]. If a greater stress is induced, beyond the ability of the adrenal cortical reserve, the patients may fall into adrenal crisis. This may easily occur during surgery for brain tumor. Steroid administration is usually necessary to maintain the adrenal reserve during and after the operative stress in such cases.

Two mechanisms have been considered to regulate the pituitary-adrenocortical reactien. One involves the negative feed back mechanism in which the reaction of ACTH is regulated in such a way that a fall in plasma corticoid level leads to an increase of ACTH secretion. This negative feed-back mechanism acts mainly under non-stress condition. The second mechanism is considered to explain the regulation during stress. During major surgical stress, plasma ACTH concentration rises even though the plasma corticoid level is already elevated. Katsuki[22)] reported the dissociation of the neural regulating centers in the hypothalamus. One is the center for the feed back mechanism and the other the center for reaction to stress.

Investigations have been pursued to test whether or not administered steroids may suppress the elevation of either corticoid or ACTH secretion induced by stress. Yates *et al*,[23)24)] proposed the "reset" theory from their experiment in

rats. They postulated that, under conditions of stress, ACTH secretion was still delicately governed by the level of corticosteroids with the regulator "reset" at a higher level than under non-stress conditions. Estep *et al.*[25] have indicated that during some major surgical operations the pituitary-adrenocortical response cannot consistently be abolished by dexamethasone. This report is contrary to the view expressed by Yates *et al.*

On the other hand Ingraham *et al.*[26] reported in 1952 the use of cortisone in the pre- and post-operative management of craniopharyngioma. Operative and postoperative states of the patient were very stable and they suggested the beneficial action to prevent development of cerebral edema. Apart from the replacement therapy for secondary adrenocortical insufficiency due to sellar lesion, many authors[27)-30)] have demonstrated the apparent beneficial effect of corticosteroid for cerebral edema. Nowadays, corticosteroid therapy for cerebral edema is used in preoperative states[29] and even in cerebral edema due to head injury[30].

The present study was designed to test the hypothesis that during stress conditions the regulation of pituitary-adrenocortical function at a higher level was affected by the feed back mechanism of reset condition as Yates *et al.*[23)24)] reported, and to test the influence of dexamethasone therapy on the hypothalamo-pituitary-adrenocortical response after brain tumor operation.

Administration of corticosteroid adequately corresponding to the adrenal response to operative stress suppresses the increased adrenocortical hypersecretion though partially in this study. Four weeks after the operation with dexamethasone therapy, the pituitary-adrenocortical function is not affected by this corticoid therapy.

MATERIALS

These investigations covered 127 patients admitted to the First Department of Surgery, Nagoya University School of Medicine, during 1961 to 1965. Among these 108 cases were subjected to craniotomy for various diseases of the brain and skull, including 93 cases of brain tumor (Table 1) and 15 cases of various brain diseases other than tumor (Table 2). Nineteen patients with Buerger's disease (Table 7, 16) in which lumbar sympathectomy was performed were selected as controls because of the comparative uniformity of the operative procedures in this clinic[31].

Anesthesia (intravenous isozol and succinyl choline chloride and endotracheal nitrous oxide, oxygen with hallothane or ether of low concentration and d-tubocurarine) and other pre-, operative and post-operative medication were standardized as far as possible. Morphine was not used as it seemed to be most effective in inhibiting the central nervous system involving the hypothalamo-

Table 1. Brain tumor cases

I. Frontal lobe tumors

1	Y.G.	57	M	Cancer metastasis (R)
2	T.O.	24	M	Astrocytoma (R)
3	E.T.	41	M	Meningioma (R)
4	H.K.	52	M	Glioblastoma (L)
5	M.S.	42	M	Cancer metastasis (L)
6	S.O.	40	F	Glioblastoma (L)
7	C.H.	29	M	Glioblastoma (R)
8	E.I.	52	M	Glioblastoma (R)
9	K.O.	28	M	Glioblastoma (L)
10	S.S.	45	M	Glioblastoma (L)
11	M.I.	53	M	Meningioma (L)
12	S.M.	42	M	Cancer metastasis (R)
13	T.Y.	28	F	Glioblastoma (L)
14	S.M.	35	M	Teratoma (L)
15	H.K.	17	M	Actinomycotic tumor (L)

II. Parietal lobe tumors

1	Y.S.	38	F	Astrocytoma (R)
2	O.K.	48	M	Glioblastoma (L)
3	H.O.	53	M	Cancer metastasis (L)
4	M.K.	30	M	Meningioma (L)
5	A.K.	40	F	Meningioma (R)
6	K.K.	41	M	Meningiema (L)
7	T.I.	56	M	Meningioma (R)
8	K.S.	60	F	Meningioma (L)
9	H.N.	19	F	Astrocytoma (L)
10	Y.M.	34	F	Meningioma (L)
11	I.W.	41	F	Cancer metastasis (R)
12	E.T.	61	M	Glioblastoma (L)

III. Occipital lobe tumors

1	Y.M.	46	M	Glioblastoma (R)
2	M.I.	31	M	Astrocytoma (R)
3	Y.I.	23	F	Astrocytoma (L)
4	H.S.	18	M	Melanoma (L)
5	H.T.	39	M	Meningioma (L)
6	S.T.	47	M	Meningioma (M)
7	H.I.	48	F	Cancer metastasis (R)

IV. Temporal lobe tumors

1	W.S.	27	M	Meningioma (L)
2	S.K.	34	M	Meningioma (L)
3	T.K.	50	M	Glioblastoma (R)
4	Y.I.	22	F	Meningioma (L)
5	H.T.	32	M	Oligodendroglioma (R)
6	T.Y.	25	M	Ependymoblastoma (L)

V. Suprasellar tumors

1	S.T.	49	M	Meningioma (R)
2	I.F.	32	M	Glioblastoma (R)
3	I.K.	61	F	Meningioma (R)

VI. Olfactory groove tumors

1	S.T.	44	F	Meningioma (R)
2	T.N.	30	M	Meningioma (L)
3	S.N.	63	F	Meningioma (M)

VII. Pinealoma

1	N.H.	19	M	Pinealoma
2	Y.O.	17	M	Pinealoma
3	T.T.	27	M	Pinealoma

VIII. Intraventricular tnmors

1	Y·K.	8	F	Ependymoma
2	M.S.	9	F	Ependymoma

IX. Brain stem tumors

1	T.T.	24	M	Astroblastoma (L)
2	R.F.	6	M	Glioblastoma (L)
3	M.H.	11	M	Glioblastoma (L)
4	T.K.	15	F	Medulloblastoma (R)
5	T.I.	31	M	Ependymoblastoma (M)

X. Cerebellar tumors

1	Y.S.	4	M	Astrocytoma (M)
2	M.K.	11	F	Astrocytoma (R)
3	S.F.	8	F	Astrocytoma (L)
4	S.S.	58	F	Angioma (M)
5	T.O.	11	M	Astrocytoma (L)
6	S.S.	38	M	Angioblastoma (M)
7	T.I.	11	F	Angioblastoma (L)
8	S.T.	39	M	Astrocytoma (M)
9	T.T.	48	F	Glioma (M)

XI. Cerebello-pontine angle tumors

1	N.A.	51	M	Neurinoma (L)
2	T.U.	52	M	Neurinoma (L)
3	H.S.	21	F	Neurinoma (R)

XII. Pituitary adenoma

1	J.Y.	42	M
2	M·K.	23	F
3	U.Y.	34	F
4	Y.M.	28	F
5	K.U·	32	F
6	M.T.	26	M
7	M.T.	34	F
8	M.K.	24	F
9	K.K.	51	F
10	M.S.	24	M
11	T.O.	41	M

XIII. Craniopharyngioma

1	O.S.	53	F
2	T.N.	38	F
3	T.S.	54	M
4	H.S.	28	M
5	K.G.	14	M
6	H.H.	16	M
7	K.N.	31	M
8	T.T.	42	M
9	K.S.	53	F
10	T.T.	42	M
11	M.I.	5	F
12	M.A.	45	M
13	S.N.	13	F
14	T.S.	54	M

Table 2. Control cases in which craniotomy was performed

No.	Name	Yrs.	Sex	Diseases
C- 1	S.M.	11	M	Depressed fracture
2	M.H.	31	M	same
3	W.S.	29	M	same
4	K.F.	9	F	same
5	K.H.	48	M	same
6	T.I.	25	M	Arachinitis optochiasmatica
7	S.K.	48	M	same
8	M.K.	11	F	same
9	M.F.	38	F	Arachinitis of lower cranial nerve
10	T.M.	19	F	Trigeminal neuralgia
11	T.K.	28	M	Subacute extradural hematoma
12	T.M.	26	M	Hemoangioma of the skull
13	N.T.	22	F	Involuntary movement (choreic)
14	Y.S.	15	M	Thalamic necrosis (Vascular)*
15	K.S.	27	M	Choreoathetosis*

*: Stereotaxic thalamic surgery was done

pituitary-adrenocortical function[32]. All cases in which the course of the disease was modified by occasional complications such as pneumonia, wound infection, thrombophlebitis, and other liver[33] or kidney dysfunction demonstrated by routine clinical examinations were excluded. The author experienced in such cases irregular elevation of the urinary total 17-hydroxycorticosteroids excretion during the postoperative course. Franksson *et al.*[7] described that if the level of 17-hydroxycorticosteroids remained high for three or more days after surgery, a postoperative complication might be suspected.

In all cases of craniotomy, 0.5 mg of atropin sulphate was injected for premedication and 125 mg of diphenylhydantoin sodium was injected preoperatively to prevent seizure attack. Urea or mannitol solution was administered intravenonsly in drip to depress the intracranial hypertension during and after the operation when necessary. Blood and fluid transfusion was administered if needed and then only in maintenance levels. Post-operatively 125 mg of diphenylhydantoin sodium was injected intramuscularly every eight hours for two or three days, then 300 mg/day of diphenylhydantoin sodium was administered orally for more than two months or more if necessary. Anabolic steroid was injected to prevent the atrophy of the adrenal gland[34)35)] which might be caused by massive glucocorticoid administration. Other medication except for corticosteroid derivatives, which was administered intentionally in this study, was standardized as strictly as possible in both craniotomy and lumbar sympathectomy.

We planned the prophylactic corticosteroids therapy to prevent cerebral edema in brain tumor operation. As suppression of the adrenocortical hyperresponse and prevention of the development of cerebral edema were intended, dexamethasone was chosen, because of its intense suppressive action on the feed

back mechanism with minimum electrolyte action[36]. Moreover, Galicich and French[37] reported that dexamethasone was the most effective corticosteroid to prevent cerebral edema. With this prophylactic corticosteroid therapy for cerebral edema, the clinical course of the postoperative patient becomes more stable.

METHOD

Urinary total 17-hydroxycorticosteroids (17-OH-CS) was measured by Kornel's method[38]. Phenylhydrazine hydrochloride used for this procedure was twice recrystallized[39], and n-butanol was redistilled[40] in contrast to Kornel's original method. Cortisone (Upjohn) was used as a standard, at a concentration of 20 ug of cortisone in 1 ml. of n-butanol. Optical densities were read by a Beckman spectrophotometer (Shimazu Seisakujo). The reproducibility of the method expressed as the coefficient of variation is 2.8%.

Urine was collected from 7 A.M. to 7 A.M. of the next day and stored in the refrigerater without preservative until asaay. When a patient was urinary incontinent, urine was obtained by means of indwelling catheters. Urine was flash evaporated by low pressure vapourizing below 50°C in cases of diabetes insipidus and was diluted with distilled water in cases where the urine volume was below 1000 ml/day.

Urinary total 17-hydroxycorticosteroids was estimated at the basal level some days before the operation and postoperatively it was estimated for 8 days including the day of surgery.

Tests on pituitary adrenocortical suppressibility were reported by Liddle[41]. In this study the original method of Liddle was utilized. 0.5 mg of dexamethasone was administered every 6 hours for two days and the total excretion of urinary 17-hydroxycorticosteroids was estimated. In cases of pituitary adenomas and craniopharyngiomas, 1 mg of dexamethasone was used every 8 hours for 2 days, because the suppression rate of these groups was abnormally low[42][43].

Urinary excretion rate of administered dexamethasone was 11.2%, which was estimated as urinary total 17-hydroxycorticosteroids in patients with absolute panhypopituitarism due to craniopharyngioma whose basal level was estimated to be zero. In dexamethasone treated cases the value was corrected by this rate.

Measurement of urinary total 17-hydroxycorticosteroids excretion has the advantage that one may observe the glucocorticoid action of the adrenocortical function during a relatively long duration, the urinary secretion representing the summation of the adrenocortical function during the observed period[3]. However, there is a disadvantage that various factors may affect the level[44]; *e.g.*, the rate of conjugation in the liver and excretion by the kidney. On the contrary plasma 17-hydroxycorticosteroids level is advantageous for observing the

change during a short interval; however, one can observe the level only at the time of estimation. Steenburg *et al.*[3] related that during the first four days the excretion of 17-hydroxycorticosteroids correlated well with the total nitrogen loss and clinical magnitude of the trauma. In my opinion the total urinary 17-hydroxycorticosteroids excretion is advantageous as a measure of the overall metabolic change.

RESULTS

1) *Basal level*

The basal level was estimated under non-stress conditions and the mean value of one to three days was taken. The basal level of the normal person, in whom neither apparent disease of endocrine disorders nor liver or kidney disease was observed in routine clinical examinations, was estimated in resting conditions. The basal level of the normal person ranged from 5.5 mg to 13.2 mg, the mean being 9.27 ± 2.03 mg/day (Table 3). The basal level was estimated for patients with brain tumor as 8.59 ± 2.26 mg/day (Table 4, 5), for patients with non-tumorous cranial diseases as 8.38 ± 2.38 mg/day (Table 6), and for Buerger's disease as 8.34 ± 1.69 mg/day (Table 7, 16). The basal level of the patient with brain tumor ($P < 0.01$) and Buerger's disease ($0.01 < P < 0.05$) is lower than that of the normal control.

2) *Suppression test*

A) Suppression test in normal person

In this study the original method of Liddle was utilized. A dose of 0.5 mg every 6 hours for two days was administered and the total excretion of urinary 17-OH-CS was observed.

Though suppression was seen even on the first day, the maximum suppression was observed on the second day; thereafter, the urinary excretion

Table 3. Normal basal level of urinary total 17-hydroxycorticosteroids (mg/day)

No.	Name	Yrs.	Sex	Bacal level	No.	Name	Yrs.	Sex	Basal level
N- 1	K.F.	59	M	9.2	14	F.M.	49	F	5.5
2	M.M.	36	M	12.6	15	T.K.	48	F	6.2
3	S.H.	58	M	7.2	16	K.T.	23	F	5.6
4	I.S.	44	M	8.7	17	S M.	20	F	8.6
5	I.M.	45	M	8.7	18	K.K.	50	F	9.1
6	I.N.	32	M	11.1	19	K.T.	30	F	8.8
7	K.T.	30	M	9.6	20	S.M.	37	F	13.2
8	K.N.	28	M	8.4	21	K.N.	30	F	10.1
9	K.K.	29	M	9.4					
10	N.M.	31	M	9.3	Mean				9.27
11	K.S.	33	M	10.9					
12	K.T.	32	M	12.2	Standard deviation				2.03
13	K.M.	31	M	10.2					

Table 4. Adrenocortical response to craniotomy in brain tumor cases (Urinary total 17-OH-CS, mg/iday)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
I- 1	6.2	16.4	24.0	16.7	9.7	10.0	7.1	8.0	6.9	19.0
2	5.0	12.3	49.1	34.1	24.8	12.4	15.2	9.3	7.6	31.8
3	4.2	15.0	19.7	24.0	24.0	18.2	13.4	12.2	9.0	19.6
4	9.1	29.4	38.9	32.1	15.4	10.9	12.7	9.9	9.1	33.7
5	12.7	46.3	60.2	37.0	37.8	23.0	10.2	5.3	3.5	47.8
6	10.9	20.2	56.5	29.9	17.5	8.8	10.5	15.4	13.4	35.5
7	11.0	38.2	50.6	50.0	46.0	24.2	12.1	14.5	15.0	46.3
II- 1	8.9	18.1	19.5	29.6	14.9	9.0	9.0	9.8	10.1	21.4
2	7.6	13.7	48.5	48.9	29.4	24.5	25.0	12.4	10.8	37.0
3	8.6	12.1	68.9	44 2	14.8	18.1	9.2	9.8	8.0	41.7
4	9.8	24.8	28.0	10.9	14.9	6.9	6.8	7.9	6.0	21.2
5	9.1	15.0	26.8	14.6	15.1	5.8	9.4	12.7	5.2	18.8
6	11.2	40.3	78.4	30.1	28.0	11.0	9.5	4.0	4.0	49.6
III- 1	8.0	36.5	44.3	35.0	10.1	17.0	14.0	15.8	8.5	38.6
IV- 1	9.7	25.9	81.7	38.6	22.8	21.4	19.4	13.6	15.8	48.7
2	8.5	14.3	45.0	28.4	15.9	17.9	16.2	12.8	10.2	29.2
V- 1	7.1	28.0	76.1	64.5	23.5	10.3	14.2	12.0	7.4	56.2
VI- 1	8.9	30.4	53.4	45.1	21.4	16.4	13.0	10.8	9.0	43.0
VII- 1	4.8	23.5	84.3	32.8	20.8	14.2	11.3	11.5	9.0	46.9
2	8.3	24.1	38.2	25.0	16.2	14.0	12 5	9.0	14.1	29.1
IX- 1	5.7	15.3	35.2	32.6	11.6	7.9	7.1	16.8	11.2	27.7
2	13.7	40 5	38.1	23.4	8.8	16.9	12.2	6.3	10.1	34.0
X- 1	9.1	17.0	21.0	27.7	17.8	12.9	6.9	2.5	7.5	21.9
2	9.6	19.7	49.0	29.6	19.8	5.1	5.2	5.3	4.1	29.4
3	6.2	30 5	51.4	45.3	20.5	15.3	12.8	6.7	7.1	42.4
4	8.9	47.4	45.3	28.4	10.9	18.0	16.3	14.0	8.5	40.4
XI- 1	10.9	20.2	63.3	50.4	18.9	7.0	17.8	15.1	13.0	44.6
2	9.3	24.6	40.8	53.8	18.3	14.2	18.4	10.3	8.8	41.7
Mean	8.67	24.78	47.71	34.82	19.26	13.97	12.41	10.46	9.03	35.64
S.D.	2.25	10.53	18.33	12.01	8.45	5.44	4.47	3.69	3.14	10.51

level was restored gradually and reached an almost normal value on the 5th day.

Suppession rate was estimated as follows:

$$\text{Suppression rate (S.R.)} = \frac{S_B - S_2}{S_B} \times 100\%$$

S_B: Total amount of urinary 17-OH-CS at the basal level

S_2: Total amount of urinary 17-OH-CS on the second day of suppression test.

Normal suppression rate in this study exceeded 60% and the mean was 73.68% (Table 8).

B) Suppression rate of brain tumor cases (Table 9)

In 5 cases, an abnormally low suppression rate was observed; I-15 H.K. a deep frontal aktinomycotic tumor, IV-4 Y.I. bilateral sphenoid ridge meningioma with sellar extension, V-3 I.K. suprasellar meningioma, VI-2 T.N. olfactory

Table 5. Adrenocortical response to craniotomy in brain tumor cases, suppressed with large doses of dexamethasone, (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
I- 8	10.8	9.8	14.3	17.0	15.7	11.0	7.1	6.9	9.5	13.7
9	9.1	11.3	12.9	9.0	6.7	2.4	2.1	3.2	1.8	11.1
10	10.7	21.0	28.0	19.0	11.6	11.5	7.8	5.0	4.5	22.7
11	9.8	22.5	34.0	19.3	13.1	8.0	5.3	9.3	6.9	24.9
12	7.5	7.8	25.8	10.3	7.0	3.0	2.5	3.0	6.8	11.2
13	9.0	20.1	28.8	20.5	25.1	13.3	8.2	7.0	5.8	23.1
II- 7	8.2	16.4	20.6	21.4	12.4	7.2	3.4	4.0	3.5	19.5
8	5.5	15.0	17.2	17.0	7.9	8.0	8.5	12.2	11.4	16.4
9	8.0	9.4	16.9	16.7	16.1	9.0	2.0	5.0	7.2	14.3
III- 2	12.8	21.8	17.2	16.1	15.0	10.7	8.9	8.7	9.2	18.4
3	8.9	10.9	18.5	13.4	12.4	2.5	2.6	1.1	3.8	14.3
4	9.1	26.6	22.0	20.2	13.3	4.6	5.4	3.0	3.2	22.9
5	10.5	20.8	23.1	15.1	13.4	9.5	10.0	9.1	5.7	19.6
6	8.5	20.0	20.7	29.4	12.7	6.3	16.2	11.8	11.7	23.4
IV- 3	10.3	10.8	16.1	18.2	17.8	12.2	8.1	7.2	9.1	15.0
4	4.0	14.8	10.6	9.3	9.0	8.2	5.4	4.7	4.8	11.5
5	6.1	19.9	10.7	12.5	9.6	4.8	3.7	1.8	2.0	14.4
V- 2	8.8	17.0	13.8	11.0	10.5	5.6	5.1	6.8	5.8	13.9
3	10.9	28.5	21.0	25.1	14.1	4.3	3.5	7.9	8.1	24.9
VI- 2	7.0	18.3	19.5	15.5	8.5	5.1	4.3	3.5	5.0	17.4
VII- 1	5.2	14.0	23.1	15.3	6.4	2.4	3.4	5.8	6.9	17.5
2	5.8	36.5	30.8	8.0	7.9	6.2	4.1	2.9	3.7	25.1
IX- 3	7.8	10.9	24.3	19.5	20.4	10.8	5.0	6.5	8.2	18.2
4	5.4	18.2	19.4	18.9	16.1	1.3	2.3	1.0	1.1	18.8
5	6.3	18.4	16.5	16.0	12.2	10.5	9.1	4.5	8.4	17.0
X- 5	9.8	24.1	15.5	7.8	3.3	2.0	1.4	2.8	3.0	15.8
6	10.9	13.2	13.8	13.3	8.3	8.8	9.0	11.2	8.9	13.1
7	6.1	14.0	12.9	5.9	6.1	5.0	4.2	2.2	3.0	10.9
8	13.4	23.3	22.6	18.1	11.9	13.3	9.7	8.1	11.5	21.3
XI- 3	9.1	18.0	10.7	5.4	3.9	4.0	4.8	4.8	2.6	13.4
Mean	8.51	17.45	19.25	14.64	11.58	6.98	5.76	5.64	6.09	17.94
S.D.	2.27	6.19	6.57	5.57	4.45	3.52	3.23	3.07	2.99	5.09

groove meningioma, IX-2 R.F. a large pontine tumor. In 29 other cases the suppression rate ranged within normal limits (mean was 72.36%).

C) Suppression rate of patients with pituitary adenoma or craniopharyngioma (Table 10, 11)

Lack of suppression was seen in a case of craniopharyngioma (XIII-8). Low suppression rate was seen in the following cases: XII-1, 3, 4, and XIII-12, 13). In these cases, the results may be explained by tumor involvement of the hypothalamus.

D) Suppression test after more than four weeks following surgery in dexamethasone treated cases (Table 12)

Table 6. Adrenocortical response to craniotomy in the control cases (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
C- 1	5.8	12.4	11.1	7.4	7.3	8.1	7.2	6.4	6.0	10.3
2	8.3	13.0	27.7	15.7	18.6	17.1	13.6	10.6	8.7	18.8
3	5.5	28.1	7.3	6.6	5.9	4.0	4.1	5.5	6.5	14.0
4	12.8	17.0	20.1	18.3	15.5	13.4	9.2	9.8	11.3	16.8
5	7.1	15.8	16.8	11.2	10.7	11.0	9.3	9.0	9.5	14.6
6	8.8	14.3	9.6	9.8	10.2	9.0	5.0	5.9	7.6	11.2
7	8.6	14.4	25.7	13.8	11.6	10.1	9.0	8.6	10.0	18.0
8	6.0	22.0	11.5	10.6	7.3	7.5	6.5	6.0	5.8	14.9
9	10.9	18.0	25.2	17.7	11.2	8.9	13.5	9.4	8.7	20.3
10	10.5	18.2	11.2	27.6	33.2	23.0	22.5	13.8	10.0	19.0
11	9.8	12.5	20.2	16.2	14.1	15.6	13.1	10.1	8.2	16.3
12	12.4	20.0	18.2	15.0	12.1	10.8	11.2	12.3	8.0	17.7
13	5.0	18.3	11.0	8.3	3.9	4.8	3.5	7.3	11.5	12.5
14	6.7	7.6	18.9	10.6	4.4	8.4	3.2	7.3	7.0	12.4
15	8.0	8.4	16.0	4.8	6.6	3.5	8.7	6.5	8.9	9.7
Mean	8.38	16.08	16.03	12.91	11.99	10.41	9.99	8.51	8.61	15.10
S.D.	2.38	5.00	6.19	5.61	7.10	5.03	4.83	2.46	1.72	3.25

Table 7. Adrenocortical response to lumbar sympathectomy in Buerger's disease cases (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
B- 1	5.6	25.6	26.2	22.3	15.6	7.4	8.5	6.5	3.9	24.5
2	8.9	10.6	16.7	14.6	7.7	12.4	10.4	5.7	8.7	13.9
3	11.0	15.6	9.1	8.9	10.4	10.0	9.1	8.5	10.2	11.2
4	8.7	9.8	16.8	20.9	9.1	8.8	8.3	7.9	8.1	15.8
5	10.5	14.7	17.5	13.6	13.4	8.9	9.2	8.3	12.4	15.3
6	9.1	9.0	20.4	18.3	16.8	14.5	10.3	9.5	9.3	15.9
7	9.8	18.3	19.6	18.4	10.5	12.1	14.3	9.7	10.3	18.8
8	8.0	22.2	18.3	17.9	13.4	4.9	5.5	11.4	5.3	10.5
9	7.4	33.8	24.7	12.5	10.3	9.4	9.4	4.7	6.6	23.7
10	7.9	17.4	12.9	17.1	15.1	6.3	10.1	11.2	8.8	15.8
11	8.3	7.9	13.0	11.7	8.3	10.1	8.9	8.4	7.5	10.9
12	6.4	18.5	36.8	20.3	12.2	14.8	13.5	7.6	5.9	25.2
13	5.9	16.4	28.7	16.8	11.0	10.2	9.0	7.5	7.4	20.6
Mean	8.27	16.84	20.10	16.40	11.82	9.98	9.73	8.24	8.02	17.78
S.D.	2.09	6.95	7.16	3.74	2.76	2.81	2.14	1.90	2.21	4.56

Nine cases were observed. Those cases in which the preoperative suppression rate was within normal limits, showed normal suppression rate. Two out of three cases (I-15 and VI-2) in whom the preoperative suppression rate was abnormally low were restored to the normal suppression rate. Only case

Table 8. Suppression test in normal person (urinary total 17-OH-CS, mg/day)

No.	Basal level	Suppression test (day)							S.R.(%)
		1st	2nd	3rd	4th	5th	6th	7th	
N- 1	9.2	5.8	1.9	2.7	6.5	8.8	10.5	12.1	79.7
3	7.2	5.2	2.0	2.8	4.3	7.0	6.8	7.0	72.3
5	8.7	6.7	2.8	4.0	6.8	7.7	8.1	8.3	67.8
6	11.1	8.1	2.6	5.6	9.7	10.8	11.3	10.9	76.7
8	8.4	6.8	3.2	3.5	7.3	8.0	7.9	8.1	62.0
9	9.4	7.1	1.5	3.1	8.0	9.5	8.6	9.0	84.1
11	10 9	9.0	3.2	2.8	7.9	9.7	9.8	10.7	74.7
16	5.6	4.4	0.8	1.0	5.0	5.4	5.2	5.5	72.2
Mean									73.68

Table 9. Pre-operative supression test in brain tumor cases and suppression rate of operation, (urinary total 17-OH-CS, mg/day)

No.	Basal level	Suppression test			S.R. (%)	S.R. (op) (%)
		1st	2nd	3rd		
I- 2	5.0	2.9	0.8	2.1	84.0	
4	9.1	7.0	1.5	4.7	83.5	
II- 3	8.6	6.1	1.6	3.5	81.4	
4	9.8	7.0	2.8	3.9	71.5	
5	9.1	6.3	2.2	4.6	75.9	
III- 1	8.0	4.4	1.7	4.1	78.8	
IV- 1	9.7	6.9	3.5	6.4	64.0	
2	8.5	5.2	2.5	3.1	71.6	
V- 1	7.1	5.3	1.2	3.4	83.1	
VI- 1	8.9	5.3	1.3	4.3	85.4	
VII- 1	4.8	2.0	1.8	2.2	62.5	
2	8.3	3.5	1.1	4.5	86.8	
IX- 1	5.9	4.7	2.2	2.7	62.6	
2	13.7	10.9	6.0	8.6	56.2*	
X- 1	9.1	5.9	1.7	4.9	81.3	
XI- 1	10.9	7.9	3.0	5.8	72.5	
I- 8	10.8	6.7	3.7	4.8	65.8	62.2
10	10.7	9.0	2.8	5.4	73.8	36.5
13	9.0	6.8	1.9	5.0	78.9	35.2
15	10.1	8.9	5.2	4.7	48.5*	37.4
II- 7	8.2	4.1	1.6	3.8	80.5	45.3
8	5.5	2.0	0.7	1.8	87.3	54.0
III- 4	9.1	5.9	1.8	5.7	80.8	35.8
IV- 4	4.0	4.3	3.4	3.8	15.0*	67.7
V- 2	8.8	5.0	2.4	4.2	72.7	61.1
3	10.9	9 8	6.8	8.5	37.6*	30.2
VI- 2	7.0	7.1	4.0	6.4	42.8*	10.7
VIII-1	5.2	4.3	1.0	2.3	81.8	50.9
IX- 3	7.8	4.7	1.6	3.6	79.5	49.0
4	5.4	3.0	0.5	3.4	90.8	47.3
5	6.3	3.6	0.9	3.3	85.7	52.4
X- 5	9.8	1.7	1.0	4.2	89.8	55.7
8	13.4	8.5	3.2	7.1	76.3	40.3
XI- 3	9.1	6.8	2.6	4.5	71.5	62.4
Mean					72.36	46.86

Table 10. Suppression test in pituitary adenoma cases (uriuary total 17-CH-CS, mg/day)

No.	Basal level	Suppression test			S.R. (%)
		1st	2nd	3rd	
XII- 1	5.9	5.7	4.3	6.3	28.8
3	14.2	12.7	7.2	10.6	49 3
4	8.4	6.2	3.7	4.8	55.9
5	9.4	5.5	2.0	3.0	78.7
6	4.2	1.2	0.9	2.7	78.5
8	10.2	7.4	3 1	5.7	69.6
10	14.3	5.8	2.8	4.3	80.4
Mean					55.88

Table 11. Suppression test in craniopharyngioma cases (urinary total 17-OH-CS, mg/day)

No.	Basal level	Suppression test			S.R. (%)
		1st	2nd	3rd	
XIII- 1	8.2	5.1	3 2	3.3	60.9
2	7.8	5.7	2.4	4.8	69.2
3	12.1	7.6	2.1	3.4	82.6
4	14.8	8.7	5.4	4.9	63.5
7	3.1	2.2	1.0	1.4	67.7
8	0.8	2.3	1.2	1.7	−50.0
12	8.4	7.8	6 0	8.5	28.5
13	1.0	0.9	0.5	0.9	50.0
Mean					46.55

Table 12. Suppression test after more than 4 weeks following craniotomy (urinary total 17-OH-CS, mg/day)

No.	Basal level	Suppression test			S.R. (%)
		1st	2nd	3rd	
I- 8	9.6	7.2	2.8	4.7	70.9
13	10.1	8.9	2.8	5.7	72.3
15	7.7	4.8	1.0	2.4	87.0
II- 7	8.5	4.9	3.2	4.2	62.4
III- 4	9.3	6.7	3.5	3.8	62.5
VI- 2	8.8	6.4	2.7	4.8	69.3
IX- 2	11.2	8.9	6.3	8.1	42.8
X- 5	6.7	3.4	0.8	1.3	88.6
XI- 3	8.9	6.1	3.5	3.9	60.7
Mean					68.50

IX-2 R.F. showed low suppression rate, in whom decomppressive craniectomy was performed. Some cases (II-7, III-4, VI-2 and XI-3) showed relatively low suppression rate though within normal range.

3) *Adrenocortical response to the operation*

Although maximum values were most often observed on the 2nd operative day in this study, the response was expressed as "Mean value of the first 3 days" or "Three days' mean" in order to quantitatively compare individual case.

$$M_3 = \frac{R_0 + R_1 + R_2}{3}$$

M_3: Mean value of the first three days
R_0 : Estimated value of total urinary 17-OH-CS on the day of surgery
R_1 : Estimated value of total urinary 17-OH-CS on the first operative day
R_2 : Estimated value of total urinary 17-OH-CS on the second operative day

A) Response to lumbar sympathectomy in cases with Buerger's disease (Table 7)

Total urinary 17-OH-CS was elevated to the maximum on the lst operative day, then gradually decreased until it became normal on the 6th post-operative day. The mean value of the first three days in these cases was 17.78 ± 4.56 mg.

B) Response to craniotomy in non-tumorous control cases (Table 6)

Maximum response was seen on the day of operation or the lst postoperative day. The mean of the first three days of these cases was 15.10 ± 3.25 mg.

C) Response to craniotomy in brain tumor cases

α) Brain tumor cases (excluding pituitary adenoma or craniopharyngioma) (Table 4)

The maximum peak was observed most frequently on the lst postoperative day. The mean of the first three days was estimated as 35.94 ± 10.51 mg, which was more intense than in other operations.

β) Pituitary adenoma and craniopharyngioma cases (Table 13, 14)

In these cases the minimum dosage of prednisolone (12.5 mg/day) was used for the replacement therapy during the first three post-operative days and was decreased gradually thereafter. The response ranged from normal to complete absence. The maximum value was observed on the second postoperative day in pituitary adenoma and in craniopharyngioma.

4) *Suppression of the operative response with dexamethasone*

As the maximum adrenal response to stress or exogenous ACTH was estimated to be 400 mg/day of hydrocortisone[21], the dose of dexamethasone equivalent to 400 mg of cortisol was estimated as follows:

$$400 \text{ mg} \times \frac{0.5 \text{ mg}}{20 \text{ mg}} = 10 \text{ mg}$$

Table 13. Adrenocortical response to craniotomy in pituitary adenoma cases (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
XII- 1	5.9	20.1	15.0	6.1	6.8	5.3	8.1	7.8	8.0	10.4
2	10.2	18.5	8.8	9 0	8.2	5.8	2.4	5.6	5.4	12.1
3	14.2	39.3	25.4	20.2	15.0	13.8	13.2	12.5	13.9	28.3
4	8.4	28.1	20.3	19.5	18.4	16.1	11.4	7.5	8.1	22.6
5	9.4	10.2	13.1	7.2	5.8	6.0	6.7	5.2	5.6	10.2
6	4.2	44.1	12.1	7.7	5.6	4.4	3.2	2.2	2.3	21.3
Mean	8.72	26.73	15.78	11.60	9.96	8.56	7.48	6.78	7.21	17.48
S.D.	3.17	11.87	5.52	5.86	4.93	4.59	3.94	3.16	3.56	6.96

Table 14. Adrenocortical response to craniotomy in craniopharyngioma cases (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
XIII- 1	8.2	15.7	25.8	25.2	32.2	26.2	20.2	11.9	8.1	22.2
2	7.8	20.0	26.0	9.2	7.2	3.8	5.8	1.8	4.4	18.4
3	12.1	36.7	37.5	28.0	16.8	8.9	10.0	9.3	9.8	34.1
4	14.8	18.4	10.1	8.4	10.3	10.1	8.1	8.8	7.0	12.3
5	7.3	21.8	34 3	22.1	16.9	10.7	8 8	7.8	6.3	26.1
6	2.6	4.1	3.8	4.3	4.0	6.9	2.0	4.5	1.7	4.1
7	1.1	3.2	3.5	2.0	1.5	2.8	1.0	1.2	1.5	2.6
Mean	7.70	16.97	20.14	14.01	12.70	9.91	7.97	6.47	5.57	17.11
S.D.	4.47	10.72	13.16	9.85	8.79	7.21	5.77	3.74	3.10	10.69

Table 15. Adrenocortical response to craniotomy in brain tumor cases treated with small doses of dexamethasone, (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
I- 14	13.1	29.4	39.4	28.5	17.1	11.0	5.2	4.7	5.5	32.4
II- 10	8.4	40.2	48.3	30.3	20.4	10.7	6.3	5.8	5.7	39.6
11	7.8	13.6	28.9	18.5	10.3	5.2	2 3	3.5	4.2	20.3
III- 7	5.9	15.8	63 2	37.7	15.2	6.0	3.9	2.8	2.2	38.9
VI- 3	10.3	45.0	73.4	41.4	27.4	17.3	15.5	16.3	12.1	53.3
X- 9	4.7	10.7	15.4	12.3	8.2	3.5	1.8	3.1	3.3	12.8
Mean	8.37	25.75	44.77	28.10	16.43	8.95	5.83	6.01	5.50	32.88
S.D.	2.75	13.33	19.64	10.13	6.37	4.64	4.59	4.71	3.19	13.26

These relations were determined by Holub[36] according to the anti-inflammatory action of corticosteroid derivatives.

Eight to 10 mg/day of dexamethasone was administered for the first three post-operative days and the dosage was decreased gradually on successive days and reduced to zero on the 6th post-operative day. In these cases, suppression seemed to be insufficient or absent on the first three postoperative days, though relatively low levels were seen on the 4th, 5th, 6th and 7th post-operative days (Table 15). Probably these minimum doses of dexamethasone could not suppress the high response from brain tumor craniotomy. On the other hand, it was reported that there was no critical dose and duration to prevent brain edema with administration of corticosteroids[27]. Because of the two reasons described above; that is, to prevent brain edema and to suppress (if possible) the high adrenocortical response after brain tumor craniotomy, more massive doses of dexamethasone were administered. This steroid treatment was performed under a constant schedule in successively decreased amounts; that is, 32 mg of dexamethasone was administered on the day of operation, 24 mg on the lst, 16 mg on the 2nd, and 8 mg on the 3rd post-operative day, and gradually decreased to 1 mg on the 6th post-operative day.

According to the statement of Reece *et al*[9] and Dobriner[45], the basal level is not an index of the ability of the adrenal cortex to respond to corticotrophin or surgery. For this reason, expression of the result as a percentage increase over the basal level may be fallacious. In this study, the effect of suppression with dexamethasone upon the adrenal cortex was expressed in comparison to the non-dexamethasone treated group. The comparison was made with three days' mean in each group.

A) Lumbar symathectomy in Buerger's disease cases (Table 16)

Only mild suppression was seen, which was insignificant even with the

Table 16. Adrenocortical response to lumbar sympathectomy in Buerger's disease cases treated with large doses of dexamethasone (urinary total 17-OH-CS, mg/day)

No.	Name	Yrs.	Sex	Basal level	Post-operative days								M_3
					0	1	2	3	4	5	6	7	
B- 14	N.M.	38	M	8.7	17.4	19.7	17.3	15.5	8.3	5.1	7.2	4.3	18.1
15	K.M.	43	M	8.6	15.4	20.2	13.0	9.2	7.5	6.5	6.0	5.5	16.2
16	Y.K.	35	M	5.4	13.4	14.9	7.3	7.3	3.6	3.2	2.4	2.6	11.5
17	S.M.	22	M	11.3	24.2	24.8	15.7	5.8	5.4	6.4	4.8	5.9	21.6
18	T.N.	54	M	9.2	12.9	12.1	11.2	11.0	9.2	8.9	8.7	8.1	12.1
19	T.W.	28	M	8.0	8.5	15.1	12.4	5.9	10.5	7.4	5.7	6.5	11.7
Mean				8.53	15.30	17.80	12.81	9.11	7.41	6.25	5.78	5.46	15.2
Standard deviation				1.81	4.82	4.28	3.30	3.41	2.34	1.79	2.09	1.76	3.99

Table 17. Adrenocortical response to craniotomy in pituitary adenoma cases treated with dexamethasone, (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
XII- 7	12.4	15.1	4.8	13.8	24.1	11.6	5.3	5.4	4.7	11.2
8	4.0	16.2	14.4	5.1	3.3	2.9	2.1	3.0	3.6	11.9
9	8.1	27.5	13.5	12.0	8.5	7.6	5.4	3.3	2.4	17.7
10	2.3	8.7	16.3	11.0	6.6	5.2	3.8	1.8	3.5	12.0
11	14.3	17.8	14.8	10.2	10.9	8.5	8.0	8.2	8.6	14.3
Mean	8.22	17.06	12.76	10.42	10.68	7.16	4.92	4.43	4.52	13.42
S.D.	4.63	6.07	4.08	2.92	7.18	2.96	1.95	2.26	2.17	2.38

Table 18. Adrenocortical response to craniotomy in craniopharyngioma cases treated with dexamethasone (urinary total 17-OH-CS, mg/day)

No.	Basal level	Post-operative days								M_3
		0	1	2	3	4	5	6	7	
XIII- 8	0.8	5.8	7.0	2.7	4.4	4.1	1.9	2.1	1.1	5.2
9	9.0	23.6	17.1	13.6	2.2	8.5	2.7	1.2	3.1	18.1
10	1.5	3.2	4.1	3.5	3.1	2.8	2.3	1.0	2.0	3.6
11	2.5	5.0	6.9	1.7	0.7	4.6	6.8	4.8	3.7	4.2
12	18.4	13.4	10.2	6.7	5.1	6.9	7.0	5.6	6.0	10.1
13	1.0	2.5	4.0	2.8	3.0	3.0	7.1	1.4	1.6	3.1
14	5.4	32.1	10.3	4.0	3.2	3.1	3.8	2.0	1.0	15.5
Mean	5.51	12.24	8.37	5.00	3.10	4.73	3.81	2.59	2.64	8.54
S.D.	5.93	10.65	4.25	3.80	1.32	2.01	2.06	1.07	1.66	5.69

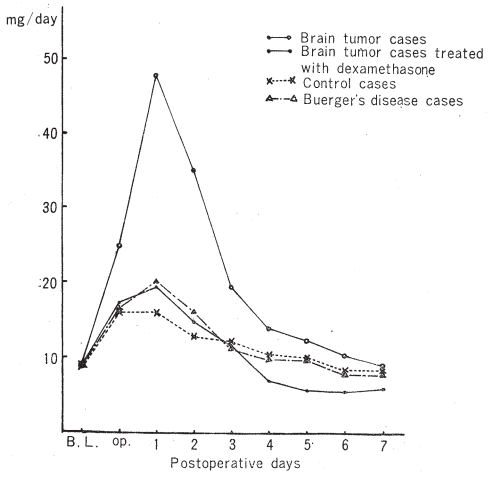

Fig. 1. Mean adrenocortical response to operations (Urinary total 17-OH-CS)

abundant dose of dexamethasone.

B) Craniotomy in brain tumor cases

Significant suppression ($P < 0.01$) was observed. When comparing the three days' mean, it was depressed from 35.64 $\pm$ 10.51 mg to 17.94 $\pm$ 5.09 mg. Fig. 1 shows the relations between the mean of each group on each day.

C) Pituitary adenoma and craniopharyngioma cases (Table 17, 18)

In most cases response was very low. However, total removal of the pituitary gland may cause adrenocortical insufficiency and result in low excretion of the

adrenal corticosteroids. In this respect, whether the suppression actually occurred or not was difficult to ascertain. Indeed, in some cases we could not maintain the patient on dexamethasone therapy during the post-operative course and were compelled to use hydrocortisone in order to save the patient. In this group suppression or treatment of brain edema was a secondary problem, compared with the replacement therapy. Twenty mg/day of cortisol or 25 mg/day of cortisone was used for replacement therapy in this absolute panhypopituitarism at resting conditions, according to the study on the maintenance dose of the adrenalectomized patient with advanced cancer of the breast[46]. However, the patient in whom the basal level of the urinary total 17-OH-CS excretion was not zero needed no special administration of the corticoid in resting conditions after the craniotomy.

DISCUSSION

1) *Basal level*

Urinary total 17-hydroxycorticosteroids excretion is maintained at a relatively constant level in each individual during non-stressful conditions[24]. Even in brain tumor cases individuals show a nearly normal level except in cases of sellar lesions, that is, craniopharyngiomas and pituitary adenomas, in which lower levels are commonly observed. However, we observed rather high basal levels in some cases of craniopharyngiomas with accompanying diabetes insipidus. Kawahara[42] reported a case of a rather high basal level. He explained that when the urine volume increased, active urinary 17-OH-CS might increase, resulting in a decrease of plasma 17-OH-CS level which then stimulated the secretion of ACTH from the pituitary gland.

In some cases, in which intracranial hypertension was progressing rapidly, high basal levels were observed. This was shown typically in case VII-3 (Table 19). After Torkildsen's operation, which had been made five years previously,

Table 19. Special cases (urinary total 17-OH-CS, mg/day)

No.	Basal level	preoperative days				ope.	postoperative days						
		−4	−3	−2	−1	0	1	2	3	4	5	6	7
I- 15	10.1	5.9	4.3	2.7	3.0	14.9	13.2	12.0	8.1	4.3	5.5	5.8	6.4
II- 12	14.8				7.2	15.6	20.3	14.2	10.3	8.8	9.0	15.8	13.0
IV- 6	15.7		7.1	5.7	3.7	5.0	9.2	9.4	9.6	17.5	5.0		
VIII-3	36.8	20.3	5.7	6.1	3.8								

I-15, II-12, IV-6: Dexamethasone was administered preoperatively to prevent advanced cerebral edema. Note high basal level in these cases.

VII-3: A pinealoma case in which rapid intracranial hypertension occurred five years after Torkildsen's operation.

his course was satisfactory; however, severe headache occurred suddenly and after 3 hours he became unconscious. Neurological examination revealed neck stiffness and bilateral papilloedema. Anticoagulant treatment was chosen because fibrinous obstruction of the Torkildsen's shunt was considered. Fourty-eight hours after the attack of headache he gradually regained consciousness and the urinary 17-OH-CS decreased, becoming normal. In other cases a relatively rapid increase in intracranial hypertension was observed in the clinical course coinciding with a high basal level. Especially high basal levels were observed in cases I-15, II-12, IV-6 (Table 19), in which we were compelled to administer dexamethasone preoperatively to prevent advanced cerebral edema. Probably rapidly increased intracranial hypertension might be a stress stimulus to ACTH secretion from the pituitary gland.

During the hours before operation the patient is more or less under psychic tension which may stimulate the adrenal cortex. Franksson *et al.*[8] described that in the preoperative patient adrenocortical function was activated and plasma 17-OH-CS elevated. This elevation is suggested to be due to psychic tension. Roche *et al.*[47] found a gradual progressive lowering of the eosinophile count as the day of operation approached. However, Halme *et al.*[10] could not find the effect of preoperative fear. In this study the mean value of the preoperative basal level was slightly lower than the normal basal level. If the basal level was influenced by the duration of intracranial hypertension, as described by Brilmayer[20], then in these cases intracranial hypertension might have persisted for a longer period since initial appearance. Uozumi[12] described that he could not find elevation of steroid excretion in intracranial hypertension, but only mild hyperresponse to the exogenous ACTH in cases of cerebellar tumor in which intracranial hypertension was common. Reece *et al.*[9] and Dobriner[45], in discussion of the basal level, indicated that it had no relation to the ability of the adrenal cortex to respond to exogenous corticotrophin (*i.e.* adrenal reserve). Nishikawa[43] showed that elevation of the basal steroid excretion was found in capsulated, expanding tumor cases and could not find elevation of the basal level in cases with destructively infiltrating brain tumor.

Brilmayer[20] mentioned that a considerable elevation of steroid excretion was observed in the patient with increasing intracranial pressure of not longer than 6 weeks duration. When the intracranial hypertension continued for longer than 6 weeks, no pathological change in steroid excretion was found. When the intracranial hypertension reaches an excessive degree after a chronic course, then the steroid excretion is significantly diminished, far below the normal range. In this study no special relation was found between the site or duration of the tumor and its basal level of urinary total 17-OH-CS excretion except in cases of sellar region. Hökfelt and Luft[42] reported abnormal urinary Porter-Silber chromogen in 3 out of 9 cases of suprasellar tumor and an absence of diurnal

rhythm. In craniopharyngiomas, these regions may be destroyed by suprasellar extension of the tumor.

2) *Response to the operation*

Many authors have written on the problem of endocrine or metabolic reactions to surgical procedures. As the adrenocortical response was rapid Hardy *et al.*[6] observed urinary excretion of corticosteroids and other metabolic changes after a major operation. Moore *et al.*[1] reported in 1955 their extensive metabolic study on the elevated urinary excretion of 17-hydroxycorticosteroids after soft tissue and bone trauma. Steenburg *et al.*[3] demonstrated that excretion of 17-OH-CS correlated well with the clinical magnitude of the trauma. On the other hand, Selye[50] mentioned that there has been evidence that trauma may affect metabolism through some other pathways, the adrenal steroids playing only a permissive role. Hetzel *et al.*[51] described that the urinary 17-OH-CS might be affected and elevated after laboratory examination or receiving an ECG or PBI test.

Halme *et al.*[10] reported that the highest level occurred on the first two or first three postoperative days, and a slightly elevated excretion persisted even on the fourth to sixth days, becoming normal on the seventh day. This was observed in cases of lung cancer, tuberculosis, thyroid tumor, gastric tumor, gastric ulcer and bone fracture. Reece *et al.*[9] emphasized the importance of estimating urinary excretion of 17-OH-CS, for the plasma level was not a true index of adrenocortical function since it resulted from a balance between the rate of secretion, the volume of distribution, the rate of conjugation and hydrogenation, the rate of destruction in the tissues, and the rate of excretion.

Swan *et al.*[5] reported on the urinary excretion of 17-OH-CS in hypothermia. The maximum level shifted from the lst to the 4th postoperative day by hypothermia.

Helmreich *et al.*[4] observed urinary 17-OH-CS levels after gastrointestinal or thoracic surgery. However, they used ether for anesthesia, and therefore emphasized the importance of the suppression of conjugation in the liver derived from the use of ether, which was considered a stimulant of adrenocortical response. Uozumi[12] noticed an intense adrenocortical response to surgical stress especially in brain tumor in comparison with pulmonary lobectomy for tuberculosis. He also found these intense responses paralleled proportionally the response to exogenous corticotrophin.

As previously cited, according to Brilmayer[20], the adrenocortical function is activated in cases with increasing intracranial pressure of not longer than 6 weeks duration. In this study, adrenocortical response to craniotomy in brain tumor cases was more intense in comparison with the lumbar sympathectomy for Buerger's disease ($P<0.01$) or even with craniotomy for non-tumorous cases

($P<0.01$), where of course intracranial pressure was normal or not so high and the post-operative brain edema not so severe. In these cases an elevated response had no significant relation to the duration of operation time or the volume of blood transfusion.

In brain tumor cases, the elevated response to stress may be caused by some involvement of the hypothalamus or of the central nervous system which in turn affects the hypothalamus. Indeed some cases in which the tumor extended to the hypothalamus showed a low suppression rate. Also in cases of sellar lesion, low suppression rates were common.

3) *Suppression of the operative response*

Many drugs may affect the adrenocortical response, such as barbiturates[52)53)], ether[54)], morphine[32)], chlorpromazin[55)] and diphenylhydantoin[56)-59)]. In this series, morphine and chlorpromazin were not used. Isozol was used in all cases in introduction of anesthesia. Ether was used in some cases only in a low concentration (3%) and its influence was only of a mild degree in comparison with the surgical stress[60)]. Diphenylhydantoin was used in all cases of craniotomy to prevent postoperative seizure attack. The effects of these drugs in this study might be neglected because these drugs were used even in the control cases of craniotomy. Ishihara[32)] described that the central suppression by corticosteroid derivatives seemed to be different from the suppression by other drugs. The former acted as hormonal suppressants rather than as pharmacological central suppressants.

Fortier[61)] classified stress in 1951 as systemic (adrenaline, cold and histamin) and neurotrophic (sound and immobilization) stimuli from his experiment in rats, following separation of the adenohypophysis from the hypothalamic center. Yates and Urquhart[24)] discussed: "systemic" stimuli were those which increased nerve traffic to the hypothalamus from below (*i. e.* from peripheral nerve and hind brain), whereas the "neurogenic" stimuli were those which increased nerve traffic to the hypothalamus from the diencephalon, or telencepnalon.

Since the experiment of Ingle *et al.*[62)] in 1938 that long term adrenocortical hormone administration caused atrophy of the adrenal cortex in animals, the concept has arisen that the rate of adrenal secretion might be the result of a feed back mechanism whereby the level of adrenal hormones in the blood influenced the release of ACTH from the pituitary. This concept, however, does not explain the observation during surgery. Egdahl and Richards[63)] observed increased adrenocortical secretion following peripheral nerve stimulation in dogs, suggesting that excitation of the central nervous system resulted in prompt activation of the pituitary adrenal axis. Richards and Pruitt[64)] also reported that the infusion of cortisol inhibited the adrenocortical response to operative trauma in dogs but did not alter the adrenal 17-OH-CS secretory response to

peripheral nerve stimulation. Sayers and Sayers[65] had reported that an inhibition of stress (cold, heat, histamin, and epinephrin) induced adrenal response by cortical hormones. Myers *et al.*[66] also observed that the infusion of either dexamethasone or triamcinolone suppressed the secretion of adrenal 17-OH-CS not only in response to surgery but also following femoral nerve stimulation in dogs. Myers *et al.*[67] also observed in man that the free plasma 17-OH-CS response to surgical operation was markedly diminished in the majority of patients in whom either triamcinolone or oxylone was administered orally prior to operation with dexamethasone infused during the operation. They emphasized that the blood level of 17-OH-CS played an important regulatory function in the release of pituitary ACTH during surgical stress in man. Though their experiments are questionable, as they used morphine and ether during the operation, these data are suggestive of the suppressibility of adrenocortical response to the operative stress by the potent exogenous corticosteroids. This concept was referred to as "steroid block". Yates *et al.*[23] proposed a "reset theory" from their experiment in rats. Their concept was derived from the application of the negative feed back theory in the electronics to the hypothalamo-pituitary-adrenocotical system. They considered that the adrenal cortical system lay under a proportional closed-loop control with variable set points; the rapid rises in plasma corticosteroid concentration which followed many varied stimuli were caused by a reset of the negative feed back control of plasma corticosteroid concentration to regulate at higher levels. According to their opinion, even the plasma corticosteroid concentration in surgical stress was under the control of a feed back mechanism at a higher level, which was "reset" by the various nervous afferent stimuli from the operated area. Estep *et al.*[25] opposed the opinion of Yates *et al.* from their clinical experience in pelvic laparotomy. They used various doses of dexamethasone and they could not gain any significant suppression. In this study, significant suppression was not obtained in lumbar sympathectomy of Buerger's disease. The elevation of the urinary excretion of 17-OH-CS in this operation was not so high, but could not be suppressed significantly even with sufficient doses of dexamethasone. However, in cases of brain tumor craniotomy, suppression was observed and the high urinary 17-OH-CS was diminished to the level of an ordinary response to surgical stress. Suppression was not observed in these cases with lower doses and also in cases of lumbar sympathectomy in Buerger's disease. Moreover, suppression in the brain tumor cases did not occur to an apparent degree. Its level was as low as was seen in non-tumorous cranial diseases or Buerger's disease. This fact that partial suppression was seen in the convalescent course was probably due to two mechanisms involved in craniotomy of brain tumor cases.

Theoretically, the following functions are ascribed to the site of suppression [16)24)].

A) Synthesis, secretion of adrenal cortex
B) Reactivity of adrenal cortex to ACTH
C) Synthesis secretion of ACTH in pituitary gland
D) Inactivation of ACTH in blood or tissue
E) Action on the hypothalamus (Secretion mechanism of CRF)
F) Action on the central nervous system affecting the hypothalamus
G) Inactivation in the liver

Among these functions, E) and/or F) play the most important role in an *in vivo* experiment[32]. The possibility of direct action of exogenous steroid on pituitary ACTH secretion or adrenal steroid biosynthesis has been discussed[68], howover in *in vivo* experiment this direct inhibitory action seems to be lesser than the suppressive action on the central nervous system affecting ACTH secretion.

A hypothesis may be presented that there are at least two factors influencing the elevation of the operative adrenocortical response in the craniotomy of brain tumor. The first factor is the unsuppression with corticosteroid which was equally observed in other operations, and the second factor the suppression which was apparently seen in brain tumor craniotomy. Ishihara[32] proposed that the unsuppressible factor was a humorally active peptide factor derived from the tissue injury and that the suppressible factor was of neurohumoral or neural origin.

Ganong[16] postulated three forces or "vectors" to explain ACTH secretion mechanism. One is the degree of hypothalamic activation, that is, pituitary driving mechanism which is made up in large part of afferent nervous activity in the limbic and reticular system. A second is the extent to which ACTH secretion is checked by the circulating corticoid level, which may be composed of more than one locus. As a third variable, he described a neural inhibitory component. If his theory is accepted, the intense response in craniotomy and the suppressibility of operative response with dexamethasone in this study, may be due to involvement of the neural inhibitory component.

4) *Relationship between the preoperative suppression test and suppression rate of craniotomy*

In this study suppression rate of operative response is defined as follows:

$$\text{S.R.(op)} = \frac{AM_3 - M_3}{AM_3}$$

AM_3: Average of the three days' mean of brain tumor cases in which dexamethasone was not used.

M_3: Three days' mean of the dexamethasone treated case

The suppression rate of the operative response intends to compare the sup-

pressibility of the individual patient with dexamethasone during and after surgery. This is, as it were, an imaginary suppression from the three days' mean of the operative response in the control cases without administration of dexamethasone, as the operative response of the patient, who was administered dexamethasone, could not be compared with his own response without dexamethasone.

Patients who demonstrated normal suppression rate (S.R. > 60%) had a relatively clear correlation to the S.R.(op), when S.R.(op) was lower than 60%.(Fig. 2). The correlation coefficient was calculated as 0.75.

Three cases showed relatively low suppression rate with a high S.R.(op) in which preoperative symptoms of intracranial hypertension seemed to be extreme. Other three cases, in which the S.R. was abnormally low, showed various S.R.(op). It was difficult to discuss whether the operative response was low or the suppression was high.

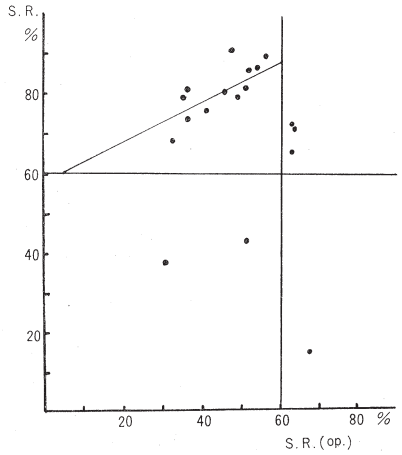

Fig. 2. Relation between preoperative suppression rate and suppression rate of operative response.

5) *Post-operative suppression rate*

After more than four weeks, the suppression test was performed on nine cases. All cases except one showed a normal S.R., though relatively low. In the abnormal case, only Torkildsen's operation was done. These data showed that after four weeks, the superphysiological doses of dexamethasone during and after the operation did not affect the suppressibility of the hypothalamo-pituitary-adrenocortical function.

Krieger[56] reported the effects of diphenylhydantoin on pituitary-adrenal interrelation. From her data, it would appear that diphenylhydantoin administration interferes with the mechanism of the integrity of the hypothalamic pituitary ACTH secretion, without affecting the basal secretion of the adrenal cortex or its ability to respond to exogenously administered ACTH. Oppenheimer *et al.*[59] reported that diphenylhydantoin did not affect the integrity mechanism. They meaured the suppression test with dexamethasone. Recently Kahnt and Neher[69] reported that diphenylhydantoin acted as an inhibitor to adrenal hydroxylase *in vitro*, and suggested that *in vivo* it might act on the steroid biosynthesis at the adrenal cortical level besides its action on the central nervous system. In this study, suppression was observed on operative response, and doses of diphenylhydantoin were lower and suppression compared with con-

trol cases in which diphenylhydantoin was used also. Further factor analysis was difficult in this study. Probably an enzymatical study will be necessary in the future.

McCarthy *et al.*[70] described that hypothalamo-pituitary function after severe head injury was depressed. Their data showed a low suppression rate with the dexamethasone test. Their patients were not administered diphenylhydantoin. Their patients reacted to ACTH and pyrogen. In this study some patients showed relatively low suppression rate within normal limits. These data are difficult to analyse, whether the low value is derived from diphenylhydantoin or superphysiological doses of the dexamethasone or surgical involvement of the central nervous system.

The mechanism of the inhibition of adrenocortical function due to exogenous glucocorticoid administration has been studied (Ingle *et al*[62], Hirama[34], and Imura[71]). Nowadays, the action of glucocorticoids on the corticotrophin releasing factor secretion is considered to be most important. Both the duration and doses of glucocorticoids are responsible for the suppression of adrenocortical function. Christy[72] described from his study in man that the former was more important than the latter. Sakauchi[73] and Hirama[34] reported that the minimum dose might not completely suppress the adrenocortical response. However, a sufficient dose and sufficient duration suppresses the adrenocortical function without fail (over 4 weeks, with a total of 45 mg dexamethasone---Hirama).

In this study large doses were administered even during a short period. The suppression after more than 4 weeks as determined by the feed back test was normal. The extensive stress sets off the suppressive faculty of exogenous large doses of glucocorticoids.

CONCLUSION

1) Preoperative basal level of urinary total 17-OH-CS was lower in brain tumor cases than in normal cases except in some cases with rapidly increasing intracranial hypertension.

2) Adrenocortical response, measured as urinary total 17-OH-CS, was more intense in brain tumor craniotomy than in other operations chosen as control.

3) Large doses of dexamethasone which were administered prophylactically in brain tumor craniotomy to prevent cerebral edema, suppressed this intense adrenocortical response, and reduced to the same degree of adrenocortical response seen in control operations.

4) In most cases suppression with dexamethasone in craniotomy had a correlation to the preoperative suppression rate.

5) More than 4 weeks after craniotomy with dexamethasone treatment, suppression test ranged within normal limit.

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REFERENCES

1) Moore, F. D., Steenburg, R. W., Ball, M. R., Wilson, G. M. and Myrden, J, A., Studies in surgical endocrinology 1. The urinary excretion of 17-hydroxycorticosteroids, and associated metabolic changes in cases of soft tissue trauma of varying severity and in bone trauma, *Ann. Surg.*, **141**, 145, 1955.
2) Moore, F. D., Endocrine change after anesthesia, surgery and unanesthetized trauma in man, *Recent Progr, Hormone Res.*, **13**, 511, 1957.
3) Steenburg, R, W., Lennihan, R. and Moore, F. D., Studies in surgical endocrinology II The free blood 17-hydroxycorticoids in surgical patients; Their relation to urine steroids, metabolism and convalescence. *Ann. Surg.*, **143**, 180, 1956.
4) Helmreich, M. L., Jenkins, D. and Swan, H., The adrenal cortical response to surgery. II Changes in plasma and urinary corticosteroid levels in man, *Surgery*, **41**, 895, 1957.
5) Swan, H., Jenkins, D. and Helmreich, M. L., The adrenal cortical response to surgery III. Changes in plasma and urinary corticosteroid levels during hypothermia in man, *Surgery*, **42**, 202, 1957.
6) Hardy, J. D., Richardson, E. M. and Dohan, F. C., The urinary excretion of corticoids and 17-ketosteroids following major operations. Correlation with other aspects of metabolism, *Surg. Gynec. Obstet.*, **96**, 448, 1955.
7) Franksson, C., Gemzell, C. A. and Von Euler, U. S., Cortical and medullary adrenal activity in surgical and allied conditions., *J. Clin. Endocr.*, **14**, 608, 1954.
8) Franksson, C. and Gemzell, C. S., Adrenocortical activity in the preoperative period, *J. Clin. Endocr.*, **15**, 1069, 1955.
9) Reece, M. W., Edwards, K. M. and Jepson, R. P., Adrenocortical response to surgery, *Surgery*, **42**, 669, 1957.
10) Halme, A., Pekkarinen, A. and Turunen, M., On the excretion of noradrenaline adrenaline, 17-hydroxycorticosteroids and 17-ketosteroids during the postoperative stage, *Acta Endocr. (Kobenhavn), supple.* **32**, 3, 1957.
11) Fisher, R. G., Copenhaver, J. H. and Naukkarinen, I., Adrenal cortical hormone output in cerebral injury and neoplasm, *Surg. Forum*, **9**, 683, 1958.
12) Uozumi, T. The adrenocortical function of brain tumor patient. *Folia Endocr. Jap.*, **38**, 1146, 1963. (In Japanese)
13) Inagaki, H , Pre- and postoperative determination of 17-OH-CS and endocrine disorders in the tumor of the sellar region, *Clin. Surg. (Tokyo)*, **19**, 1149, 1964. (In Japanese)
14) Wise, B. L., Russell, H. and Vincent, J. P., Fluid and electrolyte balance following injuries to the head, *Amer. J. Surg.*, **97**, 205, 1959.
15) Matsumoto. M., Changes in the urinary adrenocorticosteroid following to the head injuries, *Endocr.* Metab. **2**, 119, 1960. (In Japanese)
16) Ganong, W. F., The central nervous system and the synthesis and release of adrenocorticotropic hormone. *In* Advances in neuroendocrinology, Edited by A. V. Nalbandov University of Illinois press. Urbana 1963.
17) Ishihara, I., Komori, Y. and Tamura, Y., Experimental studies on neuroendocrine factors mediating environmental influences. Adrenal medullary and cortical secretion after electrical stimulation of limbic system, *Ann. Rep. Res. Inst. Environ. Med. Nagoya*

Univ., **17**, 132, 1965.
18) Bauer, H. G., Endocrine and other clinical manifestation of hypothalamic disease. (A survey of 60 cases, with autopsies), *J. Clin. Endocr.*, **14**, 13, 1954.
19) Kahana, L., Lebovitz, H., Lusk, W., Mcpherson, H. T., Davidson, E. T., Oppenheimer, J. H., Engel, F. L., Woodhall, B. and Odom, G., Endocrine manifestations of intracranial extrasellar lesions, *J. Clin. Endocr.*, **22**, 304 1962.
20) Brilmayer, H., Endocrinological aspects of intracranial hypertension. *Acta Endocr. (Kobenhavn)*, **31**, 130, 1959.
21) Nugent, C. A., MacDiarmid, W. D., Nelson, A. R. and Tyler, F. H., Rate of adrenal cortisol production in response to maximal stimulation with ACTH, *J. Clin. Endocr.*, **23**, 683, 1963.
22) Katsuki, S., Studies on the central control of adrenocortical function. *In* The central control of endocrine glands. Edited by S. Katsuki Igaku Shoin Ltd. Tokyo, 1965. (In Japanese)
23) Yates, F. E., Leeman, S. E., Glenister, D. W. and Dallman, M. F., Interaction between plasma corticosterone cencentration and adrenocorticotropin releasing stimuli in the rat: Evidence for the reset of an endocrine feedback control, *Endocrinology*, **69**, 67, 1961.
24) Yates, F. E. and Urquhart, J., Control of plasma concentration of adrenocortical hormones, *Physiol. Rev.*, **42**, 359, 1962.
25) Estep, H. L., Island, D. P., Ney, R. L. and Liddle. G. W., Pituitary adrenal dynamics during surgical stress, *J. Clin. Endocr.*, **23**, 419, 1963.
26) Ingraham, F. D., Matson, D. D. and McLaurin, R. L., Cortisone and ACTH as an adjunct to the surgery of craniopharyngiomas, *New Eng. J. Med.*, **246**, 568, 1952.
27) Blinderman, E. E., Graf, C. J. and Fitzpatrick, T., Basic studies in cerebral edema. Its control by a corticosteroid (Solu-Medrol). *J. Neurosurg.*, **19**, 319, 1962.
28) Gårde, A., Experiences with dexamethasone treatment of intracranial pressure caused by brain tumors, *Acta Neurol. Scand.*, **41**, *suppl.* **13**, 445, 1965.
29) Rasmussen, T., and Des Raj Gulati, Cortisone in the treatment of postoperative cerebral edoma, *J. Nenrosurg.*, **19**, 435, 1962.
30) Hatanaka, H., Sano, K., Kitamura, K., Kamano, H. and Masuzawa, H., Steroids and cerebral edema, *Brain Nerve (Tokyo)* **15**, 624, 1963. (In Japanese)
31) Sugihara, E., Adrenocortical function in Buerger's disease. Especially on urinary 17-OH-CS, the amount of 17-KS excreted and its fractions. *J. Nagoya Med. Ass.*, **78**, 36, 1959. (In Japanese)
32) Ishihara, I., The disturbance of diencephalone with drugs; Medicine which suppress the pituitary-adrenocortical activating system. *Jap. J. Clin. Med.*, **20**, 432, 1962. (In Japanese)
33) Peterson, R. E., Adrenocortical steroid metabolism and adrenal cortical function in liver disease, *J. Clin. Invest.*, **39**, 320, 1960.
34) Hirama, M., Study of the inhibitory effect of anti-inflammatory corticosteroids upon pituitary-adrenocortical function, *Folia Endocr. Jap.*, **39**, 342, 1963. (In Japanese)
35) Linèt, O. and Bartová, A. The effect of long-term administration of cortisol and some androgenic-anabolic steroids on the rat adrenals. *Acta Endocr* (Kobenhavn), **51**, 481, 1966.
36) Holub, D. A., Jailer, J. W., Kitay, J. I., and Fratz, A. G., Direct and indirect estimation of pituitary adrenocorticotropin reserves in man following adrenal steroid therapy, *J. Clin. Endocr.*, **19**, 1540, 1959.
37) Galicich, J, H. and French, L. A., Use of dexamethasone in the treatment of cerebral edema resutling from brain tumors and brain surgery, *Amer. Pract.*, **12**, 169, 1961.
38) Kornel, L., An improved, rapid method for free and conjugated 17-hydroxycorticos-

teroids in urine, *Metabolism*, 8, 432, 1959.
39) Iwai, K., Muranaka, H., Yahata, M., Ishizaki, Y., Manju, T. and Imura, H., Clinical method for corticoid. *Endocr. Metab.*, **2**, 184, 1960. (In Japanese)
40) Sasaki, T., Hazama, T., Yoshimura, T., Morinaga, T. and Torii, T., Method for urinary total 17-hydroxycorticosteroids, *Naibunppitsu*, **1**, 382, 1954. (In Japanese)
41) Liddle, G. W., Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome, *J. Clin. Endocr.*, **20**, 1539, 1960.
42) Kawahara, K., Diurnal variation of urinary steroids and its suppression by corticosteroid administration in human subjects, *Folia Endocr. Jap.*, **40**, 9, 1964. (In Japanese)
43) Hibino, S. and Ishihara, I., Clinical study on the central control of adrenocortioal secretion. Diurnal variation of urinary steroids and its suppression by corticosteroid administration. *In* The central control of endocrine glands. Edited by S. Katsuki Igaku Shoin Ltd. Tokyo 1965.
44) Van Brunt. E. E. and Ganong. W. E., The effects of preanesthetic medication, anesthesia and hypothermia on the endocrine response to injury, *Anesthesiology*, **24**, 500, 1963.
45) Dobriner, K., Studies in steroid metabolism. XXII. The adrenal response to ACTH in young and old men, *J. Clin. Invest.*, **33**, 222, 1954.
46) Okumura, O., Studies on the maintenance of the adrenalectomized patients with advanced cancer of the breast, *Folia Endocr. Jap.*, **40**, 1966, 1965. (In Japanese)
47) Roche, M., Thorn, G. W. and Hills, A. G., The levels of circulating eosinophils and their response to ACTH in surgery, *New Eng. J. Med.*, **242**, 307, 1950.
48) Nishikawa, M. Studies on the central control mechanism of the pituitary adrenocortical function. *In* the central control of endocrine glands. Edited by S. Katsuki Igaku Shoin Ltd. Tokyo 1965.
49) Hökfelt, B. and Luft, R., The effect of suprasellar tumors on the regulation of adrenocortical function, *Acta Endocr.* (*Kobenhavn*), **32**, 177, 1959.
50) Selye, H. "Conditioning" versus "permissive" actions of hormone. *J. Clin. Endocr.*, **14**. 122, 1954.
51) Hetzel, B. S., Schottstaedt, W. W., Grace, W. J. and Wolff, H. G., Change in urinary 17-hydroxycorticosteroid excretion during stressful life experienced in man, *J. Clin. Endocr.*, **15**. 1057, 1055.
52) Harwood, C. T. and Mason, J. W., Acute effects of tranquilizing drugs on the anterior pituitary ACTH mechanism, *Endocrinology*, **60**, 239, 1957.
53) Woodburg, D. M., Relation between the adrenal cortex and the central nervous system, *Pharmacol. Rev.*, **10**, 275, 1958.
54) Royce, D. C. and Sayers, G., Blood ACTH; Effects of ether, pentobarbital, epinephrin and pain, *Endocrinology*, **63**, 794, 1958.
55) Sevy, R. W., Ohler, E. A. and Weiner, A., Effect of chlorpromazine on stress induced adrenal ascorbic acid depletion, *Endocrinology*, **61**, 45, 1957.
56) Krieger, D. T., Effect of diphenylhydantoin on pituitary-adrenal interrelations, *J. Clin. Endocr.*, **22**, 490, 1962.
57) Krieger, D. T., Ross, F. R. and Krieger, H. P., Response to dexamethasone suppression in central nervous system disease, *J. Clin. Endocr.*, **26**, 227, 1966.
58) Bray, P. F., Ely, R. S. and Kelley, V. C., Studies of 17-hydroxycorticosteroids. VIII Adrenocortical function in patients with convulsive disorder, *Arch. Neur. psych.*, **72**, 583, 1954.
59) Oppenheimer, J. H., Fisher, L. V. and Jailer, J. W,, Disturbance of the pituitary-adrenal interrelationship in diseases of the central nervous system, *J. Clin. Endocr.*, **21**, 1023, 1961.
60) Hodges, J. R. and Vernikos, J., Circulating corticotrophin in normal and adrenalectomized rats after stress, *Acta Endocr.* (*kobenhavn*), **30**, 188, 1959.

61) Fortier, C., Dual control of adrenocorticotrophin release. *Endocrinology*, **49**, 782, 1951.
62) Ingle, D. J., Higgins, G. M. and Kendall, E. C., Atrophy of the adrenal cortex in the rat produced by administration of large amounts of cortin. *Anat. Rec.*, **71**, 363, 1938.
63) Egdahl, R. H. and Richards, J. B. The effect of stimulation of the femoral nerve on adrenal 17-hydroxycorticosteroids secretion in dogs. *Surg. Forum*, **7**, 142, 1957.
64) Richards, J. B. and Pruitt, R. L., Hydrocortisone suppression of stressinduced adrenal 17-hydroxycorticosteroids secretion in dogs. *Endocrinology*, **60**, 99, 1957.
65) Sayers, G. and Sayers, M. A., Regulation of pituitary adrenocorticotrophic activity during the response of the rat to acute stress, *Endocrinology*, **40**, 265, 1947.
66) Myers, J. L., O'Hara, E. T., Heizer, J. W., Liberman, H. and Marks, L. J., The effect of the acute administration of corticosteroids on the adrenocortical response to surgery, *Surg. Fornm*, **11**, 131, 1960.
67) Myers, J. L., Marks, L. J., O'Hara, E. T., Heizer, J. W. and Liberman, H., Regulatory function of circulating corticosteroids in the pituitary-adrenal response to surgical operation, *Ann. Surg.*, **154**, 895, 1961.
68) Langecker, H., and Lurie, R., Die Hemmung der Corticotropin-Sekretion durch Steroide, *Acta Endocr* (*Kobenhavn*) **25**, 54, 1957.
69) Kahnt, F. W. and Neher, R., Über die adrenale Steroid-Biosynthese *in vitro* III Selective Hemmung der Nebennierenrinden-Function, *Helv. Chim. Acta.*, **49**, 725, 1966.
70) McCarthy, C. E., Willis, M. R., Keane, P. M., Gaugh, K. R. and Read, A. E., The SU-4885 (Methopyrapone) response after head injury, *J. Clin. Endocr.*, **24**, 121, 1964.
71) Imura, H., Experimental studies on adrenocortical insufficiency induced by the administration of glucocorticoid, *Folia Endocr. Jap.*, **38**, 817, 1962. (In Japanese)
72) Christy, N. P., Wallace, E. Z. and Jailer, J. W., Comparative effects of prednisone and of cortisone in suppressing the response of the adrenal cortex to exogenous adrenocorticotropin, *J. Clin. Endocr.*, **16**, 1059, 1956.
73) Sakauchi, N., Suppression of the pituitary-adrenocortical system during and after prolonged corticoid treatment, *Niigata Med. J.*, **74**, 1291, 1960. (In Japanese)